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Adjunctive Nutritional Management of Cancer And Integrative Therapies

James Meschino DC, MS, ROHP

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Cancer: My Experience and Credentials

- Kept Detailed Notes for over 30 years on this subject – a great deal of which is in your note package (Not responsible for this reading for exam purposes, as these slides summarize key points, but good reference material to clarify anything that may seem confusing or if you want more details on a particular anti-cancer nutrient, or proto-oncogene)

- Faculty Member of the American Academy of Anti-Aging Medicine –in Integrative Cancer Therapy Fellowship Program – saw the world's most innovative and leading edge MD's and PhD Researchers on this topic

- Director of Nutritional Therapy at Integrative Cancer Clinic in Toronto (MD Medical Director)

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Main Topics Covered

1. Cell Cycle, Cyclins, Tumor Suppressor Genes, Proto-oncogenes
2. Typical Patient Work-Up
3. Biological Targets of Integrative and Conventional Cancer Rx
4. Nutrients That Act as Adjunctive Agents in Cancer Treatment
5. Supplement Protocol Considerations
6. Drug-Nutrient and Nutrient-Gene Interactions of Importance
7. How Chemotherapy Drugs Work
8. Other Integrative Cancer Treatments
9. Cancer Specific Diet (treatment and prevention of recurrence)
10. Other Lifestyle Factors of Importance - Exercise

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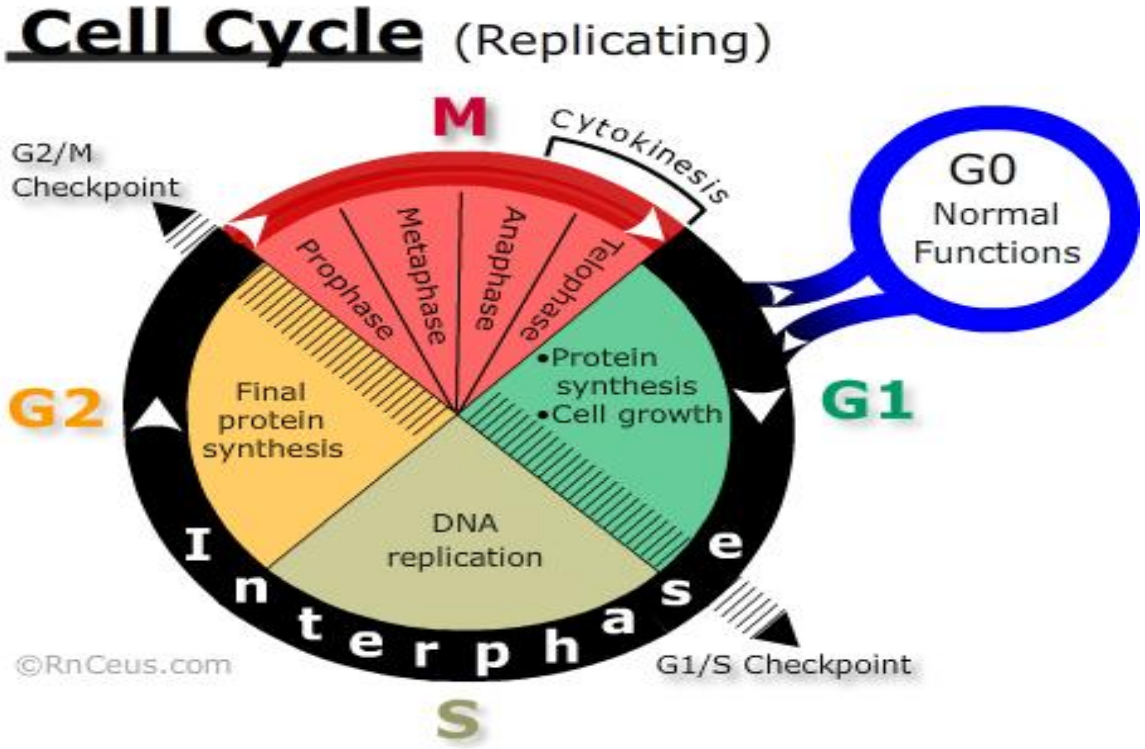
Cell Cycle- Note Checkpoints (G1 and G2) – rapid cell division rates race right through checkpoints, increasing risk of mutations.

G1 Phase: cell synthesizes mRNA and proteins in preparation for subsequent steps leading to mitosis



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G1, S-phase and G2 (Interphase)

- When a cell passes the G1 checkpoint it enters the S phase of the cell cycle. During this phase DNA is replicated. After DNA replication, the cell leaves S phase and enters G2, when the cell prepares for mitosis or meiosis.

- **S Phase**: To produce two similar daughter cells, the complete DNA instructions in the cell must be duplicated. DNA replication occurs during this S (synthesis) phase. Gap 2 (**G2**): During the gap between DNA synthesis and mitosis, the cell will continue to grow and produce new proteins

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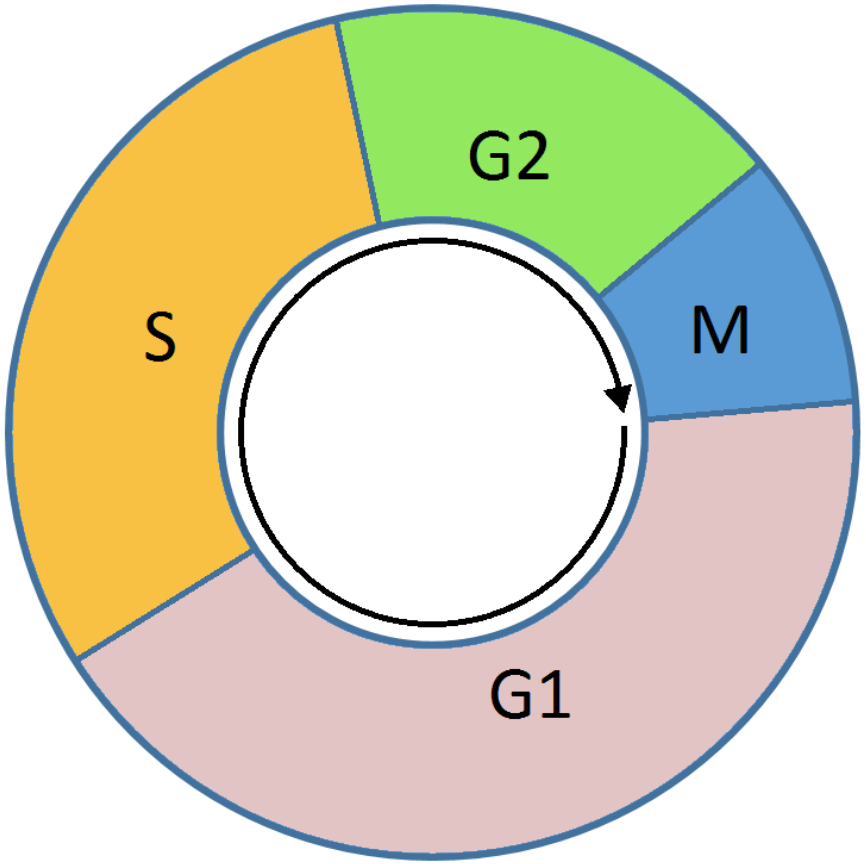
G=**G**ap; S= DNA-**S**ynthesis; M- **M**itosis



G1 - Growth

S - DNA synthesis

G2 - Growth and preparation for mitosis

M - Mitosis (cell division)

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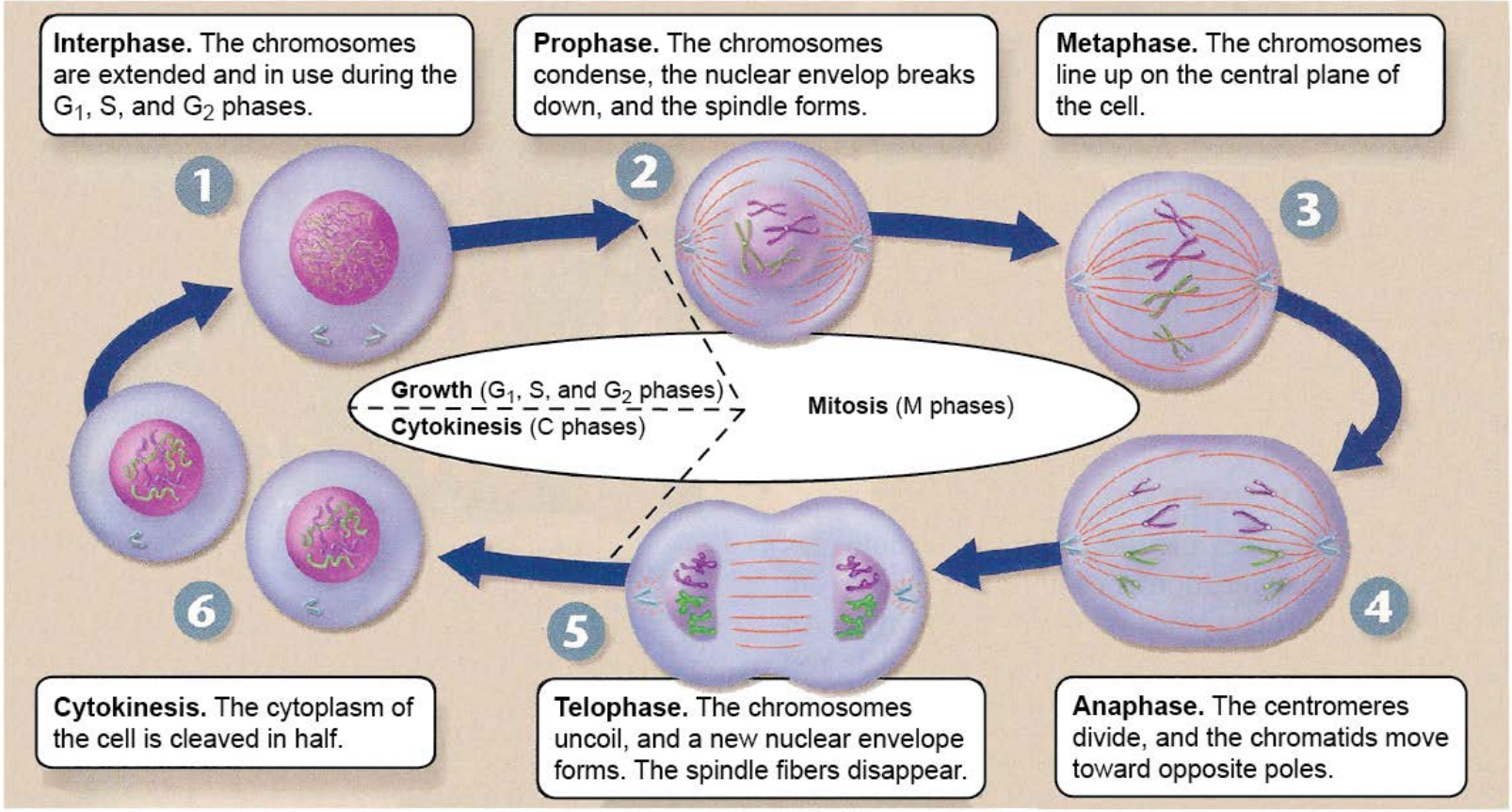
Note: Steps In Mitosis



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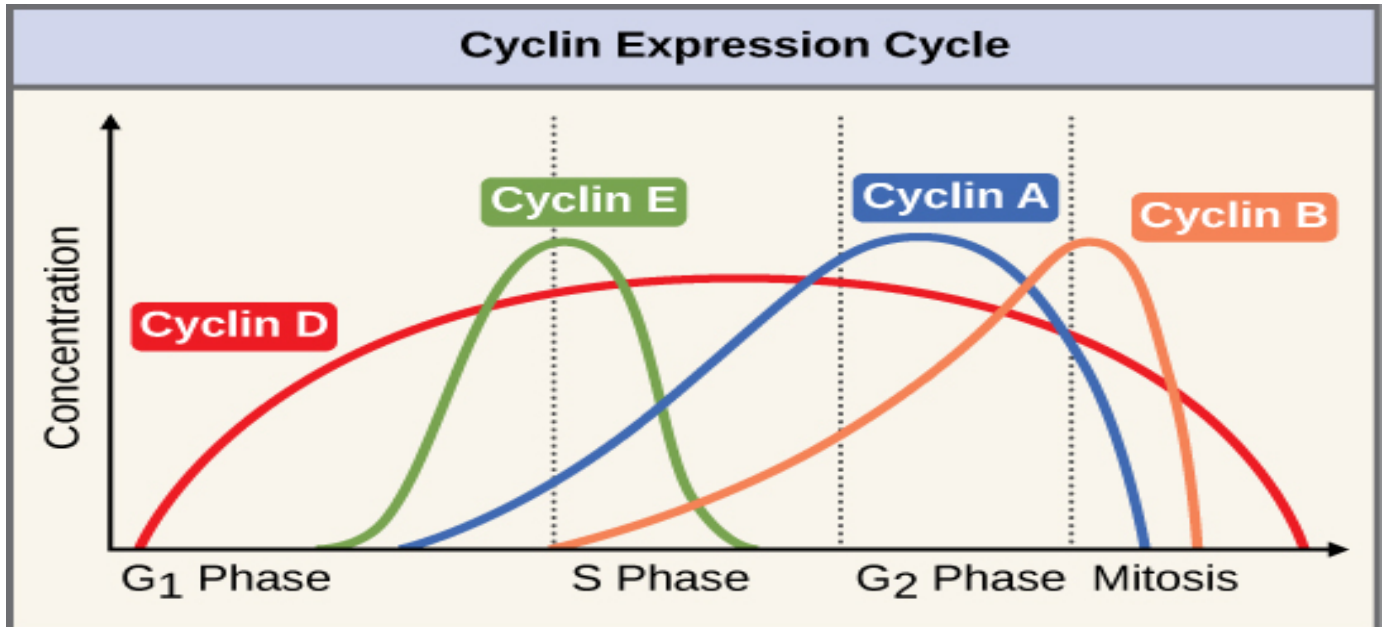
Cyclins Drive the Cell Cycle: Sustained levels of certain cyclins (i.e. cyclin D) often seen in cancer: Cyclin are peptides, turned on and off by cyclin dependant kinase enzymes (as they become phosphorylated and dephosphorylated).



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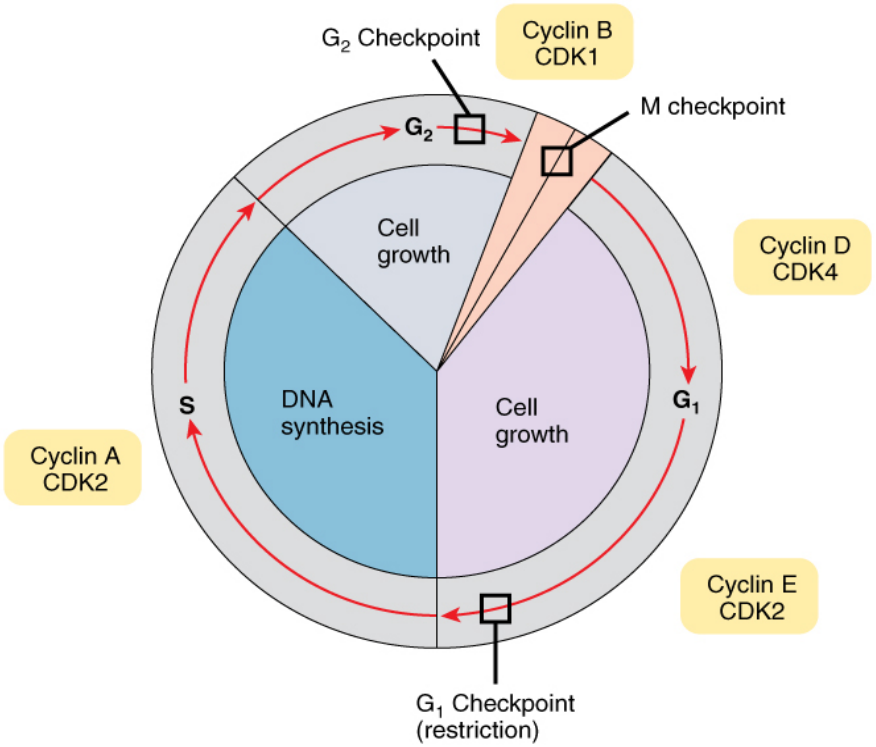
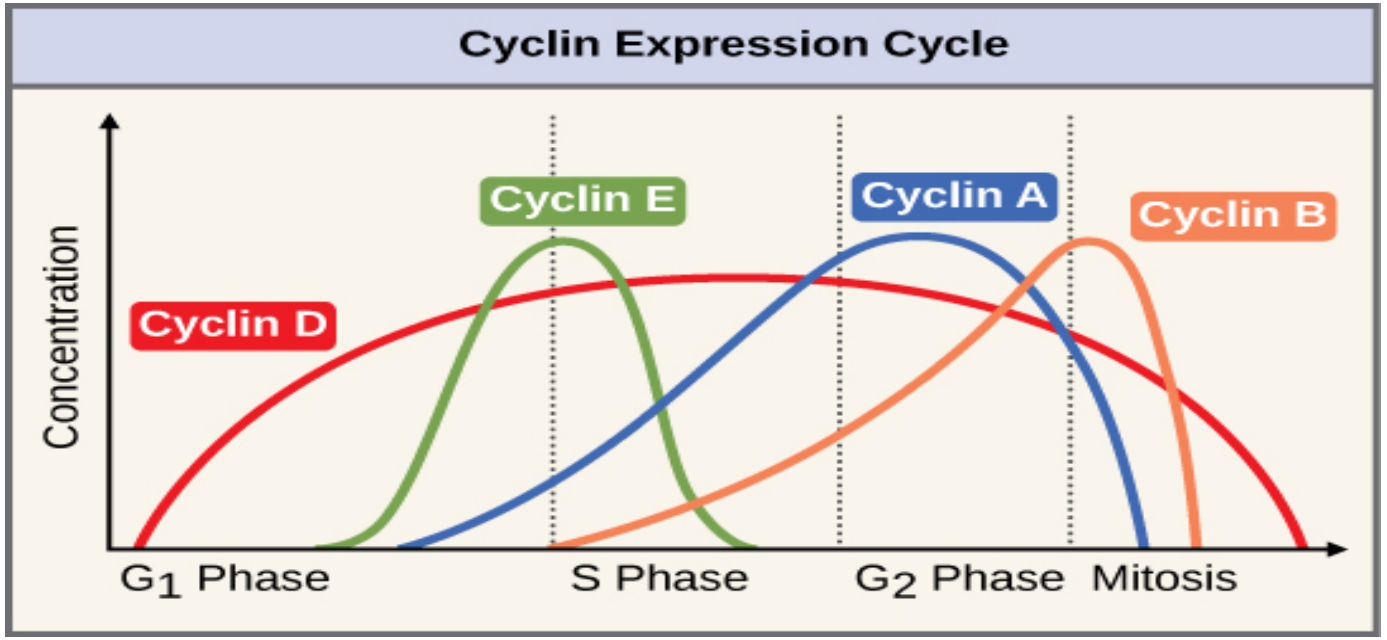
Note Cyclin Dependant Kinase 1, 4, 2





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Tumor Suppressor Genes

Functions

- Tumor-suppressor genes, or more precisely, the proteins for which they code, either have a dampening or repressive effect on the regulation of the cell cycle or promote apoptosis, and sometimes do both. The functions of tumor-suppressor proteins fall into several categories including the following:
- **Repression of genes that are essential for the *continuing* of the cell cycle**. If these genes are not expressed, the cell cycle will not continue, effectively inhibiting cell division.
- Coupling the cell cycle to DNA damage. As long as there is damaged DNA in the cell, it should not divide. **If the damage can be repaired, the cell cycle can continue.**
- If the damage *cannot* be repaired, **the cell should initiate apoptosis** (programmed cell death) to remove the threat it poses for the greater good of the organism.
- Some proteins involved in **cell adhesion prevent tumor cells from dispersing,** block loss of contact inhibition, and inhibit metastasis. These proteins are known as metastasis suppressors

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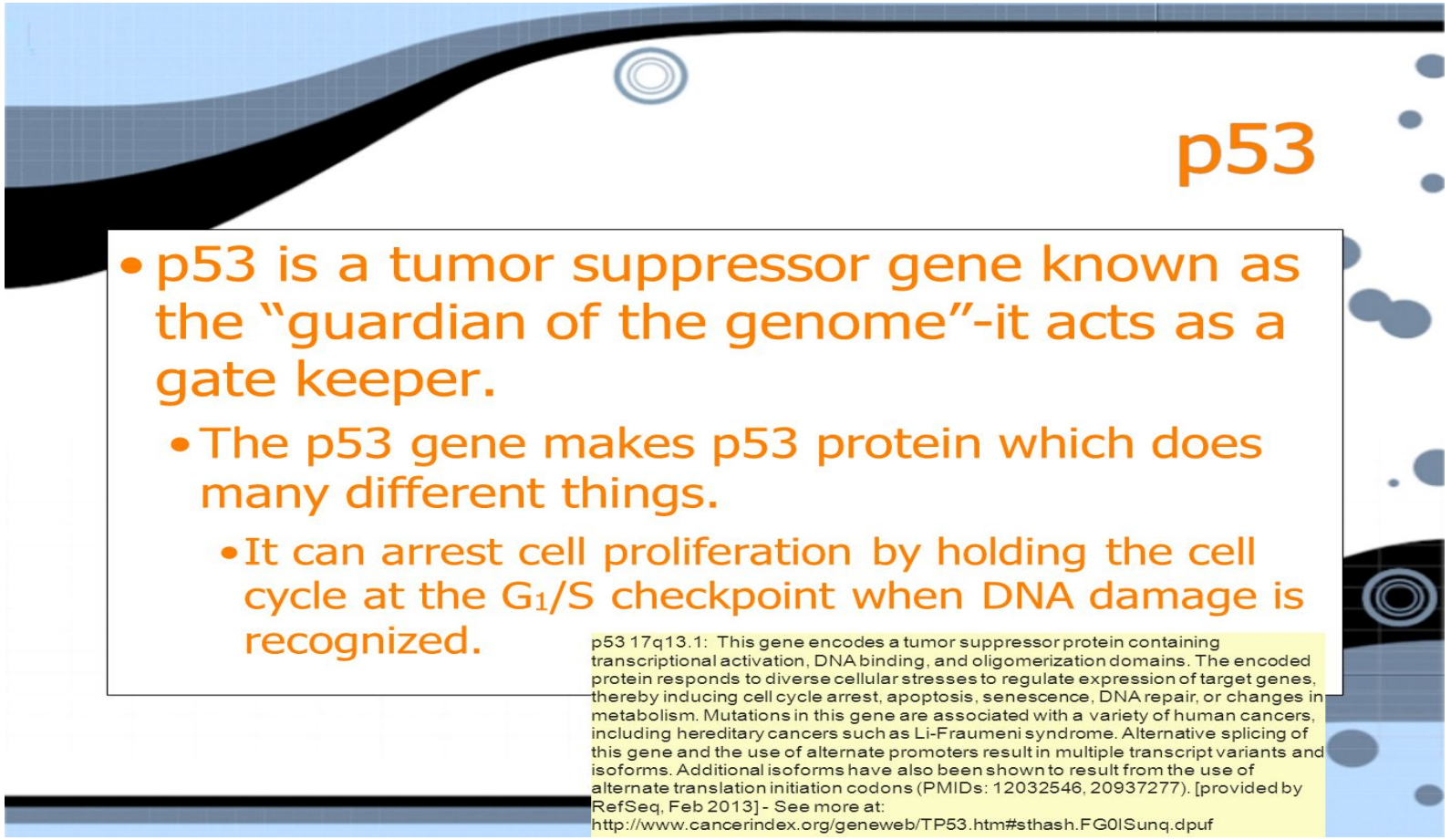
P53 Tumor Suppressor Gene- mutated in 50% of human cancers



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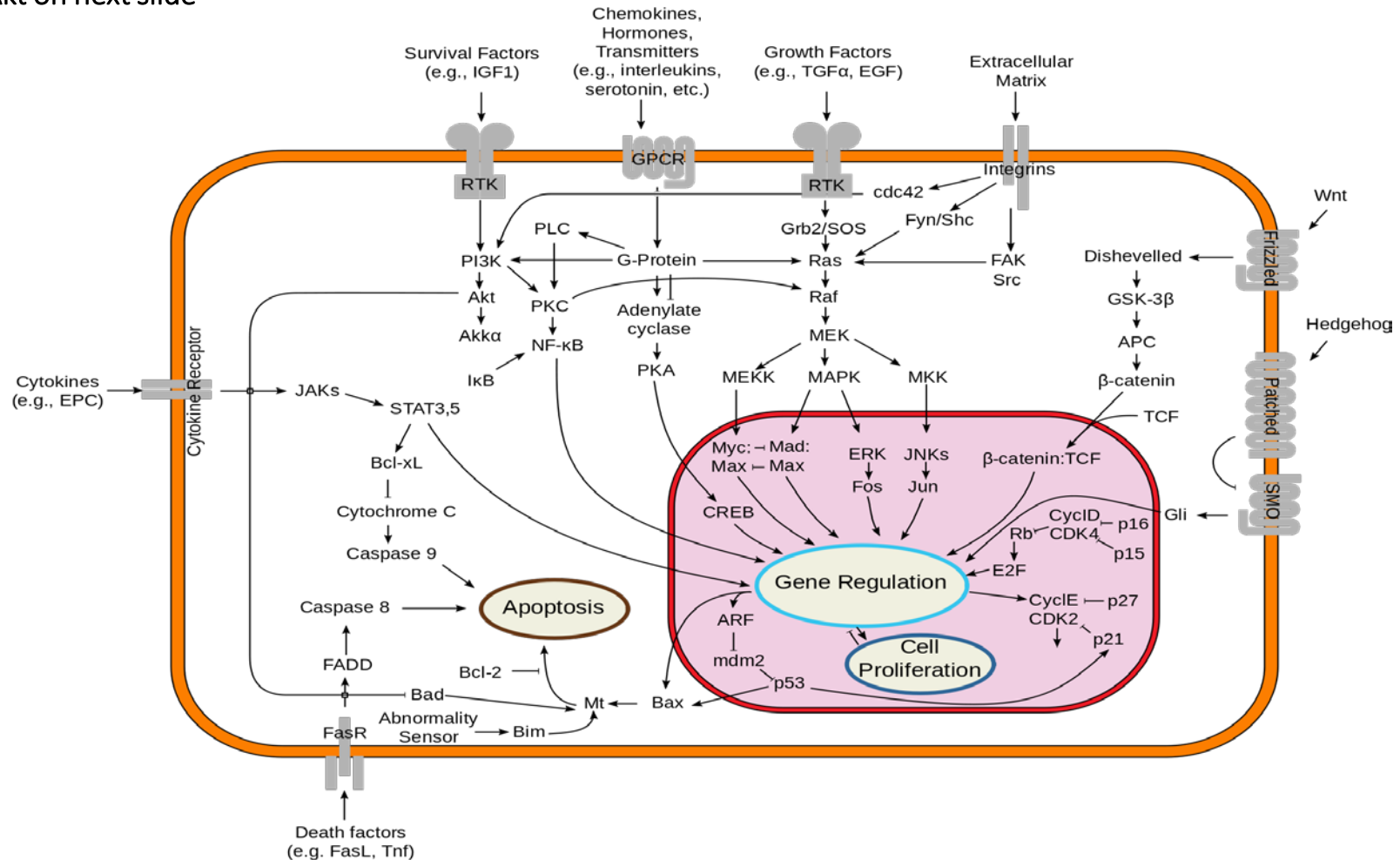
P53, Bcl-2, Stat 3, RTK-PI3K-NFkb, Ras-MAPK, Wnt-beta-catenin, P21,, Her-2, Insulin and IGF-1, Death and Cytokine receptors, Akt cmyc. central role played by the pathway that controls the activity of the retinoblastoma tumor suppressor protein (Rb), which in turn regulates the E2F transcription factor. In particular, it is now clear that the Rb/E2F pathway is critical in regulating the initiation of DNA replication. Loss of Rb tumor suppressor causing up-regulation of transcription factor E2F and this system is disrupted in virtually all human cancers.

m-TOR- via Akt on next slide



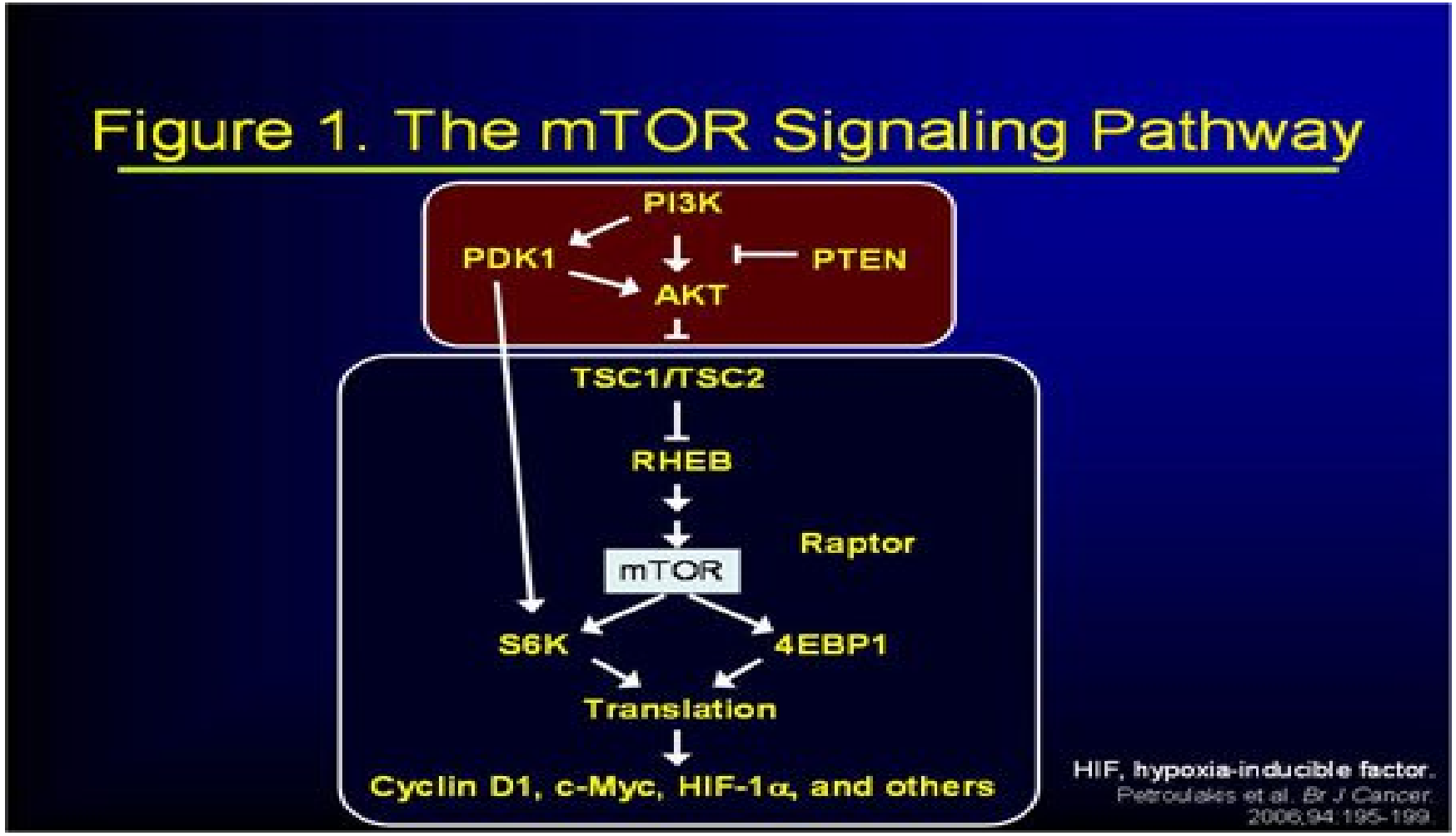
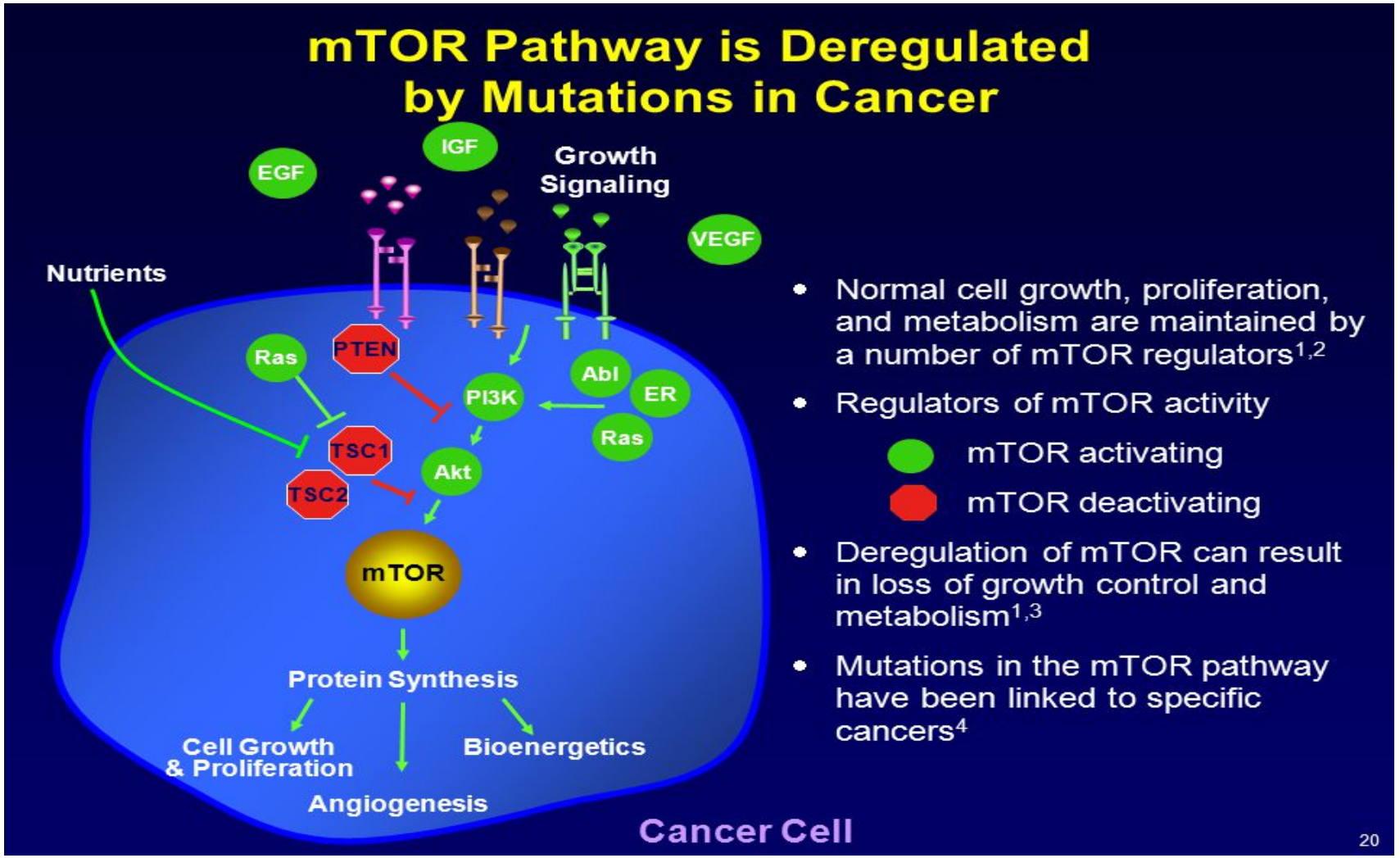


Figure 1. The mTOR Signaling Pathway
PI3K
PDK1
PTEN
AKT
TSC1/TSC2
RHEB
Raptor
mTOR
S6K
4EBP1
Translation
Cyclin D1, c-Myc, HIF-1α, and others
HIF, hypoxia-inducible factor.
Petroulakes et al. Br J Cancer. 2006;94:195-199.

mTOR Pathway is Deregulated by Mutations in Cancer



- Normal cell growth, proliferation, and metabolism are maintained by a number of mTOR regulators[1,2]
- Regulators of mTOR activity
  - mTOR activating
  - mTOR deactivating
- Deregulation of mTOR can result in loss of growth control and metabolism[1,3]
- Mutations in the mTOR pathway have been linked to specific cancers[4]

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Proto-oncogenes and Oncogenes

Define proto-oncogenes oncogene,and growth factors

* A **proto-oncogene** is a normal gene that can become an oncogene due to mutations or increased expression. The proto-onncogenes converted to ocogenes and develop cancer.

* A mutant proto-oncogene whose protien product is involved in the transformation of normal cell to cancer cell.

* An **oncogene** can be defined as an altered gene whose product acts in a dominant manner to accelerate cell growth or cell division.

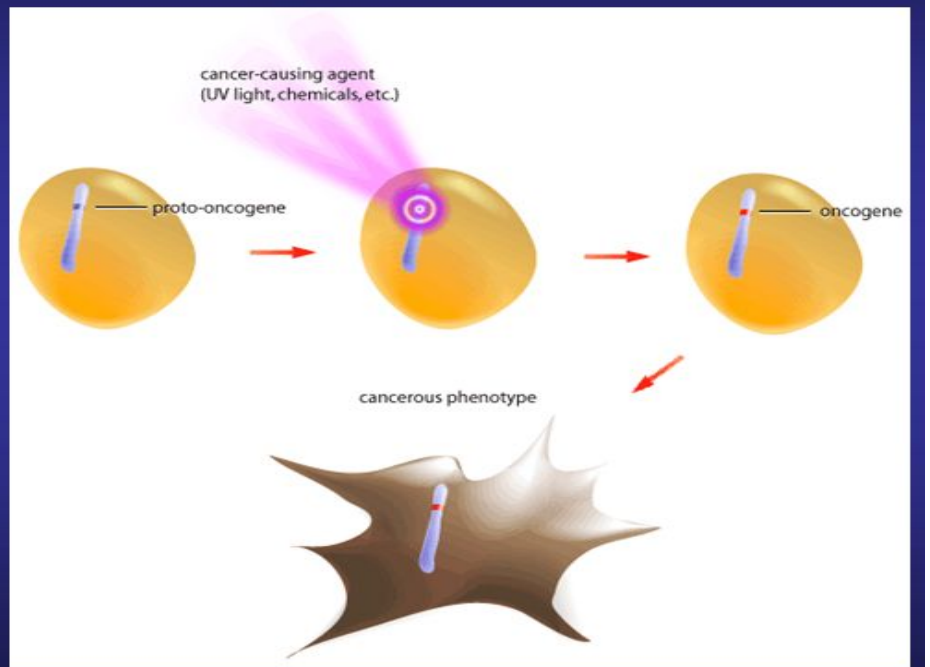
Proto-oncogenes are regulatory genes

- Products of many oncogenes are polypeptide growth factors e.g. sis gene produces PDGF
- Or Act as receptors for growth factors e.g. erb-B produces receptor for EGF.
- Some act on key intracellular pathways e.g. src product tyrosine kinase enzyme phosphorylates tyr residue-activation of intracellular events.

Oncogenes

Definition: Oncogenes are genes whose expression causes cells to become cancerous.

Tumorigenic mechanism: The normal version of the gene (termed a proto-oncogene) becomes mutated so that it is overactive. Because of their overactivity, oncogenes are genetically dominant over proto-oncogenes, that is only one copy of an oncogene is sufficient to cause a change in the cell's behavior.



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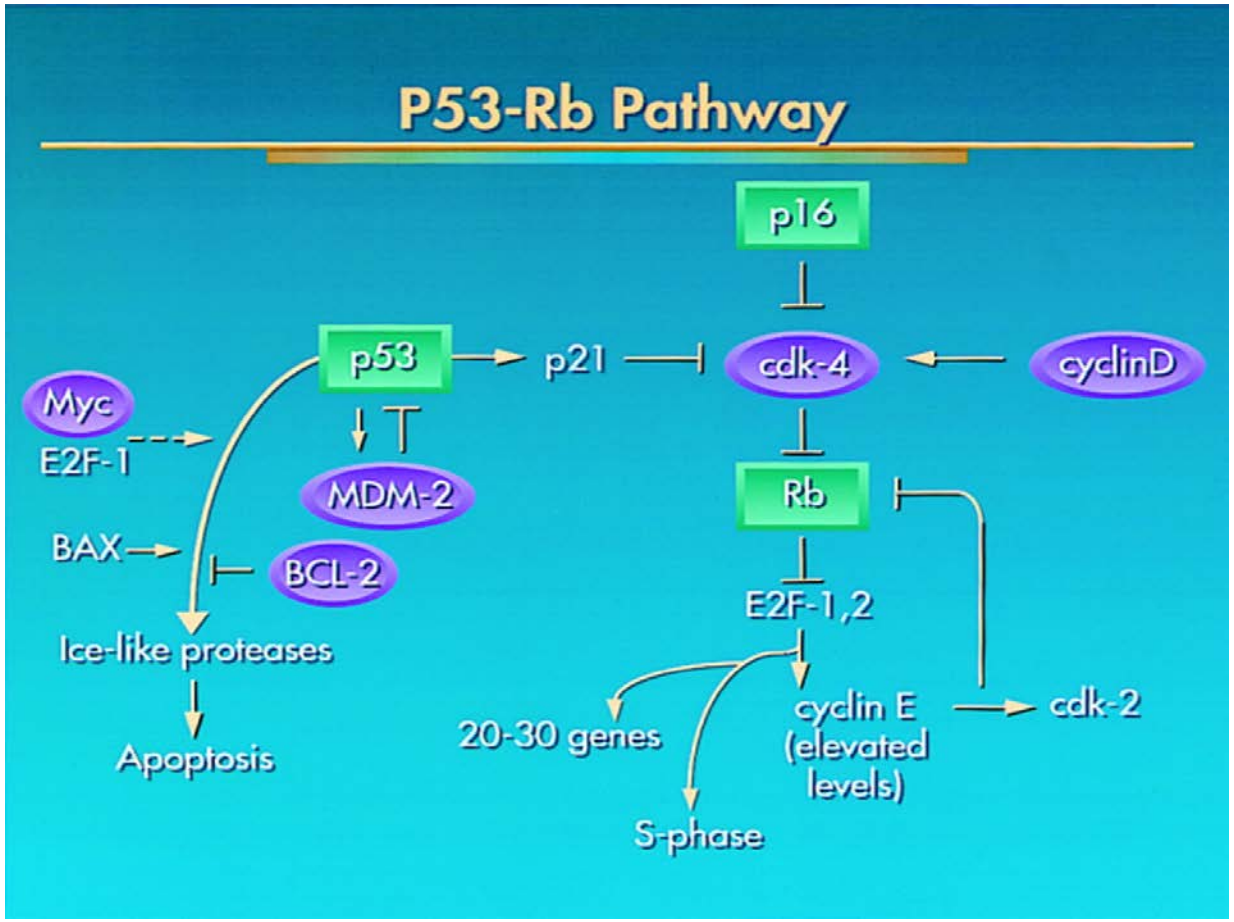
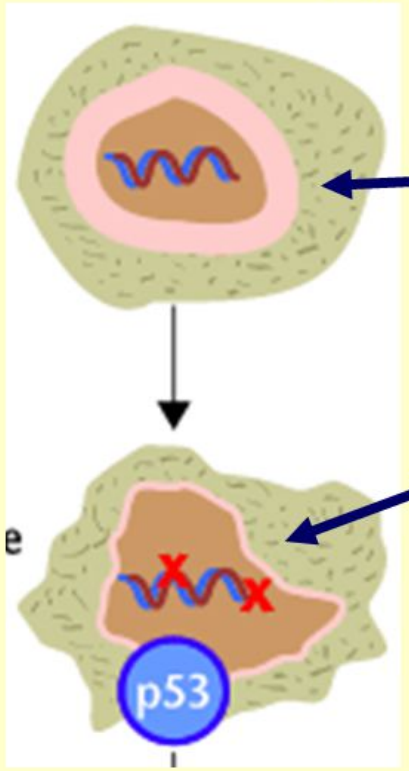
P53 and Retinoblastoma Tumor Suppressor Protein



p53 that can trigger cell apoptosis

p53 Tumor Suppressor Gene



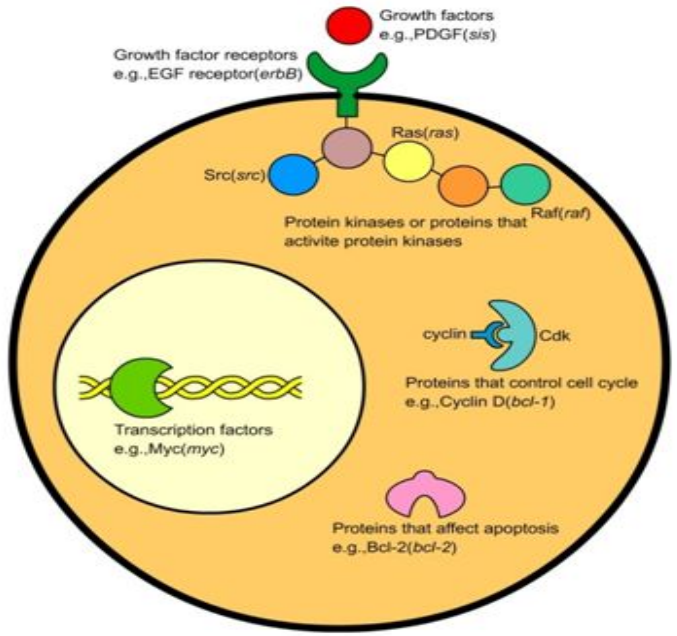
50% of all cancers
have an aberrant p53 gene

Normal cell

Cancerous cell

***ras* proto-oncogene:**

- mutations in the ***ras* gene** are found in about 30% of human cancers
- the product is the **Ras protein**
- the ***Ras* protein** is a G protein that relays a growth signal from a growth factor receptor on the plasma membrane to a cascade of **protein kinases**



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Proto-oncogenes Mutations and Cancer

Proto-oncogenes (tumor promoters)	Anti-oncogenes (tumor suppressors)
ras: cancers of bladder, lung, colon, pancreas, kidney	*BRCA-1*, *BRCA-2* (DNA repair genes): breast and ovarian cancer
N-*myc*: neuroblastoma, small cell carcinoma of the lung	*NF-1*: neuroblastoma, neurofibromatosis type 1, sarcomas
ERB-B1: squamous cell carcinoma of the lung	*APC/β-catenin*: gastric, colonic, and pancreatic cancer; familial adenomatous polyposis coli
ERB-B2: breast and ovarian cancer	*DCC*: colon cancer
TGFα: astrocytoma, hepatocellular carcinoma	*P53*: the majority of cancers, Li-Fraumeni syndrome
sis: astrocytoma, osteosarcoma	*RB*: retinoblastoma, osteosarcoma, other tumors
abl: chronic myeloid leukemia, acute lymphoblastic leukemia	*WT-1*: Wilms tumor

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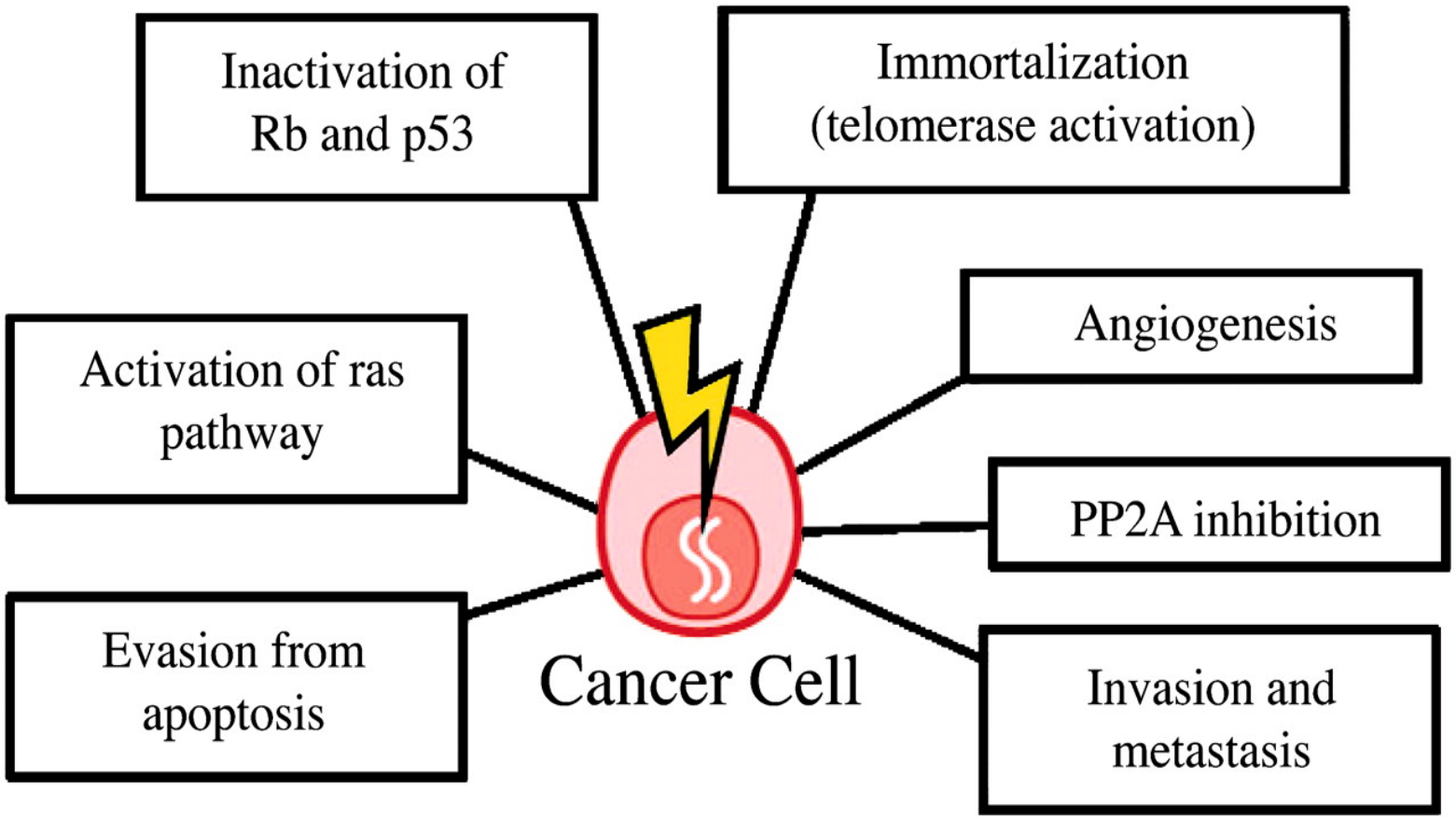
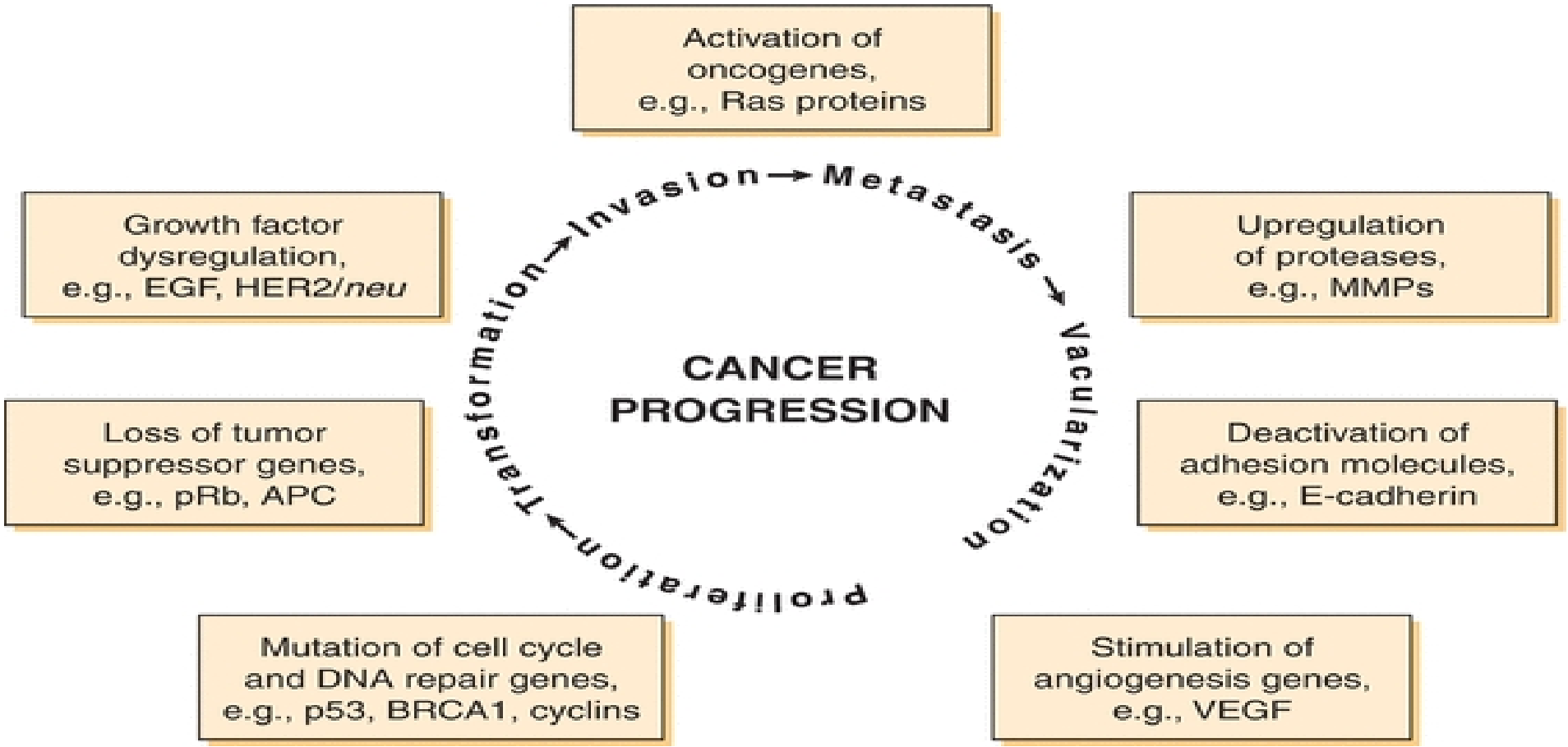
Note: Hypomethylation as Epigenetic Event increasing Cancer Risk (folic acid metabolism)

Table 4 Genetic and epigenetic events involved in cancer development

Proto-oncogenes (growth-enhancing)	
Growth factors	PDGF-B, FGF, sis
Growth factor receptors	EGFR, CSF
Signal transduction	*ras*, *abl*
Nuclear regulatory proteins	*myc*, *fos*
Cell cycle regulators	Cyclins and cdks
Tumor suppressor genes (growth-inhibiting)	
Cell surface molecules	TGF-βR
Regulate signal transduction	NF1
DNA repair, cell cycle	p53, Rb, BRCA1
Apoptosis genes	Bcl-2, Bcl-x, Bax, bad, Bcl-xS
DNA repair genes	HNPCC, XP
Epigenetic events	Methylation


Inactivation of Rb and p53
Immortalization (telomerase activation)
Activation of ras pathway
Angiogenesis
PP2A inhibition
Evasion from apoptosis
Cancer Cell
Invasion and metastasis


Activation of oncogenes, e.g., Ras proteins
Growth factor dysregulation, e.g., EGF, HER2/neu
Upregulation of proteases, e.g., MMPs
Loss of tumor suppressor genes, e.g., pRb, APC
CANCER PROGRESSION
Deactivation of adhesion molecules, e.g., E-cadherin
Mutation of cell cycle and DNA repair genes, e.g., p53, BRCA1, cyclins
Stimulation of angiogenesis genes, e.g., VEGF
Transformation → Invasion → Metastasis → Vascularization → Proliferation

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In Summary

Cancer has multiple causes

-mutated tumor suppressor genes
-mutated cell cycle regulators
-mutated repair proteins
-mutated receptor signaling
constant division, etc.

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Typical Patient Work-Up by Integrative MD's in Cancer Treatment

1. Diagnosis: Type of cancer; Stage of cancer
2. Complete Blood and Urine Work-up: Liver function, Kidney Function, Anemia, White Blood Cell and Platelet Count etc.
3. Genomic Profile of Tumor Cells: Genes Overexpressed, Under-expressed or Normal
4. Chemosensitivity Panel (blood or tumor tissue sample)
5. Immuno-Competency – Natural Killer Cell Activity
6. Co-morbidity Issues: Hypercalcemia of Malignancy, Diabetes, etc.
7. Past History of Health: Including Surgeries etc.
8. Current Medication Use
9. Current Supplement Use

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A Review of the biological mechanisms in cancer where specific nutrients can intervene and common genetic-environment interactions

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Premise Of Supplementation In Cancer Prevention and Management

In addition to antioxidants, B-vitamins for DNA methlylation and strengthening the immune system, nutritional supplementation can alter course of cancer (prevention/management) via many physiological effects such as:

- Replication Rate (uncontrolled mitosis)
- Apoptosis (programmed cell death)
- Angiogenesis/metastasis

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JNCI – Willett W. 1996

Estimates of cancer deaths avoidable by dietary change

Types of cancer	Percent avoidable Doll-Peto (1981)	Willett (1994)	Range (1994)
Lung	20	20	10-30
Colon/rectum	90	70	50-80
Breast	50	50	20-80
Prostate	(with other)	75	20-80
Pancreas	50	50	10-50
Stomach	35	35	30-70
Endometrium	50	50	50-80
Gall bladder	50	50	50-80
Larynx, bladder, cervix, mouth, pharynx, esophagus	20	20	10-30
Other types	10	10	—
Overall estimate	35	32	20-42

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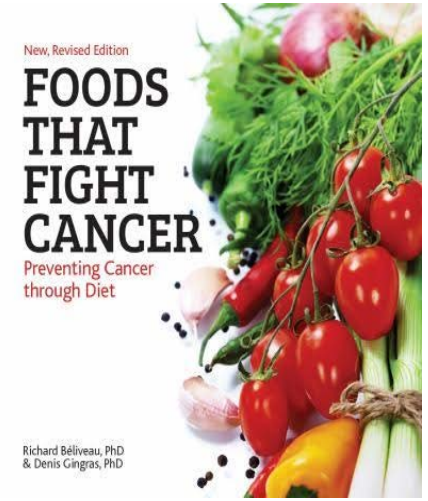
Foods That Fight Cancer: Beliveau and Gringras – Cancer Researchers

As stated in their book, “Nature supplies us with an abundance of foods rich in molecules with powerful anti-cancer properties, capable of engaging with the disease (cancer) without causing any harmful side effects. In many respects, these foods possess therapeutic properties on par with those of synthetic drugs”. More specifically, they highlight the research showing how specific food-borne bioactive molecules can:



Decrease free radical damage to DNA, which is known to produce cancerous mutations

Strengthen immune system function – as various immune cells are known to destroy cancer cells (e.g. macrophages and killer-T cells)

Inhibit angiogenesis of developing tumors

Block key signal transduction pathways required for cancer cell replication

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- Stimulate pathways that induce programmed cell death (apoptosis) of existing and emerging cancer cells
- Enhance detoxification, helping to neutralize and eliminate carcinogens in body
- Promote cellular differentiation, which decreases the risk of healthy cells from becoming cancer cells
- Block the formation of dangerous nitrosamines in the body
- Block the synthesis of dangerous forms of estrogen and testosterone, which are associated with reproductive organ cancers

- Slow the rate of cell replication, which is a key factor in reducing the frequency of genetic mutations that may occur

- Blocking receptor sites on cells to prevent over-stimulation of hormones and growth factors, which in turn, slows down the rate of cell division

- Reduce the synthesis of inflammatory prostaglandin (Series-2), which is also linked to increased cancer risk

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All of these factors are very important in cancer prevention and prevention of cancer recurrence in cancer survivors

In patients undergoing cancer treatment or who need a cancer-specific treatment diet, many of plant-based foods with anti-cancer nutrients are precluded because they also contain macronutrients that fuel tumor growth. Explained in later.

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Important Biological Targets And Physiological Factors In Cancer Prevention/Management (Proto-concogenes)

1. Epidermal Growth Factor Receptors
2. Tyrosine Kinase
3. AKT- Nuclear Factor-kappa beta
4. Transcription Factors – NF-kappa beta, Stat-3
5. Cyclin D and Cyclin B_1-activate cyclin dependent kinases
6. Death Receptors and caspase-dependent apoptosis

7. Angiogenesis (VEGF)

8. Prostaglandin-2 and Lipoxygenase (5 & 12)

9. Ornithine Decarboxylase and DNA Topoisomerase

10. Transforming Growth Factor B – decrease prolif (DAAX)

11. Cellular Differentiation (vit D, vit A, carotenes, soy isoflavones, IP-6).

11. Bcl-2 (back) – blocks apoptosis

12. mTOR cascade – cell division, angiogenesis and anti-apoptosis (branching from Akt pathway)

13. Estrogen receptors – whereby ER-beta transactivation blocks proliferative effect of ER-alpha at gene level and up-regulates quinone reductase (phase II detox enzyme inhibiting formation of reactive estrogen metabolites, which induce DNA damage in breast cells – converting catecholestrogen quinones back to hydroxycatechol estrogen, which can be conjugated and excreted

14. Aromatase inhibition, 17-betahydroxy dehydrogenase enzyme inhibition, and increased 2OH:16OH estrone – in breast cancer prevention and management

15. Inhibition of 5-alpha reductase, androgen and estrogen blockade on prostate cells and prostate cancer cells

16. Immune Modulation - multiple effects we will review

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17. Gap Junction Preservation

18. Inhibition of MDR-1 pump

19. Inhibition of Heat Shock Proteins and Glucose-Related Molecules (quercetin and genistein)

20. Inhibition of telomerase – IP-6

21. IGF-1 receptors and IGF-1 unbound hormone - cancer cells often over express IGF-1 receptor for auto-stim of cell replication and higher IGF-1 and insulin levels linked to increased cancer (mitogens) – lycopene decreases IGF-1 activity as does endurance exercise and reducing body fat.

22. Wnt Pathway – beta-catenin (colon cancer)

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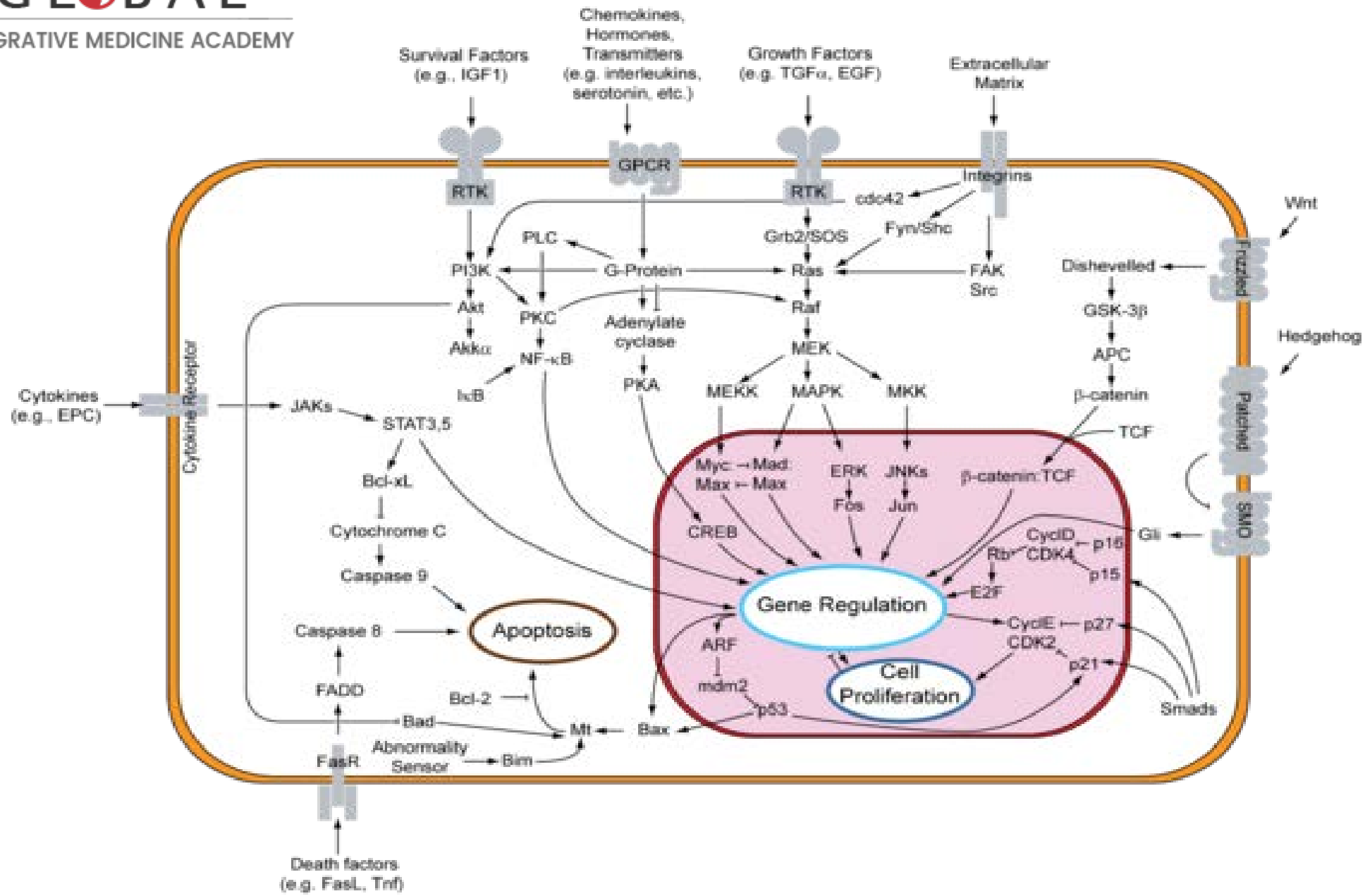

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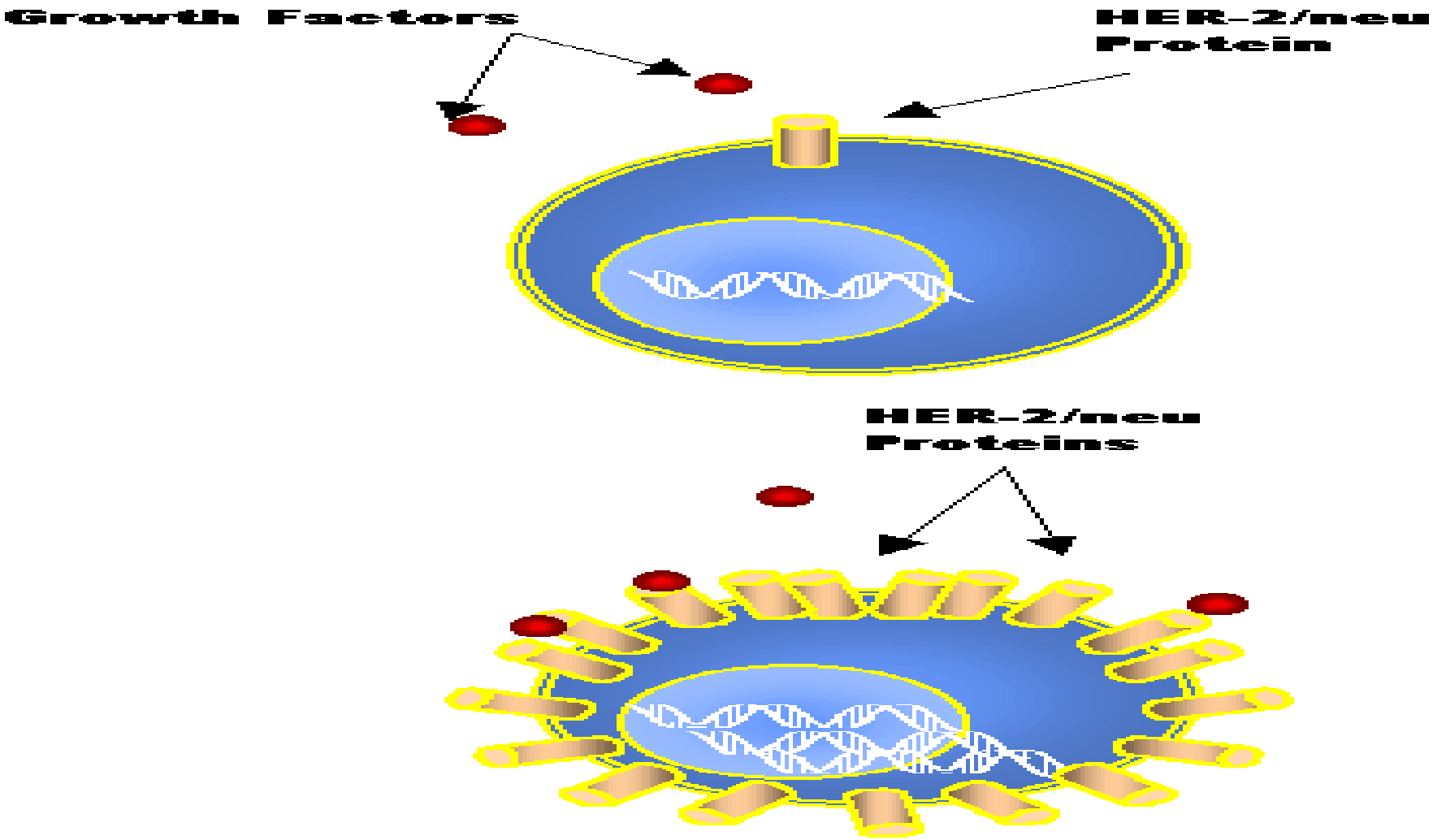
Epidermal Growth Factor Receptors HER-2(ErbB2) – breast, colon, prostate cancer



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Epidermal Growth Factors Receptors As An Oncogene

- In its proto-oncogenic form it requires binding of the growth factor molecule to enable its kinase activity. The catalytic domain then proceeds to transfer phosphate groups to its target proteins to activate them, which ultimately leads to translation of proteins involved in mitosis.

- The oncogenic form of *egfr* produces a receptor that does not require binding of growth factor, but instead is constitutively active. In this way the oncogene product is capable of always activating the pro-growth pathway in the absence of pro-growth signals

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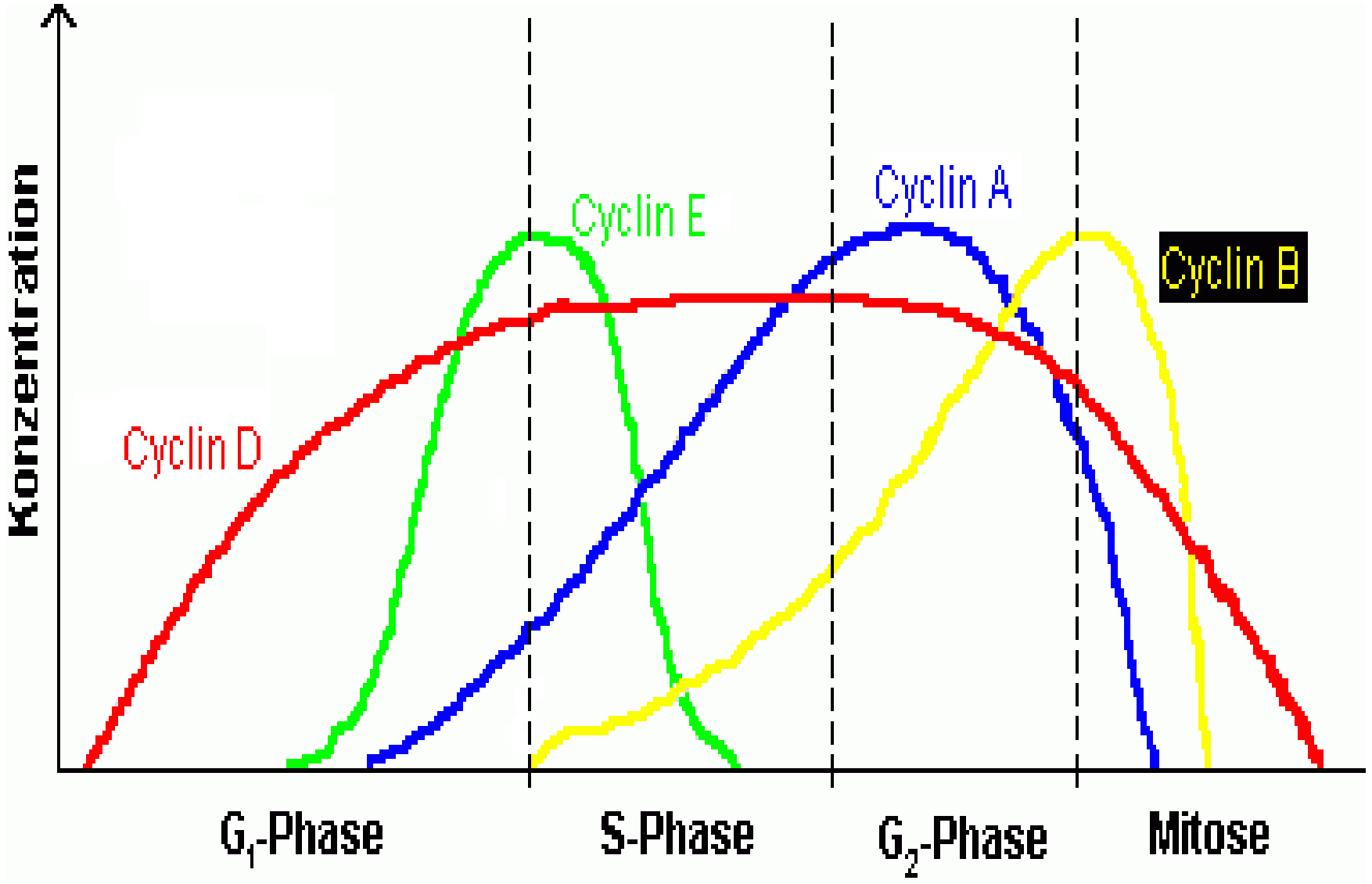
Cyclins and Mitosis



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Apoptosis (programmed cell death) may occur through 2 main signaling pathways:

- The intrinsic pathway may be triggered by DNA damage and other types of severe cell stress. It may involve the release of intracellular pro-apoptotic proteins that activate caspases, a network of proteases that ultimately destroy critical structural proteins in the cell and stimulate fragmentation of the chromosomal DNA, resulting in cell death.

- The extrinsic pathway may be triggered in response to external pro-apoptotic signals, such as endogenous Apo2L/TRAIL. Binding of this molecule to pro-apoptotic cell surface transmembrane receptors DR4 and DR5 may lead to apoptosis by initiating a signaling cascade, which results in the activation of the caspase system.

- The intrinsic and extrinsic apoptosis pathways converge via the activated caspases that ultimately trigger cell death.

References

1. Ashkenazi A. Targeting death and decoy receptors of the tumour-necrosis factor superfamily. *Nature.* 2002;2:420–430.
2. Ghobrial IM, Witzig, TE, Adjei AA. Targeting apoptosis pathways in cancer therapy. *CA Cancer J Clin.* 2005;55:178-194.
3. Jin Z, El-Deiry WS. Overview of cell death signaling pathways. *Cancer Biol Ther.* 2005;4:139-163.

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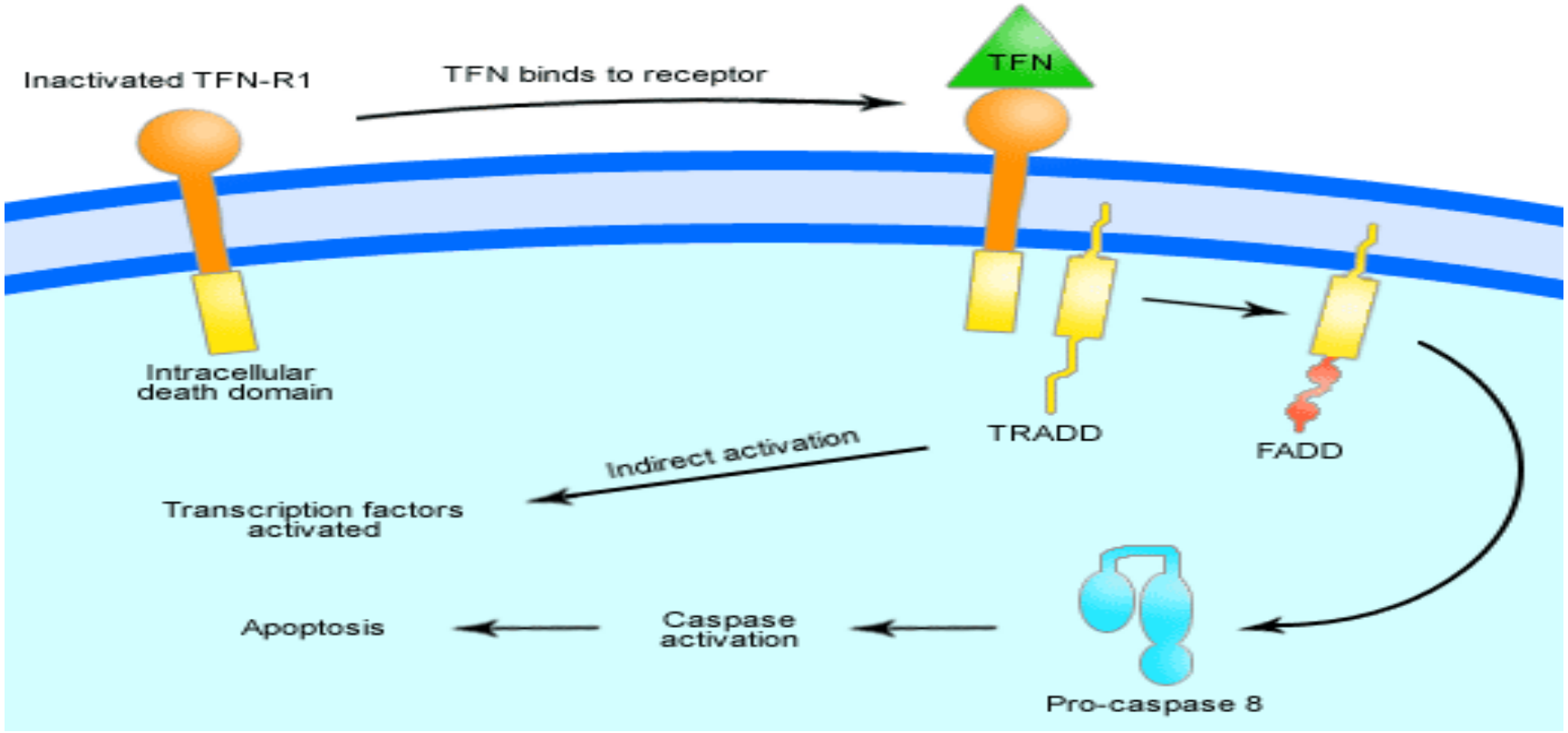
Tissue Necrosis Factor – TNF is a cytokine produced mainly by activated macrophages, and is the major extrinsic mediator of apoptosis. The binding of TNF to*TNF-R1* initiates the pathway that leads to caspase activation via the intermediate membrane proteins TNF receptor-associated death domain (TRADD) and Fas-associated death domain protein (FADD).



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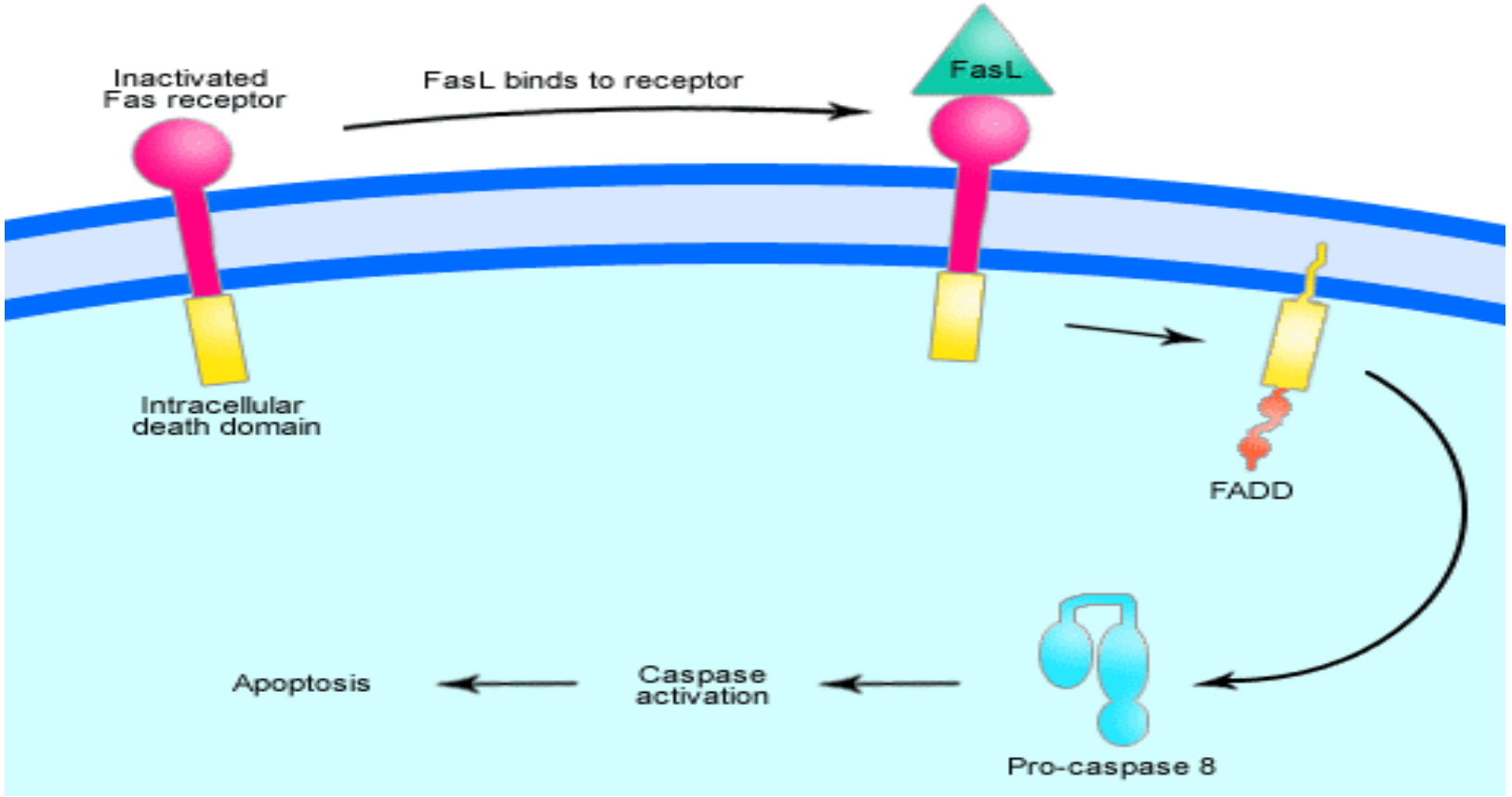
Apoptosis and Fas Receptors: Fas ligand (FasL or CD95L) is a type-II transmembrane protein that belongs to the tumor necrosis factor (TNF) family. It is a cytokine secreted by immune cells. Its binding with its receptor induces apoptosis. Dysregulation of TNF and/or Fas ligand is associated with cancer and cancer progression.



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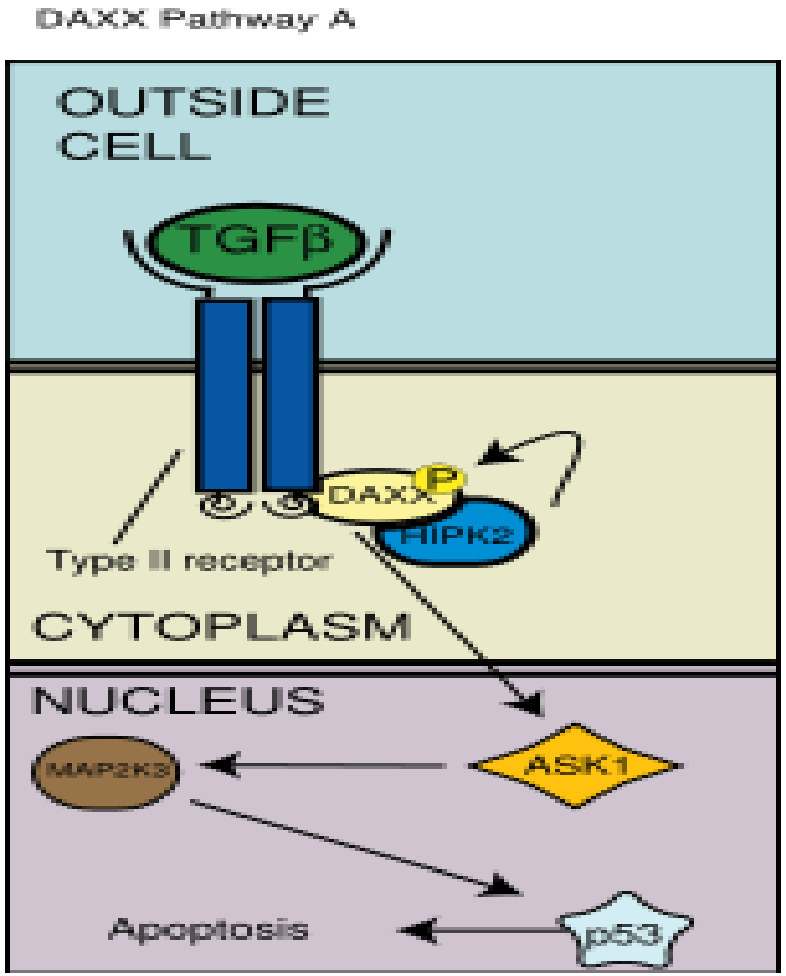
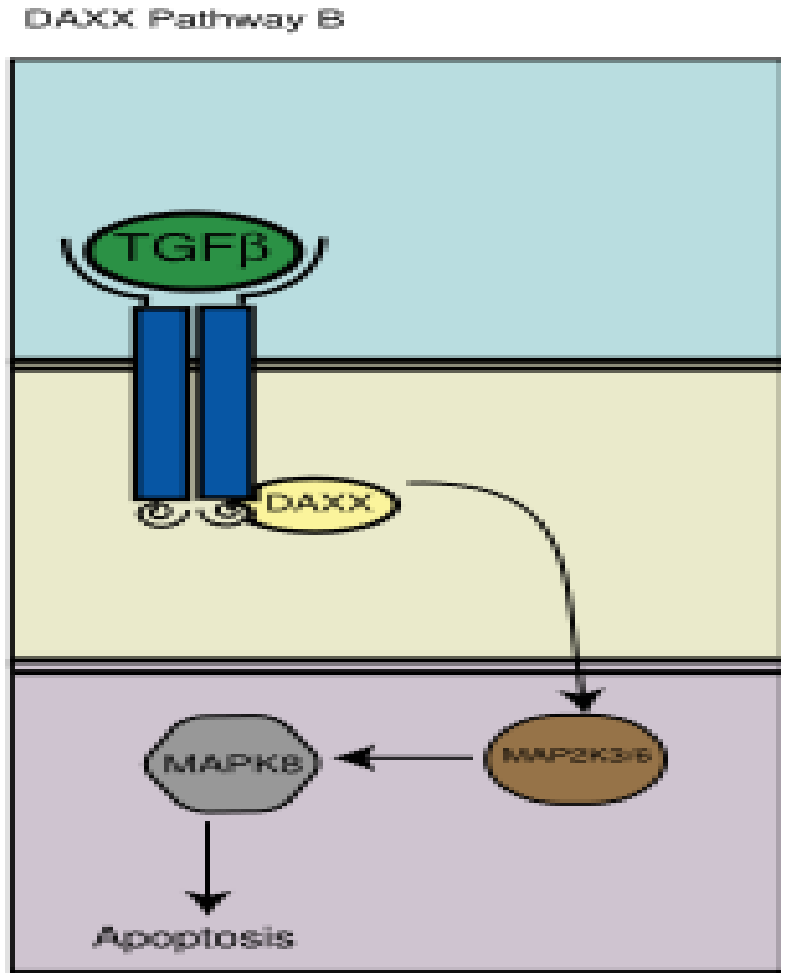
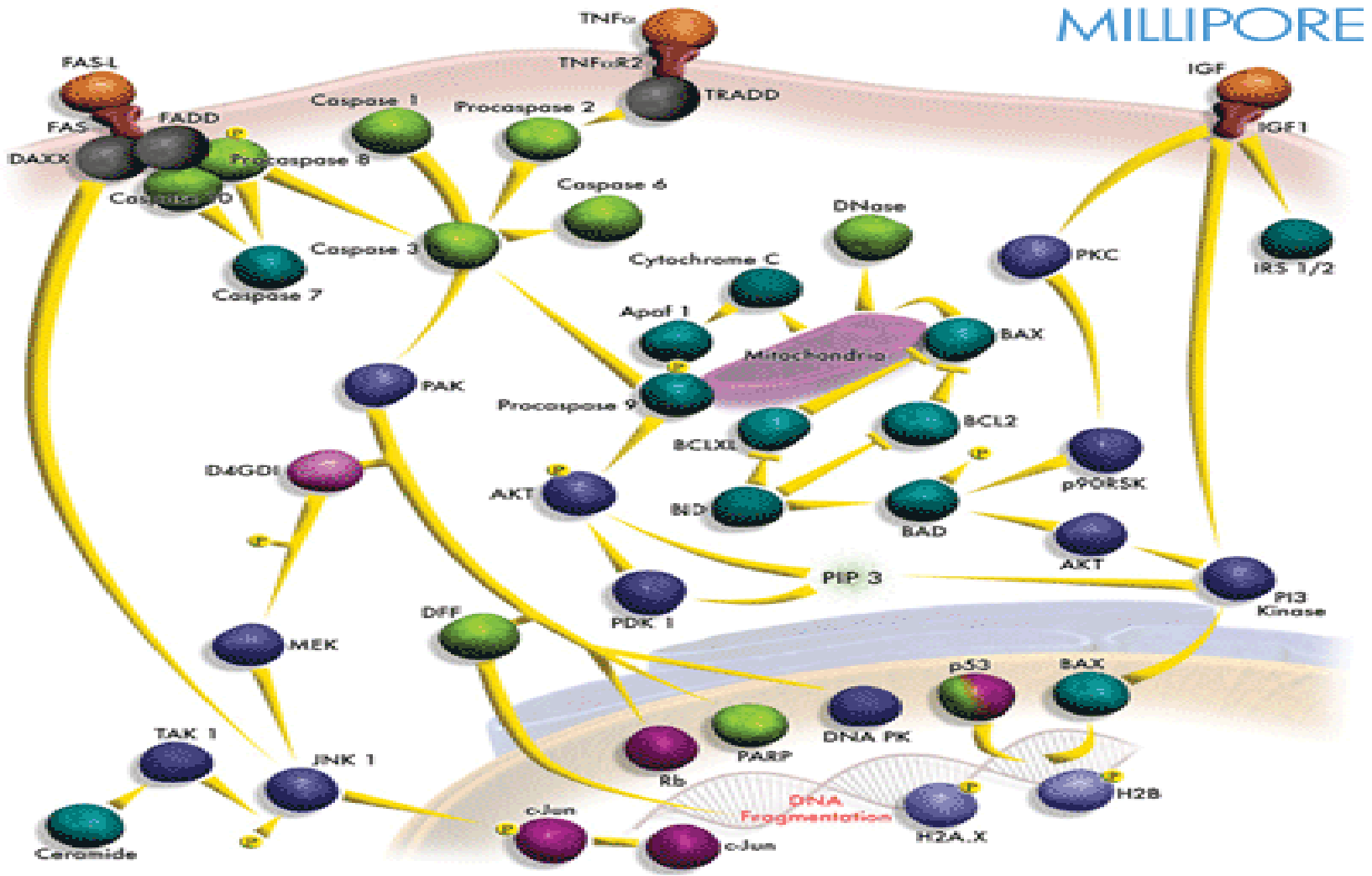
In the DAXX pathway, TGF beta may also trigger apoptosis via the death associated protein (DAXX adapter protein).







Apoptosis

upstate
now part of Millipore

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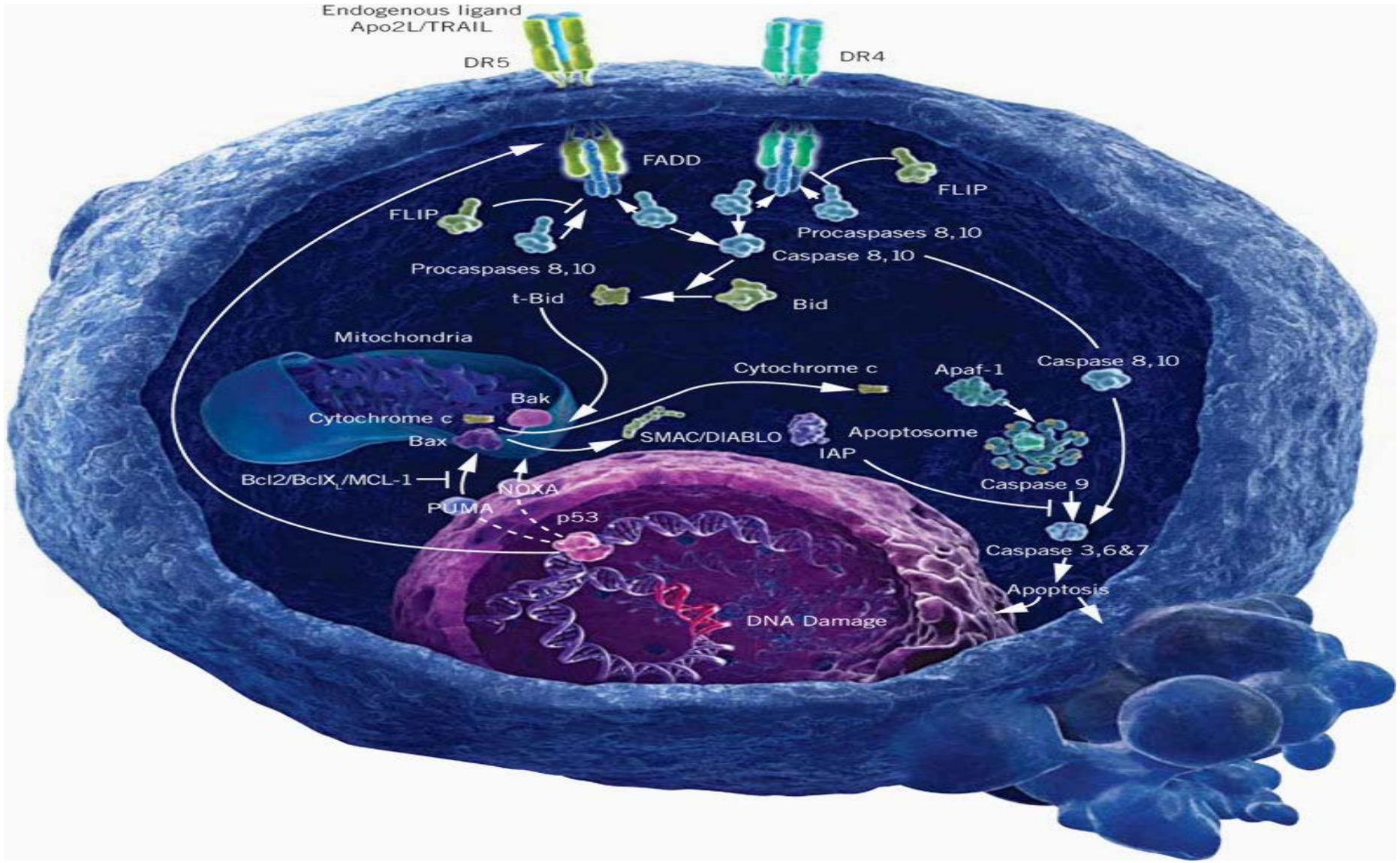

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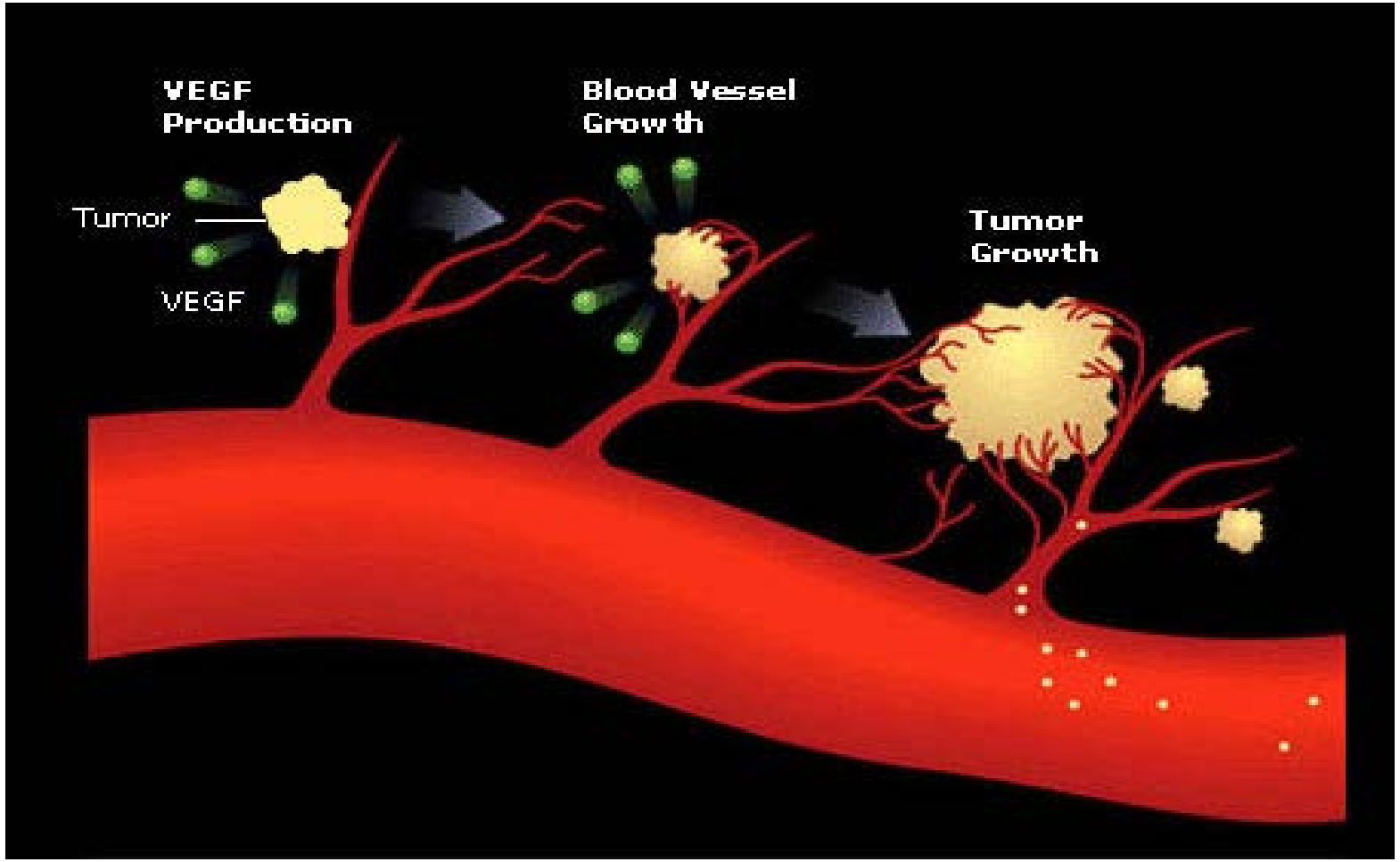
Angiogenesis and Metastasis (VEGF)



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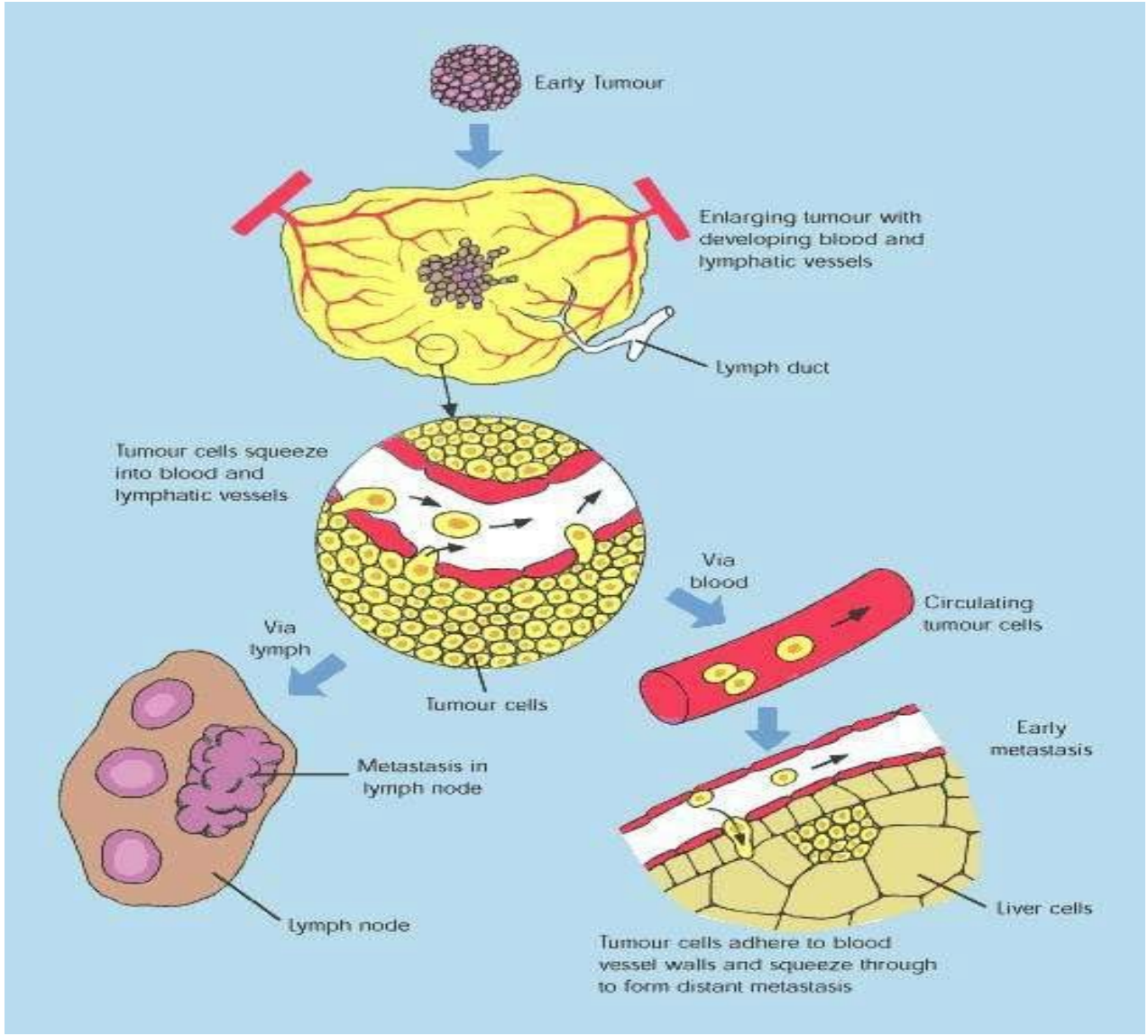
Angiogenesis and Metastasis



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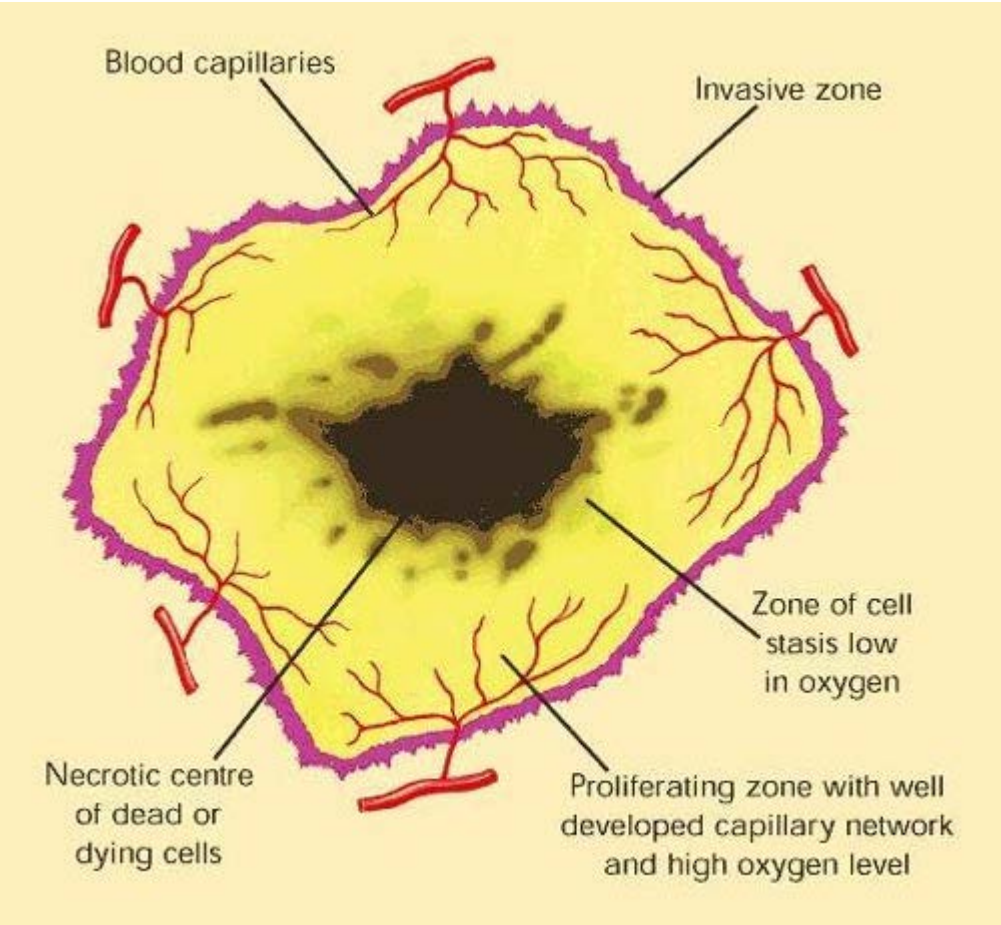
Avastin inhibits the action of VEGF by blocking VEGF receptor binding.



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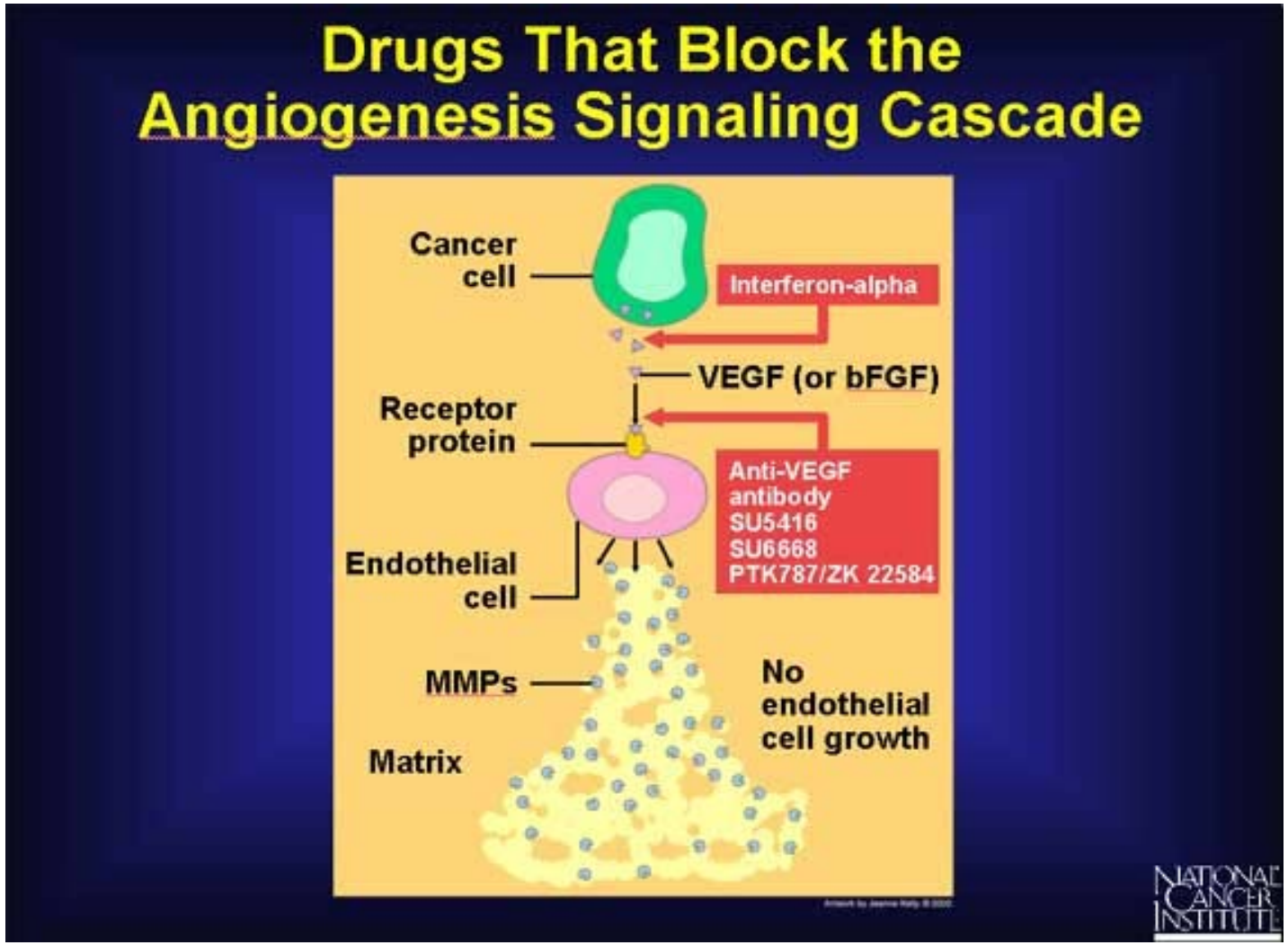
Monoclonal Antibodies Destroy VEGF Receptors



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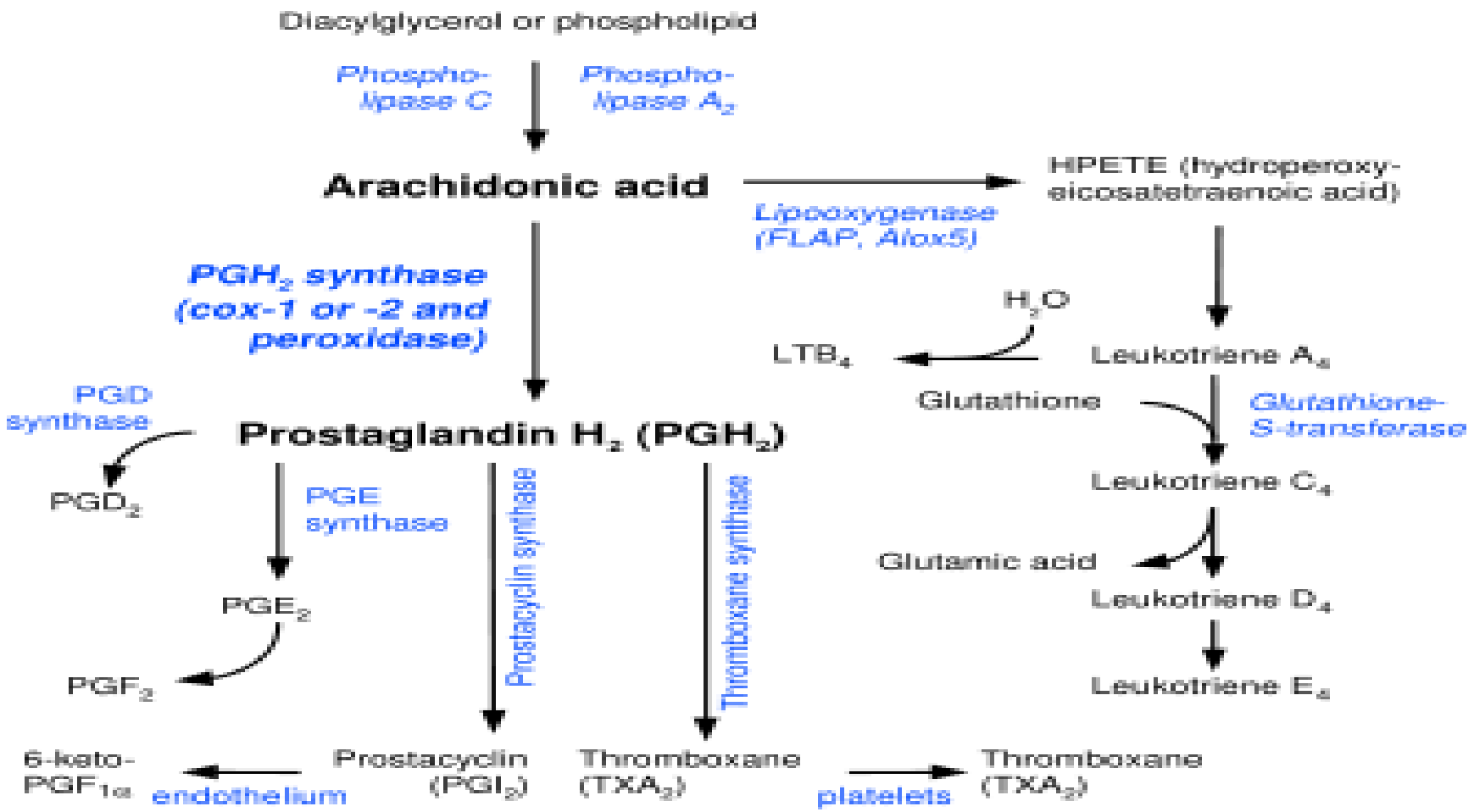
Eicosanoids From AA (HETE, LTB-4 and PGE-2)



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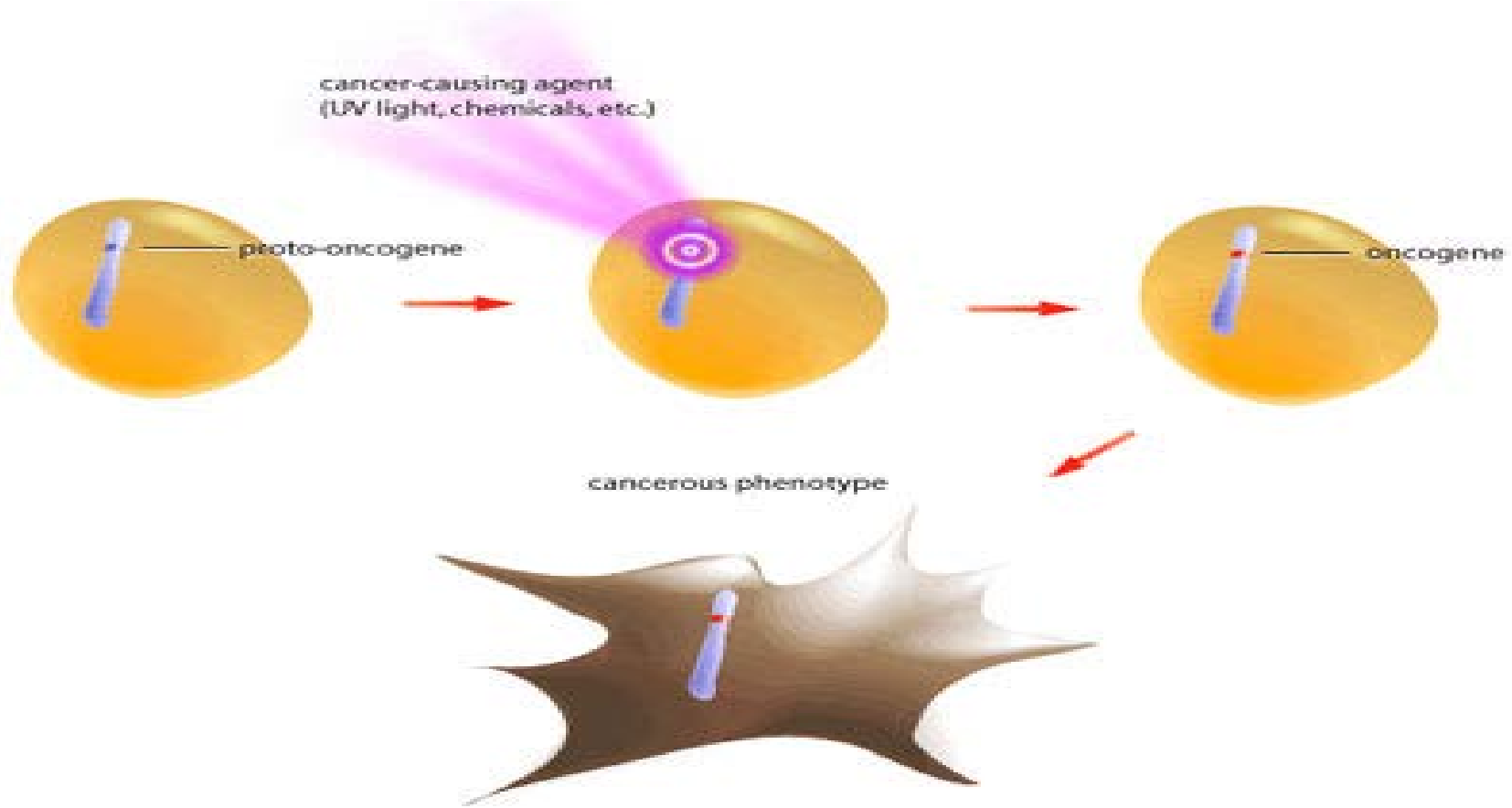
Proto-oncogenes can become oncogenes. Proto-oncogenes encode for normal cellular proteins involved in growth signaling pathways. When these genes become mutated as a result of exposure to chemicals, radiation, or other carcinogens, these

genes are called oncogenes.



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Oncogenes and Cancer

- Oncogenes are mutated genes that contribute to cancer development by disrupting a cell's ability to control its own growth and DNA repair mechanisms.

- Normally mitosis (cell division) is a carefully regulated event, requiring the activation of one protein to activate another, in what is known as a signal transduction cascade. This cascade eventually culminates in changes in gene expression that prepares the cell for mitotic events.

- When proto-oncogenes mutate to become oncogenes they retain their functionality, but are no longer capable of responding to normal regulatory signals. At present, over 100 oncogenes have been identified in various cancers .

Reference

ONCOGENES: THE (AUTOSOMAL) DOMINANT EVIL

Brandon Stott and Michelle Wyse. The Science Creative Quarterly (August 2003)

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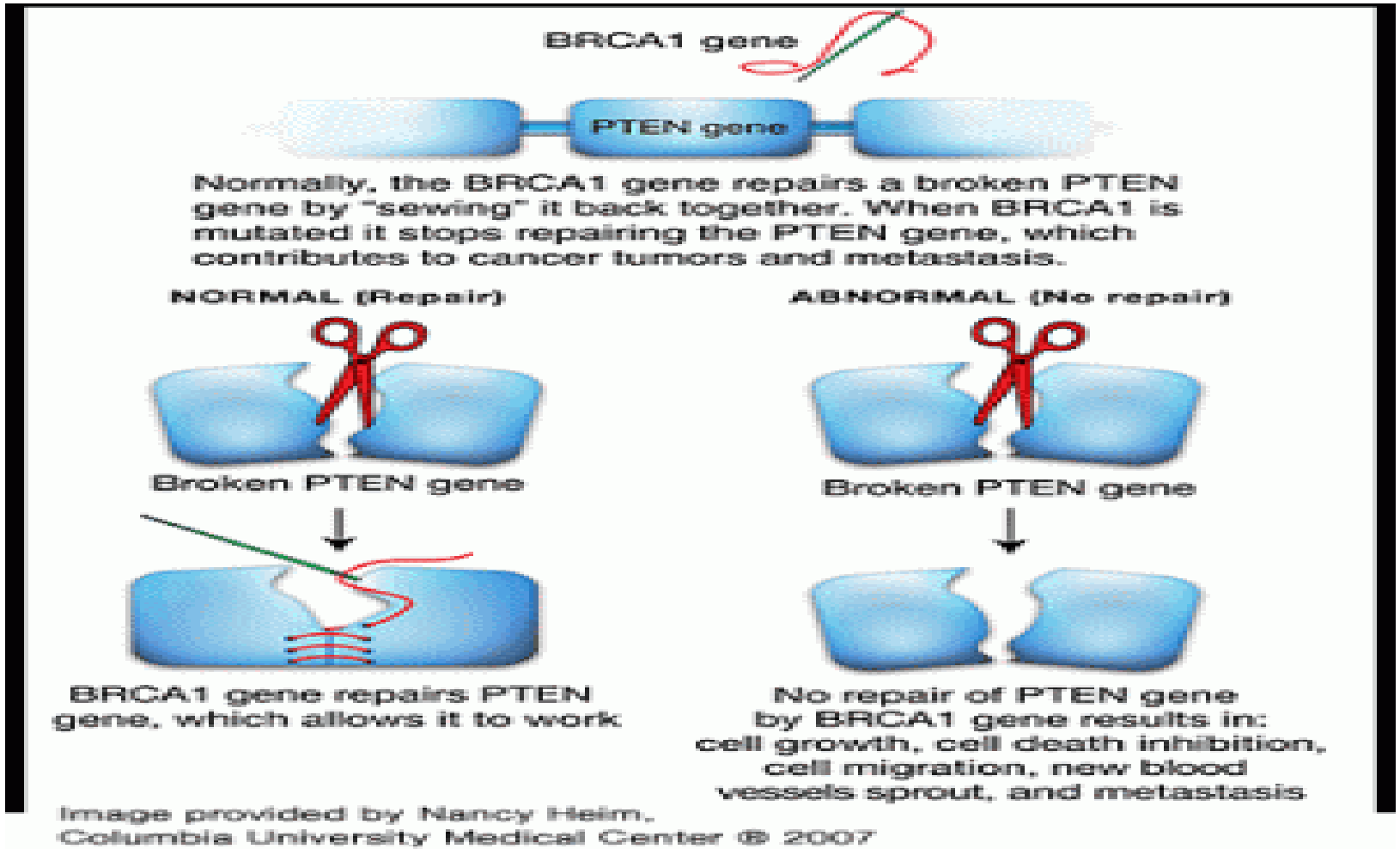
BRCA1(2) Gene Mutation And Breast Cancer (Prostate CA)



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BRCA1 Mutations And Breast Cancer

December 9th, 2007 in Medicine & Health / Genetics

- In 1997, Dr. Parsons led one of the two teams that independently discovered the PTEN, one of the most important tumor suppressor genes altered in breast cancer, as well as in brain and prostate cancers. PTEN is now recognized to be mutated in about 30 percent of all cancers, making it the second most mutated gene in cancer after p53.

- Knocking out PTEN sends a strong pro-growth signal on tumor cells. “Once a cell loses PTEN it has a growth advantage over its neighbors and starts on the road to cancer,” said Dr. Parsons.

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Breast Cancer Genetics (BRCA1&2; HER-2)

BRCA1 (**breast cancer 1)** is a human gene that belongs to a class of genes known as tumor suppressors, which maintains genomic integrity to prevent uncontrolled proliferation.

The multifactorial BRCA1 protein product is involved in DNA damage repair, ubiquitination (protein degradation), transcriptional regulation as well as other functions.

A mutated *BRCA1* gene usually makes a protein that does not function properly because it is abnormally short. Researchers believe that the defective BRCA1 protein is unable to help fix mutations that occur in other genes. These defects accumulate and may allow cells to grow and divide uncontrollably to form a tumor.

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- If a woman with a family history of breast cancer inherits a defective form of either BRCA1 or BRCA2, she has an estimated 80% to 90% chance of developing breast cancer.

- Researchers also think that the two genes are linked to ovarian, prostate, and colon cancer, and BRCA2 likely plays some role in breast cancer in men. ("Where is the ERBB2 gene located?" in Genetics Home Reference, U.S. National Library of Medicine, 2004, http://ghr.nlm.nih.gov/geneerbb2 (accessed February 8, 2005)

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Genes vs Environment

- Several recent studies reported higher rates of *BRCA1* and *BRCA2* gene mutations in Ashkenazi (Eastern and Central Europe ancestry) Jewish women than in the general population in different countries.

- This fact has also been associated with a higher lifetime risk of developing ovarian and breast cancer among Ashkenazi women, the latter ranging from 38% by age 50 to 59% by age 70.

- Different from the reported scientific literature about a higher breast cancer incidence among Ashkenazi women in North America and Europe than in the general population, breast cancer seems to present a moderate pattern of occurrence among Brazilian Ashkenazi women suggesting that dietary and lifestyle factors can suppress breast cancer in high women with genetic vulnerability.

- In other words, these results suggest that BRCA-1 (and 2) mutations seem insufficient to induce higher breast cancer risks by themselves, but environmental interaction would also be necessary to modulate gene expression related to familial breast cancer. (Koifman S**.** *Breast Cancer Res* 2001, **3:**270-275)

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BRCA1 & 2 Assoc With EGFR Over expression (van der Groep P, et al)

Research shows that invasive breast carcinomas in patients with a BRCA1 or BRCA2 germline mutation also show high frequency of EGFR overexpression

They urge further investigation into mechanisms of EGFR overexpression and into new preventive strategies through EGFR targeting. (van der Groep P, et al). e.g curcumin, vitamin E succinate, vitamin D, monoclonal antibodies against HER-2 Receptors

Up to 40% of Breast Cancer Cases Involve Overexpression of Erb-2 (HER-2) Receptors (hyperproliferation)

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Medicine's New Biological Targeted Therapies

1 Monoclonal antibodies

2. Small molecules – block certain pathways

3. Heat Shock Proteins and Glucose-related Proteins - High levels of HSPs and GRPs occur in cancer and virally transformed cells They facilitate malignant transformation by **enhancing** the activity of many oncogenic growth factor receptors, kinases and transcription factors. GRPs have been shown to **upregulate tyrosine kinase** activity in cancer cells and the presence of HSPs and GRPs make cancer cells more **resistant to chemotherapy and radiation and apoptosis**. Medicine is creating HSP inhibitors

4. Ligand-based strategies - Toxin conjugated ligands are generated by conjugating a potent cellular toxin with one of the ligands of the HER family receptor.

5. **Targeting Akt -** 17-AAG, an indirect inhibitor of Akt activity, is an **ansamycin antibiotic** which has shown antitumor effects in HER-2-overexpressing breast cancer cell lines in several preclinical experiments.

4. **Agents targeting PI3K/Akt pathway** - **Targeting mTOR.** The mTOR pathway is a key growth factor-mediated signal transduction pathway that regulates cell growth, closely related to the PI3K/Akt pathway. mTOR-dependent growth factor signaling include estrogen, HER-2/neu and IGF-1, all of which can be inhibited by mTOR inhibition, resulting in G1 arrest of the cell cycle.

CCI-779 is an m-TOR inhibitor with activity seen in breast cancer cells, both in vitro and in vivo, and is the only agent of this category in later stages of clinical development in breast cancer

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Part 2

Anti-Tumor Effects of Individual Nutrients

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Anti-Tumor Effects of Individual Nutrients

1. Curcumin
2. Chinese scullcap
3. Essential Fatty Acids
4. Reishi Mushroom Extract
5. Astragalus
6. Vitamin E Succinate
7. Selenium
8. Vitamin C
9. Vitamin D
10. Immune Modulators
11. Beta-Carotene
12. Parthenolide
13. Flaxseed Lignans
14. Isoflavones
15. Lycopene
16. Quercetin
17. Induribin
18. Indole-3-Carbinol (Cruciferous Vegetables)
19. Other Anti-Angiogenic Agents
20. Pomegranate Juice – 8 oz per day in localized or advanced prostate cancer

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Curcumin

1. Pan Erb Inhibitor and RTK (Epid Growth Factor) – breast, colon and prostate cancer
   - Compared to monoclonal antibody drug Herceptin
   - Up to 40% breast CA involves ErbB-2
   - Used successfully in familial polyposis to block recurrence at 480 mg, three times daily (with 60 mg quercetin)- decreased number and size of polyps and more benign histological feratures.

2. Inhibits 12 Lipoxygenase (decrease prolif)
3. Inhibits VEGF – decrease angiogenesis
4. Induces apoptosis – via dissociating heat shock protein complex
5. Inhibits action of NF-kappa beta
6. Decrease prostate cancer cell changes required for bone mets
7. Enhances chemo killing effect (experimental evidence)

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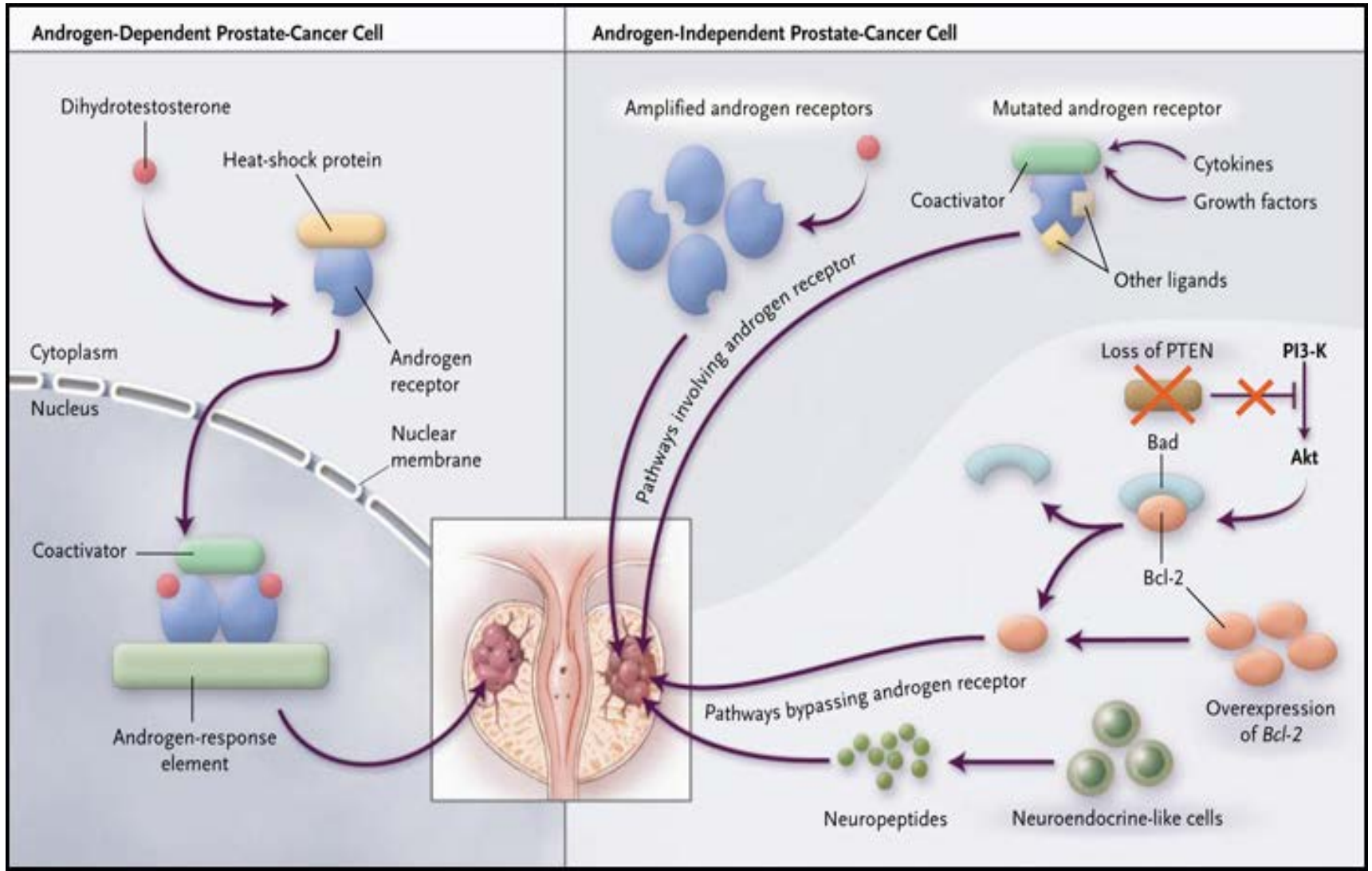
Heat Shock Proteins and Glucose-Related Proteins Upregulate Cell Proliferation



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Baicalein Flavonoid (Chinese scullcap)

1. Inhibits 12 lipoxygenase (very few molecules can do this – baicalein and curcumin) – this effect associated with increased apoptosis and decreased angiogenesis. 12 LOX is over expressed in many types of cancer including breast, colon and prostate.

Inhibition of 12 lipoxygenase in prostate cancer cells produced:

a. decreased cyclin D1, D3 via activation (dephosphorylation) of retinoblastoma protein (pRB) (https://www.ncbi.nlm.nih.gov/pubmed/22820424)

c. increased apoptosis via decreased AKT activation (Bcl-2) and loss of survivin (survivin inhibits caspase enzymes and is often overexpressed in cancer cells)

2. Angiogenesis – unknown pathway (http://journals.sagepub.com/doi/abs/10.1258/ebm.2011.010395)

One additional note – baicalein prevents build up of synuclein in Parkinson's nerve cells (experimental)

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Flaxseed, Fish And Borage Seed Oil

1. Low AA and LA diet: recommended to decrease synthesis of 5 and 12 HETE, other leukotrienes and PGE-2 made from AA

2. EPA: a. Competes with AA for CO and LO

b. EPA- derived prostanoids and leukotrienes decrease proliferation and inflammation (this is why ASA associated with decreased cancer risk – but side effects)

c. Inhibits release of PLA-2 (decrease AA activate)

3. DHA: can be converted into EPA (fish oil)

4. ALA: a. Inhibits conversion of LA to AA (elongase/desataturase)

b. ALA converted to EPA

5. DGLA (from GLA) GLA supplementation shown to raise DGLA:

a. Competes with AA for CO and LO

a. Blocks AA to Leukotrienes

b. Produces Anti-inflammatory prostaglandins

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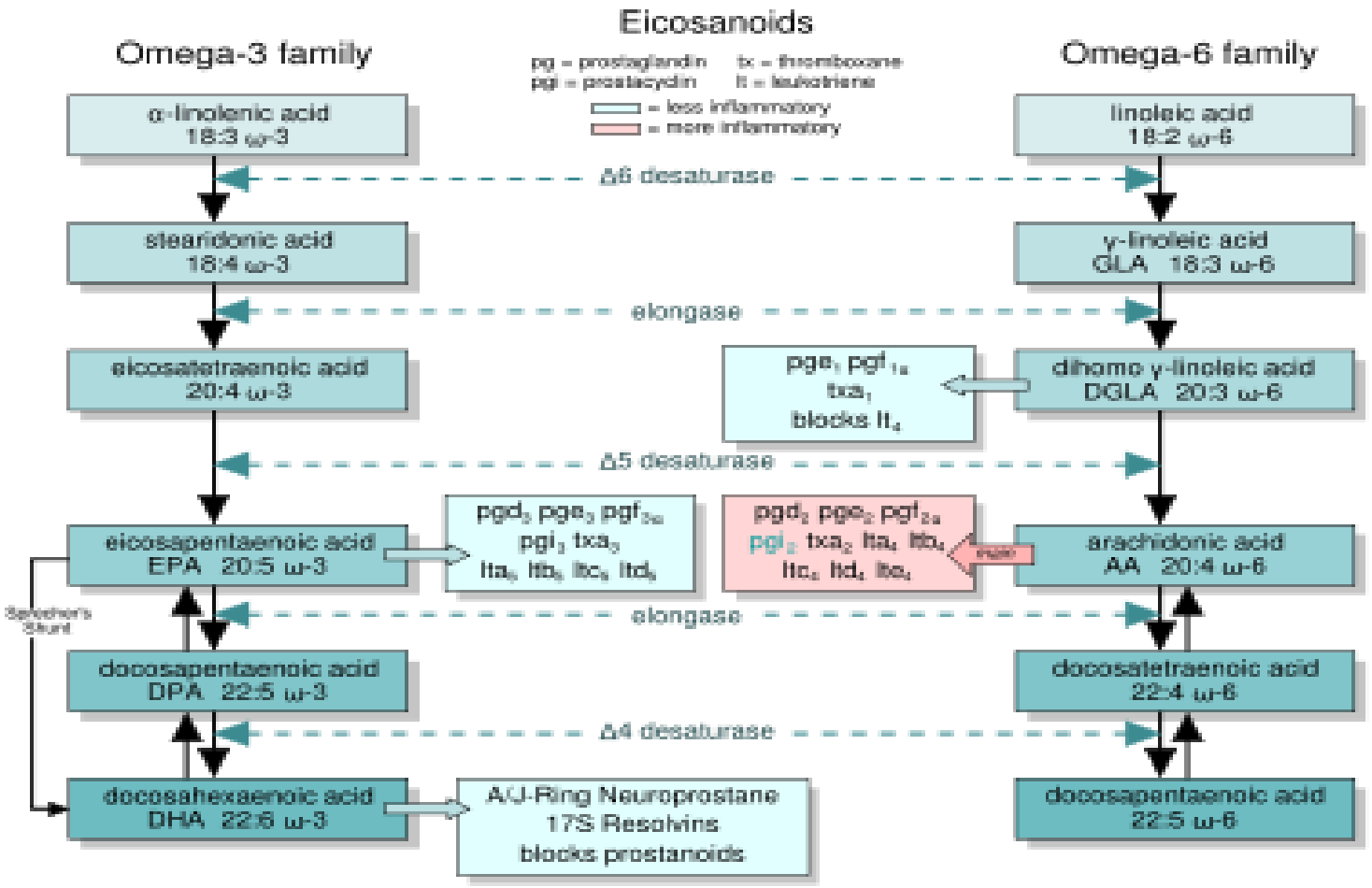
ALA Blocks Conv of Linoleic to AA via delta 6 competition
ALA uses up delta-5 desaturase enzyme, enabling GLA to competes with AA
Omega-3 also inhibits TNF-alpha and Interleukin-1 (pro-inflammatory cytokines)



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Example of Essential Fatty Acid Supplement

One capsule contains:

1. Fish Oil – 400 mg (30% EPA/20% DHA = 50% EFA)
2. Flaxseed Oil – 400 mg (58% ALA)
3. Borage Seed Oil – 400 mg (22% GLA)

Dosage: 3-4 capsules per day for therapeutic purposes

90 Capsules Per Bottle

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5 lipoxygenase converts AA to LTA_4 (up-regulates proliferation messengers and oncogenes involved in cancer

Other Natural Inhibitors of 5 Lipoxygenase and COX:

1. Boswellia
2. Ginger
3. White Willow Bark Extract (primarily COX inhibitor like other NDAIDs – aspirin)
4. Quercetin - also inhibits phosphoinositol-3 kinase (P13K – important second messenger in proliferation)

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Example of Natural Anti-Inflammatory

One capsule contains:

1. Curcumin – 200 mg (cox and lox)
2. Boswellia – 200 mg (70% boswellic acids) (lox)
3. White Willow Extract – 33.3 mg (15% salicin) (cox)
4. Ginger Root Extract – 50 mg (5% gingerols) (cox and lox)

Dosage – 3-4 capsules, 3x daily

90 Capsules Per Bottle

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Immune System In Cancer

Apoptosis - Cytotoxic T-cells (NK) are able to directly induce apoptosis in cells by opening up pores in the target's membrane and releasing chemicals which bypass the normal apoptotic pathway. The pores are created by the action of secreted **perforin**, and the granules contain **granzyme B**, a protease which activates a variety of caspases that induce apoptosis.

Interferon - sometimes used in cancer therapy, is a protein made by immune cells that upregulates the function of cytotoxic T- cells (natural killer cells), helping them stimulate apoptosis of cancer cells.

Tissue Necrosis Factor – TNF is a cytokine produced mainly by activated **macrophages**, and is the major extrinsic mediator of apoptosis. The binding of TNF to *TNF-R1* has been shown to initiate the pathway that leads to caspase activation via the intermediate membrane proteins TNF receptor-associated death domain (TRADD) and Fas-associated death domain protein (FADD).

Hence – natural immune modulators (reishi m ext, astagalus) shown to boost levels of these apoptotic-triggering cytokines

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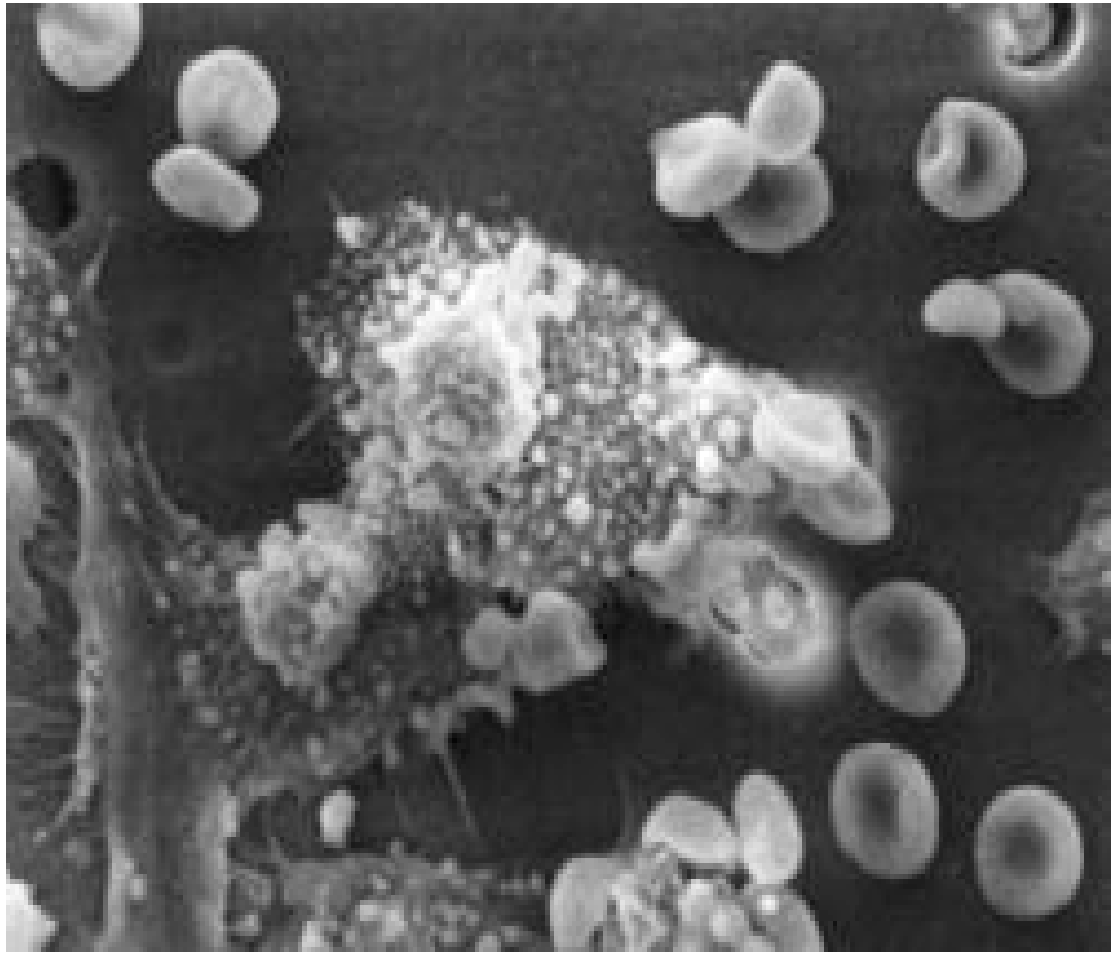
Macrophages have identified a cancer cell (the large, spiky mass). Upon fusing with the cancer cell, the macrophages (smaller white cells) will inject toxins that kill the tumor cell.



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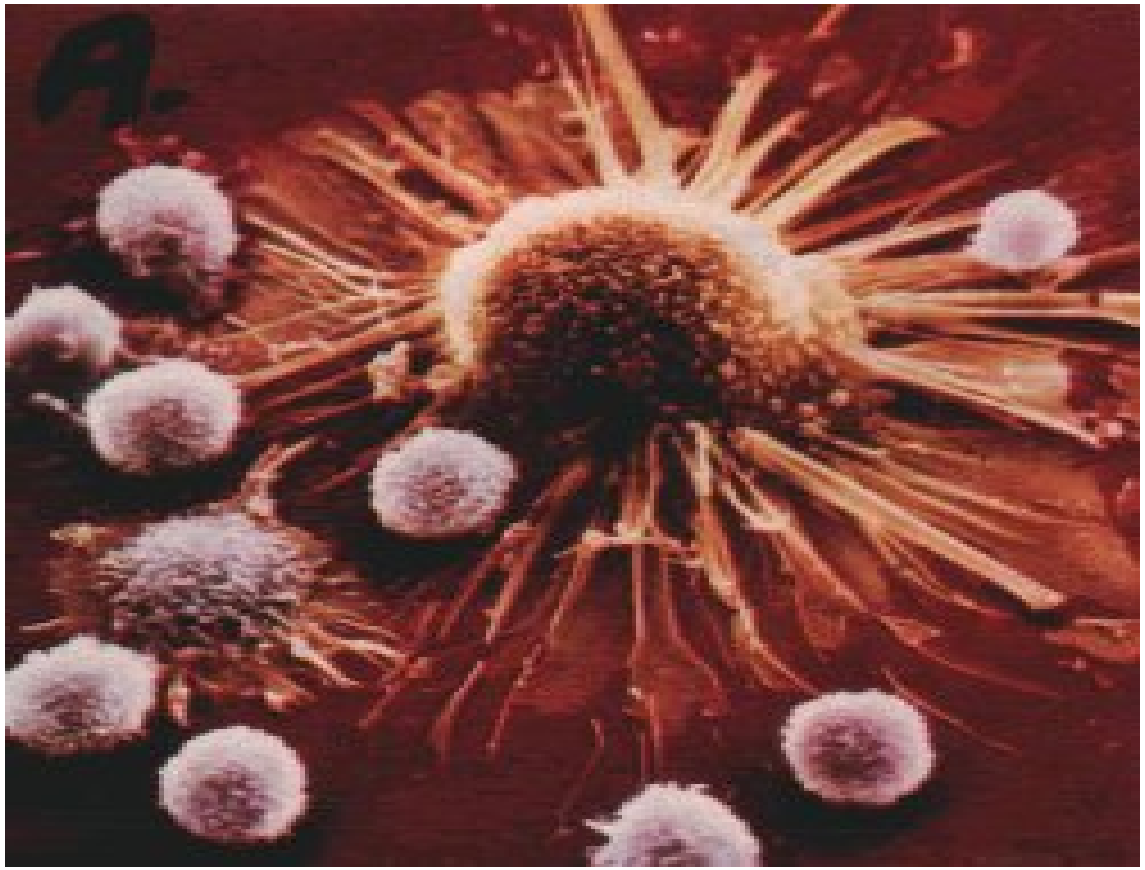
Before

A fully intact cancer cell surrounded by the immune systems killer t-cells.

The cancer cell is surrounded and attacked by the killer T-Cells of the immune system. Scanning electron microscope pictures shows killer t-cells attacking the cancer cell. Notice the tenticles of the cancer cell



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After

Notice how the cancer is completely flattened and totally destroyed.
During the killing process, granules in a T-Cell fuse with the cell membrane and release units of the protein PERFORIN. These combine to form pores in the target cell membrane. Thereafter fluid and salts enter so that the target cell eventually bursts.

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Reishi Mushroom Extract

- (Ganoderma lucidum) “the mushroom of immortality” in China and has been used in Oriental Medicine for over 2,000 years.

- **Modulates Immune Function Via**: Specific Polysaccharides - in the form of Beta-D-glucans bound to amino acids. These agents are known to possess immune-modulating and anti-cancer properties

- **Apoptosis**: Reishi M extract shown to induce apoptosis of many types of cancer cells via increased secretion of anti-tumor cytokines (TNF-alpha and IFN-gamma), acting on death receptors. It also suppresses phosphorylation of Akt, followed by down regulation of cyclin D1 and cyclin dependent kinase-4 (anti-proliferative)

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Astragalus

- Shown to reduce side effects of chemotherapy and radiation treatment in human studies. A large clinical study of 572 cancer patients demonstrated that Astragalus supplementation was able to protect adrenal cortical function during radiation and chemotherapy treatment. It also helped to greatly minimize bone marrow depression and gastrointestinal side effects, such as nausea, vomiting and intestinal tract ulcerations in these patients - 500mg, 3X daily (2:1 extract)

- In patients with very low white blood cell counts, as a side effect of drugs, radiation or chemotherapy, Astragalus supplementation has been shown to help significantly increase the number of circulating white blood cells, helping to restore normal function of the immune system in these severely immune-compromised patients

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- The biological activity that can account for these outcomes is related the active constituents in Astragalus, primarily its triperpene glycosides and polysaccharide content, which have been shown to significantly increase the proliferation of lymphocytes, enhance interferon and interleukin-2 production, which enhance the effectiveness of immune cells, activate T cell blastogenesis, increase T cell cytotoxicity, enhance the secretion of tumor necrosis factor (TNF), enhance phagocytosis by immune cells, and increase natural killer cell cytotoxicity.

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Example: Immune-Detox Supplement

One capsule contains:

1. Reishi M Extract – 30 mg (10% polysacch)
2. Astragalus – 100 mg (2:1 extract)
3. Milk Thistle – 150 mg (80% silymarin)
4. Indole-3 carbinol – 25 (97% grade)

Dosage: 1-2 capsules per day for health promotion and 4 capsules, 2-3 times per day in cancer support

60 capsules per bottle

Also use: 2-4 teaspoons per day or 14 mushroom blend available from www.mushroomharvest.com

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Vitamin E Succinate

1. Apoptosis:
   a. Inhibits Bcl-2
   b. Stimulates Fas Death Receptor
   c. Stimulates c-jun apoptosis pathway

2. Inhibits Erb-2 receptors and related second messengers in breast cancer cells

3. Decreases expression of androgen receptors – required for prostate cancer

4. Angiogenesis: Inhibits release of VEGF

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Vitamin E Succinate Shows Potent and Consistent Anti-Cancer Properties

- Over a number of years a unique form of vitamin E known as vitamin E succinate (alpha-tocopheryl succinate) has shown the most impressive anti-cancer properties, compared to all other forms of vitamin E, including the tocotrienols.

- Experimental studies continue to show that only this form of vitamin E (vitamin E succinate) causes rapid production of reactive oxygen species (free radicals) selectively within cancer cells, triggering cell death (apoptosis), while being non-toxic to normal healthy cells.

- In addition, Vitamin E succinate also inhibits the anti-apoptotic function of Bcl-2 and Bcl-xl, normally expressed by tumor cells. Malignant cells typically try to block signals that lead to programmed cell death (apoptosis). One of the clever ways they do this is by blocking an important apoptotic signaling pathway that is controlled by the p53 tumor suppressor gene.

- Normally, when a cancer cell is emerging it is detected by a network of internal surveillance genes (tumor suppressor genes), which in turn respond by up-regulating the synthesis of the Bax protein. The Bax protein translocates to the mitochondria and exerts effects that lead to mitochondrial disruption and fragmentation. This prevents cancer cells from generating vital ATP energy, which in turn, triggers programmed cell death (apoptosis).

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- The synthesis of the Bax protein is under control of the p53 tumor suppressor gene. However, malignant cells block the apoptotic effects of Bax protein by synthesizing the Bcl-2 protein, which inhibits the effects of the Bax protein, thereby enabling cancer cells to survive and thrive, even though tumor suppressor genes are sending signals directed at programmed cell death

- Vitamin E succinate is one of only a few compounds ever shown to inhibit the anti-apoptotic function of Bcl-2 and Bcl-xl (by blocking their BH3 domains www.ncbi.nlm.nih.gov/pubmed/10816098). This may also explain, to some extent, how vitamin E succinate has been shown to sensitize cancer cells to other anti-cancer drugs, thereby improving their chemotherapy-killing effects (1).

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Vitamin E Succinate May Also Kill Cancer Cells are Via Oxidative Stress

- The emerging studies show that cancer cells that are able to protect themselves against reactive oxygen species (free radicals) are less likely to undergo apoptosis.

- Thus, some experimental studies show that antioxidant fortification via superoxide dismutase, N-acetylcysteine, coenzyme Q10, and possibly other forms of vitamin E, provide cancer cells with a survival advantage due to their antioxidant properties.

- However, vitamin E succinate has the opposite effect – it increases accumulation of free radicals within cancer cells, which leads to cell death.

- This has been shown to occur via the unique ability of vitamin E succinate's capacity to bind to complex II within the mitochondria, thus preventing binding of coenzyme Q10 at this point in the mitochondrial chain.

- As such, coenzyme Q10 becomes unable to transfer electrons to complex II, and thereby releases them within the cell. The unpaired electrons interact with cellular oxygen to form various reactive oxygen species, such as the superoxide anion (free radicals), which accumulate and trigger programmed cell death.

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- This mitochondrial disruption killing-effect of cancer cells has recently been demonstrated in a mouse model of breast cancer, in which many tumors showed over-expression the Her-2 receptor. The positive Her-2 receptor breast cancer phenotype is known to be highly aggressive and a stubborn form of cancer to kill.

- Anticancer agents that target mitochondria disruption leading to programmed cell death are termed mitocans, which represent a new investigative and promising area of oncology research. Vitamin E succinate is a one of the most promising mitocans discovered to date (1,2).

- In addition, vitamin E succinate has shown other multi-modal anticancer properties that have been reviewed by several researchers over the years (3,4).

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Human Studies Underway

- The impressive experimental cancer-killing effects of vitamin E succinate, coupled with our understanding of its observed anticancer properties (particularly reactive oxygen species-induced apoptosis, and inhibiting the anti-apoptotic effects of Bcl-2 and Bcl-xl), prompted researchers to test vitamin E succinate in a recent human case of mesothelioma.

- Malignant mesothelioma is a form of lung cancer caused by exposure to asbestos and is highly resistant to radiation and chemotherapy. In this single case study administering vitamin E succinate to a patient with malignant mesothelioma the researches stated, “the data revealed a significant clinical benefit with vitamin E succinate therapy, causing a reduction in tumour volume and improved the well-being of our subject who had a lethal type of neoplastic pathology”.

- This outcome was published in *Lancet* in 2005. These researchers are currently preparing to set-up a larger clinical trial in which a cohort of mesothelioma patients will be treated with vitamin E succinate (1). Experimental studies in the past have demonstrated the efficacy of vitamin E succinate in killing human malignant mesothelioma cells *in-vitro* (2,3).

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References

1. Dong LF, Low P, Dyason JC, Wang XF, prochaxka L et al. Alpha-tocopheryl succinate induces apoptosis by targeting ubiquinone-binding sites in the mitochondrial respiratory complex II. Oncogene. 2008. 27, 4324-4335. http://www.nature.com/onc/journal/v27/n31/full/onc200869a.html
2. Neuzil J, Wang XF, Dong LF, Low P, Ralph SJ. Molecular mechanism of mitocan-induced apoptosis in cancer cells epitomizes the multiple roles of reactive oxygen species and Bcl-2 family proteins. FEBA Lett. 2006. 580(22):5125-9.
3. Kline K, Weiping Y, Sanders. Vitamin E: Mechanism of actions as tumor cell growth inhibitors. J Nutri. 2001. 131(1):161s-163s.
4. Prasad KN, Kummar B, Yan XD, Hanson AJ, Cole WC. Alpha-tocopheryl succinate, the most effective form of vitamin E for adjuvant cancer treatment: a review. J Am Coll Nutr. 2003. 2:108-117.

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Selenium

- At supraphysiological levels of intake, selenium has been shown to exhibit a number of anti-cancer properties beyond the activation of the antioxidant enzyme, glutathione peroxidase.

- The present view is that selenium metabolites (i.e., methylated forms of selenium), rather than simply the saturation of L-selenocysteine synthesis alone, are key factors in selenium's cancer preventive effects.

- During periods of supraphysiological intake (supplementation), once L-selenocysteine levels are saturated, Se is rapidly methylated to **dimethyl selenide and other *methylated forms including the monomethylated form, and trimethylselenonium.***

- Experimental studies highlight the fact that these methylated forms of selenium (metabolites) possess direct and indirect chemopreventive effects that are not attainable by the action of glutathione peroxidase acting alone.

- Reduced Risk of colon cancer occurs at selenium blood levels 120 micrograms per liter (may reduce risk more than 50%)

Thus, selenium supplementation (100-400 mcg per day) increases the levels of methylated selenium metabolites that appear to account for many of selenium's cancer preventive effects. These general mechanisms include:

1. Apoptosis – detectable towards the upper limit of plasma selenium concentrations (approx 5 umol/L)
2. Growth-inhibitory effects of cancer cells
3. Induction of p53 tumor suppressor gene, which gives rise to proteins that arrest cell cycle division when DNA mutations occur, allowing DNA repair enzymes to correct the error.
4. Protects against DNA damage
5. Anti-promotional agent, discouraging cancer cell division.

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Vitamin C

Apoptosis:

a. Interferon – increase release of interferon from various immune cells causes increase activation and release perforin and granzyme B proteins from NK cells and T lymphocytes

b. Up regulation of caspase-3 enzyme mediated apoptosis has been shown in cancer cells treated with vitamin C

c. Upregulation of p53 tumor suppressor-mediated apoptosis in cancer cells treated with vitamin C

Proliferation – Vitamin C shown to inhibit NF-kappa beta in infected cells and thought to do the same in cancer cells – decreasing proliferation

Gap Junction Preservation – preserves cell-to-cell communication whereby healthy cells shut off communication with infected and and cancer cells – blocking spread of infection and cancer

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Vitamin D and Cancer

- Cancer cells maintain Vitamin D receptors, enabling them to convert 25-hydroxycholecalciferol into 1,25 dihydroxycholecalciferol (Calcitriol)

- Calcitriol slows rate of replication of human prostate, breast and colon cancer cells, under experimental conditions, as well as non cancerous cells, decreasing risk of cancer development (above 85nmol/L)

- Calcitriol promotes newly formed cells to mature to their full adult potential (differentiation), which decreases the chance of these cells being transformed into cancer cells by some external influence.

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- Calcitriol exerts a favorable effect on immune function, which is thought to account for some of its anti-cancer influences.

- Calcitriol also has been shown to transform the appearance of human cancer cells (e.g., prostate cancer cells) back to healthy, nonmalignant-looking cells, and inhibit their replication, an effect that is lost once the calcitriol is no longer administered.

- Slows the PSA doubling time in prostate cancer patients **(see next slide)**

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- In this study (Woo TSC, 2005) 15 prostate cancer patients were given **2,000 IU** (50 ug) **of cholecalciferol** daily and monitored prospectively every 2-3 months.

- In 9 patients, the PSA level decreased or remained unchanged (no further rise) and these results were sustained during the 21-month course of vitamin D administration.

- Analysis also showed that there was a statistically significant decrease in the rate of PSA rise after administration of cholecalciferol compared with that before cholecalciferol administration. The median PSA doubling time increased from 14.3 months prior to cholecalciferol administration to 25 months after commencing cholecalciferol. There were no side effects reported by any patient.

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- The marked prolongation of PSA doubling time is an extremely important outcome to the administration of cholecalciferol in these patients, according to the recent work of Partin and fellow researchers (J Urol, 2003).

- Partin and fellow researchers showed that the risk of distal metastasis of prostate cancer (with respect to relapse after prostate cancer surgery) at 5 years was 65% to 75% when PSA doubling time was less than 10 months compared with 10-20% when PSA doubling time was greater than 10 months

- Many practitioners now administer 10,000 - 50,000 IU per day of vitamin D to cancer patients, but blood levels of cholecalciferol must be monitored (under 250nmol/L)

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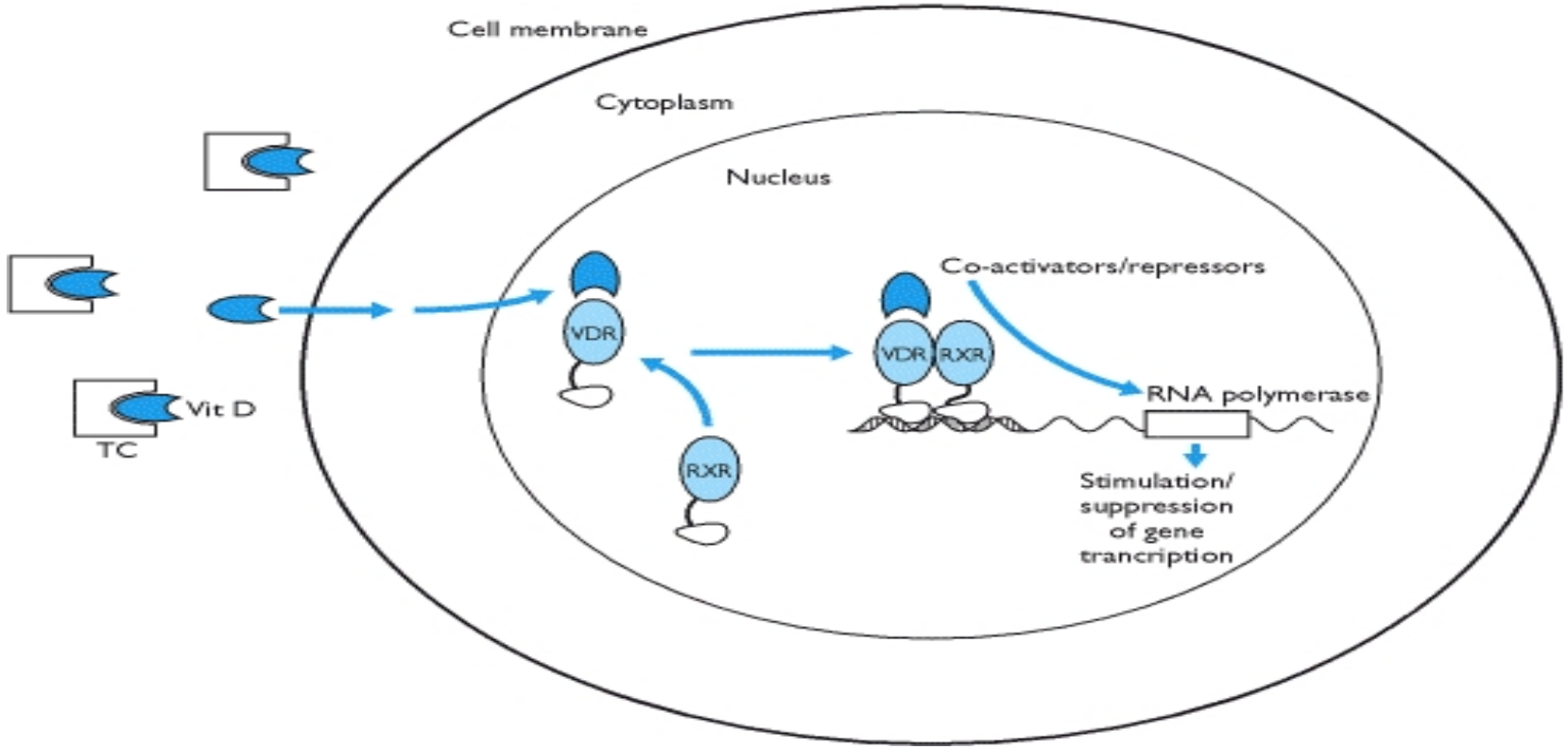
Vitamin D Slows Cell Division and Promotes Cell Maturation

- In circulation vitamin D is bound to the globulin, transcalciferin (TC), with only a small fraction existing in free form. The free form crosses the cell membrane and the nuclear membrane where, in target cells, it interacts with a vitamin D receptor (VDR). This induces dimerization with the retinoic acid receptor (RXR), DNA binding and interaction of receptors with transcription factors resulting in stimulation or inhibition of gene transcription



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Vitamin D and Cancer: 2017 Review Paper: Clinical Therapeutics

https://www.clinicaltherapeutics.com/article/S0149-2918(17)30194-7/fulltext

- In the past, studies found that the asset of vitamin D was modified in patients with various forms of cancer, but it was not until recent that it was found that vitamin D actually has a modulating effect on cancer cells: 1,25(OH)2 D stimulates the expression of cell cycle inhibitors p21 and p27 and the expression of the cell adhesion molecule E-cadherin, while inhibiting transcriptional activity of β-catenin. These actions should block the proliferative potential of these cells.

- In keratinocytes 1,25(OH)2 D promotes the repair of DNA damage induced by ultraviolet radiation and increases p53 expression in damaged cells. Epidemiologic evidence supports the importance of adequate vitamin D administration (including sunlight exposure) for the prevention of different types of cancer is extensive, as shown in recent studies.

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- Vitamin D exerts anticancer activities by targeting key molecules involved in cell cycle regulation. These include c-Myc and c-Fos, two known proto-oncogenes involved in the cell cycle regulatory machinery and overexpressed in several tumors.

- It has been found that vitamin D suppresses the expression of the oncogene c-Myc and, thus, promotes the increased expression of its antagonist, the transcriptional repressor MAD1/MXD1, an effect mediated by a cellular regulator referred to as F-box protein.

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- However, as reviewed by Farlandin, there appear to be more mechanisms through which vitamin D could have an anticancer effect. It has strong antiproliferative effects, increasing the expression of insulin-like growth factor–binding protein 3, thus inhibiting mitogenic signaling by growth factors such as insulin-like growth factor-1 and inducing apoptosis by suppressing antiapoptotic genes such as *BCL2*.

- It also has anti-inflammatory effects, which explains why vitamin D is capable of having positive effects in both tumors and autoimmune diseases.

- Vitamin D stimulates differentiation and inhibits invasion and metastasis through increased expression of E-cadherin, a gene inversely correlated to tumor's metastatic capacity.

- In addition, inhibition of angiogenesis, through suppression of vascular endothelial growth factor, reduces invasion and growth potential of the tumor.

- The biological actions of vitamin D are mediated by the VDR, mostly by genomic actions. Vitamin D binds to the VDR, thereby causing its dimerization with the retinoid X receptor, binding of the complex to vitamin D response elements in multiple regulatory regions located at promoters and distal sites of target genes, and the recruitment of co-modulators.

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- Overall, mechanisms through which vitamin D works are still not totally understood, but it appears that vitamin D levels have a positive impact on the type and outcome of the tumor, and they may even have a positive effect in preventing the development of BC.

- However, note that some of the mechanisms summarized above have been observed only in particular forms of cancer: that is, Bcl-2 and E-cadherin in PCa and differentiation in leukemic cells. Thus, it appears that there is not a single common underlying mechanism through which vitamin D is an anticancer agent.

Reference

Pandolfi F, Franza L, Mandolini C, Conti P. Immune Modulation by vitamin D: Special emphasis on its role in prevention and treatment of cancer. Clinical Therapeutics. 39 (5):884-893. 2017
https://www.clinicaltherapeutics.com/article/S0149-2918(17)30194-7/fulltext

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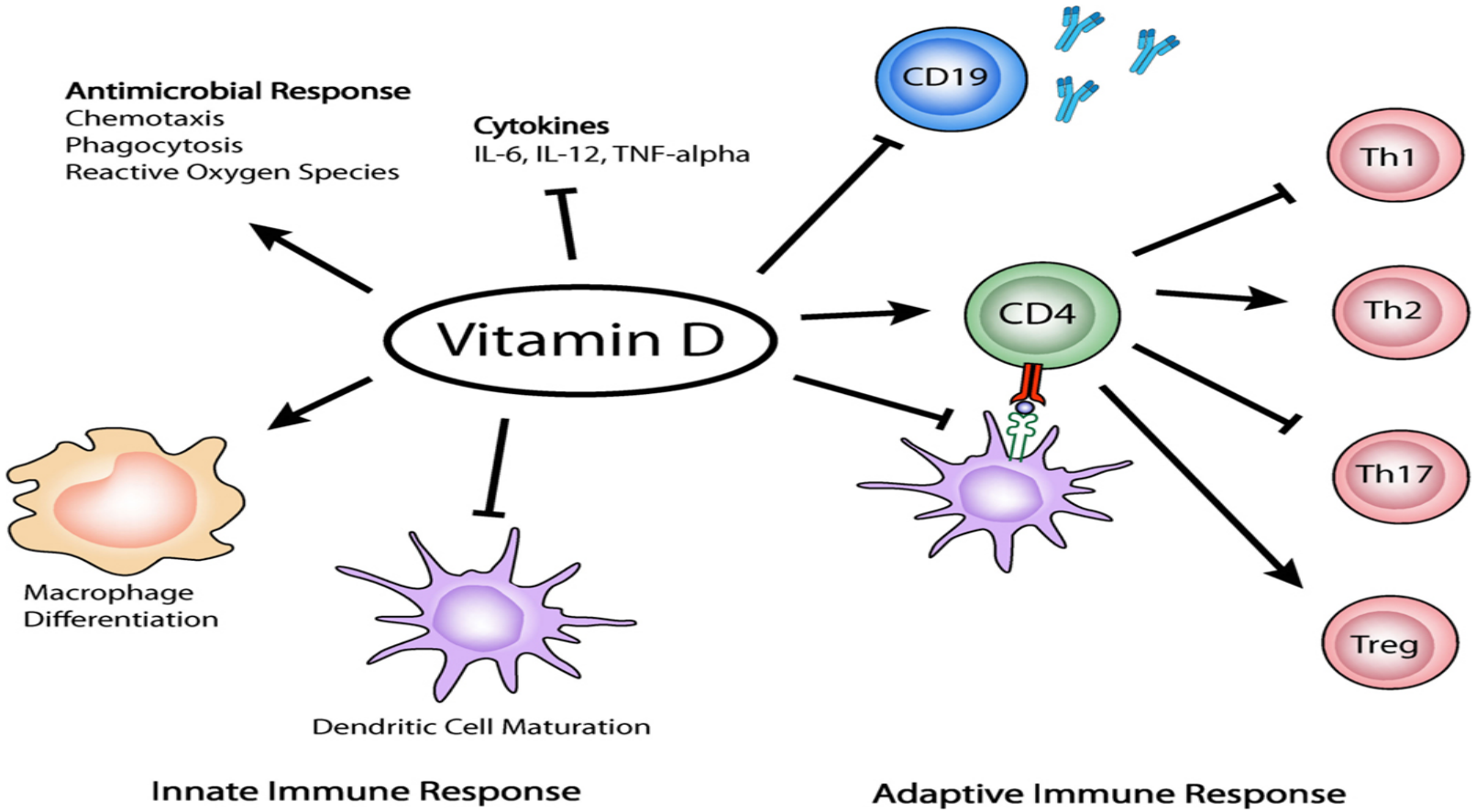
Vitamin D and Immune System



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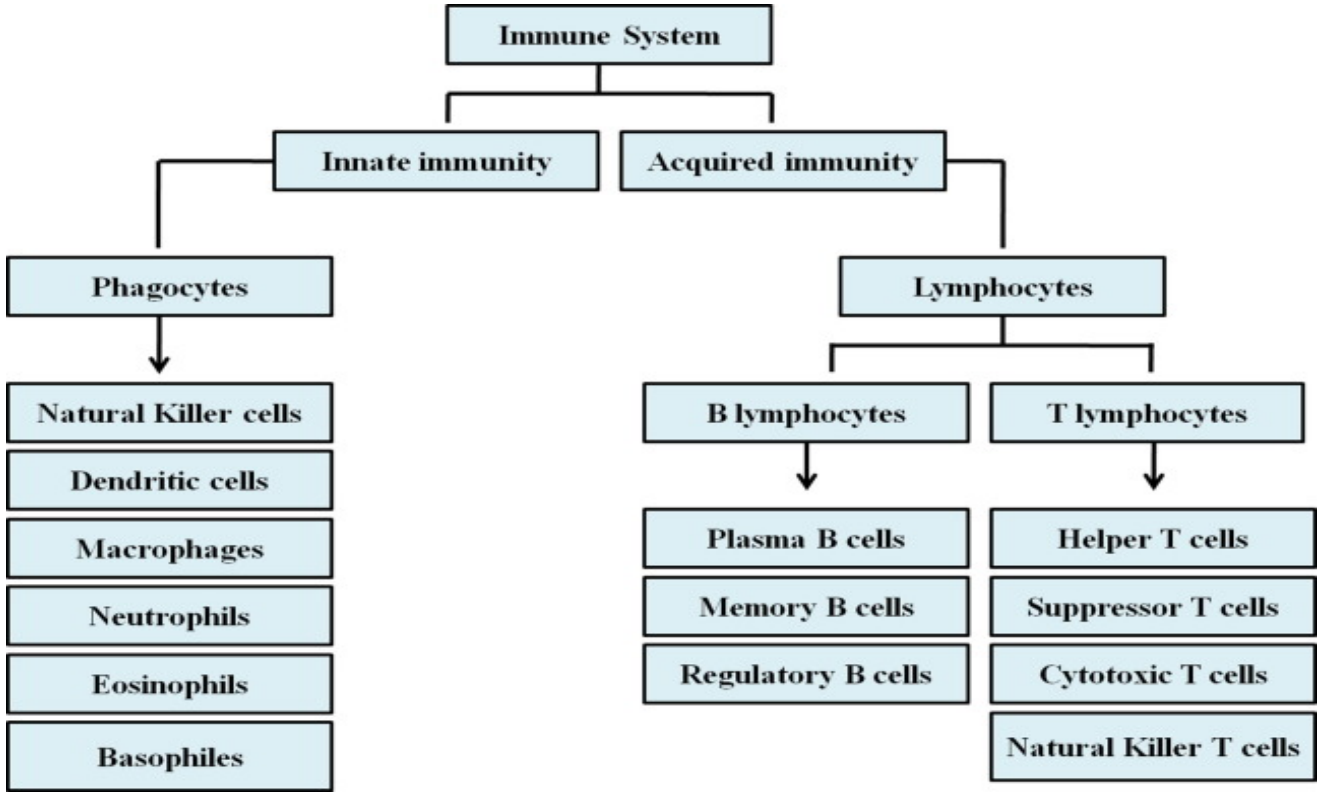
Closer Look At Immune System



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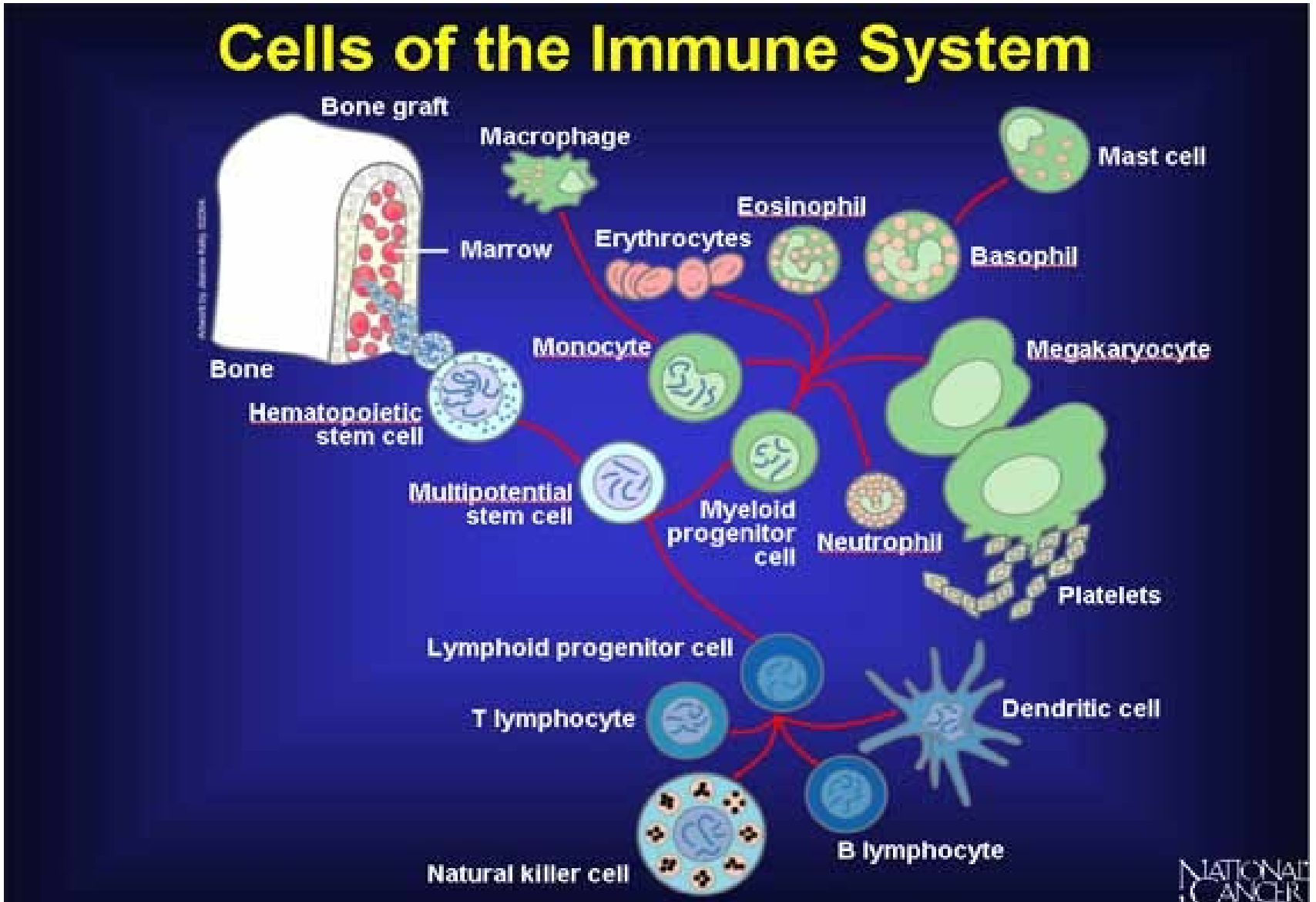
Immune Cell Differentiation



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The Immune System: Essential Review

- Bone Marrow Stem Cells give rise to B lymphocytes, natural killer cells, granulocytes (neutrophils, basophils, eosinophils) and immature thymocytes, in addition to red blood cells and platelets

- **Immature thymocytes** leave the bone marrow and migrate to thymus, where they further develop and mature and are then released to the circulation:
  - **T-helper cells** (CD4+ cells) modulate activity of other immune cells, but do not kill anything themselves.
  - **T-killer cells** (Cytotoxic T lymphocytes, Suppressor T-cells, or CD8+ cells) are activated by CD4+ cells to kill virally-infected cells, other antigen-containing cells, as well as tumor cells.
  - Activation occurs in lymphoid tissues, but CD4+ and CD8+ cells are found throughout the body

- **Natural killer cells** (NK cells) are a subset of killer T cell subset (CD8+ cells). They function as effector cells that directly kill certain tumors such as melanomas, lymphomas and viral-infected cells, most notably herpes and cytomegalovirus-infected cells.

- NK cells, unlike the CD8+ cells**, kill their targets without a prior conditioning in lymphoid organs with CD4+ cells**. However, NK cells activated by cytokines from CD4+ T cells kill tumors or viral-infected targets more effectively.

- **B lymphocytes** – main function is **production of antibodies** in response to foreign proteins of bacteria, viruses, and **tumor cells.** Antibody production and binding to a foreign substance or antigen, is a critical means of signaling phagocytotic cells (macrophages, neutrophils, CD8+ cells) to engulf, kill or remove that substance from the body.

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- **Macrophages** (from monocytes) **can directly kill foreign cells (including tumor cells) via phagocytosis and TNF release etc., but are also antigen-presenting cells (APC), which ultimately up-regulate production of tumor antibodies produced by B-lymphocytes and plasma cells**

  CD4+ cells condition CD8+ cells (T-suppressor or cytotoxic T-cells, and NK cells to target antigen-containing microorganisms and tumor cells

- **Dendritic cells**, derived from myeloid (from monocytes) and lymphoid progenitor cells, can kill tumors via phagocytosis, but **are also the most important APC**, with respect to generating a global immune response against tumor cells.

- **Dendritic cell failure is thought to be largely responsible for tumor tolerance and progression of cancer.**

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Immune System Has The Ability To Kill Cancer Cells

The Evidence:

- Cancer risk increases in immune-suppressed individuals (from drugs, AIDS, other infections)
- Solid Tumors Show Infiltration Of Various Immune Cells
- Monoclonal Antibody Model proven to induce immune response against tumor cells, once antibody binds to target receptor (eg. Her-2 and Herceptin)
- Spontaneous Remission of Cancer Shown To Involve Removal Of Tumor By Immune Cells
- Immune Activation (via Coley's Toxin, Syphyllis and other methods) has shown benefits in reversing certain cancer cases.

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Conclusion – "it is possible that many early tumors rejected by the immune system do not progress to form clinical cancer, and only those that the immune response fails to eliminate do progress to a clinically-detectable stage. This could account for the high incidence of malignancies in immune-suppressed individuals"

(Nzula S et al. Cancer Therapy 2003. The role of B lymphocytes in breast cancer: a review and current status)

- Immune Suppression can also occur from high cortisol levels (physical or psychological stress) and depression and despair (hopelessness, helplessness)

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Immune Cell Behavior In Cancer

A. Immune Cells Shown To Infiltrate Solid Tumors:

- Cytotoxic T Cells (CD8+)
- T-helper lymphocytes (CD4+)
- Macrophages
- Dendritic Cells
- NK cells
- B- Cells (B- lymphocytes)

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B. Coordination Of Innate and Adaptive Immune System In Cancer:

Innate Immunity and Cancer

- Innate leukocytes include: Natural killer cells, mast cells, eosinophils, basophils; and the phagocytic cells including macrophages, neutrophils and dendritic cells.

- **NK-cells, macrophages, neutrophils and dendritic cells** are most important cells of innate immunity with respect to cancer. They are all phagocytic cells, **except NK- cells.** NK-cells kill cancer cells exclusively by secreting perforin to lyse the cell membrane and granzyme B to induce apoptosis, as can CD8+ cells

In addition to attacking cancer cells, the innate immune cells activate the **complement system** – a biochemical cascade requiring the release of plasma proteins synthesized in the liver by hepatocytes which:

- Trigger recruitment of inflammatory cells.
- Tag" pathogens for destruction by other cells by *opsonizing*, or coating, the surface of the pathogen.
- Disrupt the plasma membrane of an infected or cancerous cell, resulting in cell lysis.
- Rid the body of neutralized antigen-antibody complexes.

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Macrophages

- Macrophages enter the areas between cells in pursuit of invading pathogens and cancer cells. They are the **most efficient phagocytic cells.**

- In addition to phagocytosis, macrophages also function as **antigen-presenting cells** (APC)

T Lymphocytes never act as antigen-presenting cells, but B Lymphocytes do, as well as dendritic cells and macrophage cells

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Macrophages And Apoptosis

Macrophages can also induce apoptosis of cancer cells via release of Tumor Necrosis Factor –alpha and/or Fas ligand (stimulation of FADD and TRAAD Receptors)

Macrophages represent major extrinsic pathway of apoptosis of cancer cells

A major problem in cancer is insufficient activity of macrophages against cancer cells (phagocytosis, apoptosis, APC function)

Some Drs administer **Macrophage-Activating Factor** (INF-gamma) to up-regulate macrophage activity

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T- helper cells

- T-helper cells (CD4+ cells) are activated by APC (dendritic cells and macrophages) to enhance the killing effect of CD8+ cells, B-cells, macrophages and neutrophils to attack cancer cells or microorganism displaying antigen.

- T-helper cells (CD4+ cells) also stimulate B-lymphocytes to produce antibodies against the cancer cell (or microorganism) and for some B-lymphocytes to morph into plasma cells, which generate large volumes of antibodies.

- The antibodies mark the cells for other immune cells to attack and destroy them via phagocytosis (macrophages, dendritic cells, neutrophils, B lymphocytes etc.), and up-regulate the Complement System.

- Antibodies can also signal natural killer cells and macrophages to kill tumor cells, viral or bacterial-infected cells.

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Cytotoxic T Lymphocytes (CTL)

- Cytotoxic T Lymphocytes (CD8+) - **most abundant immune cells in tumors** and are major contribution to immune response against tumors. They do not require antigen recognition, but it improves their killing effects when initiated this way. Thus CD4+ cell modulation improves the cancer-fighting ability of CD8+ cells.

- CTL release **perforin and granulysin:** cytotoxins which form pores in the target cell's plasma membrane, allowing ions and water to flow into the infected cell, and causing it to burst or lyse.

- CTL release granzyme B, a serine protease that enters cells via pores to induce apoptosis.

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Natural killer cells (subset of CD8+ cells):

- **NK-cells** destroy compromised host cells, such as tumor cells or virus-infected cells, recognizing such cells by a condition known as **"missing self."**

- “Missing self” describes cells with low levels of a cell-surface marker called MHC class I (major histocompatibility complex I), which are usually present on all self-cells.

- NK-killer cells do not require activation to kill “non-self” cells

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Dendritic cells

- **Dendritic cells (derived from myeloid and lymphoid sources)** are present in tissues in contact with external environment, mainly the skin (Langerhans cells), and the inner mucosal lining of the nose, lungs, stomach and intestines.

- In addition to phagocytosis, dendritic cells are the **most important antigen presenting cells (APC),** boosting the involvement of CD4+ cells to recruit CD8+ cells and B-lymphocytes into the fight within lymphoid tissue.

- **Dendritic cell failure** is common problem in development of immune system tolerance of tumor cells

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Neutrophils

- Similar to macrophages, neutrophils attack pathogens by activating a respiratory burst such as hydrogen peroxide, free oxygen radicals and hypochlorite.

- Neutrophils are the **most abundant type of phagocyte**, normally representing 50 to 60% of the total circulating leukocytes, and are usually the first cells to arrive at the site of an infection.

- Neutrophils do not require antigen activation to kill cancer cells.

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- As we age, neutrophils are less able to generate optimal concentrations of hydrogen peroxide to kill cancer cells and pathogens.

- The administration of neutrophils from young healthy donors is being evaluated as a cancer treatment method (Unmatched allogenic)

- The bone marrow of a normal healthy adult produces more than 100 billion neutrophils per day, and more than 10 times that many per day during acute inflammation.

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Adaptive Immunity: How It Works

Lymphocytes

- The peripheral blood contains 20–50% of circulating lymphocytes; the rest move within the lymphatic system.

- B cells and T cells are derived from the same multipotent hematopoietic stem cells, and are indistinguishable from one another until after they are activated.

- B cells play a large role in the humoral immune response, whereas T-cells are intimately involved in cell-mediated immune responses.

- T-cells travel to and develop in the thymus

Peripheral lymphoid organs contain mixture of B and T Lymphocytes in at least three stages of differentiation:

1. **Naive cells** that have matured, left the bone marrow or thymus, have entered the lymphatic system, but that have yet to encounter their cognate antigen

2. **Effector cells** that have been activated by their cognate antigen, and are actively involved in eliminating a pathogen (e.g. activated CD8+ cells, activated B Lymphocytes)

3. **Memory** T and B cells – the long-lived survivors of past infections.

- **Memory In Infection** - Upon resolution of an infection, most of the effector cells will die and be cleared away by phagocytes, but a few of these cells will be retained as memory cells.

  Upon a later encounter with the same antigen, these memory cells quickly differentiate into effector cells, dramatically shortening the time required to mount an effective response.

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- **Interdependence Of Innate and Adaptive Immune Processes In Cancer**:

  The innate and adaptive portions of immune system work together. The adaptive arm would be unable to function without modulation by CD4+ cells, and CD4+ cells are useless without antigen-presenting cells to activate them.

  Likewise B lymphocytes are crippled without CD4+ help.

- As well, the innate system would likely be overrun with pathogens without the specialized action of the adaptive immune system, in cases of infection

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Why Don't Immune Cells Kill Cancer Cells Very Well In Real Life

1. Most solid cancers express **small amounts of Tumor-Associated Antigens (TAAgs)**, which may also be cryptic and not readily available for recognition by APC immune cells (dendritic cells, macrophages, B-cells)

2. Tumor cells tend to **lack co-stimulatory** molecules that normally drive clonal expansion of T cells, the production of key regulatory cytokines, and development into tumor cell specific cytotoxic T lymphocytes (CTLs).

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Dendritic Cell Dysfunction In Cancer: key findings explaining immune failure in cancer

- In most tissues dendritic cells capture and process Ags, which are then displayed as MHC-peptide complexes on the DC surface.

- Essential co-stimulatory molecules are upregulated on DCs as they migrate to secondary lymphoid organs (the spleen and lymph nodes) where they liaise with naïve T cells, inducing the transformation to CD4+ cells with activation and proliferation of Ag specific cytotoxic T lymphocytes (CD8+ cells).

- Tumor cells shown to secrete **Interleukin 10** which inhibits differentiation of circulating dendritic cells, down-regulates expression of key co-stimulatory signals, and blocks production and secretion of dendritic cells and T-cell regulatory molecules.

- Some tumors also secrete soluble factors which inhibit dendritic cell function

Result = Dendritic Cell Failure to activate T – cells, with immune tolerance towards tumor antigens

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Other Factors Suppressing Immune Response In Cancer:

1. Tumor cells secrete Fas Ligand, which induces apoptosis of immune cells by activating their FADD

2. Secretion of Prostaglandin series-2

3. Increased acidity of tumor environment

4. Fibrous coat around tumor cells (disguising them and reducing accessibility)

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Immune Modulators

Nutritional Supplements Shown To Enhance Tumor-Killing Effect Of Immune Cells:

- Medicinal Mushrooms
- Astragalus
- Echinacea
- CoQ10
- Antioxidants (plus selenium and zinc)

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Reishi Mushroom Continued

Anti-Cancer Effects:

- Potentiates the tumoricidal activity of Macrophages and T-Cells
- Apoptosis –in leukemic cells and induces cellular differentiation in 40-45% of leukemic cells
- Increase secretion of anti-tumour cytokines – TNF-alpha and Interferon-gamma
- Inhibits Nuclear Factor Kappa –beta in human breast cancer cells
- Inhibits activation of Akt with down regulation of cyclin D1 and cyclin dependent kinase-4
- **Therapeutic Dosage**: 250 mg, 1-4 times daily (std to 10-12.5% polysaccharide content)

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Astragalus Continued

Immune Modulation To Combat Cancer:

- Increase number of proliferating lymphocytes
- Enhances Interferon and interleukin-2 production and efficacy
- Activates T-cell cytotoxicity
- Enhance secretion of TNF
- Enhances phagocytosis by various immune cells
- Increase Natural Killer Cell cytotoxic activity
- Increases activity of peritoneal macrophages
- Direct anti-viral effects

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Astragalus Continued

Human Study:

- **Small Cell Lung Cancer** – patients treated with medical intervention plus Astragalus showed better results than medical treatment alone (longer survival time was outcome measured)

- Experimental evidence shows efficacy against renal cell carcinoma in mice

- Also increases sperm motility along with L-carnitine and zinc

- **Therapeutic Dosage:** 500 mg, 3-4 times daily (std to 2:1 extract)

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CoQ10 In Cancer Therapy

- Increases macrophage activity (1)

- Tumor Regression in breast cancer patients with tumor of as large as 1.5-2.0 cm (2)

Dosage: 300 -400 mg required for tumor regression (expensive)

1. Folkers K. et al.(1993) Survival of cancer patients on therapy with CoQ10. Biochemical and Biophysical Research Communication 192:1: 241-245
2. Lockwood K et al. (1994) Partial and complete regression of breast cancer in relation to dosage of coenzyme Q10. Biochemical and Biophysical Research Communication. 199:1504-1508

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Antioxidants As Immune Modulators

Multi-modal Immune Effects Of Orthomolecular Doses Of:

- Vitamin C: 1000 – 10,000 mg/d
- Vitamin E: 400 – 3200 IU/d
- Beta-carotene: 25,000-100,000 IU/d-
- Vitamin A: 50,000 – 100,000 IU (Lipid Soluble by Genestra)
- Selenium: 200 – 600 mcg/d
- Zinc: 15-40 mg/d

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Mistletoe (Immune Modulator)

Originally conceived by Rudolf Steiner (Austrian scientist), Iscador is trade name of mistletoe preparation used by European physicians since 1920.

Iscador consists of fermented extracts of European Mistletoe (*Viscus Album*), and some forms combined with metals to produce certain desired, anti-cancer effects

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Animal Studies:

- Kills cancer cells
- Stimulates Immune System – **especially NK cells**
- Inhibit tumor formation

Human Studies:

- Improved survival in breast, bronchial, skin, lung, stomach, colon, ovaries (including stage III ovarian CA) and cervical cancer patients
- Enhanced radiation treatment outcomes in patients with cervical cancer
- Reduced malignant transformation of bladder papillomas

Mistletoe Must Be Administered Via IV only (can not take orally)

Reference: Definitive Guide To Cancer. Future Medicine Publishing Inc (Diamond WJ et al editors). Pages 830-831 (References on page 1086)

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Beta-Carotene and Cancer

- Beta-Carotene demonstrates a number of anti-cancer properties and has been shown to reverse leukoplakia as well as early-stage cervical dysplasia. (50,000-100,000 I.U)

- Linxian China study - combination of modest dosages of Beta-Carotene, Vitamin E, and selenium significantly reduced stomach and esophageal cancers, as well as total cancer incidence in high-risk individuals, compared to other vitamin and mineral combinations.

- Beta-Carotene is an antioxidant, an immune system modulator and enhances cellular differentiation of epithelial cells. All of these effects associated with cancer prevention and reversal of some early stage cancers and dysplasias

- May not be appropriate for smokers and lung cancer pts

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Lycopene Research

- Inhibitory effect on migration of cancer cells

Huang CS, Liao JW, Hu ML. "Lycopene inhibits experimental metastasis of human hepatoma SK-Hep-1 cells in athymic nude mice." J Nutr. 2008 Mar;138(3):538-43.

- Ability to reduce levels of circulating insulin-like growth factor (IGF)

Vrieling A, Voskuil DW, Bonfrer JM, Korse CM, van Doorn J, Cats A, Depla AC, Timmer R, Witteman BJ, van Leeuwen FE, Van't Veer LJ, Rookus MA, Kampman E. "Lycopene supplementation elevates circulating insulin-like growth factor binding protein-1 and -2 concentrations in persons at greater risk of colorectal cancer." Am J Clin Nutr. 2007 Nov;86(5):1456-62

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- Trap platelet-derived growth factor (PDGF) - which can act through signal transduction to promote cancer cell division or angiogenesis

Chiang HS, Wu WB, Fang JY, Chen DF, Chen BH, Huang CC, Chen YT, Hung CF. "Lycopene inhibits PDGF-BB-induced signaling and migration in human dermal fibroblasts through interaction with PDGF-BB." Life Sci. 2007 Nov 10;81(21-22):1509-17.

Wu WB, Chiang HS, Fang JY, Hung CF. " Inhibitory effect of lycopene on PDGF-BB-induced signalling and migration in human dermal fibroblasts: a possible target for cancer." Biochem Soc Trans. 2007 Nov;35(Pt 5):1377-8.

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- Stimulated the expression of connexins (gap junction proteins)

Fornelli F, Leone A, Verdesca I, Minervini F, Zacheo G. " The influence of lycopene on the proliferation of human breast cell line (MCF-7)." Toxicol In Vitro. 2007 Mar;21(2):217-23.

- In vitro studies clearly show the anti-proliferative effect of lycopene on different types of cancer cells.

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- Vrieling et al. tested the effect of lycopene supplementation on IGF levels in 71 individuals with a family history of colon cancer.

- Lycopene supplementation significantly increased levels of IGF-binding proteins (type 1 and type2) but did not alter IGF levels.

Vrieling A, Voskuil DW, Bonfrer JM, Korse CM, van Doorn J, Cats A, Depla AC, Timmer R, Witteman BJ, van Leeuwen FE, Van't Veer LJ, Rookus MA, Kampman E. "Lycopene supplementation elevates circulating insulin-like growth factor binding protein-1 and -2 concentrations in persons at greater risk of colorectal cancer." Am J Clin Nutr. 2007 Nov;86(5):1456-62

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- Overexpression of cyclin D1 is often observed in many breast cancer tumors.

Nahum and co-workers investigated the effect of lycopene on cultured human breast cancer cells and found that lycopene reduced the mitogenic effect IGF1 by reducing the level of cyclin D1, which normally up-regulated by IGF-1

Nahum A, Zeller L, Danilenko M, Prall OW, Watts CK, Sutherland RL, Levy J, Sharoni Y. " Lycopene inhibition of IGF-induced cancer cell growth depends on the level of cyclin D1." Eur J Nutr. 2006 Aug;45(5):275-82.

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Lycopene and Prostate Cancer

- Lycopene inhibited growth of the androgen-independent DU145 and PC-3 prostate cells more than androgen-dependent LNCaP (up to 50% inhibition)

- Also saw tumor growth rate inhibited by 55.6 and 75.8% in mice treated with 100 and 300 mg/kg lycopene, respectively, compared with controls.

- In addition, no tumors formed in 1 month in mice treated with DU145 cells that had been pretreated with 20 µmol/L lycopene

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- Flow cytometry revealed that lycopene caused DU145 cells to accumulate in the G0/G1 phase and to undergo **apoptosis** in a dose-dependent manner.

- These results suggest that lycopene may specifically inhibit the growth of androgen-independent prostate cancers.

Reference: Lili Tang et al. Lycopene Inhibits the Growth of Human Androgen-Independent Prostate Cancer Cells In Vitro and in BALB/c Nude Mice. Nutrition and Cancer. J. Nutr. 135:287-290, February 200

Human Studies now confirm reversal of prostate cancer with lycopene supplement – we will see this in Prostate Cancer Section

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Quercetin (Flavonoid)

- Down regulation of mutant P53 protein – re-establishing ability to arrest cell cycle in G2-M phase
- G1- phase arrest of cancer cells (controlled by P53 gene)
- Tyrosine Kinase Inhibitor (IV application has shown this effect in advanced human cancer patients)
- Inactivates Phosphatidylinositol-3 kinase pathway to slow cell replication of cancer cell
- Estrogen Receptor Binding Capacity (ER-II (beta) receptor) – providing growth inhibition

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Quercetin continued

- Inhibition of Heat Shock Proteins

- Inhibition of Ras Protein Expression

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Quercetin Continued

- Increases efficacy of cisplatin and cyclophosphamide and protects renal tubular cells from cisplatin toxicity

- Anti-angiogenesis (decreasing VEGF)

- May decrease resistance to chemotherapy in those over expressing MDR-1 and MDR genes, by inhibiting the action of these efflux glycoprotein pumps

Dosage: 1000-2000 mg per day in divided doses

Quercetin References:

Lamson DW et al. Antioxidants and Cancer III: Quercetin. Alternative Medicine Review. Vol 5, No3: 196-208. 2000

Ren W et al. Flavonoids: Promising Anticancer Agents. Medicinal Reserarch Reviews. Vol 23, No4:519-534. 2003

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Indirubin

- Indirubin is an active constituent of a traditional Chinese preparation and has been proven to exhibit anti-leukemic effectiveness in chronic myelocytic leukemia.

- Indirubin is a potent inhibitory potential towards cyclin-dependent kinases (CDKs).

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- This novel family of compounds holds strong promise for clinical anticancer activity and might be useful also in several important noncancer indications, including Alzheimer's disease or diabetes.

Journal of Cancer Research and Clinical Oncology 2004 https://link.springer.com/article/10.1007/s00432-004-0579-2

- Other researchers have shown that induribin identify is a potent inhibitor of the SFK/Stat5 signaling pathway leading to **apoptosis of human Chronic Myelogenous Leukemia cells**.

- Molecular Oncology 2012 https://febs.onlinelibrary.wiley.com/doi/full/10.1016/j.molonc.2012.02.002

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Parthenolide (feverfew)

Preliminary studies suggests anticancer properties of PN:

- Potent inhibitor of DNA synthesis and cell proliferation in various human cancer cell lines.

- Patel and co-workers reported PN sensitizes breast cancer cells to the chemo effects of paclitaxel via its **inhibitory effect on nuclear factor kappa Beta**

- PN is potent inhibitor of NF-B signaling pathway, which also contributes to its anti-inflammatory activity.

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- **Apoptosis** - PN was shown to increase TRAIL activity (tumor necrosis factor-related apoptosis-inducing ligand) , which induces apoptosis via caspase-3 activation, overriding the anti-apoptotic effects of XIAP protein (protein X-linked inhibitor of apoptosis), common in resistant breast cancer cells.

- **Leukemia and Parthenolide -** Experimental studies demonstrate that parthenolide destroys acute myeloid leukemia (AML) cells, leaving normal bone marrow cells relatively unscathed. Moreover, the compound may get at the root of the disease because it also kills stem cells that give rise to AML. (Blood, online February 1, 2005)

- Phase I Trial – 4 mg of parthenolide non toxic to humans

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Flaxseed Lignans

Plant lignans, such as secoisolariciresinol (SECO) and matairesinol, richly supplied by ground flaxseed are transformed by intestinal microbiota into mammalian lignans enterodiol (END) and enterolactone (ENL).

Flaxseed contains 800-times more of these mammalian lignan precursors than any other food (i.e. beans, nuts)

Anticancer Mechanisms of ENL and END:

a. Inhibit estrogen receptors – binding as weak estrogen

b. Inhibit aromatase enzyme (fat, breast adrenals etc)

c. Inhibit tyrosine kinase and DNA topoisomerase enzymes in many types of cancer cells leading to apoptosis (breast, prostate, colon, lung)

Animal Studies: secoisolariciresinol diglucoside (SLD), isolated from flaxseed, metabolized into both END and ENL, and shows chemopreventive properties in DMBA-induced mammary tumor model in rats

Inverse association between a high enterolactone (ENL) concentration in both urine and serum, and the risk of breast cancer found in epidemiological studies suggests a chemopreventive action for ENL

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Human Studies:

- In pilot human studies, dietary flaxseed given preoperatively to newly diagnosed breast cancer patients markedly reduced **c-erb2** of the breast cancer tissue, suggesting direct antiproliferative effects. As expected, there was a marked increase in the urinary excretion of mammalian lignans after the ingestion of flax.

- Antiproliferative effect on the breast, similar to that of other selective estrogen receptor modulators, such as tamoxifen and raloxifen

- Decrease the synthesis of 16-alpha hydroxyestrone and increase the synthesis of 2 hydroxyestrone. A higher 2 hydroxyestrone to 16-alpha hydroxyestrone ratio (urinary metabolites) has been shown to be related to a decreased risk of breast cancer in women.

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- Flaxseed supplementation produces longer luteal phase, with increased progesterone:estradiol ratios during the luteal phase, fewer anovulatory cycles, and a decreased tendency to ovarian dysfunction; all of which are linked to a reduced risk of breast cancer in women

- Reversal of Fibrocystic Breast Disease – 50 gm per day (Toronto St Michaels Hospital Study)

- Increase sex hormone-binding globulin (SHBG), decreasing levels of free unbound sex hormones

- A recent study of short-term flaxseed supplementation and fat restriction in diet additionally showed significantly lower proliferation rates and higher rates of apoptosis in prostate cancer of men before operation. (Cancer Epidemiol Biomarkers Prev 2008;17(12):3577–87)

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Other Nutrients With Anti-Angiogenesis Effects In Experimental Studies

Milk Thistle and the Silymarin flavonoids - In the laboratory, silymarin demonstrates strong activity against a variety of tumours by downregulation of vegf and egfr. Silymarin suppresses vegf when used as a single agent against human ovarian cancer.

Quercetin – Quercetin flavone inhibits angiogenesis through multiple mechanisms, including interaction with the cox-2 and lipoxygenase-5 enzymes, egfr, the *HER2* intracellular signaling pathway, and the nf-κb nuclear transcription protein. Quercetin may enhance the anticancer effects of tamoxifen through anti-angiogenesis

Artemisinin (Chinese Worm Wood) - is the active constituent extracted from the plant *Artemisia annua. and* used clinically as an anti-malaria drug. More recently, shown to be cytotoxic to cancer cells through induction of apoptosis and lowered vegf expression by tumour cells. Artemisinin also inhibits the activation of nuclear factor kappa-B and kills cancer cells via free radical damage to its cell membrane via iron-induced free radicals

- **Dogfish Shark and Squalamine** - Squalamine is a steroid isolated from the liver of the dogfish shark. Squalamine significantly blocks vegf in human vascular endothelial cells. Squalamine is anti-angiogenic for ovarian cancer xenografts, and it appears to enhance the cytotoxic effects of cisplatin chemotherapy, independent of *HER2* status.

- Overexpression of *HER2* is normally associated with resistance to cisplatin and promotion of tumour angiogenesis. In a phase II trial of patients with advanced small-cell lung cancer, squalamine was administered at a dose of 300 mg/m2 by continuous infusion for 5 days, with paclitaxel and carboplatin given on day 1. Patient survival data and a satisfactory safety profile indicated that the combination should be explored further.

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The Soy Controversy

Experimental data show that soy isoflavones may increase or decrease prolif of normal breast and breast cancer cells (?)

A recent study showed that 200 mg of soy isoflavones given to women with breast cancer decreased the mitosis:apoptosis ratio (shrinking tumor) and did not increase mitosis in non breast cancer subjects.

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Anti-Cancer Soy Effects

1. Acts as weak estrogen toning down effects of potent estrogens
2. Powerful tyrosine kinase inhibitor
3. Inhibits key enzymes to decrease available estradiol in breast cancer cells
4. Inhibits DNA topoisomerase (cell cycle arrest)
5. Increase TGF-B
6. Stimulates ER-beta receptors which decrease cell proliferation
7. Form heterodimer with ER-alpha receptors silencing their prolif effects
8. Up-regulates quinone reductase – phase II detox enzyme that prevents build up of reactive estrogen metabolites (free radicals) such as catecholestrogen quinones. (Bianco NR, 2005)
9. Inhibits angiogenesis (genistein the strongest isoflavone in this regard) (Shu-Jem Su 2004)
10. Induces Apoptosis of cancer cells (Shu-Jem Su 2004)
11. Anti-oxidant (isoflavones)
12. Protease inhibitor – inhibits matrixmetallo protease activity (helping to block direct spread of cancer to adjacent tissues)

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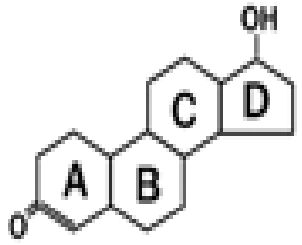
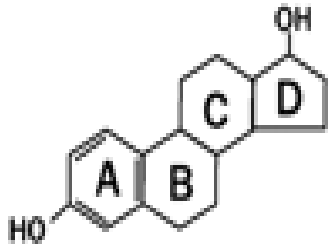
Recent study showed that 200 mg of soy isoflavones increased the apoptosis/mitosis ratio in women with breast cancer awaiting surgery

Nutrition and Cancer Journal

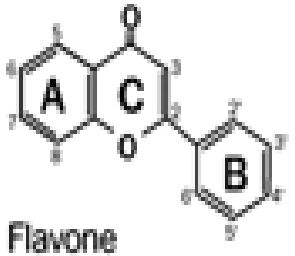
Soy isoflavones (100 mg per day) also significantly slowed the PSA double rate in men with localized prostate cancer



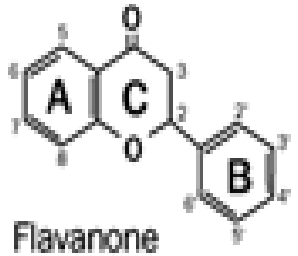
Testosterone



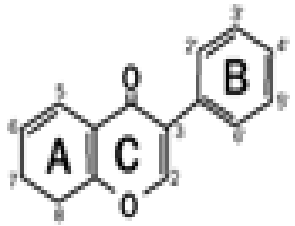
17β–Oestradiol



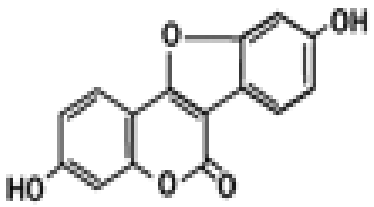
Flavone



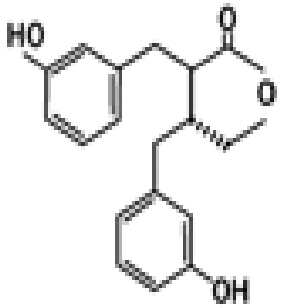
Flavanone



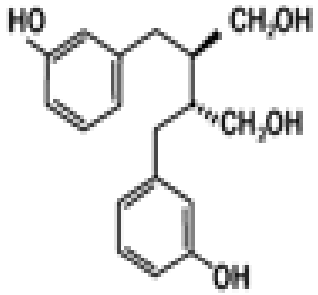
Isoflavone



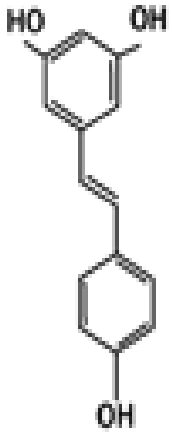
Coumestrol



Enterolactone



Enterodiol



trans-Resveratrol

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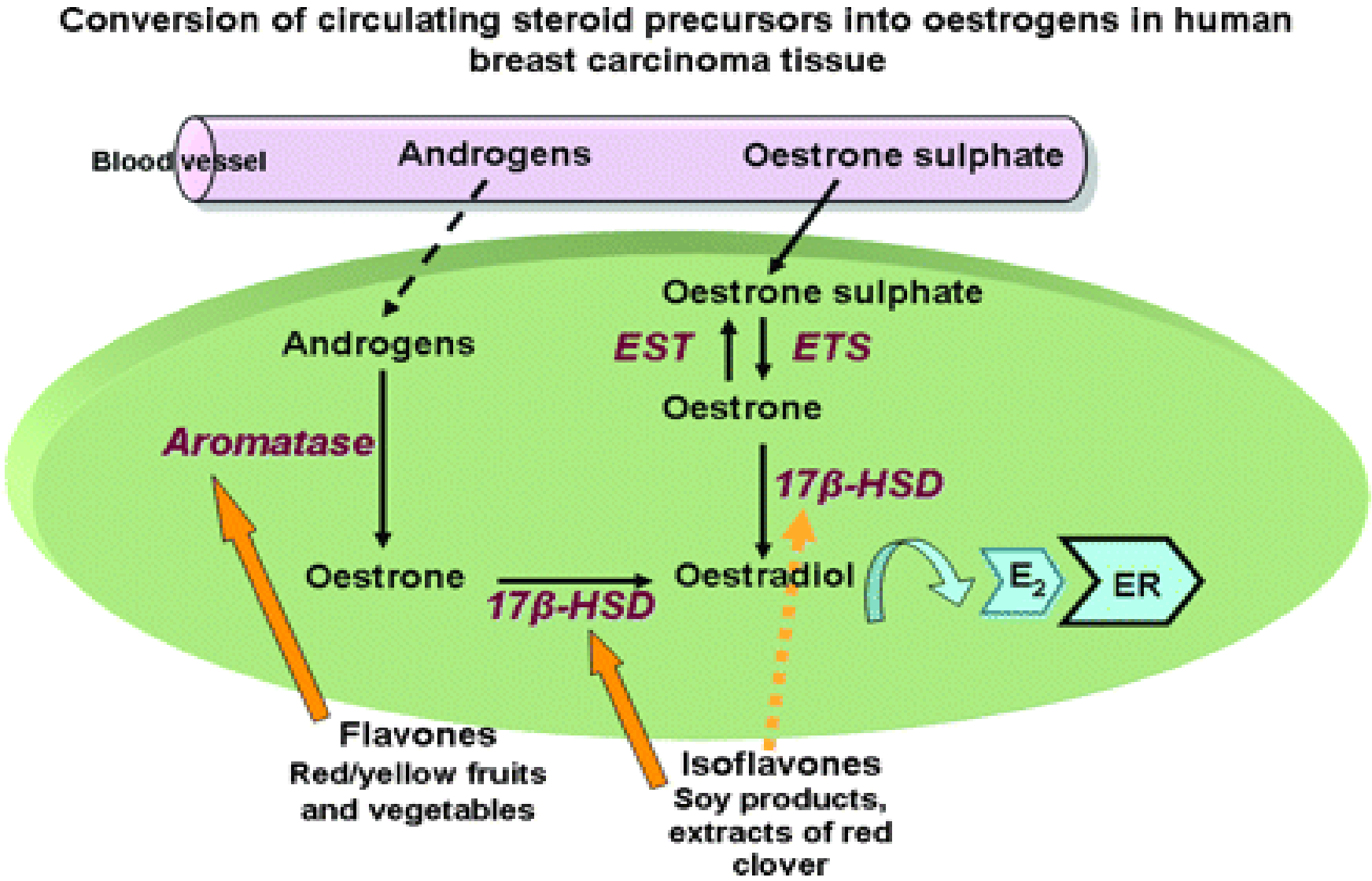
Aromatase inhibitors include: isoflavones, flavones (quercetin) indole-3 carbinol and ENL and END

17 beta HSD inhibitors include genistein and diadzein –soy isoflavones



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Indole-3 Carbinol

Indole-3-carbinol (C_9H_9NO) is produced by the breakdown of the glucosinolate glucobrassicin

Shown *in vivo* to protect against chemically induced carcinogenesis in animals (2–7).

Clinical benefits shown in human trials for:

cervical dysplasia (8), breast cancer (9, 10), respiratory papillomas (14), and vulvar intraepithelial neoplasia VIN (see reference in slide)

Metabolism And Effects:

In an acidic milieu (stomach), indole-3-carbinol undergoes spontaneous dehydration and condensation to form diindoylmethane and a series of oligomeric products (12, 13), **all of which** exhibit *in vitro* antiproliferative activities against cancer cells (14–18).

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Mechanism of Action:

Evidence indicates that indole-3-carbinol facilitates growth arrest and apoptosis by targeting a broad range of signaling pathways pertinent to cell cycle regulation and survival, including those mediated by:

- Akt, nuclear factor- B (NF- B)
- Bcl-2
- Mitogen-activated protein (MAP) kinases
- Cyclin-dependent kinase (CDK) inhibitors p21 and p27, and cyclin D1 (19–23)

- Indole-3 carbinol also shown to induce anti-angiogenesis effects in many tumor cells (25)

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Cervical CIN Study: Gynecological Oncology 2000: Reference 8
https://www.ncbi.nlm.nih.gov/pubmed/10926790

OBJECTIVE: Most precancerous lesions of the cervix are treated with surgery or ablative therapy. Chemoprevention, using natural and synthetic compounds, may intervene in the early precancerous stages of carcinogenesis and prevent the development of invasive disease. Our trial used indole-3-carbinol (I-3-C) administered orally to treat women with CIN as a therapeutic for cervical CIN.

METHODS: Thirty patients with biopsy proven CIN II-III were randomized to receive placebo or 200, or 400 mg/day I-3-C administered orally for 12 weeks. If persistent CIN was diagnosed by cervical biopsy at the end of the trial, loop electrocautery excision procedure of the transformation zone was performed. HPV status was assessed in all patients.

CONCLUSIONS: There was a statistically significant regression of CIN in patients treated with I-3-C orally compared with placebo. The 2/16 alpha-hydroxyestrone ratio changed in a dose-dependent fashion.

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3,3′-diindolylmethane (DIM) and Breast Cancer: Reference 9

Nutrition Review 2016 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5059820/

- A placebo-controlled, double-blind trial on BR-DIM was conducted in 19 postmenopausal women with early-stage breast cancer. Women were randomized to receive 108 mg of BR-DIM or placebo daily for 30 days.
- When compared with placebo, BR-DIM resulted in a significant increase in 2OHE and a modestly protective shift in the 2OHE:16αOHE ratio.
- The ability of DIM to induce CYP enzymes responsible for catalyzing hydroxylation could be responsible for the enhanced production of 2OHE and the limited production of 16αOHE.
- Additionally, administration of BR-DIM to premenopausal women improves symptoms of cyclical mastalgia, a potential indicator of increased breast cancer risk.
- To date, many trials evaluating DIM and breast cancer have been conducted in samples of less than 50 subjects, limiting the interpretation of study findings. Several trials evaluating the role of DIM in breast cancer prevention are currently under way

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Indole-3 Carbinol in Women at High-Risk for Breast Cancer: 2005
Cancer Epidemiol Biomarkers Prev 2005;14(8):1953–60
https://pdfs.semanticscholar.org/72b5/a3d5a155d0120135bfc2283bc0381df6bf3b.pdf

- I3C has been shown to have pronounced chemopreventive effects against development of both spontaneous and chemically induced tumors in rats, mice, and trout.

- These reports involved the use of polycyclic aromatic hydrocarbons, nitrosocompounds, heterocyclic aromatic amines, and aflatoxin as initiating agents.

- In addition, chemopreventive effects of I3C were reported against tumor development in mammary gland, liver, lung, cervix, and gastrointestinal tract.

- The project reported here, a phase I trial of I3C in humans, provides a further step in this development. Because the chemopreventive effects of I3C were observed in mammary gland and because I3C has been proposed as a potential chemopreventive agent for breast cancer in particular, we chose to carry out this phase I study in a population of women at elevated risk for breast cancer

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Intervention:

- We completed a phase I trial of indole-3-carbinol (I3C) in 17 women (1 postmenopausal and 16 premenopausal) from a high-risk breast cancer cohort.

- After a 4-week placebo run-in period, subjects ingested 400 mg I3C daily for 4 weeks followed by a 4-week period of 800 mg I3C daily.

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Results:

- Comparing the results from the placebo and the 800 mg daily dose period, CYP1A2 was elevated by I3C in 94% of the subjects, with a mean increase of 4.1-fold.

- In subjects with high NAT-2 activities, these were decreased to 11% by I3C administration but not altered if NAT-2 activity was initially low.

- Lymphocyte glutathione S-transferase activity was increased by 69% in response to I3C.

- The apparent induction of CYP1A2 was mirrored by a 66% increase in the urinary 2-hydroxyestrone/16A-hydroxyestrone ratio in response to I3C.

- The maximal increase was observed with the 400 mg daily dose of I3C, with no further increase found at 800 mg daily.

- If the ratio of hydroxylated estrone metabolites is a biomarker for chemoprevention, as suggested, then 400 mg I3C daily will elicit a maximal protective effect. (Cancer Epidemiol Biomarkers Prev 2005;14(8):1953–60)

Vulvar Intraepithelial Neoplasia (VIN)
Gynecol Cancer 2006

Example of Reported Phase II Studies

- Therapeutic benefits of indole-3-carbinol (I3C) in the management of vulvar intraepithelial neoplasia (VIN)
  - Women (n=12) with histologically confirmed high-grade VIN were randomized to receive 200 and 400 mg/day of I3C
  - Symptomatology by visual analog scale and vulvoscopic appearance were assessed at recruitment, 6 weeks, 3 months, and 6 months
  - Tissue biopsy to determine histologic response was obtained at completion of the study period
  - Urine samples were obtained at each visit to determine 2-hydroxyestrone to 16-alpha-hydroxyestrone ratios.
  - There was a significant improvement in symptomatology with the introduction of I3C (itch, P= 0.018; pain, P= 0.028). Lesion size and severity were also significantly reduced (size, P= 0.005; appearance, P= 0.046)
  - also a significant increase in 2-hydroxyestrone to 16-alpha-hydroxyestrone ratio following commencement of I3C, P= 0.05
  - tissue biopsy from the worst-affected vulval areas revealed no improvement in grade of VIN during the 6-month period, P= 0.317
  - no significant differences in results between those women taking 200 mg/day of I3C and those on 400 mg/day
  - study has shown significant clinical improvement in symptomatology and vulvoscopic appearance of VIN with I3C therapy. Further clinical and scientific investigations are required to support these preliminary findings.

Naik R et al., Int J Gynecol Cancer, 2006 Mar-Apr;16(2):786-90

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Antioxidants During Chemotherapy - Controversy

During chemo some doctors discourage antioxidant administration as they fear it will decrease efficacy of chemo (by mopping up cytotoxic free radicals). However, most chemo drugs (exception is Bleomycin) don't kill via ROS, but by other means (e.g. DNA intercalation), which requires mitotic stage.

In the presence of ROS generated by chemo drugs cancer cells enter quiescence (G_0 stage), which allows them to survive chemo and begin replicating again once chemo is completed. Antioxidant supplementation, therefore, enhances chemo effects by encouraging normal cancer cell mitosis during chemo administration. This explains why slow growing tumors (lung ca) are highly resistant to chemotherapy – long G_0 stage). (Conklin, K.A.2000, Nutr. Can – see additional course notes)

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Further, during chemo and radiation cancer killing effects are enhanced by molecules that stimulate death receptors, inhibit angiogenesis, decrease proliferative transcription factors, inhibit EPGF receptors, inhibit tyrosine kinase, enhance cell differentiation etc

As such, there is sound scientific support to recommend Reishi M extract, Astragalus, Vitamin D, Curcumin, Baicalein, and EFA's, even if Antioxidants excluded from mix

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Part 3

Common Supplementation Protocols For Cancer and Other Supplement Considerations

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Common Supplementation Protocol Considerations For Cancer

1.High potency multivitamin and mineral

2.Vitamin E Succinate – 1600 -3,000 IU/d

3.Vitamin C – 3,000-10,000 mg/d

4. Selenium – 500-800 mcg

5. Beta-carotene – 50,000-100,000 IU/d (not in lung cancer cases)

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6. Vitamin A (lipid emulsion) – 100,000 IU for 3 mths, followed by 50,000 IU (liver function tests) – Genestra

7. Essential Fatty Acids -3-6 capsules per day (fish, flax, borage seed)

8. Natural Anti-Inflammatory Combo – 9-12 caps per day (Curcumin, Boswellia, Ginger, White Willow Extract)

9. Chinese scullcap - Baicalein content of 150-200 mg

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10. Immuno-Detox Supplement – 6 caps per day (reishi m extract, astragalus, indole-3 carbinol, milk thistle)

11. 14 Mushroom Blend (www.mushroomharvest.com)

12. Coenzyme Q10 – 200-300 mg/d (Lockwood 1994, Mol Asp Med)

    CoQ10 also inhibits the cardiotoxicity (arrhythmias and reduced ejection fraction) induced by anthracylines, by protecting the mitochondria of cardiac muscle cells (Moss R., 2001-7th International Symposium for Biologically Closed Electric Circuits in Biomedicine

13. Vitamin D – 10,000 – 50,000 IU/day

14. Quercetin – 1000 mg, twice daily

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Colon CA: Add

1. Calcium – 1,500 mg/d - decrease proliferation and decreases secondary sterols

2. Wheat Bran – 15 gms/d

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Breast CA: Add:

1. Isoflavones – consider - 200 mg per day – increases apoptosis:mitosis ratio

2. Melatonin – 10-20 mg/d – requires physician monitoring (liver function tests)

3. Green Tea Catechins- 600 mg per day

4. Ground Flaxseed

Breast Cancer Survivors: Antioxidants have improved survival, as well as ingestion of soy (isoflavones), higher vitamin D blood levels, **exercise,** lower body weight, avoid smoking

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Vitamin D Doubles Breast Cancer Survival

- A study published in March 2014 in the journal Anticancer Research has now shown that breast cancer survivors would be well advised to keep their vitamin D blood level within the ideal range. The study by B. Sharif et al showed that breast cancer patients with high levels of vitamin D in their blood were twice as likely to survive the disease compared to women with low levels of vitamin D.

- These researchers analyzed data from five large breast cancer studies, involving a total of 4,443 breast cancer patients, with an average follow-up period of nine years. ***The data showed that women who had an average vitamin D blood level of 30ng/ml experienced survival rates double that of women who had an average blood vitamin D blood level of 17ng/ml.***

- The researchers pointed out that the average vitamin D blood level in patients with breast cancer in the United States is 17ng/ml (5).

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- In Canada blood levels of vitamin D is usually reported in nmol/L, not ng/ml. Thus, for Canadians it is worth noting that 30ng/ml is equal to about 75nmol/L, whereas 17ng/ml is equal to about 42nmol/L.

- In their concluding statements B. Sharif et al suggest that breast cancer patients may be well advised to increase their blood level of vitamin D to 80ng/ml (approximately 200nmol/L), based on all available evidence.

Reference:

Sharif B. Mohr, Edward D. Gorham, June Kim, Heather Hofflich And Cedric F. Garland. Meta-analysis of vitamin D sufficiency for improving survival of patients with breast cancer. Anticancer Research 34(3): 1163-1166, 2014

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Soy and Breast CA Recurrence

- A study presented in 2011, at the *102nd American Association for Cancer Research 102nd Annual Meeting* (April 2-6), showed that the consumption of soy products by **breast cancer** survivors reduced their risk of cancer recurrence and progression, compared to **cancer** survivors who ingested little or no soy foods.

- The report featured data that combined four National Cancer Institute-funded studies: the *Shanghai Breast Cancer Survival Study*; the *Life After Cancer Epidemiology Study*; the *Women's Healthy Eating and Living Study*; and the *Nurses' Health Study*. Together this included 18,312 women between the ages of 20 and 83 years, who had previously been diagnosed with invasive primary **breast cancer**.

- Nine years after the initial **diagnosis of breast cancer** diagnosis the combined **data showed the following:**

- Those who consumed the highest amounts of soy isoflavones (**more than 23 mg per day)** were compared with the outcomes of those whose intake was lowest (0.48 mg per day or lower). Women in the highest intake category of more than 23 mg per day had a **9 percent reduced risk of mortality and a 15 percent reduced risk for recurrence, compared to those who had the lowest intake level**.

Reference:

American Association for Cancer Research (2011, April 5). Soy isoflavones not a risk for breast cancer survivors, study finds. *ScienceDaily*.

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Multivitamin and Antioxidant Supplements Shown to Reduce Breast Cancer Recurrence

Study published in Breast Cancer Research and Therapy (Nov 2011)

Study followed women who had been treated for breast cancer looking at their survival and relapse rates during the 2-yr follow-up period after breast cancer treatment

Results:

- Study showed that women who were in the top 25% of following a healthy lifestyle, who regularly took a multiple vitamin supplement, had a 60-70% reduction in risk of dying from any cause during the study

- A healthy lifestyle was defined as a healthy diet (consuming at least 5.5 servings of fruits and vegetables per day) and being at least moderately physically active (being non-sedentary for 16 hours/week).

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Results showed that the addition of the multiple vitamin supplement **enhanced survival outcomes by 60-70% in these women**

However, in women who didn't follow a healthy lifestyle (diet remained poor and were non active) the addition of a multiple vitamin supplement **alone** did not improve survival to any degree.

Take Home Message:

That's why they're called supplements – they are intended to supplement or enhance the metabolic effects of a healthy diet and exercise.

Supplements by themselves, in many cases, can't reverse the effects of unhealthy dietary and lifestyle practices.

Previous study showed similar outcome:

- A Shanghai China study followed 4,877 breast cancer survivors and examined antioxidant supplement use (vitamin C, vitamin E, and/or multivitamins) during the first six months post-diagnosis.
- Results showed that supplement use was associated with decreased risk of cancer recurrence by 22% and overall mortality by 18%.

Reference:

- Kwan ML, Greenlee H, Lee VS, Castillo EP, Gunderson EP, Habel LA, et al. Multivitamin Use and Breast Cancer Outcomes in Women with Early-Stage Breast Cancer: The Life After Cancer Epidemiology (LACE) Study. Breast Cancer Res Treat. 2011 Nov; 130(1): 195–205.

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Lifestyle modifications for patients with breast cancer to improve prognosis and optimize health. Can Med Ass J 2917 http://www.cmaj.ca/content/189/7/E268

Research from systematic reviews and meta-analyses published within the past 10 years.

KEY POINTS:

- Physical activity has the strongest effect on reducing the risk of breast cancer recurrence and death.
- All patients with breast cancer (except for those who have an abnormally low body mass index before diagnosis) should avoid gaining weight.
- Patients who are obese and those who smoke have a higher risk of cancer recurrence, but it is unclear whether their prognosis can be improved by weight loss or smoking cessation.
- Soy consumption is not harmful.

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Prostate CA: Add:

1. Prostate Herbal Combination Supplement (block DHT, apoptosis, androgen blockade etc.)

2. Melatonin – 10-20 mg/d (Physician Supervision)

3. Soy Isoflavones – 200 mg per day

4. Pomegranate Juice – 8 oz per day (PomWonderful)

5. Green Tea Catechins: 600 mg per day

6. Lycopene Supplementation – 20-30 mg per day. Recent studies show lycopene can reverse PSA levels in localized prostate cancer.

In one study, 26 men with prostate cancer were randomly assigned to receive lycopene (15 mg twice a day) or no lycopene for three weeks before undergoing prostate surgery. Prostate tissue was then obtained during surgery and examined. Compared to the unsupplemented men, those receiving lycopene were found to have significantly less aggressive growth of cancer cells. In addition, a case report has been published of a 62-year-old man with advanced prostate cancer who experienced a regression of his tumor after starting 10 mg of lycopene per day and 300 mg of saw palmetto, three times per day.

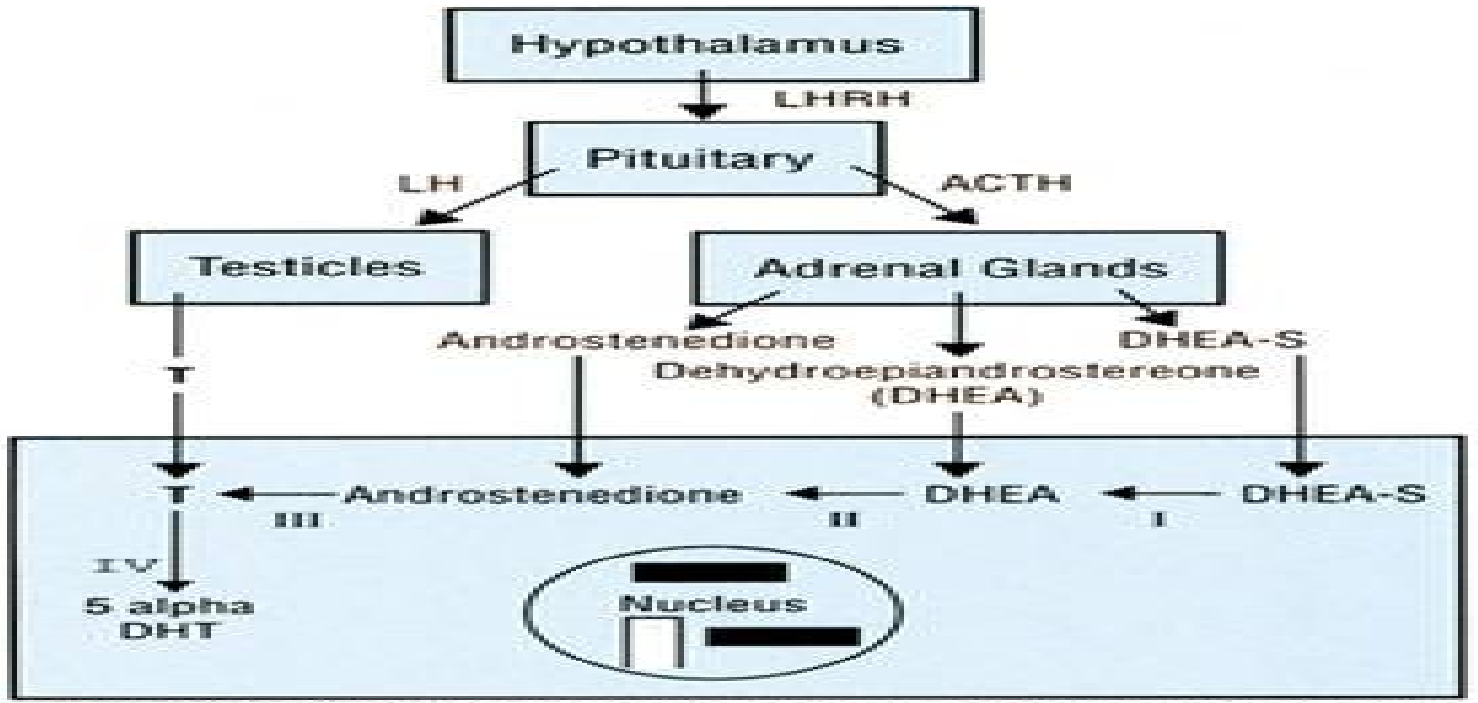
7. Pomegranate Juice – unknown agent shown to reverse PSA levels in 2 studies in men with localized prostate cancer

8. Ground Flaxseed – 50 gm per day shown to decrease proliferation of localized prostate cancer cells while men were awaiting surgery.

8. Modified Citrus Pectin - blocks galectin-3 receptor preventing cancer cells from adhering to each other, discouraging their ability to form colonies (tumor mass). If cancer cells are deprived of their own adhesive ability, they fail to thrive and can be more easily destroyed by the body's immune system.

Dosage - 5 gms, three times per day

But many Integrative Doctors fail to see results with this.



The Prostate Cell & Intra-Prostatic Synthesis of Androgens

Legend
I = Sulfatase
II = 3 beta hydroxysteroid dehydrogenase
III = 17 beta hydroxysteroid dehydrogenase
IV = 5 alpha reductase
Androgen receptor
Androgen receptor blocked

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Reversing BPH With Natural Supplements

- 1. Saw Palmetto
  - 160 mg, twice per day-std 85-90% FA & Sterols
  - As effective as Proscar, possibly better
  - Fewer side effects (erectile dysfunction)
  - Action: inhibits 5-alpha-reductase enzyme, androgen blockade, estrogen blockade (phytoestrogen), anti-inflamm (PG-2)
  - Berries only 1% FA and Sterols

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Reversing BPH

2. Pygeum Africanum (bark of tree)

- 100-200 mg-std to 12-14% triterpenes
- Action: decreases blood levels of LH, prolactin, which increase uptake of testosterone by prostate, reduces prostate synthesis of cholesterol (statin drugs shown to reduce BPH)

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Reversing BPH

3. Beta-sitosterol

- Dosage: 65 mg, twice per day, or 20 mg, three times per day
- Action: inhibits 5-alpha-reductase enzyme, blocks estrone synthesis in fat cells, apoptosis of prostate cancer cells (via signal transduction)

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Reversing BPH

4. Soy Isoflavones

- 25-75 mg per day associated with decreased prostate cancer and enlargement
- Actions: inhibits 5-alpha-reductase enzyme, apoptosis of prostate cancer cells, inhibit proliferative enzymes, increase SHBG, inhibits estrone synthesis in fat cells, antioxidant, anti-angiogenisis, androgen and estrogen blockade

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Reversing BPH

5. Stinging Nettle (urtica dioica)

- Action: inhibits binding of DHT to cell nucleus
- Dosage: 20-60 mg usually in prostate combo products

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Source: *Clinical Cancer Research*, 2009 *"Dietary Omega-3 Fatty Acids, Cyclooxygenase-2 Genetic Variation, and Aggressive Prostate Cancer Risk"*

Authors: V. Fradet, I. Cheng, G. Casey, J.S. Witte

- Researchers performed a case-control analysis of 466 men diagnosed with aggressive prostate cancer and 478 healthy men. Diet was assessed by a food frequency questionnaire and researchers genotyped nine COX-2 single nucleotide polymorphisms.

- Researchers divided omega-3 fatty acid intake into four groups based on quartiles of intake. Men who consumed the highest amount of long chain omega-3 fatty acids had a 63 percent reduced risk of aggressive prostate cancer compared to men with the lowest amount of long chain omega-3 fatty acids.

- The researchers then assessed the effect of omega-3 fatty acid among men with the variant **rs4647310** in COX-2, a known inflammatory gene. Men with low long chain omega-3 fatty acid intake and this variant had a more than five-fold increased risk of advanced prostate cancer. But men with high intake of omega-3 fatty acids had a substantially reduced risk, even if they carried the COX-2 variant.

- "The COX-2 increased risk of disease was essentially reversed by increasing omega-3 fatty acid intake by a half a gram (500 mg) per day," said Witte. "If you want to think of the overall inverse association in terms of fish, where omega-3 fatty acids are commonly derived, the strongest effect was seen from eating dark fish such as salmon one or more times per week."

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Reversing BPH

- 6. Cernilton (rye grass pollen extract)
  - Contains hydroxamic acid and other bioactive agents, which reduce prostate inflammation
  - Hydroxamic acid shown to inhibit replication of prostate cancer cells
  - Dosage: 63 mg, twice per day

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Lycopene And Prostate Cancer: Human Studies

Study 1. In one study, the effect of tomato sauce on apoptosis in benign prostate hyperplasia (BPH) tissue and carcinomas was examined. 26 patients who were scheduled for prostatectomy were given tomato sauce pasta entrees (30 mg/day of lycopene) to eat daily for 3 weeks before surgery.

- Patients scheduled for surgery who did not receive the tomato sauce pasta entrees served as control subjects.

Results: Those who consumed the tomato sauce pasta entrees exhibited decreased serum PSA levels and increased apoptotic cell death in BPH tissue and carcinomas

Reference: Kim HS, Bowen P, Chen L, et al.: Effects of tomato sauce consumption on apoptotic cell death in prostate benign hyperplasia and carcinoma. Nutr Cancer 47 (1): 40-7, 2003.

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Study 2. In a 2004 open-label study, patients with hormone-refractory prostate cancer (HRPC) received lycopene supplements daily (10 mg/day of lycopene) for 3 months.

- Of the study's participants, 50% had PSA levels that remained stable, 15% showed biochemical progression, 30% showed a partial response, and one patient (5% of the total sample) exhibited a complete response after treatment.

Reference: Ansari MS, Gupta NP: Lycopene: a novel drug therapy in hormone refractory metastatic prostate cancer. Urol Oncol 22 (5): 415-20, 2004 Sep-Oct

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Study 3. Prostate Cancer Patients received lycopene supplements (30mg/day) or no intervention twice daily for 3 weeks prior to radical prostatectomy.

- Patients who received the lycopene supplements had smaller tumors and lower serum PSA levels than patients who did not receive the supplements.

- These results suggest that lycopene may be beneficial in prostate cancer treatment

Reference: Kucuk O, Sarkar FH, Djuric Z, et al.: Effects of lycopene supplementation in patients with localized prostate cancer. Exp Biol Med (Maywood) 227 (10): 881-5, 2002.

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Study 4. A 2006 study investigated whether lycopene supplements (10 mg/day) would affect PSA velocity in patients with localized prostate cancer.

- There was a statistically **significant decrease** in PSA velocity following lycopene treatment as well as a large, but not statistically significant, increase in PSA doubling time

Reference: Barber NJ, Zhang X, Zhu G, et al.: Lycopene inhibits DNA synthesis in primary prostate epithelial cells in vitro and its administration is associated with a reduced prostate-specific antigen velocity in a phase II clinical study. Prostate Cancer Prostatic Dis 9 (4): 407-13, 2006.

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Study 5. Patients with high-grade prostate intraepithelial neoplasia (HGPIN) received 4 mg of lycopene twice a day or no lycopene supplementation for 2 years.

Results: A greater decrease in serum PSA levels was observed in those treated with lycopene supplements compared with those who did not take the supplementation.

- During follow-up, adenocarcinomas occurred more often in patients who had not received the supplements than in patients who had received lycopene.

- These findings suggest that lycopene may be effective in preventing HGPIN from progressing to prostate cancer

Reference: Bunker CH, McDonald AC, Evans RW, et al.: A randomized trial of lycopene supplementation in Tobago men with high prostate cancer risk. Nutr Cancer 57 (2): 130-7, 2007

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Study 6 - In a Phase II clinical trial (Vaishampayan U et al, 2007) researchers investigated the efficacy of lycopene alone or in combination with soy isoflavones on serum PSA levels in men with prostate cancer.

To be eligible for the study, men with prostate cancer had to have rising serum PSA following local therapy or while on hormone therapy. The study population included 71 patients who had 3 successive rising PSA levels or a minimum PSA of 10 ng/ml at 2 successive evaluations prior to starting therapy.

- Subjects were randomly assigned to receive a tomato extract capsule containing **15 mg of lycopene alone** (n = 38) **or together** with a capsule containing **40 mg of a soy isoflavone** mixture (n = 33) twice daily orally for a maximum of **6 mo.** One patient on the lycopene arm did not receive therapy due to his inability to ingest the study pill.

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- There was no decline in serum PSA in either group. However, 35 of 37 (95%) patients in the lycopene group and 22 of 33 (67%) patients in the lycopene plus soy isoflavone group achieved stable disease, meaning that they achieved **stabilization in serum PSA level.**

- The data suggest that lycopene and soy isoflavones have important adjunctive effects in prostate cancer patients with PSA relapse disease and may delay progression of both hormone-refractory and hormone-sensitive prostate cancer.

Reference:

Vaishampayan U, Hussain M, Seren S, Sarkar F, Fontana J et al. Lycopene and Soy Isoflavones in the Treatment of Prostate Cancer. Nutri and Cancer**.** 2007; 59 (1): 1-7

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H. Saw Palmetto and Lycopene (A case report)

A 62-year-old man with androgen-independent metastatic prostate cancer that had failed to respond to multiple treatment regimens stopped all conventional therapy and began 10 mg/day of lycopene and 300 mg of saw palmetto 3 times per day.

- The prostate-specific antigen (PSA) level decreased from 365 ng/ml to 140 ng/ml after 1 month and to 8.1 ng/ml after 2 months. A repeat bone scan revealed an improvement of bony metastases. He has continued the lycopene and saw palmetto and has remained asymptomatic for an unspecified period of time.

- Note – Saw Palmetto contains Beta-sitosterol, which in experimental and animal studies has shown an ability to induce programmed cell (apoptosis) death of certain prostate cancer cell lines. Most researchers attribute the dramatic disease reversal effect in the above case to this biological process.

Reference:

Matlaga BR, Hall MC, Stindt D, Torti FM. Response of hormone refractory prostate cancer to lycopene. J Urol 2001;166:613.

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Pomegranate Juice

- Two clinical studies shown that men with established prostate cancer realized a marked slowing of their disease when they drank 8 ounces of pure pomegranate juice each day.

- Reporting at the 104th Annual Meeting Scientific Meeting of The American Urology Association, researchers presented findings showing that men, who had undergone prostate surgery or radiation treatment for localized **prostate cancer,** benefited from drinking 8 ounces per day of pomegranate juice if their PSA levels were still continuing to rise.

- In men giving the pomegranate juice the doubling time of their PSA was extended to 60 months, compared to only 15.4 months prior to pomegranate juice administration.

- Previously, a study in the Journal of Clinical Cancer Research in 2006 showed that men, with established prostate cancer, extended the PSA doubling time from 15 months to 54 months when they began drinking 8 ounces of pomegranate juice each day

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How Does Pomegranate Juice Work?

No one knows for sure but the juice is very rich in a class of unique polyphenol antioxidants known as ellagitannin compounds.

It's possible that these, or other compounds, slow the rate at which prostate cancer cells replicate and/or trigger mechanisms that encourage programmed cell death of existing prostate cancer cells.

Phase II and III trials are planned to better understand the extent to which pomegranate juice can protect the prostate gland and be used in adjunctive management of established prostate cancer cases.

Note: Pomegranate Juice contains carbohydrate calories, and thus, is precluded from the ketogenic diet plan.

However, it can be used to help prevent prostate cancer and as follow-up intervention in prostate cancer survivors (post-treatment)

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Antioxidants and Low Animal Fat Diet –

In the September 2005 issue of *The Journal of Urology*, Dr Dean Ornish published a study testing the effectiveness of an intensive dietary and lifestyle program as the sole treatment of prostate cancer in men with low to moderate Gleason Scores.

The program consisted of a low animal fat diet (with the exception of some fish, and emphasis on fruits, vegetables, legumes, soy products and other vegetarian foods (and dairy-free). He also supplemented these men with antioxidants (vitamin C, selenium and vitamin E), and included moderate aerobic exercise, and stress management interventions in the treatment group.

The daily antioxidant supplement dosages were:

- Vitamin C – 2000 mg
- Vitamin E – 400 IU
- Selenium – 200 mcg

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- Ornish studied 93 men who had chosen not to undergo conventional invasive treatment for prostate cancer.

- Half of these men were randomly allocated to the Ornish program, while the remainder served as a non-treated comparison group.

- After 12 months, the PSA of the treated group of men decreased an average of 0.25 ng/ml or 4%,and the PSA of the non-treated group of men increased an average of 0.38 ng/ml or 6%.

Reference:

Ornish Dean et al: Intensive lifestyle changes may affect the progression of prostate cancer. The Journal of Urology Vol.174:1065, 2005

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Catechins - Prevent Prostate Cancer in High-risk Men (2006)

Cancer Res. 2006 Jan 15;66(2):1234-40.

Chemoprevention of human prostate cancer by oral administration of green tea catechins in volunteers with high-grade prostate intraepithelial neoplasia: a preliminary report from a one-year proof-of-principle study.

Bettuzzi S[1], Brausi M, Rizzi F, Castagnetti G, Peracchia G, Corti A.

Author information

- [1]Department of Medicina Sperimentale, Sezione di Biochimica, University of Parma, Via Volturno 39, 43100 Parma, Italy. saverio.bettuzzi@unipr.it

Abstract

Green tea catechins (GTCs) proved to be effective in inhibiting cancer growth in several experimental models. Recent studies showed that 30% of men with high-grade prostate intraepithelial neoplasia (HG-PIN) would develop prostate cancer (CaP) within 1 year after repeated biopsy. This prompted us to do a proof-of-principle clinical trial to assess the safety and efficacy of GTCs for the chemoprevention of CaP in HG-PIN volunteers. The purity and content of GTCs preparations were assessed by high-performance liquid chromatography [(-)-epigallocathechin, 5.5%; (-)-epicatechin, 12.24%; (-)-epigallocatechin-3-gallate, 51.88%; (-)-epicatechin-3-gallate, 6.12%; total GTCs, 75.7%; caffeine, <1%]. Sixty volunteers with HG-PIN, who were made aware of the study details, agreed to sign an informed consent form and were enrolled in this double-blind, placebo-controlled study. Daily treatment consisted of three GTCs capsules, 200 mg each (total 600 mg/d). After 1 year, only one tumor was diagnosed among the 30 GTCs-treated men (incidence, approximately 3%), whereas nine cancers were found among the 30 placebo-treated men (incidence, 30%). Total prostate-specific antigen did not change significantly between the two arms, but GTCs-treated men showed values constantly lower with respect to placebo-treated ones. International Prostate Symptom Score and quality of life scores of GTCs-treated men with coexistent benign prostate hyperplasia improved, reaching statistical significance in the case of International Prostate Symptom Scores. No significant side effects or adverse effects were documented. To our knowledge, this is the first study showing that GTCs are safe and very effective for treating premalignant lesions before CaP develops. As a secondary observation, administration of GTCs also reduced lower urinary tract symptoms, suggesting that these compounds might also be of help for treating the symptoms of benign prostate hyperplasia.

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Catechins Improve Clinical Profile In Men With Localized Prostate Cancer (2009)- Cancer Prevention Research

Tea Polyphenols Decrease Serum Levels of Prostate-Specific Antigen, Hepatocyte Growth Factor, and Vascular Endothelial Growth Factor in Prostate Cancer Patients and Inhibit Production of Hepatocyte Growth Factor and Vascular Endothelial Growth Factor *In vitro*

1. Jerry McLarty[2,4],
2. Rebecca L.H. Bigelow[1,2],
3. Mylinh Smith[2],
4. Don Elmajian[2,3],
5. Murali Ankem[5], and
6. James A. Cardelli[1,2]

+ Author Affiliations

1. ***Authors' Affiliations:*** *[1]Department of Microbiology and Immunology, [2]Feist-Weiller Cancer Center, [3]Department of Urology, and [4]Department of Medicine, Louisiana State University Health Sciences Center; and [5]Overton Brooks VA Medical Center, Shreveport, Louisiana*

1. **Requests for reprints:**
James A. Cardelli, Department of Microbiology/Immunology, Louisiana State University Health Sciences Center at Shreveport, 1501 Kings Highway, Shreveport, LA 71130. Phone: 318-675-5756; Fax: 318-675-5764; E-mail: jcarde@lsuhsc.edu.

1. **Note:** J. McLarty and R.L.H. Bigelow contributed equally to this work.

Abstract

The purpose of this study was to determine the effects of short-term supplementation with the active compounds in green tea on serum biomarkers in patients with prostate cancer.

Twenty-six men with positive prostate biopsies and scheduled for radical prostatectomy were given daily doses of Polyphenon E, which contained 800 mg of (−)-epigallocatechin-3-gallate (EGCG) and lesser amounts of (−)-epicatechin, (−)-epigallocatechin, and (−)-epicatechin-3-gallate (a total of 1.3 g of tea polyphenols), until time of radical prostatectomy. Serum was collected before initiation of the drug study and on the day of prostatectomy. Serum biomarkers hepatocyte growth factor (HGF), vascular endothelial growth factor (VEGF), insulin-like growth factor (IGF)-I, IGF binding protein-3 (IGFBP-3), and prostate-specific antigen (PSA) were analyzed by ELISA. Toxicity was monitored primarily through liver function enzymes. Changes in serum components were analyzed statistically using the Wilcoxon signed rank test. Cancer-associated fibroblasts were treated with EGCG, and HGF and VEGF protein and mRNA levels were measured.

HGF, VEGF, PSA, IGF-I, IGFBP-3, and the IGF-I/IGFBP-3 ratio decreased significantly during the study. All of the liver function tests also decreased, five of them significantly: total protein, albumin, aspartate aminotransferase, alkaline phosphatase, and amylase. The decrease in HGF and VEGF was confirmed in prostate cancer-associated fibroblasts *in vitro*.

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Green Tea Catechins and Prostate CA

High-Grade Intra-prostatic Neoplasia (carcinoma in situ)

- A 2006 study showed that green tea catechins (GTCs) were highly effective in reversing premalignant prostate lesions (high grade prostate intra-epithelial neoplasia); an established precursor to prostate cancer.
- Treatment group ingested daily GTCs supplements (total 600 mg/d).
- After 1 year, only 1 tumor was diagnosed among the 30 GTCs-treated men, whereas 9 cancers were found among the 30 placebo-treated men (3% vs 30% prostate cancer incidence).
- Men in GTCs treated group also had PSA levels that were constantly lower than the placebo-treated group throughout the study period.
- Supplementation with GTC's also improved symptoms of prostate enlargement and reduced lower urinary tract symptoms.
- No significant side effects or adverse effects were reported by the men supplementing with GTCs

Reference:

- Bettuzzi S, Brausi M, Rizzi F et al. Chemoprevention of Human Prostate Cancer by Oral Administration of Green Tea Catechins in Volunteers with High-Grade Prostate Intraepithelial Neoplasia: A Preliminary Report from a One-Year Proof-of-Principle Study. Cancer Res January 15, 2006 *66;* 1234

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Green Tea Catechins In Localized Prostate Cancer

- Based on success of 2006 study described previously, a second study using GTCs was published in 2009 (Cancer Prevention Research).
- In this study GTCs were provided to men with **established localized prostate cancer**, who were awaiting surgical treatment involving radical prostatectomy.
- 26 men with positive prostate biopsies ingested a supplement containing 800 mg per day GTCs, until time of radical prostatectomy (median dosing period was 34.5 days).
- Serum was collected before initiation of the study and on the day of prostatectomy.

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The study showed that GTCs supplementation in these men produced a decrease in many prostate cancer biomarkers, including:

- Prostate Specific Antigen (PSA)

- Hepatocyte Growth Factor (HGF) – the stromal tissue around cancer cells is known to secrete this growth factor, which promotes cancer cell division and increased tumor vascularization to promote metastasis. High HGF signifies higher risk for metastasis.

- Vascular Endothelial Growth Factor (VEGF) – this growth factor promotes the growth of new blood vessels to feed the tumor and promote metastasis. High VEGF levels signified higher risk for metastasis

- Insulin-like Growth Factor and its Binding Proteins (IGF-I, IGFBP-3, and the IGF-I/IGFBP-3) – Higher IGF-1 and lower IGF-1 Binding Protein levels encourage more rapid cell division of cancer cells. In this study the IGF-I/IGFBP-3 ratio decreased significantly during the study.

- Liver Function Tests – In this study all of the liver function tests also decreased, five of them significantly: total protein, albumin, aspartate aminotransferase, alkaline phosphatase, and amylase.

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Proposed Mechanism of Action:

- (EGCG and ECG) shown to inhibit the HGF/c-Met signaling pathway in both breast and prostate carcinoma cells, in experimental studies.
- Hepatocyte Growth Factor (HGF) is normally secreted by mesenchymal cells and acts primarily upon epithelial cells and endothelial cells, but also acts on haemopoietic progenitor cells.
- It has been shown to have a major role in embryonic organ development, specifically in myogenesis, in adult organ regeneration and in wound healing.
- The C-Met receptor is normally expressed by cells of epithelial origin. HGF normally stimulates the c-Met receptor on target tissues, which prompts them to replicate via up-regulation of the tyrosine kinase pathway. Thus, it plays an important role in embryonic growth and wound healing.
- In prostate cancer, the transmembrane receptor c-Met is often over-expressed (a greater number of c-Met receptors than is considered normal) in primary tumors and metastases.

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- High levels of c-Met are directly correlated with a higher Gleason score and associated with poorly differentiated tumors. Additionally, high serum levels of the c-Met ligand, HGF, have been found to be associated with metastatic disease and decreased overall survival.

- Often the overproduction of HGF occurs in cancer-associated fibroblasts located in the stromal tissue surrounding the tumor. Many studies have now shown that the tumor stroma plays a very important role in cancer progression. A number of cells associated with the stroma, including macrophages, endothelial cells, and fibroblasts, provide factors that facilitate proliferation, survival, and invasion of tumor cells.

- As such, studies show that dysregulation of the HGF/c-Met pathway leads to increased proliferation, motility, and invasion of cancer cells.

- Other *in vitro* experiments show that GTCs also block the production of VEGF and HGF in at least two different prostate cancer–associated fibroblast cell lines

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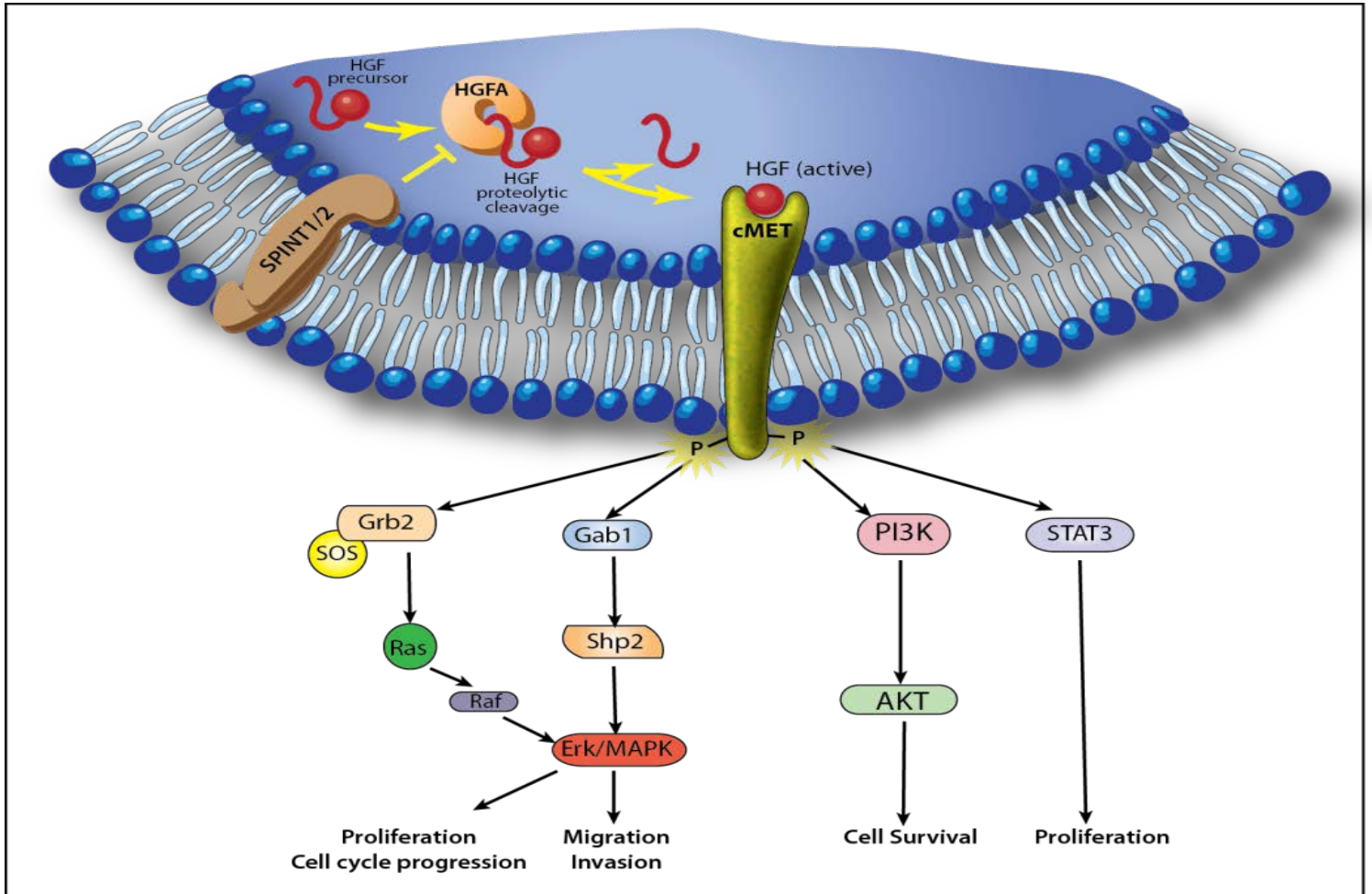
HGF/Met C Signaling Pathway



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Summary

- Overall, data suggests that supplementation with green tea catechins could be useful adjuvant therapy in men with prostate cancer by lowering the levels of cytokines (HGF, VEGF) that contribute to prostate cancer progression

- Prostate cancer is the second leading cause of cancer mortality in men in the United States, with 27,000 dying each year. Rates of recurrence for early-stage disease are relatively high, and mortality rates for late-stage disease have not improved significantly over the past 10 years

- In regard to prostate cancer prevention as much as 75% of prostate cancer is attributable to dietary and lifestyle factors, according to data published in the Journal of the National Cancer Institute.

Reference:

- McLarty J, Bigelow R, Smith M et al. Tea Polyphenols Decrease Serum Levels of Prostate-Specific Antigen, Hepatocyte Growth Factor, and Vascular Endothelial Growth Factor in Prostate Cancer Patients and Inhibit Production of Hepatocyte Growth Factor and Vascular Endothelial Growth Factor *In vitro.* Cancer Prev Res July 2009 *2;* 673

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Vegan Diet Reduces Prostate Cancer Risk by 35%: Considerations in Prostate Cancer Survivors

Jan 2016 study in American Journal of Clinical Nutrition **(**Part of Adventists Health Study-2)

Showed - Men who are Vegans had a 35% Lower Risk of Prostate Cancer compared to non-vegan men

Study Followed over 26,000 men. During study, 1079 men developed prostate cancer

Researchers showed – Vegan Men had a 35% lower risk of Pr CA compared to non-vegans

Especially true for white males, with similar trend for black male vegans, although assoc. not quite as strong.

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Not surprising, as many plant foods contain nutrients shown to inhibit prostate cancer.

Examples:

- Cruciferous vegetables – broccoli, Brussels sprouts, cabbage, cauliflower, bok choy, turnips
- Tomatoes – lycopene
- Soy beans and soy products – isoflavones and protease inhibitors
- Peas and Beans – lignins, protease inhibitors
- Green Tea – catechins (polyphenols)
- Pomegranate Juice –ellagic acid
- Ground Flaxseed – EL and ED

Many studies show consumption of theses foods associate with decreased prostate cancer

And Supplements using ingredients from some of these plant-based foods have been used as Adjunctive Treatment to Help Improve Outcomes in Pr CA patients (isoflavones, lycopene, flaxseed, catechins)

Take Home Message:

Most patients not going to become strict vegans, but encouraging them to including more plant foods with anti-cancer properties appears prudent to help prevent Pr CA

Pr CA - accounts 27% of all male cancers, and is 2nd leading cause cancer death in men

For women – Many of the same plant foods that reduce Pr CA, also shown to reduce risk of Br CA.

Reference : http://ajcn.nutrition.org/content/103/1/153.abstract

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Adjunctive Nutrition and Supplementation Recommendations For Patients With Prostate Cancer or a PSA Level Above 2.5 or a PSA Velocity that has Increased Abruptly Within a One year Period

Dietary and Lifestyle Prescription:

- No red meat, pork, lamb, duck
- No deep fried foods, no foods that are cooked to completion via pan-frying in oil
- No cheese, no milk or yogurt above 1% milk fat, no egg yolks, no butter, no cream, no mayonnaise
- No frozen yogurt or ice cream
- No sugar, honey or brown sugar in coffee or espresso
- No alcohol of any kind (including red wine)
- Eat at least one cruciferous vegetable per day (broccoli, cabbage, Brussels sprouts, kale, bok choy, cauliflower)
- Eat soy products if possible (stir fry tofu with mixed vegetables, edamame, roasted soy nuts, soy milk)
- No high fat pastries (cheat with a biscotti, or low fat muffin)
- Eat beans and peas daily if possible - including vegetarian lentil soup
- 8 ounces of pomegranate juice per day
- Drink 3-5 cups of green tea daily
- Need 30 mins of aerobic exercise at least 4 days per week for insulin and glucose control – these influence the rate of cell division and growth.

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Supplements

1. High-Potency Multiple Vitamin and Mineral – antioxidant enriched, B-50 complex. 1000 IU vitamin D etc.)

2. Essential Fatty Acids – (1200 mg capsules) - 3 capsules per day – Or 1200 mg fish oil supplement (twice daily) (at least 30% EPA/20%DHA)

3. Vitamin D – (at least another 3,000 IU per day) – have vitamin D blood level checked. It needs to be at or above 85nmol/L (35ng/ml)

4. Prostate Formula – 2 capsules, twice per day

5. Melatonin – 3-5 mg 90 mins before bedtime

6. Green Tea Catechins supplement - 600 mg of catechins/polyphenols daily

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7. Lycopene – 20 mg per day

8. Ground flaxseed – 25 gms (1 heaping tablespoons) once per day – mix into low fat yogurt or protein shake or juice.

9. Soy Isoflavones – 200 mg per day (find a supplement that contains this amount)

10. Optional – Indole-3 carbinol/sulforaphane supplement

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Other Supplement Considerations in Cancer

1. Haelen 951
2. Carnivora
3. Ukrain
4. C-Statin
5. Inositol Hexaphosphate (IP6)
6. Carctol
7. Artemisinin
8. Glutathione Precursors (N-acetyl cysteine, alpha-lipoic acid, silymarin, L-glutamine)
9. EGCG (catechins) – from decaffeinated green tea

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- **Haelan 951 (a fermented soy beverage):** showed excellent protection from the adverse side effects of chemotherapy and radiation in a clinical study involving 318 patients (276 receiving chemotherapy and the balance radiation).

- Haelan 951 reduced the side effects, and none of the patients required a blood transfusion nor did anyone have to discontinue a scheduled course of treatment because of physical weakness ($1,020.00 case- 20 – 80z bottles)

- Haelan 951 shows similar benefits to soy isoflavone research, in experimental studies:

1. Anti-angiogenesis
2. Apoptosis
3. Slow cancer cell replication

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Carnivora ® - patented phytonutrient extract of the Venus flytrap plant(Dionaea muscipula)

It is non-toxic and contains properties that are immunomodulatory, anti-viral, antitumoral, antiparasitic, antimicrobial & antibacterial.

Cancer Studies reported in the Book "German Cancer Therapies" by Dr Morton Walker. Studies of Carnivora® were conducted by professor Dieter Kurt Todorov M.D., D.Sc., chief of laboratories in oncopharmacology at the National Oncological center of Bulgaria

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Carnivora Cont-d

Experimental Studies By Dr Todorov:

- Ovarian cancer cells in a rat model – reduced tumor size
- Glioblastoma – reduced number of cancer cells
- Human sarcoma cells – reduced number of cancer cells
- Human leukemia cells showing multidrug resistance were exposed to 200ng/ml Carnivora ®. Within seventy-two hours, the abnormal, immature, and leukemic white blood cells responded well to Carnivora ® and were reduced in number from 2,250 to 570. He claims that Leukemia is successfully treated with squeezed juice of the Venus' Flytrap.

Helmut Keller MD, a world renown Cancer physician, first discovered the anti-leukemic properties of Carnivora in 1973. In his experience treating leukemias using Carnivora ®, he suggests that many blood dyscrasias may be considered reversible and curable.

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Ukrain (NSC-631570) - a semi-synthetic compound derived from the greater celandine weed (*Chelidonium majus* L.)

It contains a range of unique **alkaloids** shown to have anticancer properties

- At the Bristol Cancer Help Centre, United Kingdom, they indicate that Ukrain is the only known product that reduces tumor cells, does not destroy healthy cells, and boosts the immune system (**Miller S. Ukrain. *Bristol Cancer Help Centre 'handout' dated 05/03/2004.* 2004**)

- Ukrain is most commonly **administered intravenously** and consists of one molecule thiophosphoric acid conjugated to three molecules of chelidonine alkaloid.

- Oral administration of greater celandine in humans has been associated with several cases of **toxic hepatitis.**

- It has a drug license in several states of the former Soviet Union.

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- Research on Ukrain started about 20 years ago and numerous in-vitro studies, animal experiments, case reports, and case series have emerged.

- Collectively, data suggests that Ukrain has anticancer activity in a wide range of cell lines, which could be of clinical value.

- However, many of the studies used inferior research methodology, and thus, concrete conclusions can not be drawn

- It has been postulated that the antineoplastic effect is due to the alkaloids interfering with the metabolism of cancer cells, diminished synthesis of DNA, RNA and proteins, the inhibition of cellular oxygen consumption, and the induction of programmed cell death in malignant cells.

Reference:

Ukrain – a new cancer cure? A systematic review of randomized clinical trials

***BMC Cancer.* 2005; 5: 69. Published online 2005 July**

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C-Statin

C-Statin contains MPGC (Muramyl polysaccharide-glycan complex), **a cell wall** extract from the bacterium *Lactobacilus fermentum.*

MPGC regulates the production of a potent **angiogenesis inhibitor**, interleukin 12 (IL-12).

A well known commercial product is manufactured by Aidan Incorporated as C-Statin

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C-Statin References

1. NEUROIMMUNOMODULATION 1999 JUL-AUG; 6(4): 261-83.

2. U.S. PATENT PENDING, 2000 MENG ET AL.

3. IMMUNOLOGY 2000 JAN; 99(1): 1-7.

4. SCANNING MICROSC 1995 MAR; 9(1): 159-73.

5. PIZZORNO JE, MURRY, M. A TEXTBOOK OF NATURAL MEDICINE. BASTYR UNIVERSITY PUBLICATIONS; BOTHELL, WA 1996.

6. BOIK J. CANCER AND NATURAL MEDICINE: A TEXTBOOK OF BASIC SCIENCE AND CLINICAL RESEARCH. OREGON MEDICAL PRESS; PRINCETON, MN 1996.

7. MOL CELL BIOCHEM 1999 JUN; 196(1-2): 99-108.

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Inositol Hexaphosphate (IP-6)

Experimental Data:

1. Inhibits cell proliferation of many types of human cancer cells

2. Increases **differentiation** of malignant cells, often resulting in a reversion to normal phenotype.

3. Exogenously administered IP6 is rapidly taken into the cells and dephosphorylated to lower-phosphate inositol phosphates, which interfere with signal transduction pathways and **cell cycle arrest.**

4. Enhanced **immunity** and **antioxidant** properties have also been shown

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5. Up-regulates activity of Natural Killer Cells

- However, the molecular mechanisms underlying this anticancer action are not fully understood.

- Because it is abundantly present in regular diet (cereals and legumes), efficiently absorbed from the gastrointestinal tract, and safe, IP6 holds great promise in our strategies for the prevention and treatment of cancer.

Reference: Ivana Vucenik et al. Cancer Inhibition by Inositol Hexaphosphate (IP6) and Inositol: From Laboratory to Clinic J. Nutr. 133:3778S-3784S. 2003

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IP6 plus inositol In Advanced Colon Cancer Patients

Clinical Study With IP6 (Mayo Clinic)

- Enhanced antitumor activity without compromising the patient's quality of life was demonstrated in a pilot clinical trial involving six patients with **advanced colorectal cancer with multiple liver and lung metastasis**.

- IP6 plus inositol given as adjuvant to chemotherapy according to Mayo protocol. One patient with liver metastasis refused chemotherapy after the first treatment, and she was treated only with IP6 plus inositol; her control ultrasound and abdominal computed tomography scan 14 mo after surgery showed significantly reduced growth rate.

A reduced tumor growth rate was noticed overall **and in some cases a regression of lesions was noted**.

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- Additionally, when IP6 plus inositol was given in combination with chemotherapy, side effects of chemotherapy (drop in leukocyte and platelet counts, nausea, vomiting, alopecia) were diminished and patients were able to perform their daily activities..

Reference: Druzijanic, N., Juricic, J., Perko, Z. & Kraljevic, D. (2002) IP-6 & inositol: adjuvant to chemotherapy of colon cancer. A pilot clinical trial. Rev. Oncologia 4: 171.

Dosage: 2-8 gm per day

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Carctol

- **Carctol - comprised of 8 Indian Herbs** (Hemidesmus Indcus, Tribulus Terrestris, Piper Cubeba Linn, Ammani Vesicatroria, Lepidium Sativum Linn, Blepharis Edulis, Smilax China Linn, and Rheum Emodi Wall)

- Created by Dr Nandlal Tiwari of India, who has been treating cancer patients with it for 20 years.

- He has case files of 1,900 patients treated with Carctol, many of whom had been considered beyond medical help. According to Tiwari's records, 25 per cent of patients reported a 75 per cent to 100 per cent improvement in their condition, and 30 percent reported up to 75 per cent improvement with Carctol (not clear what these percentages mean, or how they were measured)

- Carctol appears to be especially effective in treating gastro-intestinal and haemotological cancers.

Dosage: Two capsules, four times a day.

Dr Tiwari also recommends a vegetarian diet, and prohibits sour and acidic food and drink. The patient must drink up to six pints of boiled, refrigerated water a day. The patient also takes digestive enzymes with the remedy

CAM-CANCER (Complementary and Alternative Medicine For Cancer Website) State The Following:

- Carctol is a mixture of 8 herbs.
- Neither pre-clinical studies nor controlled trials of Carctol for the treatment or palliation of cancer exist.
- Its safety is uncertain.
- Neither pre-clinical studies nor controlled trials of Carctol for the treatment or palliation of cancer exist. Its safety is uncertain

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Arteminisin (Sweet Wormwood) – from South-East Asia

- Artemisinin annua (Qing Hao) is used as treatment for quinine-resistant malaria. When artemisinin comes into contact with unsequestered iron in malaria-affected red blood cells it generates free radicals that blow up the cell, killing the parasite.

- Artemisinin has been shown to act the same way in cancer cells, which are also rich in iron

- A University of Washington study shows Artemisinin selectively kills several cancer cell lines in the test tube.

- It worked against breast cancer cells but was most effective for aggressive forms of **pancreatic and leukemia cell lines** (1,2). More recently we have seen that it works against a wide variety of cancer cells (Willoughyby JA Sr et. 2008)

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- Artemisinin damages cell membranes by reacting with iron, high concentrations of which are found in both the malaria parasite and quickly dividing cancer cells (including cancer cells).

- Researchers observed cancer cells resistant to chemotherapy were still killed by artemisinin (3)

References:

1. *Selective cancer cell cytotoxicity from exposure to dihydroartemisinin and holotransferrin*, Cancer Letters 91 {1995} 41-46)
2. *The anti-malarial artesunate is also active against cancer*, International Journal of 16)Oncology, 18 {2001} 267-773
3. *International Journal of Oncology* 18; 767-773, 2001 by Efferth, et al

Artemisinin can cross blood-brain barrier in brain cancer, along with Poly MVA

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Artemisinin, Cancer and Iron

- Iron-hungry cancer cells typically have significantly more transferrin receptors, and researchers have bound Artemisinin to Transferrin.

- Inside the cancer cell, the iron is released and reacts with the Artemisinin, generating free radials that kill the cancer cells

- Artemisinin-tagged transferrin was 34,000 times more effective in selecting and killing the cancer cells than normal cells

- Artemisinin alone is 100 times more effective

(Lai H. 1995)

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Other Anti-Cancer Actions:

1. Anti-angiogenesis & Apoptosis (Gammill, 11/29/04).

2. Anti-proliferative response due to a G1 cell cycle arrest. The G1 phase of the cell cycle can be regulated by the interactions of cyclins, cyclin-dependent kinases and cyclin-dependent kinase inhibitors. Artemisinin in shown to act as an inhibitor of CDK-2 and CDK-4

Reference: Willoughby JA Sr et al. Artemisinin Blocks Prostate Cancer Growth and Cell Cycle Progression by Disrupting Sp1 Interactions with the Cyclin-dependent Kinase-4 (CDK4) Promoter and Inhibiting CDK4 Gene Expression. The Journal of Biological Chemistry (nov. 17, 2008)

Dosage: 500 mg twice daily of Artemisinin, taken with Essential Fatty Acids (but not food, iron or antioxidants) for best absorption

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Glutathione Precursors:

1. **N-acetylcysteine** – In vitro studies suggest it can form stable covalent compound with electrophilic alkylating agents and platinum complexes, which activates these cancer drugs.

Animal studies show that it prevents hemorrhagic cystitis (bladder mucosa damage) from cyclophosphamide or ifosfamide

NAC shown to reduce cisplatin-induced nephrotoxicity and protects against bleomycin genotoxicity (as do other antioxidants). But it may inactivate the drugs' cancer fighting effects

Conklin KA. Nutr and Cancer 2000

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2. Glutamine – human studies show that it has effectively reduced stomatitis and diarrhea (secondary to gut lining damage) when used to reduce the side effects of a variety of chemotherapy drugs.

Dosage: 6 gm, 3x daily – beginning 3 days before regime and lasting 18 days, on average, of continued supplementation

Can swish in mouth 4 gm, twice daily for stomatitis prevention.

Conklin KA. Nutr and Cancer 2000

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3. Alpha-lipoic Acid:

A. **Increases Insulin Sensitivity** and thus, may improve effects of Insulin Potentiation Therapy in cancer treatment

B. May **Repair Nerve Damage** from Chemotherapy Drugs (diabetic neuropathy studies) – vitamin B6 can also help (100-200 mg per day)

C. Shown to **induce apoptosis** of cancer cells in experimental studies

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References (alpha-lipoic acid)

- Gedlicka C, Scheithauer W, Schüll B, Kornek GV. Effective treatment of oxaliplatin-induced cumulative polyneuropathy with alpha-lipoic acid. *J Clin Oncol*. 2002;20:3359-3361

- van de Mark K, Chen JS, Steliou K, Perrine SP, Faller DV. Alpha-lipoic acid induces p27Kip-dependent cell cycle arrest in non-transformed cell lines and apoptosis in tumor cell lines. *J Cell Physiol*. 2003;194:325-340.

- Ziegler D, Nowak H, Kempler P, Vargha P, Low PA. Treatment of symptomatic diabetic polyneuropathy with the antioxidant alpha-lipoic acid: a meta-analysis. *Diabet Med*. 2004;21:114-121.

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4. Silymarin (Milk Thistle): Experimental Data Show These Effects:

- Angiogenesis inhibitor
- Cell cycle Inhibition of cancer cells
- Apoptosis of cancer cells

Studies show these results in the following cancer cells under experimental conditions:

- Prostate
- Colon
- Ovarian
- Skin
- Lung
- Breast
- Cervical cancer

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Example of Glutathione Precursor Supplement

1. N-acetylcysteine
2. L-glutamine
3. Alpha lipoic acid
4. Milk thistle (silymarin)

Also consider as adjunctive supplement unless genetic profile shows increased activity of glutathione synthesizing enzymes (Gamma GC)

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References Silymarin

1. Zi X, Agarwal R. Silibinin decreases prostate-specific antigen with cell growth inhibition via G1 arrest, leading to differentiation of prostate carcinoma cells: implications for prostate cancer intervention. *Proc Natl Acad Sci USA* 1999; 96: 7490-7495.

2. Yang SH, Lin JK, Chen WS, Chiu JH.Anti-angiogenic effect of silymarin on colon cancer LoVo cell line. *J Surg Res*. 2003; Jul;113(1):133-8.

3. Gallo D, Giacomelli S, Ferlini C, Raspaglio G, Apollonio P, Prislei S, Riva A, Morazzoni P, Bombardelli E, Scambia G. Antitumour activity of the silybin-phosphatidylcholine complex, IdB 1016, against human ovarian cancer. *Eur J Cancer*. 2003; Nov;39(16):2403-10.

4. Singh RP, Agarwal R, Flavonoid antioxidant silymarin and skin cancer, *Antioxid Redox Signal*. 2002 Aug;4(4):655-63.

5. Sharma G, Singh RP, Chan DC, Agarwal R, Silibinin induces growth inhibition and apoptotic cell death in human lung carcinoma cells, *Anticancer Res*. 2003 May-Jun;23(3B):2649-55.

6. Zi X, Feyes DK, Agarwal R, Anticarcinogenic effect of a flavonoid antioxidant, silymarin, in human breast cancer cells MDA-MB 468: induction of G1 arrest through an increase in Cip1/p21 concomitant with a decrease in kinase activity of cyclin-dependent kinases and associated cyclins, *Clin Cancer Res*. 1998 Apr;4(4):1055-64.

7. Bhatia N, Zhao J, Wolf DM, Agarwal R, Inhibition of human carcinoma cell growth and DNA synthesis by silibinin, an active constituent of milk thistle: comparison with silymarin, *Cancer Lett*. 1999 Dec 1;147(1-2):77-84.

8. Mokhtari MJ, Motamed N, Shokrgozar MA. Evaluation of silibinin on the viability, migration and adhesion of the human prostate adenocarcinoma (PC-3) cell line. *Cell Biol Int.* 2008 Aug;32(8):888-92. Epub 2008 Apr 8.

9. Tyagi A, Sharma Y, Agarwal C, Agarwal R. Silibinin impairs constitutively active TGFalpha-EGFR autocrine loop in advanced human prostate carcinoma cells. *Pharm Res*. 2008 Sep;25(9):2143-50. Epub 2008 Feb 6.

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Green Tea Polyphenolic Compounds: Shown to have the following anticancer effects under experimental conditions:

1. Antioxidant effects

2. Induction of detoxification enzymes

3. Regulate abnormal cell growth and cancer
   (cell cycle arrest, apoptosis, anti-angiogenesis)

4. Improves the function and growth of beneficial intestine bacteria

Weisburger JH, Chung FL. "Mechanisms of chronic disease causation by nutritional factors and tobacco products and their prevention by tea polyphenols." *Food Chem Toxicol* 2002 Aug;40(8):1145-54.

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EGCG Studies

Studies with human cancer cell lines have demonstrated that epigallocatechin-3-gallate (EGCG), a major tea polyphenol, inhibits:

1. Mitogen-activated protein kinases
2. Cyclin-dependent kinases
3. Growth factor-related cell signaling
4. Activation of activator protein 1 (AP-1) and nuclear factor B (NF B)
5. Topoisomerase I
6. Matrix metalloproteinases as well as other potential targets.
7. Angiogenesis

References:

Joshua D. Lambert and Chung S. Yang. Mechanisms of Cancer Prevention by Tea Constituents. J. Nutr. 133:3262S-3267S, 2003

Demeule M et al. Green tea catechins as novel antitumor and antiangiogenic compounds. Curr Med Chem Anticancer Agents. 2(4):441-63, 2002

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Catechin Human Cancer Studies

Prostate: Catechins from Green Tea have decreased conversion of premalignant cells to full-blown prostate cancer vs placebo in one year study

Prostate: Catechins from Green Tea have decreases important biomarkers of metastasis and progression in men with localized prostate cancer

Breast Cancer: Catechins from Green Tea have decreases important biomarkers of metastasis and progression in women with breast cancer

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Part 4

Understanding Chemotherapy Agents

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Principles Of Cancer Chemotherapy

Overview Of Topic

1. The Normal Cell Cycle

2. Three States Of Tumor Cells Within The Tumor Mass

3. Types of Chemotherapy Drugs And Their Effects In Combination Chemotherapy Approach:

- Alkylating Agents
- Anthracylcins
- Anti-metabolites
- Targeted Agents
- Endocrine Therapies

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1. The Normal Cell Cycle:

G0 Phase – resting diploid cells that are not dividing

G1 Phase – cells that have recently divided and are committed to continued proliferation

S Phase – follows G1 phase whereby cells undergo DNA synthesis

G2 Phase – premitotic rest interval (check point to see if DNA has properly reproduced itself)

M Phase – mitotic phase, chromosome condensation with cell division

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***2. Tumor Mass* – contains three types of cell:**

1. Non-dividing cells that are terminally differentiated

2. Cells that continue to proliferate

3. Non-dividing cells that are currently quiescent but may be recruited into cell cycle

Large tumors harbor **more non-proliferating cells,** which potentially make them more resistant to agents that selectively target dividing cells

Slow growing tumors (non-small cell lung cancer and chronic lymphomas) that have many non-dividing cells are also more resistant to chemo drugs.

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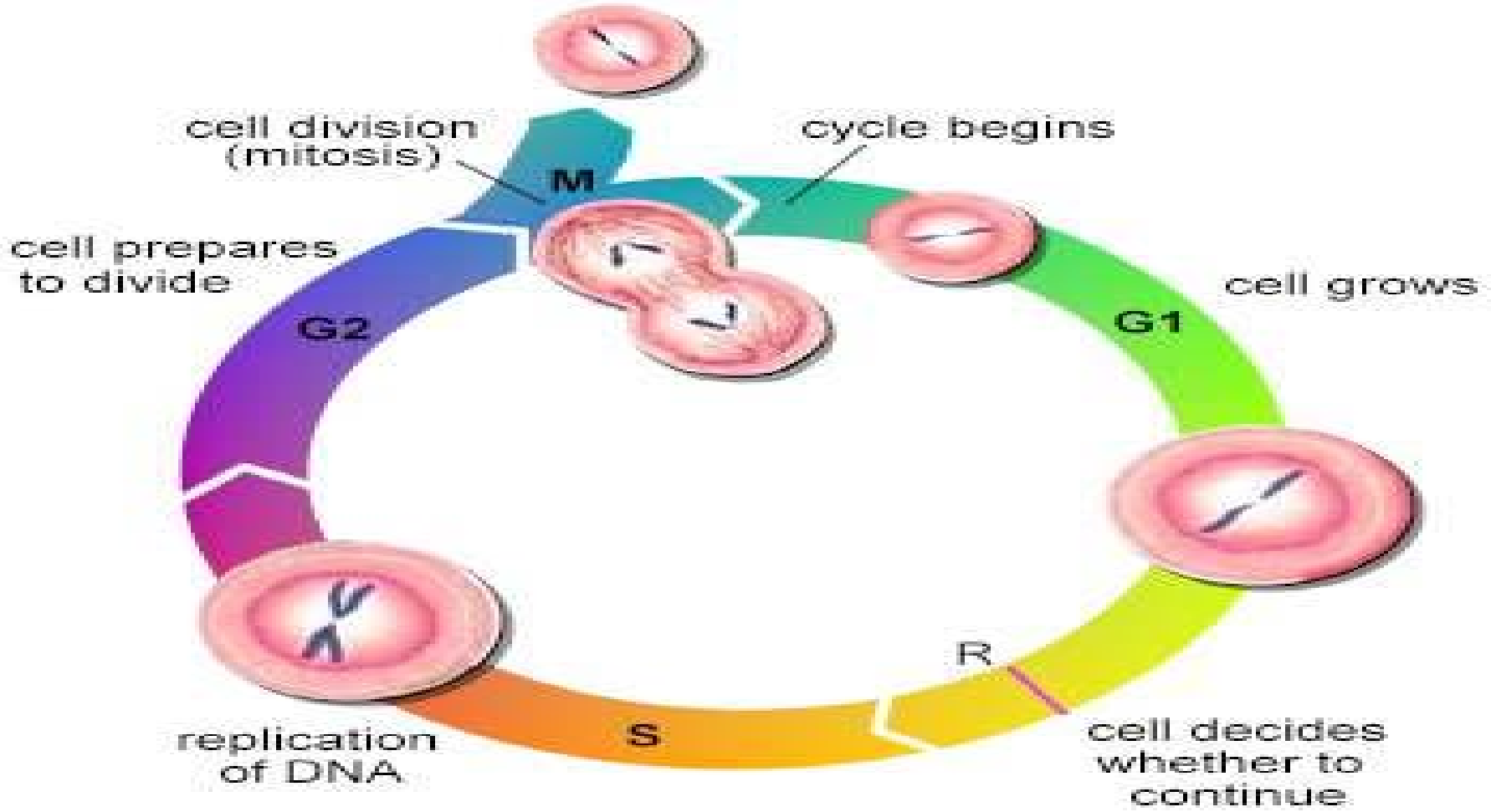
Overview Of Cell Cycle



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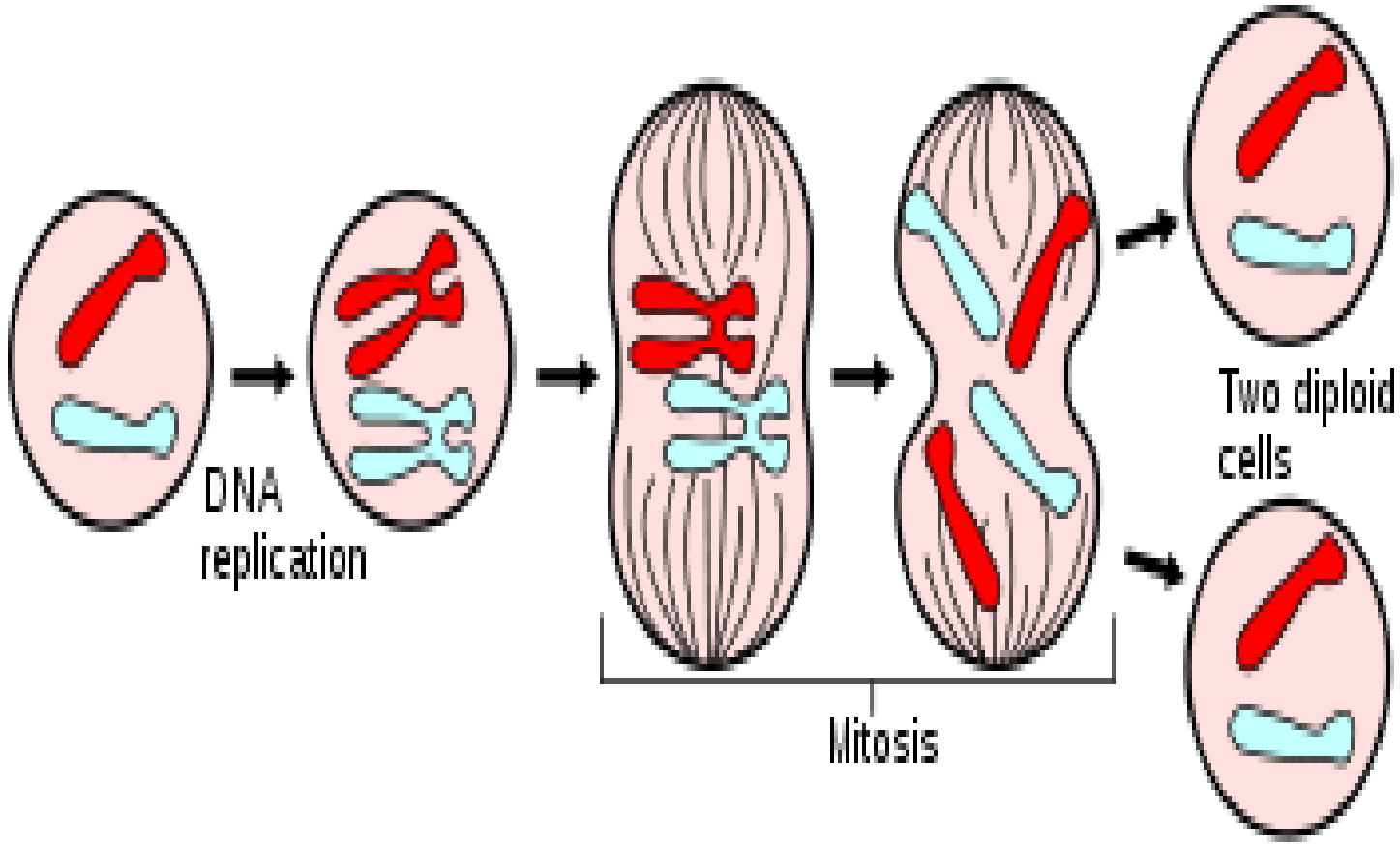
Note Formation Of Microtubules Prior To Mitosis



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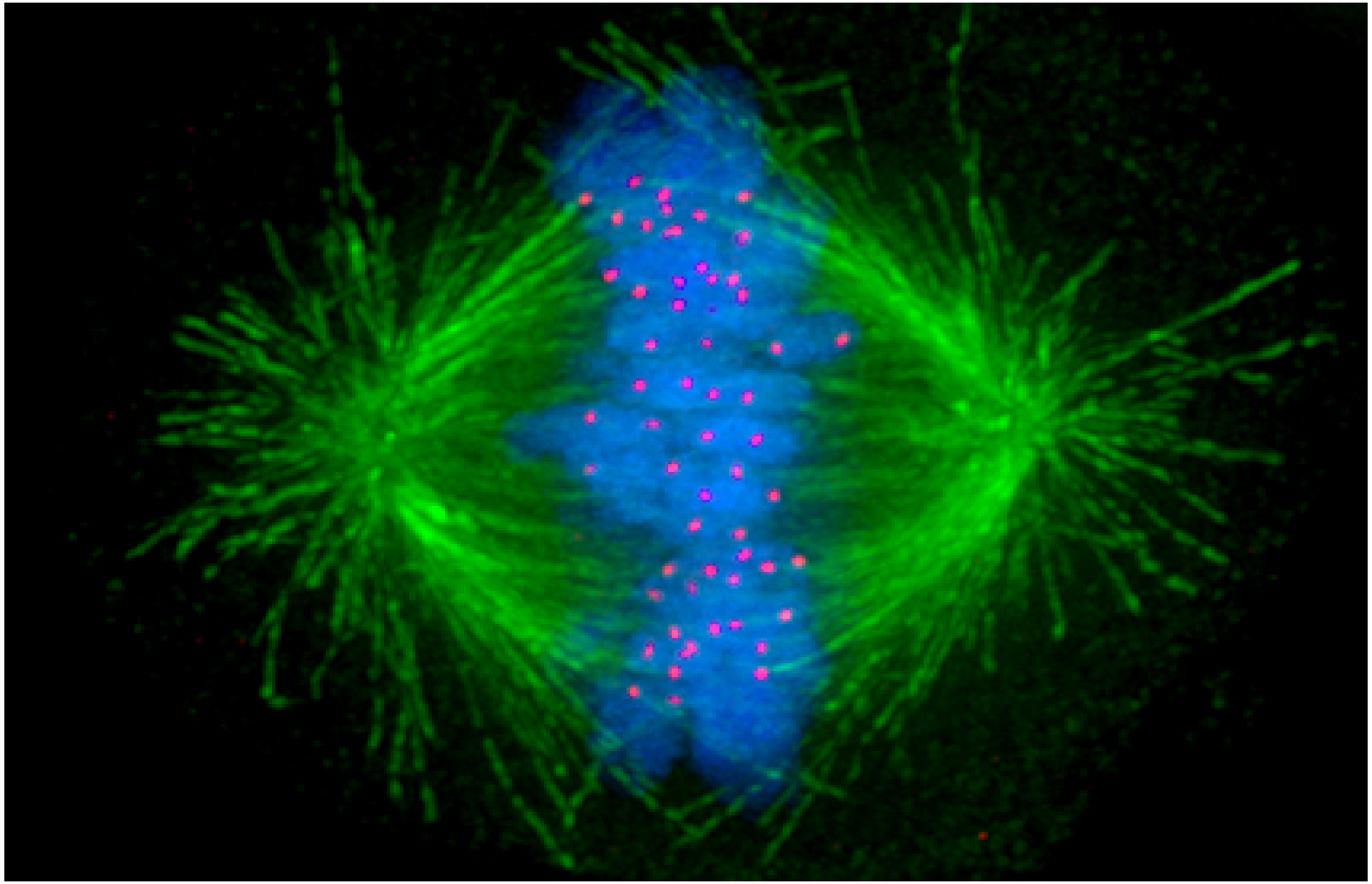
Human cell showing microtubules in green, and chromosomes (DNA) in blue



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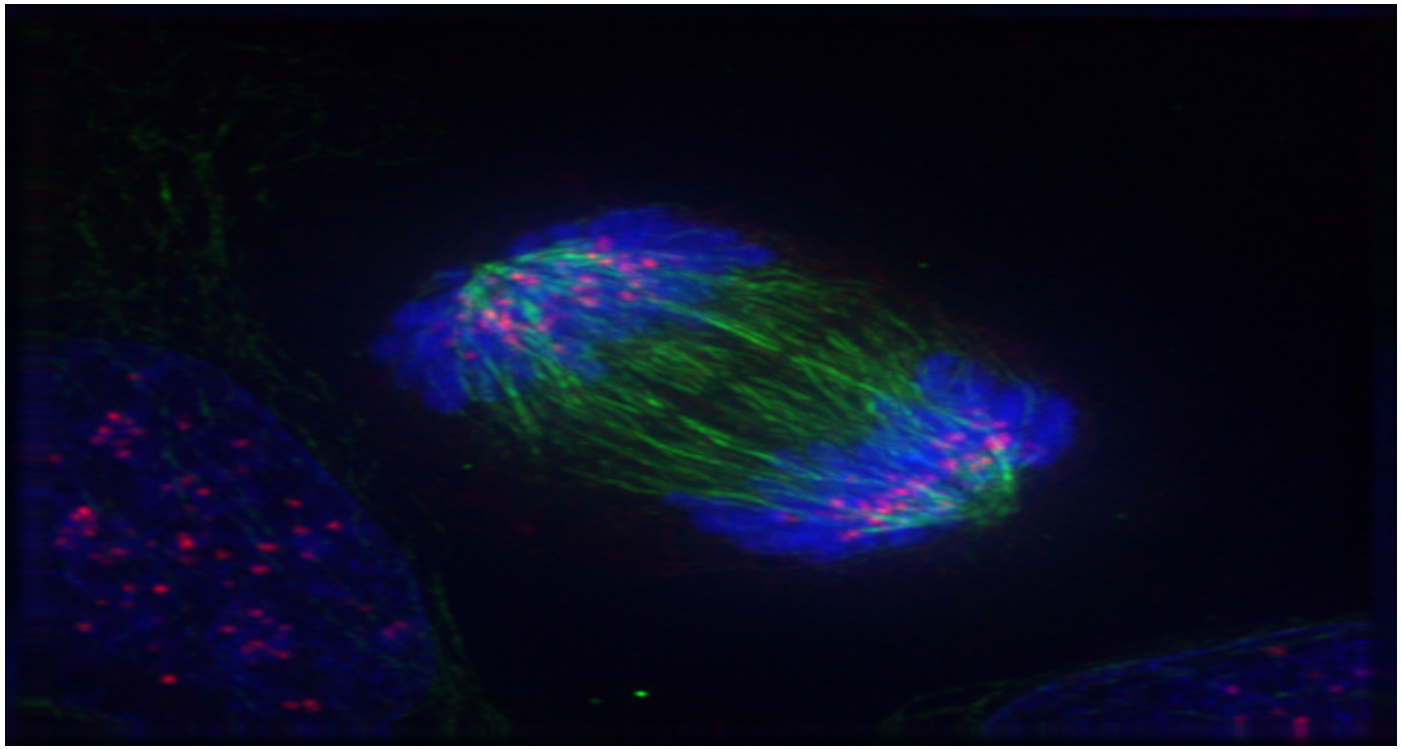
Anaphase

- **Anaphase** - chromosomes separate and each chromatid pulled to opposite poles of the cell by microtubules



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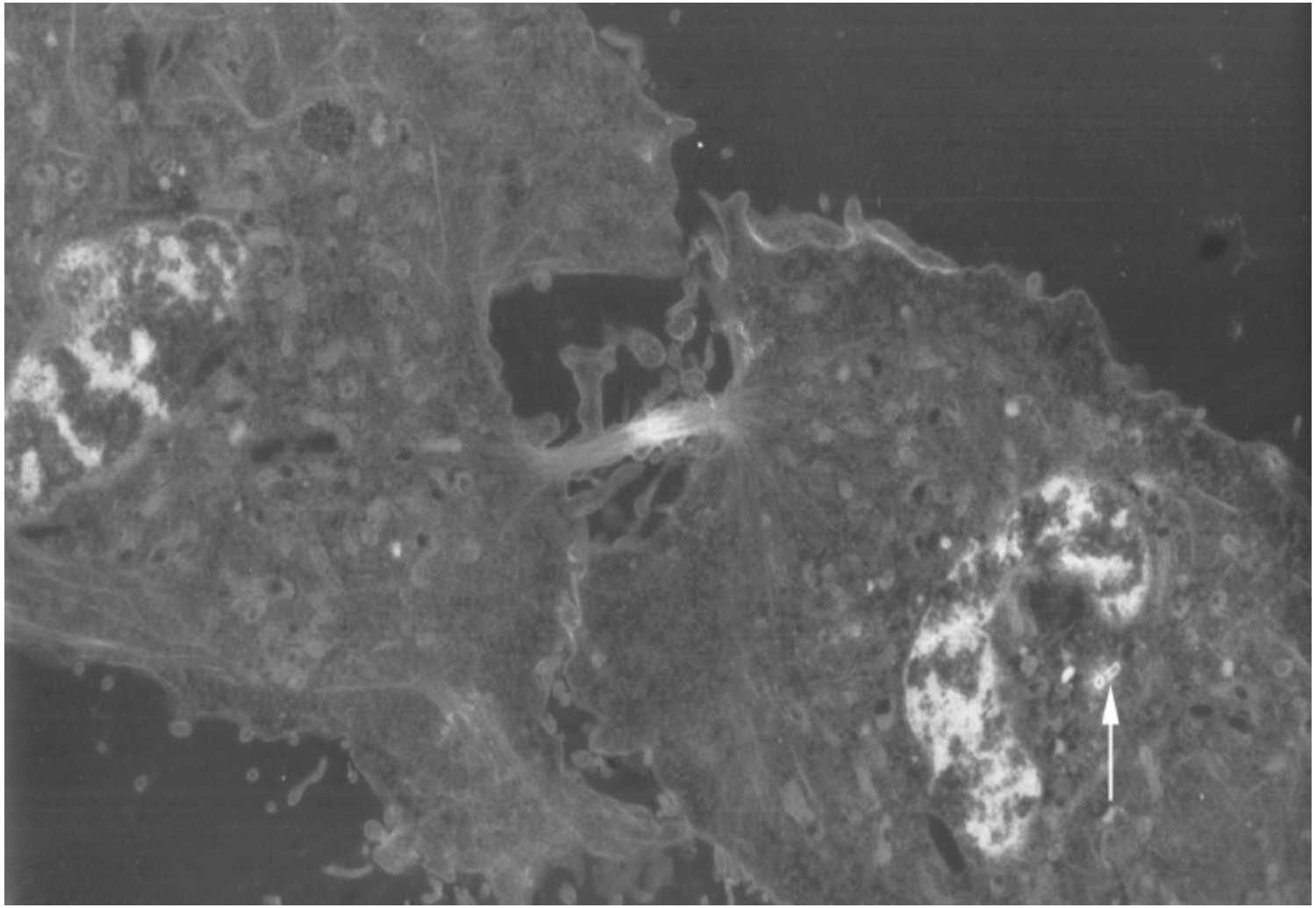
Cytokinesis – cell divides into 2 daughter cells



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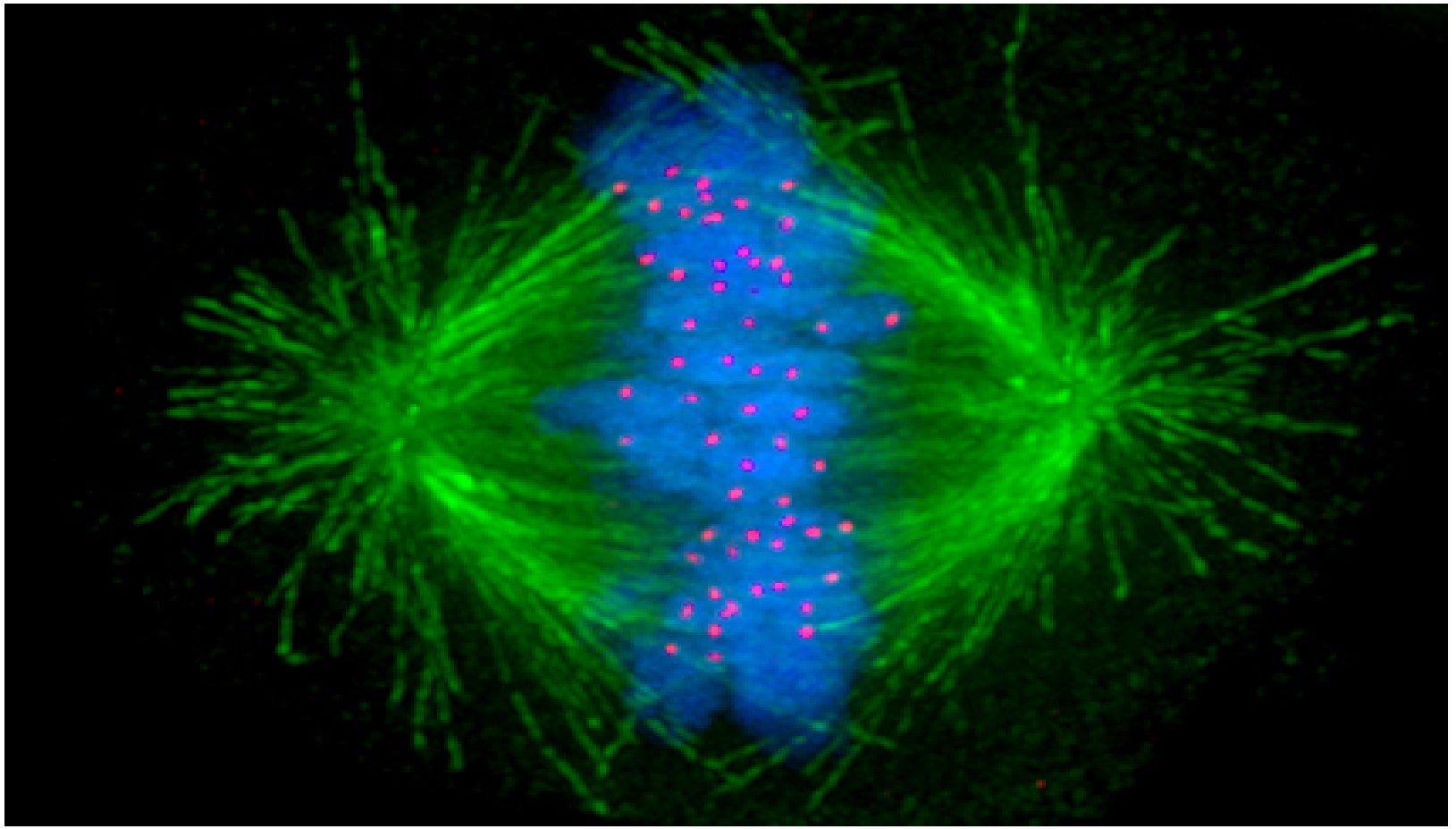
Human cell showing microtubules in green, chromosomes (DNA) in blue, centromeres in red



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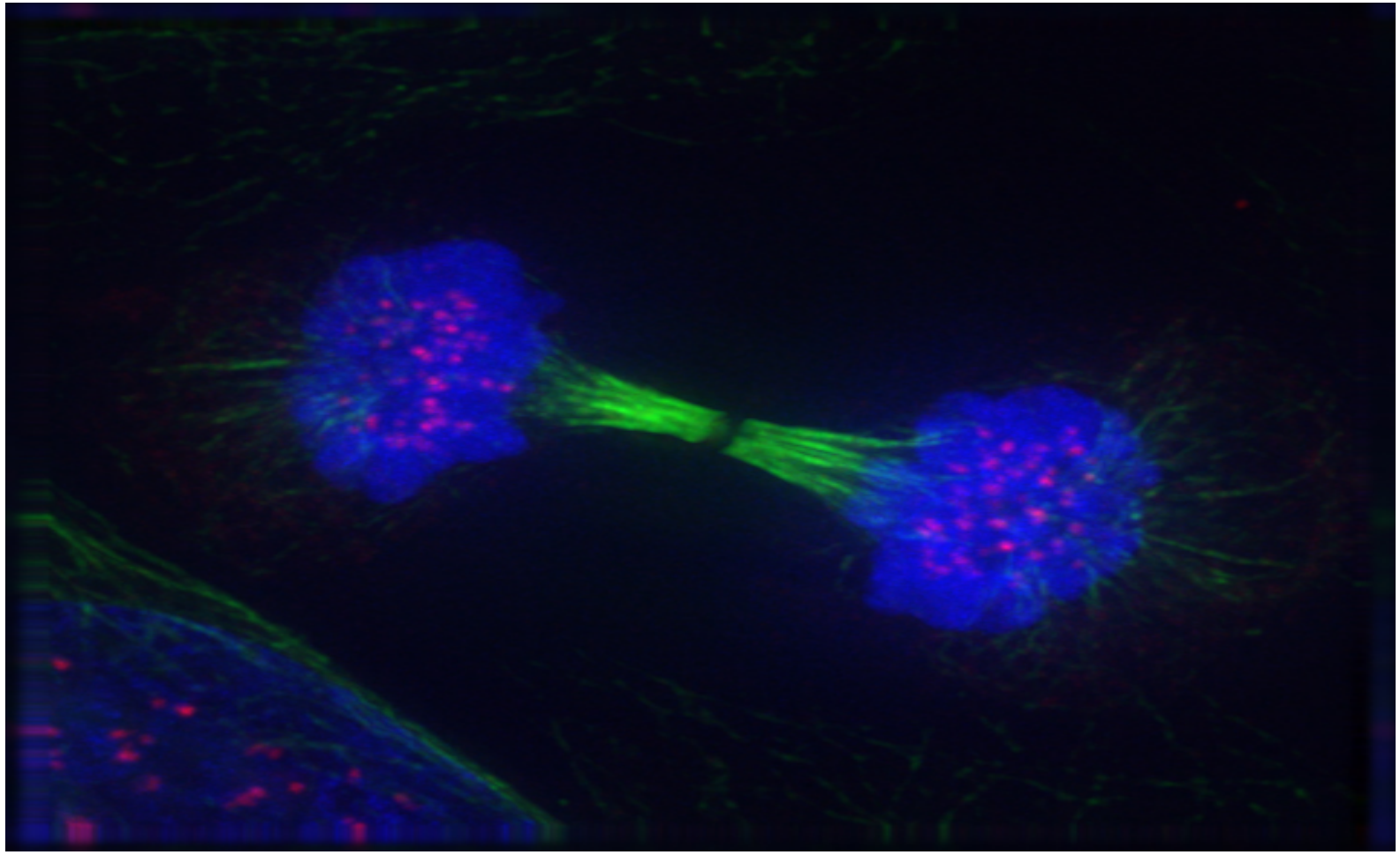
Telophase



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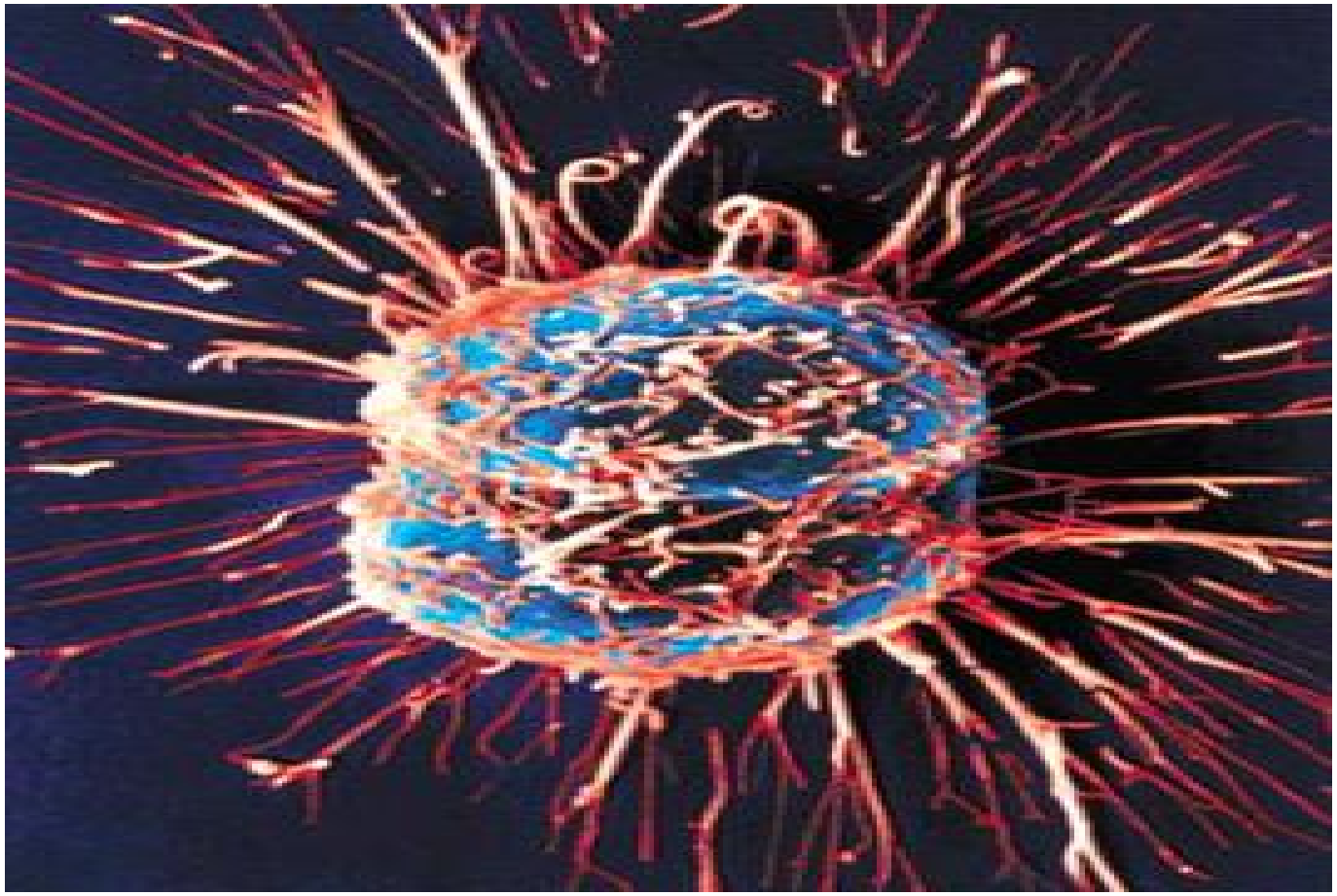
A Cancer Cell Near The End Of Cell Division



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3. Combination Chemotherapy Approach:

Uses a combination of chemo drugs that target all phases of cell cycle (Go, G1, S, G2 and M-phases) – get superior additive effects

Different classes of chemotherapy agents target specific phases of cell cycle

Combination approach also reduces overall toxicity of chemotherapy by not compounding toxicities of drugs that work via a similar mechanism of action.

This approach also reduces drug-resistance problems

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Classes Of Chemotherapy Agents:

1. Cell Cycle or Phase-Specific Drugs

2. Non Cell Cycle or Non- Phase-Specific Drugs

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1. Cell Cycle or Phase Specific Drugs:

- Anti-Metabolites
- Plant Alkaloids
- Etoposide (other Epipodophyllotoxins)
- Taxanes (Paclitaxel)
- Miscellaneous Agents

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2. Non Cell or Non Phase-Specific Drugs:

- Alkylating Agents
- Anthracyclines (antitumor antibiotics)
- Hormonal Therapies (Tamoxifen) - blocking cell receptors

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1. Cell Cycle or Phase-Specific Drugs:

A. Have greatest killing effect when cell is dividing

B. Certain drugs target specific cell phases (e.g. M-phase):

G1 Phase:

- Asparaginase
- Corticosteroids – e.g. prednisone

S-Phase (DNA Is Replicating):

Anti-Metabolites – drugs that are structural analogues to naturally occurring metabolites involved in DNA and RNA synthesis. These drugs alter critical pathways to prevent cancer cells from synthesizing DNA or RNA.

Exert their cytotoxic effects either by competing with normal metabolites for the catalytic or regulatory sites of a key enzyme or by substituting for a metabolite that is normally incorporated into DNA or RNA.

Examples Include: capecitabine – (converted to Fluorouracil - 5FU), doxorubicin, floxuridine, gemcitabine, mercaptopurine, prednisone, thioguanine, cytarabine, fludarabine, hydroxyurea, methotrexate, procarbazine)

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G2 Phase: (MAJOR CHECK POINT PHASE OF CELL CYCLE)

- Bleomycin – an antibiotic that generates free radicals to destroy DNA. Thus, concurrent antioxidant supplementation may reduce efficacy

- Irenotecan and Topotecan – derived from the Chinese ornamental Campototheca acuminate:

  Inhibit DNA topoisomerase I, which interrupts the elongation phase of DNA replication.

  Topoisomerase enzymes normally separate the strands of DNA so they can be copied.

  Theses drugs used in treatment of certain leukemias, lung, ovarian, GI, and other cancers.

- Mitoxantrone – also a topoisomerase II inhibitor

Note: Topoisomerase II inhibitors increase risk of developing a second cancer – acute myelogenous leukemia, as early as 2-3 years after drug was given

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M Phase Or Mitotic Inhibitors (cell division stage):

Mitotic Inhibitors are often plant alkaloids and other compounds derived from **natural products.** They inhibit mitosis or inhibit enzymes from making proteins needed for cell replication. They work primarily in the M-phase, but can damage cells in all phases. They are used to treat many different cancers including – breast, lung, myelomas, lymphomas, and leukemias. They often cause **peripheral nerve damage** (alpha-lipoic acid may reduce this side effect or help repair nerve damage)

1. **Vinca Alkaloids** – derived from the **periwinkle plant** (Vinca rosea) – **block polymerization of microtubules** resulting in impaired mitotic spindles (e.g. vinblastine, vincristine, vinorelbine)

2. **Podophyllotoxins or Epopodophyllotoxins** (compounds derived from the **podophyllum peltatum** or poisonous Mayapple - inhibits DNA topoisomerase II activity, **blocking DNA synthesis (e.g. etopiside)**

3. **Taxanes** (paclitaxel or Taxol, docetaxel) – semi-synthetic compounds from the yew plants. These promote microtubular assembly and stability blocking cell cycle mitosis

4. **Epithilones (eg. Ixempra)** - Epothilones were originally identified as metabolites produced by the soil-dwelling myxobacterium *Sorangium cellulosum – work similar to taxanes*

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Periwinkle Plant (Vinca alkaloids)

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Podophyllum peltatum or poisonous Mayapple (etoposide)

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Yew Shrub (tree) – the pacific yew or western yew has been studied intensively (taxanes)

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2. Non Cell Cycle or Non Phase-Specific Drugs: These drugs often remain in the cell and wait for cell division to occur, upon which they exert their anti-cancer effects, or bind to key enzymes inhibiting their function

A. Alkylating Agents – impair cell function by forming covalent bonds with amino, carboxyl, sulfhydryl and phosphate groups in biologically important molecules – most important sites are DNA, RNA and Cellular Proteins.

These are also known as **intercalating agents**

Examples of Alkylating Agents:

- Nitrogen Mustards – bind to DNA (e.g. **cyclophosphamide)**
- Nitrosureas – lipid soluble, can enter brain (form free radicals) – (e.g. streptozocin)
- **Platinum Agents** (heavy metal complex producing inter-strand breaks of DNA with cross-linking adducts – thus inhibiting DNA synthesis **(cispatinum, carboplatinum, oxaplatinum)**
- Alkyl Sulfonates: e.g. busulfan
- Triazines: e.g. Dacarbazine
- Ethylenimines: e.g. hexamethylmelaninine

B. Anthracyclines (tumor killing antibiotics)- antitumor antibiotics that interfere with enzymes involved in DNA replication.

They work in all phases of the cell cycle and thus, are used widely in various cancers. **They can permanently damage the heart if given in high doses**. Lifetime dose limits are often placed on these drugs for this reason.

Concurrent supplementation with **Coenzyme Q10** has been shown to protect the heart muscle mitochondria in cases of **Adriamycin** use, helping to prevent heart failure – a major concern with these drugs

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Examples of Anthracyclines: (cancer killing antibiotics)

Doxorubicin

Adriamycin

Danorubicin

Epirubicin

Idarubicin

Actinomycin-D

Bleomycin – kills via free radical attack

Mitomycin-C

Mitoxantrone – an anti-tumor antibiotic that is similar to doxorubicin, including potential for heart damage. It is also a topoisomerase II inhibitor, and can lead to the development of leukemia. It is used in the treatment of prostate and breast cancer, and in lymphoma and leukemia

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3. Targeted Agents:

A. Monoclonal Antibodies – antibodies that target specific protein antigens (receptors, signal transduction enzymes or proteins) that are dysregulated in a cancer cell, thereby destroying the protein and inhibiting its mitotic-driving effects.

Examples:

Rituxan – targets CD20 antigen found on B-cell lymphocytes in non-Hodgkins lymphoma

Herceptin – targets HER-2 in up to 40% of breast cancer patients

Campath – targets CD52 antigen in B-cell and T-cell lymphocytes in chronic lymphocytic leukemia

Avastin and Related MAB's – destroys receptors on blood vessels to prevent stimulation from VEGF, thus preventing new blood vessel growth into tumor

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B. Small Molecules – these inhibit some key pathways that drive cancer cell division **(particularly tyrosine kinase inhibitors):**

Examples:

Imatinib (Gleevec) – binds to ATP binding site **inhibiting tyrosine kinase** from phosphorylating its substrates

Gemfitinib – inhibits **EGFR-tyrosine kinase** signal transduction

Erlotinib – blocks **HER-1- tyrosine kinase** signal transduction in NSC Lung Cancer

Sunitinib – **tyrosine inhibitor** associated with EGFR and VEGFR

Sorafenib – another **tyrosine inhibitor** similar function to Sunitinib

Velcade – a proteoasome inhibitor used in multiple myeloma that **ultimately blocks NF-Kappa beta a**nd its effects on cell division

Torisel – **blocks mTOR protein** involved in proliferation and angiogenesis

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C. Endocrine Therapy:

- Tamoxifen and Raloxifene – selective estrogen receptor modulators (SERMs) that compete with estrogen for binding to estrogen receptors – **slowing cellular proliferation**

- Aromatase Inhibitors – block aromatase enzyme (estrogen synthase) in fat cells, stromal cells, breast cancer cells, that converts androstenedione into estrone.

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Chemotherapy Hematological Side Effects:

- Myelosuppression - significant decrease in neutrophils, erythrocytes, and megakaryocytes within bone marrow.

- **Platelets and WBC are first to decrease**, followed by anemia later. Anemia requires supplementation with folate, B12 and iron (Neutropenia big concern)

Other Hematological Effects:

- Poor dietary intake of iron (appetite suppression)
- B12 and folate deficiencies
- RBC lysis
- Microangiopathic bleeding
- Depletion of erythropoietin due to nephrotoxicity

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Drug-Resistance To Chemotherapy Agents – occurs when cancer cell up-regulates production of certain enzymes and efflux pumps:

Examples:

- **Increased glutathione conjugation** – do not supplement with glutathione in these cases

- **Increased MDR-1 glycoprotein pump** (calcium channel blockers may be helpful to inhibit pump)

- **Increased MDR-associated protein** known as MRP and Breast Cancer-Resistant Protein efflux pumps

(We will see these again later in the Drug-Nutrient Interaction Section That Follows)

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Part 5

Drug-Nutrient and Gene-Nutrient Interactions

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Drug-Nutrient Interactions:

Before Recommending Any Supplements Must Consider

General Considerations: For All Patients (cancer and non-cancer patients):

Should always be screening for these, including patient self-medication practices

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Six Biggest Concerns with Drug-Nutrient Interactions:

1. Bleeding Disorders
2. Brain Chemistry Imbalances (serotonin and cholinergic syndromes)
3. Adverse Cardiovascular Effects: Heart muscle (myocardial) dysfunction and Hypertension
4. Internal Organ Damage and/or toxicity (Liver and Kidneys) and Related Effects
5. Adverse Immune Effects
6. Glucose Intolerance

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1. Bleeding Disorders

A number of herbal and vitamin supplements, when ingested at or above specific dosages, are known to have anti-coagulant effects.

In certain instances, these products taken alone, or in combination with other anti-coagulant drugs have resulted in bleeding disorders

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A. Ginkgo Biloba Extract

Ginkgo biloba extract contains active ingredients known to decrease platelet aggregation.

Case 1: ASA plus Gingko (40 mg twice per day resulted in bleeding into the iris after one week)

Case 2: Warfarin plus Ginkgo (no dosage reported)

Case 3: Ginkgo alone (Bilateral subdural hematoma) – 60 mg twice daily

Case 4: Ginkgo alone – (subdural hematoma) – 50 mg, three times daily

- These bleeding episodes stopped in all cases reported above after Ginkgo was discontinued.

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B. Garlic

Garlic contains disulfide compounds (e.g. ajoene) that:

1. Decrease platelet aggregation
2. Increase fibrinolytic activity

Case 1 - Elderly man ingesting 2,000 mg of garlic (4 cloves) daily for an undetermined period of time, developed a spontaneous epidural hematoma (the patient denied use of any anti-clotting medication or anti-inflammatory).

Case 2 - A patient taking garlic prior to cosmetic surgery experienced bleeding complications and had a clotting time of 12.5 minutes. After cessation of garlic consumption, her clotting time dropped to 6 minutes and there were no complications during a second procedure.

As such, S. Mills and K Bone suggest that garlic intake and garlic supplementation should be discontinued 10 days prior to surgery. This also applies to Vitamin E (or any vitamin E containing supplements, as well as other anti-coagulant natural substances)

- N.B. Equivalent of one clove of garlic reduces platelet aggregation to the same degree as one aspirin (Ajoene content appears to be most responsible for anti-coagulant properties of garlic.

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Don’t recommend Garlic if patient taking:

1. NSAIDs
2. Plavix
3. Coumadin
4. Warfarin
5. Any other anti-coagulant medication

C. Ginseng

- One case report of ginseng altering prothrombin time (INR).

- Ginseng antagonizes the effects of warfarin, **decreasing prothrombin time,** which returns to normal with discontinued use of ginseng.

D. Angelica Species (Dong Quai, e.g.,)

Case - A 46-year-old woman taking warfarin experienced increased strength of the anticoagulant properties of the drug after starting to use dong quai for menopause. Her bleeding tendency returned to normal after discontinuing the dong quai.

- Dong quai contains at least six coumarin derivatives, which decrease platelet clotting function and increase risk of photosensitivity-induced dermatitis

Other Coumarin-containing herbs Used by Women:

1. Licorice – may also increase blood pressure due to presence of glycyheritinic acid

2. Red Clover – may also increase photosensitivity-induced dermatitis and bleeding disorders.

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E. Coenzyme Q10 Supplementation

Cases - 4 case reports where CQ10 supplementation has interfered (countered) with the ant-coagulant effects of warfarin on prothrombin time (increases clotting)

- Coenzyme Q10 molecule resembles vitamin K and thus, may have procoagulant tendencies as a result

- Taking CoQ10 with anticoagulant requires monitoring of INR

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F. Cranberry

Cases - at least five case reports suggesting that cranberry juice increases the activity of warfarin, possibly by inhibiting the breakdown of warfarin in the body.

Because of this potential interaction, people taking warfarin should avoid, or limit the intake of, cranberry juice.

Women taking cranberry extract supplements to prevent urinary tract infections require INR monitoring if taking an anticoagulant drug

G. Devil's Claw

Case - was associated with purpura (bleeding under the skin) in a patient treated with warfarin.

People taking warfarin should avoid taking devil's claw. The harpogoside content may potentiate the effect of warfarin

Devil's claw has also re-activated old peptic ulcers.

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H. St John's Wort (Hypericum perforatum) – may upregulate detoxification enzymes

- According to a preliminary report, volunteers taking 900 mg per day of St. John's wort were given a single dose of an anticoagulant similar in action to warfarin. There was a significant drop in the amount of the drug measured in the blood.

- Seven case studies reported to the Medical Products Agency in Sweden also found a decrease in the anticoagulant activity of warfarin when St. John's wort was taken at the same time. This may have occurred because constituents in St. John's wort activate liver enzymes that are involved in the elimination of some drugs.

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Other Popular Natural Health Products – potentially affecting prothrombin time (no human cases yet reported)

1. Ginger – gingerols exhibit anti-platelet clotting properties
2. Feverfew – parthenolide exhibits anti-clotting properties
3. White Willow Bark Extract – contains salicylic acid. At low concentration (15% std grade) studies do not demonstrate an anti-platelet clotting tendency
4. Turmeric – curcumin affects prostaglandin synthesis
5. Essential oils (Borage, Flaxseed, Fish oil) – Omega-3 fats decrease platelet clotting behavior via effects PG-3
6. Vitamin E - Safe up to 400 I.U. per day in conjunction with warfarin or aspirin. Testing at 800 I.U. and 1,200 I.U. per day yield equivocal results on safety with respect to altering the INR
7. Bromelain enzymes – may decrease platelet clotting tendency and increases fibrinolysis
8. Papain enzymes – these proteolytic enzymes may also potentiate the effect of warfarin]
9. Saw Palmetto

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2. Brain Chemistry Effects

A. **Ginseng** and MAOI Anti-depressants – reports of mania behavior (headache, euphoria, CNS stimulation and tremors)

B. **Valerian Root** – excessive sedation if taken concurrently with barbiturates or anti-histamines.

Valerian should be avoided by patients taking benzodiazepines, barbiturates, opiates, anti-histamines and alcohol, as their effects may be prolonged and/or amplified.

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C. Mild Serotonin Syndrome

St. John's Wort, and possibly 5-Hydroxytryptophan can increase brain levels of serotonin and thereby potentiate the effects of:

- Serotonin reuptake inhibitors (SRRI) (e.g. Prozac)
- Monoamine oxidase inhibitors (MA0)
- Tricyclic Antidepressants (TAD)

Although 5-HTP can be used if proper monitoring is in place. It may enhance drug effect and patient outcomes.

In this instance there is an increased risk of serotonin syndrome, which involves the following signs and symptoms:

1. Muscle rigidity
2. Hyperthermia
3. Autonomic instability
4. Mental confusion
5. Myoclonus
6. Delerium
7. Coma

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D. **Coma From Kava**

Kava plus alprazolam (benzodiazepine) has induced coma.

It is imperative not to recommend Kava or Valerian supplements in combination with any drugs that induce a sedative or anti-anxiolytic effect.

E. **Seizures and Ma Huang (ephedra)**

- Ma Huang (ephedra) can induce seizures in otherwise normal individuals

- It should not be used by epileptics.

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F. **California Poppy and Opioid Drugs**

As the alkaloids from California poppy also bind to opioid and serotonin receptors, this drug-nutrient combination may potentiate effects of opioids and cause coma or depressed respiration, with life-threatening consequences.

California poppy can be used as night-time medication in place of opioid dose to help with sleep in patients with night-time pain induced insomnia

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3. Heart Muscle Dysfunction

A. Digitalis/Digoxin Toxicity

- **Hawthorn and Ginseng** are known to potentiate the action of other cardioglycoside medications, such as digitalis/digoxin (elevates serum digoxin levels)- very dangerous situation.

- Ginseng slows drug detoxification in liver

- Hawthorn increases cyclic AMP, increasing force of contraction of the heart (as does digitalis via increased intracellular calcium)

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B. Hypertension and Licorice

- Licorice root alone or in combination with tricyclic antidepressants can elevate blood pressure.

- Licorice root also affects renin-angiotensin-aldosterone system and has produced hypokalemia leading to heart arrhythmias and as well as hypertension. This effect is caused by glycyrrhizin or glycyhrrhitinic acid.

- DGL chewable tablets contain deglycyrrhizinated licorice, which does not affect heart or blood pressure, as it heal ulcers

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Side Note - Most of the Licorice candy available in North America is flavored with anise oil, not Licorice.

- Authentic Licorice candy contains between 0.26 mg/g and 7.9 mg/g of glycyrrhizin; while medicinal Licorice products range from 0.30 mg/g to 47.1 mg/g of glycyrrhizin.

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C. Heart Attack and Sudden Death From Ephedra:

- **Ma Huang** (ephedra) has caused sudden death from heart attack, tachycardia, stroke and myocardial arrhythmias when taken alone

N.B.: The most commonly reported herbal product to produce adverse reactions with more than 17% of all adverse reactions reported dealing with side effects from Ma Huang (over 800 reports)

- As a result the FDA proposed limits on the use of ephedrine-containing products: a maximum of 8 mg/dose and 24 mg/day for no more than a week, and combined with no products that contain caffeine.

- The Drug Enforcement Agency proposed that products containing over 2% ephedrine be subject to the Controlled Substances Act. Individuals with cardiovascular or thyroid disease and diabetes should avoid these products altogether, as should those consuming caffeine, theophylline, cardiac glycosides, and monoamine oxidase (MAO) inhibitors

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D. **Glucosamine and Hypertension**

In rare instances glucosamine supplementation has increased blood pressure marginally. In patients with a blood pressure above 130/80 or those on anti-hypertensive drugs, blood pressure should be monitored during the first few week of glucosamine supplementation.

The mechanism of action has not be elucidated, but the presence of sulfate is not responsible in glucosamine sulfate. Glucosamine sulfate does not contain sodium contrary to myths promoted by certain supplement companies.

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4. Internal Organ Damage and Related Effects

A. St. John's Wort

- Can reduce action of concurrent medications because it accelerates liver detoxification centers (i.e., digoxin, theophylline, cyclosporine, phenprocouman (longer acting coumarin type drug)

- Increases risk of photosensitivity-induced dermatitis.

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B. Kava Kava

- Long-term use can produce abnormal liver function tests, yellow scaly rash and increased cholesterol.

- A total of 11 patients who used kava products had liver failure and underwent subsequent liver transplantation . On March 25, 2002, in response to five such case reports (four in Europe and one in the United States), the Food and Drug Administration (FDA) issued a consumer advisory and subsequently completed an investigation already underway of a similar U.S. case.

- This report presents the investigation of the two U.S. cases of liver failure associated with kava-containing dietary supplement products and summarizes the European cases.

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C. Radioactive Iodine Therapy and Kelp – human cases have shown that patients receiving radioactive iodine to treat thyroid cancer (or Grave's Disease) should not take Kelp or any form of iodine supplementation (and prescribed a low iodine diet).

- Iodine from supplements (like Kelp) can compete with radioactive iodine for uptake by thyroid cells (and thyroid cancer cells), decreasing the effectiveness of the treatment.

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D. **Vitamin A and Accutane**

Any supplement dosage of Vitamin A above 2500 IU per day should be discouraged in patient taking Accutane for acne treatment. Vitamin A can increase risk of side effects:

Liver Damage – rising liver enzymes

High Lipids

Headaches etc.

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5. Adverse Immune Effects

Echinacea

Can exacerbate autoimmune conditions through overstimulation of the immune system (possibly Ginseng and Astragalus as well)

6. Glucose Intolerance

Glucosamine Sulfate

- Experimental studies and a few human reports suggest that there is a potential for Glucosamine supplementation to increase insulin resistance in a diabetic or pre-diabetic patient.
- As such, diabetic (both type 1 and 2) and prediabetic patients should have their blood glucose monitored during the first month of glucosamine supplementation.

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Other Consideration:

1. Zinc Toxicity in Macular Degeneration Rx and Treatment of Colds and Sore Throat:

- Some supplements used therapeutically to help manage macular degeneration, contain high doses of zinc. You must be careful not to cause zinc toxicity by providing additional zinc from a multiple vitamin (or other vitamins or functional drinks or bars) that together result in total zinc supplementation at or above 60 mg/d, which is threshold level at which some people show signs of zinc toxicity. Many supplements used to treat macular degeneration contain 40 – 70 mg of zinc in the daily dosage.

- Zinc toxicity can occur in both acute and chronic forms. Acute adverse effects of high zinc intake include nausea, vomiting, loss of appetite, abdominal cramps, diarrhea, and headaches. One case report cited severe nausea and vomiting within 30 minutes of ingesting 4 g of zinc gluconate (570 mg elemental zinc) e.g. treat sore throat.

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- Intakes of 150–450 mg of zinc per day associated with such chronic effects as low copper status, altered iron function, reduced immune function, and reduced levels of high-density lipoproteins.

- Reductions in a copper-containing enzyme, a marker of copper status, have been reported with even moderately high zinc intakes of approximately 60 mg/day for up to 10 weeks.

- Zinc dosage used in the AREDS study (80 mg per day of zinc in the form of zinc oxide for 6.3 years, on average) has been associated with a significant increase in **hospitalizations for genitourinary causes**, raising the possibility that chronically high intakes of zinc adversely affect some aspects of urinary physiology.

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FDA (U.S.A.): Special Nutritionals Adverse Event Monitoring System

(searchable database of MedWatch: http://vm.cfsan.fda.gov/`dms/aems)

Of the limited number of dietary supplement adverse event reports to the FDA in 1998:

- 7% involved St. John's Wort
- 8% involved Ginkgo Biloba
- ≥17% involved ephedra-containing products; 800 reports of adverse effects:
  - Nervousness
  - Insomnia
  - Irritability
  - Psychosis
  - Headache
  - Dizziness
  - Seizures
  - Stroke
  - Premature ventricular contractions
  - Increased Blood Pressure
  - Myocardial Infarction (heart attack)
  - Death

Final Considerations: Herbal products should be discontinued 2 weeks before elective surgery, and their use reported to the anesthesiologist before any surgical procedure because of the potential for unexpected effects

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Patient Contra-indications and Precautions Questionnaire (General)

- Have you ever had an allergic reaction to a vitamin supplement in the past?
- Do you suffer from sickle cell anemia? (Vitamin C) – although this is now changing (See Kyolic Review)
- Do you suffer from a hemolytic anemia due to glucose-6 phosphate dehydrogenase deficiency? (Vitamin C)
- Do you suffer from kidney failure or are you currently receiving dialysis treatment? (All supplements and dietary recommendations require physician approval)
- Have you ever had a kidney stone? (Keep Vitamin C supplementation at or below 750 mg per day)
- Do you have Wilson's disease? (Copper)
- Do you have hemochromatosis? (Iron)
- Have you received an organ transplant of any kind? (All supplements and dietary recommendations require physician approval, especially immune boosting agents)

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- Are you taking an immuno-suppressive drug (i.e., Azathioprine, Cyclosporine, Methotrexate) (Any immune-boosting supplement may counter drug effects)

- Have you ever been diagnosed with Crohn's Disease or Ulcerative Colitis? (All supplements and dietary recommendations require physician approval)

- Are you an insulin-dependent diabetic? (Chromium can alter insulin need)

- Do you have only one functioning kidney (due to one kidney being removed or one kidney known to be non-functional)? (All supplements and dietary recommendations require physician approval)

- Are you taking the drug digitalis or digoxin? (Hawthorn is contra-indicated)

- Do you have an active ulcer? (white willow extract, garlic supplements are contra-indicated)

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- Are you under 12 years of age? (white willow extract)

- Are you taking a blood thinner drug (i.e., Coumadin, Warfarin, Clopidogrel (Plavix®), Heparin, etc.) and/or a non-steroidal anti-inflammatory drug (aspirin, ibuprofen)?

  (many anti-inflammatory herbs, garlic, ginkgo biloba, red clover, licorice root, omega-3 fats, Vitamin E above 400 IU per day, can increase anti-coagulant effect – requires INR monitoring)

- Do you have a pacemaker? (CoQ10 and Hawthorn require physician approval)

- Are you taking drugs to correct a heart arrhythmia problem? (CoQ10 and Hawthorn require physician approval)

- Are you taking any medications for Alzheimer's or dementia? (all mood altering supplements are contra-indicated, such as St John's Work, 5-hydroxytryptophan)

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- Are you allergic to aspirin? (white willow extract)

- Do you suffer from hemophilia? (any supplement that decreases blood coagulation such as many anti-inflammatory herbs, garlic, ginkgo biloba, red clover, licorice root, omega-3 fats, Vitamin E above 400 IU per day)

- Are you presently experiencing a flare up of gout (gouty arthritis)? (High doses of niacin above 50 mg)

- Do you have advanced liver disease? (All supplements and dietary recommendations require physician approval)

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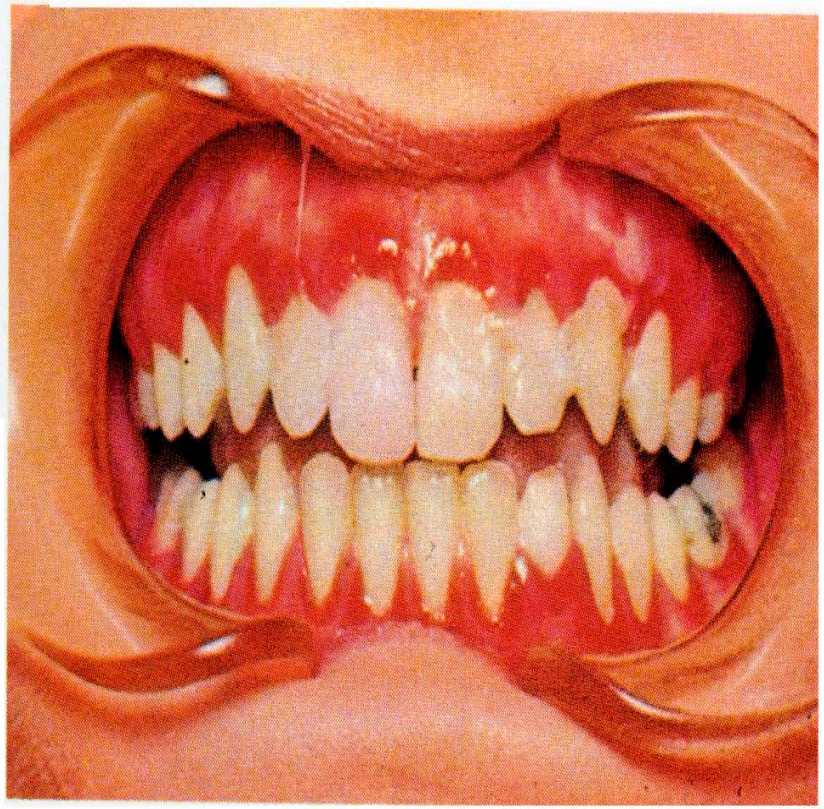
- Do you suffer from hyperparathyroidism or sarcoidosis? (Vitamin D)
- Are you taking a drug a called Methotrexate? (Folic acid above 400 mcg)
- Are you presently taking any chemotherapy drugs or undergoing radiation therapy for the treatment of cancer? (All supplements and dietary recommendations require physician approval)
- Are you currently taking any drugs for depression or to treat a psychological disorder of any kind (e.g., bipolar disease, schizophrenia, obsessive compulsive disorder, etc.)? (any mood altering supplement is contra-indicated such as St John's Wort, 5-hydroxy tryptophan)
- Are you taking the drug, Accutane (usually for acne)? (Vitamin A above 2500 IU) – See Next Slide
- Are you Pregnant? (only prenatal vitamin, plus essential fatty acids)
- Are you Breast Feeding? ((only prenatal vitamin, plus essential fatty acids)
- Are you a woman who has had a history of breast or ovarian cancer? (do not recommend any phytoestrogen supplements without consent of physician)

Vitamin A toxicity

74 Hypervitaminosis A. Acute toxicity causes nausea, vomiting and headache due to raised intracranial pressure (pseudotumour cerebri) and peeling of the skin. Chronic poisoning results in loss of weight, low-grade fever, tenderness over the long bones and skull changes (see below) and a pruritic rash. Bright red marginal discolouration of the gingiva as shown here is characteristic.

74



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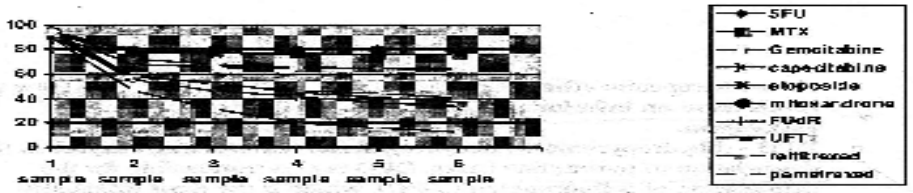
Genetic Testing Of Circulating Tumor Cells Or Tumor Sections Provides Clues To Gene-Nutrient Interactions



NAME	RELATED	RESULTS
CES1 &2 (carboxyesterase)	Resist to camptothecin	Normal
E2F1	Transcr. Fact of TS & topol	Normal
p180	Tymsin kinase growth f.	50% over control
p27	Cell arrest (G_0)	45% over control
DPD	Resist to 5FU	Normal
UP	Resist to 5FU	Normal
NP	Resist to pyrim. antagonist	Normal
TP	Resist to 5FU	Normal
Gamma GC	Resist to alkyliacing drug	Normal
p53	Cell cycle regulator	55% over control
p16	Apoptosis	70% over control
VEGF	Angiogenesis	80% over control
FGF	Angiogenesis	75% over control
PDGF	Angiogenesis	60% over control
COX2	Tumour Growth	Normal
5-LOX	Tumour Growth	Normal
MMP	Metastases	40% over control
TS	Rapid cell cycle (THFA)	Normal
DHFR	Rapid cell cycle (THFA)	Normal
SHMT	Rapid cell cycle (THFA)	Normal
GARFT	Rapid cell cycle(THFA)	Normal
NFκB	Transcription fact	30% over control
IκB (a,d,e)	Inhibitor of NFκB	25% below control
Ribonucleoside reductase	DNA synthesis	Normal
DNA methyltransferase I	DNA methylation	Normal
DNA demethylase	DNA methylation	Normal
O6-methylguanin-DNA-tran.	DNA methylation	Normal
TGF-b	Tumour Growth	20% over control
EGF	Tumour Growth	65% over control
IGF	Tumour Growth	Normal
CypB1	Xenobiotic metaholism	Normal
Histone deacylase -dispeptide	DNA coiling(nucleosome)	Normal
c-erb-B2	Her/neu2	Normal
c-erb-B1	Her1	Normal
Ber-abl	Resist phenotype	Normal
h-TERT (Human telomerase)	M2 crisis-aggresive phen.	25% over control

From the investigation above we concluded to the following :

1. From the whole neoplasmic population we have an expression of MDR1 in a percentage of 65% over control sample ,(positive in the check of resistance)
2. The activity of GST is stable in the low limits (no resistance to platinum compounds)

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Additional Adverse Drug-Nutrient and Gene-Nutrient Interactions In Cancer Patients

1. **Over Expression Of Gamma GC:** Gamma GC (gamma-L-glutamyl-cysteine synthase or gamma-GCS) increases production of glutathione (rate limiting step enzyme) to protect cancer cells from free radicals induced by alkylating agents.

   Thus, concurrent supplementation with glutathione precursors (Alpha-lipoic acid, N-acetyl cysteine, L-glutamine, Silymarin) may be contra-indicated.

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2. Hypercalcemia of Malignancy– Must be careful with Vitamin A and Vitamin D supplementation, although 25 hydroxycholecalciferol is often on the low side in patients in patients with hypercalcemia of malignancy

- Hypercalcemia commonly occurs from release of Parathyroid Hormone-related Protein (PTH-rP) by tumor cells, which further increases blood calcium levels due to bone resorption of calcium.

- Hypercalcemia can lead to decreased glomerular filtration rate, with excess water and sodium loss and dehydration

- Occurs in 8-10% of cancer patients

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3. Supplementation Concerns Prior To Surgery – refrain from all supplements, especially ones known to increase risk of bleeding:

Garlic, Ginkgo, Ginseng, Cranberry, Omega-3 fats, vitamin E above 400 IU per day, Angelica Species (don quai), red clover, licorice, curcumin, ginger, white willow extract, devil's claw etc.

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4. **Antioxidants and Radiation Treatment** – some concern that antioxidants may counter effect of radiation free radical damage to cancer cells.

5. **Antioxidants and Bleomycin** – antioxidants potentially quench free radicals induced by bleomycin to destroy cancer cells

6. **Methotrexate and Folic Acid** – methylfolate may be better option

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Synergistic Drug-Nutrient and/or Gene-Nutrient Interactions

1. **Over Expression Of MDR-1:**

Curcumin counters effects of Multi-drug Resistant (MDR-1) over expression (membrane-bound P-glycoprotein ATP-pump), which otherwise pumps organic compounds out of the cell (e.g. chemo drugs).

Curcumin and Quercetin inhibit the pump, thereby potentiating the chemo effect.

Haelen 951 (nutritional supplement derived from fermented soybeans) inhibits this pump as well.

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3. Antioxidants and Chemotherapy

Reference:

Impact of antioxidant supplementation on chemotherapeutic efficacy: A systematic review of the evidence from randomized controlled trials
Cancer Treatment Reviews. 2007. *Volume 33, Issue 5, Pages 407-418*
K. Block, A. Koch, M. Mead, P. Tothy, R. Newman, C. Gyllenhaal

Results

- Of 845 articles considered, 19 trials met the inclusion criteria. Antioxidants evaluated were: glutathione (7), melatonin (4), vitamin A (2), an antioxidant mixture (2), vitamin C (1), N-acetylcysteine (1), vitamin E (1) and ellagic acid (1). Subjects of most studies had advanced or relapsed disease

Conclusion

- None of the trials reported evidence of significant decreases in efficacy from antioxidant supplementation during chemotherapy. Many of the studies indicated that antioxidant supplementation resulted in either increased survival times, increased tumor responses, or both, as well as fewer toxicities than controls; however, lack of adequate statistical power was a consistent limitation. Large, well-designed studies of antioxidant supplementation concurrent with chemotherapy are warranted.

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4. Over Expression of VEGF – natural agents help block VEGF secretion:

- Curcumin
- Chinese scullcap
- Vitamin E Succinate
- Genistein from Soy
- Green Tea Catechins

Others: Milk Thistle
Quercetin
Indole-3 carbinol
Artemisinin (Chinese Worm Wood)
Squalamine steroid from dogfish shark

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5. Over Expression of COX-2 Enzyme – many natural agents help to suppress this enzyme:

- Omega-3 fats and GLA
- White Willow Extract
- Curcumin
- Ginger
- High Dose Antioxidants (vitamin E, Selenium, Vitamin C, Beta-carotene)

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6. Over Expression Of 5-LOX – some natural agents suppress this enzyme:

- Chinese scullcap (and 12 LOX)
- Boswellia
- Curcumin
- Ginger
- Omega-3 fats and GLA

7. Over Expression Of MMP (matrix metalloproteinases) – some natural agents can inhibit enzyme or increase mortar between bricks:

- Curcumin – inhibits MMP

- Glucosamine – shown to increase glycosaminoglycan and proteoglycan density between cells (McCarty. Medical Hypothesis)

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8 Over Expression Of NF-KB – several natural agents shown to suppress NF-KB:

Very few drugs or chemo agents inhibit NF-kb, but many natural agents show this potential effect. Over expression of NF-kb is commonly seen in genetic testing of tumor cells

The next slide lists natural agents inhibiting NF-kb

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Natural Agents Inhibiting NF-kb

Curcumin (plus LOX, COX, Her-2 inhibition)
Ginger
Reishi mushroom extract
Quercetin
Antioxidants (Vitamin C, Vitamin E)
Anthocyanidins (berrries)
EPA and DHA
N-acetyl cysteine (NAC)
Isoflavones
Pomegranate
Baicalein
Parthenolide
Artemisinin

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9. Over Expression Of EGFR (HER-2) – several natural agents shown to down-regulate HER-2 receptor (and tyrosine kinase – Akt and Ras signaling):

- Curcumin
- Vitamin E Succinate
- Vitamin D
- Ground Flaxseed
- Milk Thistle (silymarin)
- Quercetin
- Chinese Wormwood (Artemisinin)
- Squalamine steroid from dogfish shark- **see next slide**
- Rhubarb and Buckthorn – Emodin
- EPA (omega-3 fat)

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Squalamine and HER-2

- Overexpression of *HER2* is normally associated with resistance to cisplatin and promotion of tumor angiogenesis.

- In a phase II trial of patients with advanced small-cell lung cancer, squalamine was administered at a dose of 300 mg/m2 by continuous infusion for 5 days, with paclitaxel and carboplatin given on day 1.

- Patient survival data and a satisfactory safety profile indicated that the combination should be explored further.

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10. Over Expression of IGF-1 – some natural agents can tone down IGF-1 receptor of decrease its stimulation:

- Lycopene
- Low Glycemic Diet
- Reduce body fat if over weight

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Part 6

Evidence-based Integrative Cancer Therapies Other Than Diet and Supplementation

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Insulin Potentiation Therapy

Insulin Potentiation Therapy:

Most cancer cells require glucose, from which they produce ATP energy using primarily glycolytic pathways, building up pyruvic acid and lactic acid.

Cancer cells have few mitochondria, and thus do not rely on aerobic metabolism

Cancer cells pump acids out to extracellular space using various efflux pumps (creating acid environment, which they seem to like)

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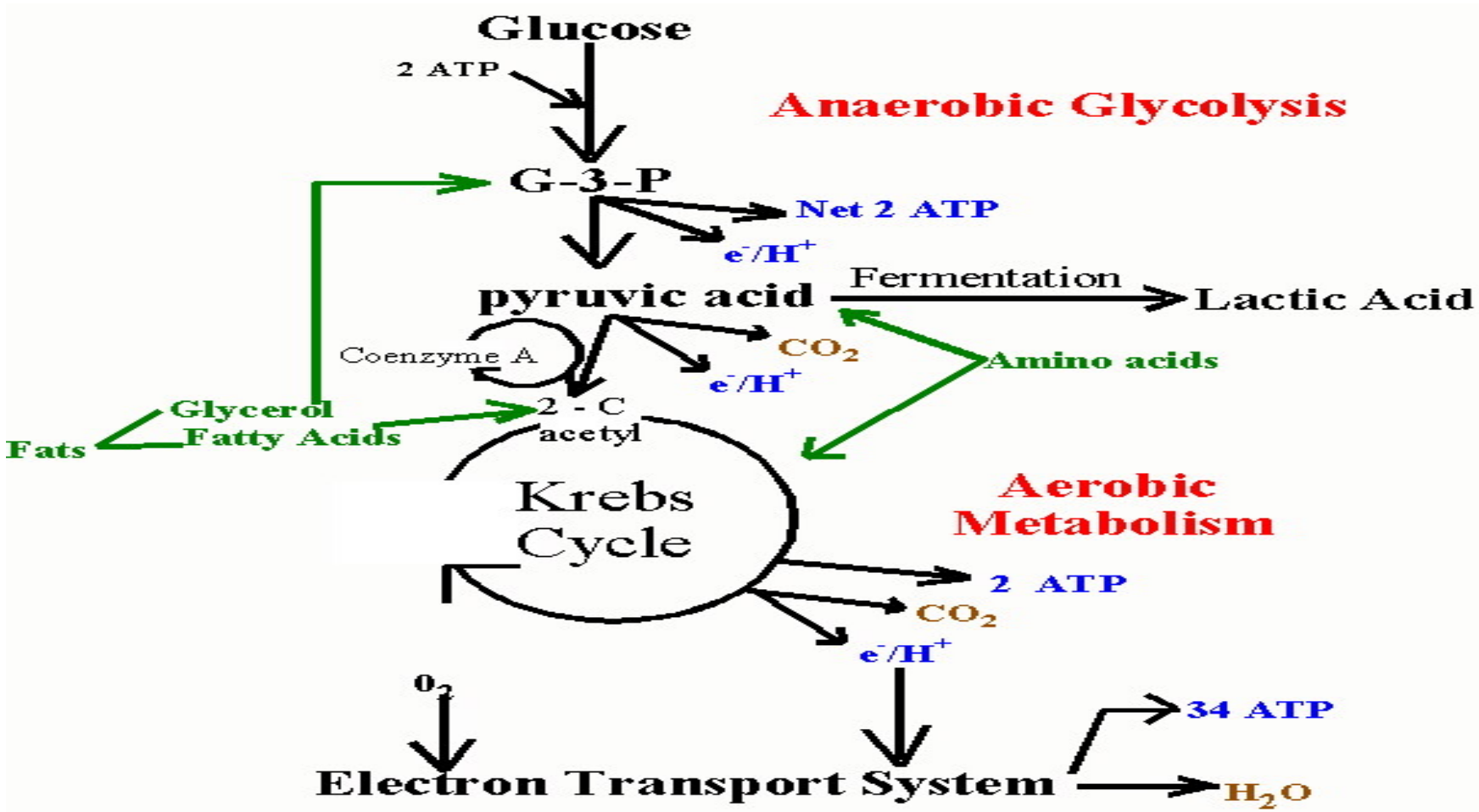
Glycolysis and Aerobic Metabolism



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- Cancer cells have 6-17 times more insulin receptors than do normal cells. Normal cells have 100 – 100,000 insulin receptors

- Cancer cells also over express IGF-1 receptors, which increases cancer cells activity into S- phase (DNA replications)

- **Cancer cells in S- phase are most susceptible to chemodrug death.**

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- Insulin provided to cancer cells increases the killing capacity of chemodrugs. Cancer cells more rapidly pick up chemodrugs when stimulated by insulin.

- **Insulin increases number of cancer cells in S-phase** (insulin increases cell division via insulin and IGF-1 receptors), which make them more susceptible to chemodrug killing effect (example **66%** in S-phase post insulin administration, compared to **37%** in S-phase, in breast cancer cell studies)

- This is one way that insulin potentiation therapy selectively increases killing of cancer cell with chemo, enabling use of only 10% of usual dose of chemo drug.

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IPT Protocol:

- Overnight fast to produce low blood sugar state (cancer cells desperate for glucose and over express insulin receptors)
- Patient injected with bolus of insulin (based on body wt) upon arrival in clinic in morning
- Once blood sugar drops very low, the patient is given low dose chemotherapy (90% lower dose than prescribed dose), which is often based on the results from chemosensitivity testing of tumor or circulating tumor cells (usually combination chemotherapy approach)

- Chemodrugs are often combined with glucose mimickers (glutathione, vitamin C) and glucose receptor sensitizing agents (alpha-lipoic acid) to enhance the rate at which cancer cells extract chemotherapy drugs from circulation.

- Hyaluronic acid also increases uptake of chemodrugs by cancer cells.

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- Insulin also increases uptake of chemo drugs by cancer cells

- Insulin also increases uptake of vitamin C by cancer cells, where it creates free radicals leading to greater cancer cell death (cancer cells are deficient in catalase and peroxidase antioxidant enzymes)

- IPT with low dose chemo (90% less) helps spare healthy cells, lowering toxicity to patient, targeting cancer cells and keeping the immune cells in the fight.

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Common Integrative Medical Protocol Used With IPT

Immune Modulation Stage - During first week to 10 days the patient receives IV of immune stimulating agents and cancer sensitizing agents (mistletoe, vitamin C-25 gm, homeopathic agents, vitamin & minerals, hyaluronic acid). They also receive the flu vaccine on several occasions to charge up immune response.

Chemo Sensitivity Panel - During this period the clinic is awaiting the results of the chemosensitivity panel, the genomic testing panel and the immune panel.

Once these results are available, then the IPT with targeted chemotherapy and other appropriate agents is initiated. The IPT is administered twice per week.

Off- Day Vitamin C IV - On the off-days the patient sometimes receives Vitamin C (75 gm with K3), and/or hydrogen peroxide, and/or sodium bicarbonate

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- High Dose Vitamin C – acts as a pro-oxidant in cancer cells. Cancer cells have deficiency in catalase and peroxidases to protect themselves from hydroxy radicals initiated from vitamin C's interaction with metals (iron, copper) and oxygen. These cells rapidly build up H00H (hydrogen peroxide) with Vitamin C uptake.

- Vitamin C looks like glucose, and thus is picked up rapidly by cancer cells, forming free radicals that destroy the cancer cell and/or induce apoptosis

- High Dose Vitamin C also boosts interferon production, up-regulating immune function

- High Dose Vitamin C shown to enhance efficacy of chemotherapy drugs (e.g. Taxol, carboplatin)

- Alpha Lipoic Acid enhances Vitamin C cancer killing effect via unknown mechanism, but may enhance Vitamin C uptake (as insulin sensitizer) and recycles Vitamin C from Dihydroascorbate back to Ascorbic acid, so it can continue to interact to form free radicals (Stoyanovski D/1995)

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Contra-indications for Vitamin C Therapy:

1. Hemochromatosis
2. Glucose-6 phosphate dehydrogenase deficiency (leading to hemolytic anemia)

References For High Dose Vitamin C In Cancer Treatment

- Gonzalez,Miranda/2002
- Riordan HD/2004
- Riordan/2005
- Chen Q/2005
- Padayaty JS/2006 CMAJ
- Pathak/2002
- Murata/1982

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Hydrogen Peroxide IV– evidence suggests that it produces free radicals within cancer cells (killing them) and also in microbes that may have injected their RNA or DNA into cells to produce cancer cells.

Thus, hydrogen peroxide IV can kill many microbes linked to cancer and chronic infections

Sodium Bicarbonate – an IV of sodium bicarbonate has also been reported to kill many microbes related to cancer and infection, and also elevates pH of cancer tissue, which suppresses their ability to thrive

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Off-Label Use Of Products In Cancer Treatment:

1. Thalidomide – inhibits NF-kappa beta, VEGF and fibroblast growth factors (anti-angiogenic).

It also provides immune enhancing and anti-inflammatory effects.

It is highly teratogenic (flipper children) and should not be taken by pregnant women (Dosage: 200 mg at bedtime at least one hour after a meal)

2. Calcium Channel Blockers – used when MDR-1 pump is over expressed. Calcium channel blockers can inhibit efflux pumps to some degree. Thus, blocks ability of cancer cells to pump chemo drugs and acid by-products of metabolism out of cell (e.g. nifidepine)

3. Cimetidine – stimulates immune function, blocks histamine receptors on cancer cells (inhibiting growth) and blocks cancer cell adhesion similar to modified pectin fiber.

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4. Cesium Chloride – this molecule reported to inhibit the uptake of glucose by cancer cells. CC accumulates in cancer cells via potassium-sodium pump mechanism, and is unable to be pumped out.

Once inside cancer cells it raises pH level to approximately 8.0, which produces cancer cell death.

Dosage: 1-6 gms per day (usually 3 gm/d). Must be taken with food. Cesium competes with potassium for uptake into cells, thus potassium replacement therapy is required under physician supervision and monitoring

Best to administer cesium chloride via IV, which is most efficient delivery system

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5. **Poly-MVA** – this is an alpha-lipoic/palladium complex. Within cancer cells it promotes rapid ion flux along mitochondria electron transport system, resulting formation of free radicals (superoxide anion, hydrogen peroxide and hydroxy radicals), as cancer cells cannot deal with overstimulation of oxidative system. Free radical end-products promote apoptosis

6. **Tramadol** – pain killer that also stimulates NK cells and shown to inhibit metastasis in lung cancer. Binds to opioid receptors to reduce cancer pain (dose – 50-100 mg per 24 hours)

7. **Selective COX-2 Inhibitors** (eg. celecoxib) – these are most appropriate when cells over express COX-2 enzymes. Giving patient IV of indomethacin is also used

8. **5- LOX Inhibitors** (zileuton asthma drug) – most appropriate when cells over express 5-LOX enzyme

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9. Valproic Acid and Hydralazine – helps to restore P16 expression. P16 controls cell cycle proliferation during G1 phase by inhibiting the ability of cyclin D/CDK-pRb pathway, which is dysregulated in many cancers and indicates poor prognosis. P16 has inhibition effect on this pathway, halting cell replication

10. Reolysin – a proprietary formulation of the human reovirus. Most of us have been affected by reovirus as it is a common constituent of sewage and water supplies.

Reolysin is administered as an IV. Cancer cells with up-regulated Ras protein (24% of all cancers) can not activate the anti-viral response cellular protein. Thus, reovirus replicates within cancer cells eventually killing the cancer cell (Oncolytics Company have clinical trials showing efficacy in several cancers)

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11. Mistletoe – a parasite that grows on many trees. It is given by injection at tumor site or intra-abdominally, not orally. Mistletoe extract shown to kill cancer cells and boost immune function:

- Increases natural killer activity
- Increases interleukin 1 and 6
- Activates macrophages
- Induces apoptosis of cancer cells
- Protects DNA of normal cells during chemotherapy

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12. Amygdalin – a cyanide-based molecule extracted from apricot pits or almonds by boiling with ethanol. This product is made in Mexico from crushed apricot pits

In the US Laetril is a semi-synthetic product that includes the amygdalin molecule

Evidence suggests that amygdalin releases cyanide to tissues with these outcomes:

1. Induces apoptosis of cancer cells in various human cancer cells
2. Induces DNA damage in colon cancer cells
3. Animal studies showed up to 80-90% decrease in metastatic activity with Laetril injection (Dept of Physiology, College of Medicine – Kyung Hee University – South Korea – 2008)

Ralph Moss was fired as head of media relations of Sloan-Kettering Cancer Center for not being willing to lie about Laetril. After reviewing the research he refused to endorse the notion that Laetril was of no value and should not be explored further in cancer treatment studies.

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13. Interferon Alpha 2 (IFNa2) – normally produced by macrophage cells, it has anti-viral, and anti-proliferative properties.

Interferon treatment is used in adjuvant therapy of many cancers to up-regulate immune function

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Other Medical Cancer Treatment Interventions

1. Radiation
2. Surgery and Peri-surgical Considerations
3. Thermal Therapy (local or systemic)
4. Cimetidine
5. Photodynamic Therapy
6. Radio Frequency
7. Radioactive Seeds (prostate)
8. HIFU (prostate)
9. Stem Cell Transplant (Hemopoetic cancers)
10. Radioactive Iodine (thyroid)
11. Hyperbaric Oxygen

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Other Forms Of Cancer Treatment

1. Radiation – radiation kills cancer cells via free radicals. Thus, concurrent high dose antioxidant supplementation may reduce efficacy.

   However, concurrent supplementation with non-antioxidant agents that enhance immune function, induce apoptosis, inhibit angiogenesis etc. may still be beneficial during radiation treatment

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2. Surgery

Use of peri-operative agents have been shown to reduce cancer metastasis. Surgery can encourage spread of cancer, and some anesthesia drugs used in surgery are shown to suppress immune function, resulting in cancer recurrence and metastasis.

Cancer patients scheduled for surgery should consider:

1. Supplementation with **Modified Citrus Pectin-** inhibits tumor cell adhesion by binding to galectin-3, preventing aggregation and invasion of cancer cells (Pienta/1995 and Guess/2003)

   Dosage: 15gms, 4x daily

2. Supplementation with **AHCC mushroom complex** – supports immune system (increases NK, macrophages and cytokines) – shown to increase survival in patients undergoing liver surgery (Matsui/2002)

   Dosage: 500 mg, twice daily

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3. Use of **Cimetidine (Tagamet)** - Many cancer cells contain histamine receptors whereby histamine stimulation is required to stimulate cell growth. Cimetidine blocks cancer cell histamine receptors.

Cimetidine also shows immune-enhancing effects.

Cimetidine also has anti-tumor adhesion effects by blocking expression of E-selectin (similar effect as modified citrus pectin)

Histamine often released during surgery. Thus, cimetidine can help prevent cancer cell stimulation from histamine and maintain more optimal immune system function as peri-operative agent. (Matsumoto/2002; Rossing/2009; Sviland/1987)

Dosage: 800 mg at night

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4. Thermal Therapy (local or systemic)

Dr Joan Bull MD (https://med.uth.edu/internalmedicine/faculty/joan-m-bull-md/)

Heating cancer cells to 39-42 degrees C used to treat cancer:

- Heat is cytotoxic to cancer cells – killing them
- Heat amplifies killing effect of chemo drugs and radiation by increasing the blood flow and cell membrane permeability
- Heat enhances immune function
- Heat damages tumor RNA and slows DNA repair

5. Photodynamic Therapy – using 5 Amino levulinic acid (5 ALA) in conjunction with red laser light (See next slide)

6. Radio Frequency

7. Radioactive Seeds (e.g. inserted in prostate)

8. High Intensity Focused Ultrasound HIFU (prostate) – sections of the prostate gland are destroyed by heating them to high temperatures via HIFU (see demo at www.hifu.ca)

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Photodynamic Therapy - 5-Aminolevulinic acid And PTD - Photodynamic Therapy (PDT) involves administration of a tumor-localizing photosensitizer (5-aminolevulinic acid [5-ALA], a precursor in the heme biosynthetic pathway), with resulting cell death upon activation by wave lengths from red light spectrum (630-635nm) – most ideally 632.5nm

- The singlet oxygen produced during the transfer of energy from light source to 5-ALA disrupts plasma, nuclear and mitochondrial cell membranes, resulting in apoptosis.

- Tumor necrosis is evident within 2-24 hours

- Porphyrins cleared from the body within 24-48 hours, reducing risk of skin phototoxicity, as often occurs with Photofrin – a microvascular and stromal photosensitizing agent

- Studies show higher accumulation of 5-ALA-derived protoporphyrin (PpIX) in rapidly proliferating cells, providing biologic rationale for clinical use of 5-ALA-based PDT and diagnosis

- Cancer cells have been shown to accumulate 5-ALA and down-stream intermediates of metabolism in heme synthesis, which are prone to mass free radical formation upon red light exposure

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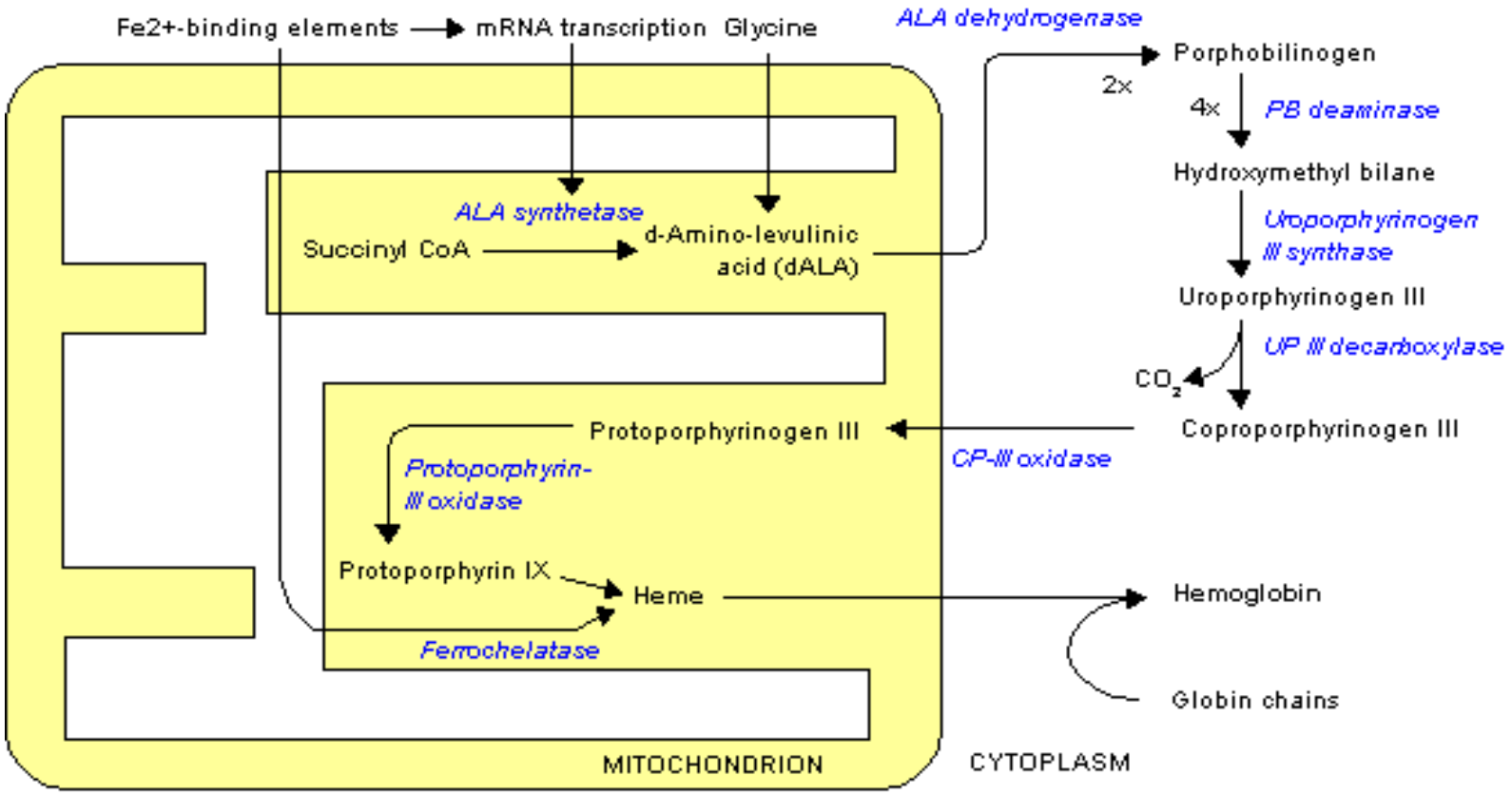
Heme Synthesis Note: addition of glycine to succinyl CoA to form ALA in mitochondria



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Activation of 5-ALA in cancer cells causes tumor ablation via direct killing effect, extensive free radical damage, damage to microvasculature, with induction of various signal transduction pathways leading to apoptosis, most notably:

- AMP- Activated Protein Kinase (AMPK)
- Mitogen Activated Protein Kinas (MAPK)
- Caspase-9
- Caspase-3

- Up-regulation of local immune response has also been shown

Note: Experimental studies indicate that concurrent supplementation with N-acetylcysteine decreases the killing effect, probably due to antioxidant function

(Molecular Cancer. 2010.Ji et al)

(Annals of Surgical Oncology. 2004. Cuenca et al)

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PDT Protocol:

1. Patient ingests (orally) loading dose of 5-ALA, then waits 4 hours (20 mg/kg)

2. Shine red light up to 4 inches into body at exact location where solid tumor resides to get killing effect – our clinic uses "Big Red", which has built in liquid cooling system to allow deep penetration of red light without burning the patient – developed by Tom Kerber (penetration studies conducted at the University of Toronto)

   Kerber Applied Research Inc.

Side Effects: Local pain (usually quite painful) from tissue destruction and inflammation

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9. Hematopoietic Cell Transplantation – the IV infusion of hematopoietic progenitor cells (stem cells) designed to re-establish bone marrow and immune function in patients with a variety of acquired or inherited malignant and nonmalignant disorders:

- Leukemia
- Lymphoma
- Multiple Myeloma
- Aplastic Anemia (non malignant acquired marrow disorder)
- Genetic Disorders Involving Hematopoietic System (thalassemia, sickle cell, severe combined immunodeficiency)
- High Dose Chemotherapy – whereby marrow destruction with severe anemia and leukopenia result form drug toxicity (eg. Breast and ovarian cancer Rx)

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Types Of Stem Cell Transplantation:

- Matched Allogenic – transplant of stem cells from a sibling or family member with same HLA antigen (or one antigen mismatch HLA system).

- Unrelated matched allogenic - transplant of stem cells from a non-first-degree relative with similar HLA match.

HLA Matching:

Typing of large numbers of individuals has shown that full HLA matches exist in the general population, making allogenic matched, and unrelated matched transplants, a possibility (kept in a computer filing system. Individual is contacted if match is identified to help a patient in need.

Allogenic transplants rarely involve the exact HLA match and thus, rejection is a common problem and the relapse rate is higher than for autologous transplants

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- Autologous Transplants – the patient's own bone marrow is harvested and cryopreserved prior to administration of chemotherapy and/or high dose radiation treatment.

Or the patient's own marrow stem cells are collected from peripheral blood (blood is collected on a cell separator and frozen to be utilized after chemo and/or high dose radiation)

Or circulating marrow stem cells from a donor can also be used where there is a genetic identical twin (syngenic transplant)

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Bone Marrow Cell Extraction (allogenic donor or autologous) – often taken from the individual's posterior iliac crest

Allogenic BMT Indications:

Leukemia

Non-Hodgkin Lymphoma

Aplastic Anemia

Myleodysplasia

Leukemia in relapse

Autologous BMT Indications:

Acute Myelogenous Leukemia in remission

Lymphoma

Hodgekins Lymphoma

Multiple Myeloma

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Overall, these hematopoietic stem cells **differentiate into healthy RBC's and WBC's** and many **become health immune cells** that are able to **kill any cancer cells** that were not destroyed by the chemotherapy and/or radiation used prior to their infusion into the blood stream, or transplantation into the bone marrow itself.

World Authority On BMT – Dr Dipnarine Maharaj MD. Medical Director and founder of the South Florida Bone Marrow/Stem Cell Transplant Institute.

Also – transplant neutrophils from young people into cancer patients (matched allogenic) – H2O2

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10. Radioactive Iodine (thyroid) – in thyroid cancer patients and Grave's disease, patients given oral dosages of radioactive iodine, which is taken up by thyroid cells.

The radioactivity kills the thyroid cells and thyroid cancer cells. The patient is then required to use thyroid replacement therapy to maintain normal thyroid stimulation of body cells

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11. Hyperbaric Oxygen Treatment

Hyperbaric oxygen – 100%-inhaled oxygen (can also control degree of atmospheric pressure. (e.g. 1 ATA, 2 ATA, 2.5 ATA, 3 ATA)

Since 1967 all published reports show that hyperbaric oxygen therapy in human subjects decreases cancer growth and increases long-term survival. Many studies with head and neck cancers (including brain), especially.

Animal studies support anti-cancer effects of HBO for many solid tumors.

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Mechanism of Action:

1. Anti-angiogenesis
2. Increases susceptibility to chemodrug killing effect on cancer cells
3. Inhibits metastasis
4. Enhances the effect of radiation therapy – cancer cells that contain more oxygen are 2-3 times more susceptible to radiation therapy
5. Tumor cells appear to need oxygen to undergo apoptosis

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As cancer cells experience hypoxia they are more inclined to secrete VEGF to gain more blood and move towards metastasis to start new colonies in more favorable vascularized environments.

Thus, happy oxygenated cancer cells behave in a less aggressive way in regards to forming new blood vessels and metastasis. They have no driving force to become more invasive

Happy oxygenated cancer cells are less invasive (Fenton et al)

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Choosing The Atmospheric Pressure:

1. Up to 2.5 ATA does not increase ROS

2. Over 2.5 ATA increase ROS, but can provide simultaneous IV of Vitamin C (25 gm) as antioxidant. This is maybe useful in:

- Autism
- Neurodegenertive Diseases (MS, ALS, Parkinson, disease, Alzheimer' disease)
- Stroke Rehab

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Protocol of Leading Integrative MD:

In addition to the use of Insulin Potentiation Therapy this doctor has used over the years the following integrative therapies in his comprehensive approach to cancer treatment. Many other Integrative Doctors use similar interventions.

Immuno-Therapy:

1. Zadaxin (Thymus Alpha-globulin peptide)

Zadaxin has proven immune-modulating properties and is used primarily to treat viral hepatitis (https://www.ncbi.nlm.nih.gov/pubmed/15992078)

It is typically administered at 1.6 mg, twice weekly, via subcutaneous injections (each vial is 1.6 mg) in adjunctive cancer treatment.

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In Lung Cancer - Proleukin (interleukin-2):
http://clincancerres.aacrjournals.org/content/2/7/1115.full.pdf

Interleukin-2 is important for an adequate immune response to cancer, but parenteral administration may cause severe toxicity.

For patients with primary or secondary lung cancer, inhalation of the interleukin-2 has been found to be effective with minimal to zero side effects.

Each vial of Proleukin is 22 million units; 1/3 of a vial is used with each treatment, which is administered 6 days per week.

Administration: Each dose of Proleukin is placed in a nebulizer with 3 ml of water or saline.

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- Interleukin-2 is in the class of medications called biologic response modifiers. It is a cytokine that works to increase the production and function of various components of the body's immune system.

- This protein is normally produced in the body, but in small amounts. By increasing levels of IL-2, the immune system gets a kick-start (specifically T cells and natural killer cells) to attack the cancer cells.

- https://www.oncolink.org/cancer-treatment/oncolink-rx/interleukin-2-proleukin-r-il-2-aldesleukin

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2. Mistletoe Injections

- Injections should be performed subcutaneously (27 g needle is adequate) in abdominal fat or in the fat on the proximal thigh.

- Therapy is divided into the induction and the maintenance phase. In the induction phase, a very small dose in the form of “Series 0,” is first used to observe the individual reaction of the patient. For the induction phase, 2 packages of Series 0 (fourteen 1 ml ampules) are used for SC injection 3 times per week (Monday, Wednesday, Friday).

A one week pause ensues after the 14 injections. If Series 0 is well tolerated and no local reactions have arisen, the dose can be increased until the patient’s individual reaction dose is reached with Series I. If no local reaction is seen with Series 1 after 14 injections, after a one week pause, the patient should repeat the above procedure with Series II.

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Mistletoe Continued

- The maintenance phase is reached if a sufficient immunological response occurs (local reaction with swelling up to a maximum of 5 cm around the inoculation site, or an increase in temperature up to 100.4 Fahrenheit). Typically, with a sufficient immune response, one will observe an increase in total white blood cells, lymphocytes, eosinophils, as well as interleukin-2 receptor.

- Duration of therapy is not limited and depends on the risk of recurrence and/or the patients' clinical status. However, a duration of at least 5 years is recommended with treatment pauses increasing gradually.

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3. Ukrain

- **Method of administration**: may be administered intravenously or intramuscularly, **but intravenous application is preferred**. Inject slowly, at a rate not more than 5 ml per minute. UKRAIN® should not be added to other injection or infusion solutions.

- Tests have shown that smaller doses (5 mg) have an immune modulating effect and larger doses (20 mg) a malignocytolytic effect.

- Because UKRAIN® accumulates in tumor or metastases areas very quickly after injection and influences the immune system of different patients in different ways, the dosage is not selected according to body weight or surface, but according to the immune status of the patient.

- A single dosage is 5 to 20 mg per injection depending on tumor mass, speed of growth, the extent of the disease and the immune status of the patient.

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3. Ukrain Injections

Dosing schedule:

- 1st day (Thursday): 1 amp. i.v. undiluted or diluted with 5 ml 5% glucose
  2nd day (Friday): 2 amp. i.v. undiluted or diluted with 10 ml 5% glucose
  3rd day (Saturday): 0 (break)
  4th day (Sunday): 0 (break)
  5th day (Monday): 3 amp. i.v. undiluted or diluted with 15 ml 5% glucose
  6th day (Tuesday): 0
  7th day (Wednesday): 0
  8th day (Thursday): 4 amp. i.v. undiluted or diluted with 20 ml 5% glucose
  12th day (Monday): 1 amp. i.v. undiluted or diluted with 5 ml 5% glucose
  15th day (Thursday): 4 amp. i.v. undiluted or diluted with 20 ml 5% glucose
- and then once a week 1 ampoule and 4 ampoules in turn (e.g. Monday 1 ampoule, Thursday 4 ampoules etc.), by carefully watching the reactions. If there are reactions, the dosage should not be reduced, as it shows that UKRAIN is working. You may use a thin needle 27G.
- The first series of injections should be for 8 weeks, followed by a break of 8 to 10 days. If a tumor is very small, or if only a stabilization is to be achieved, the dosage can be twice or three times a week one ampoule each.

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4. Proprietary Cancer Vaccine – administered outside of US

5. Coley's Toxin (vaccine) – administered outside of US and Canada (alternative is BCG and/or flu vaccine)

6. Vitamin C – IV

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7. Goleic (GcMAF) – this is the body's precursor to Macrophage-Activating Factor (MAF). MAFs (or "macrophage-activating factors") are protein mediators produced by T-cells, which direct the immune system response by signaling between its cells. One of the functions of this immune response is to make macrophages cytotoxic to tumors

Nagalese is an enzyme (its scientific name is "alpha-N-acetylgalactosaminidase") which blocks the conversion of Gc protein into to GcMAF, thereby preventing the immune system from recognizing and destroying cancer cells.

Thus, elevated nagalase inhibits Gc from forming into GcMAF, which results in a significant decline in the immune system's ability to address cancer.

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- There is some controversy surrounding direct supplementation of GcMAF, even though there is over a decade of clinical experience without any evidence of adverse effects from injection of this glycoprotein.

- Research papers have been published in highly respected mainstream journals such as *Frontiers*, the *International Journal of Cancer Research and Treatment*, the *American Journal of Immunology* and the *Journal of Translational Oncology*, on its efficacy.

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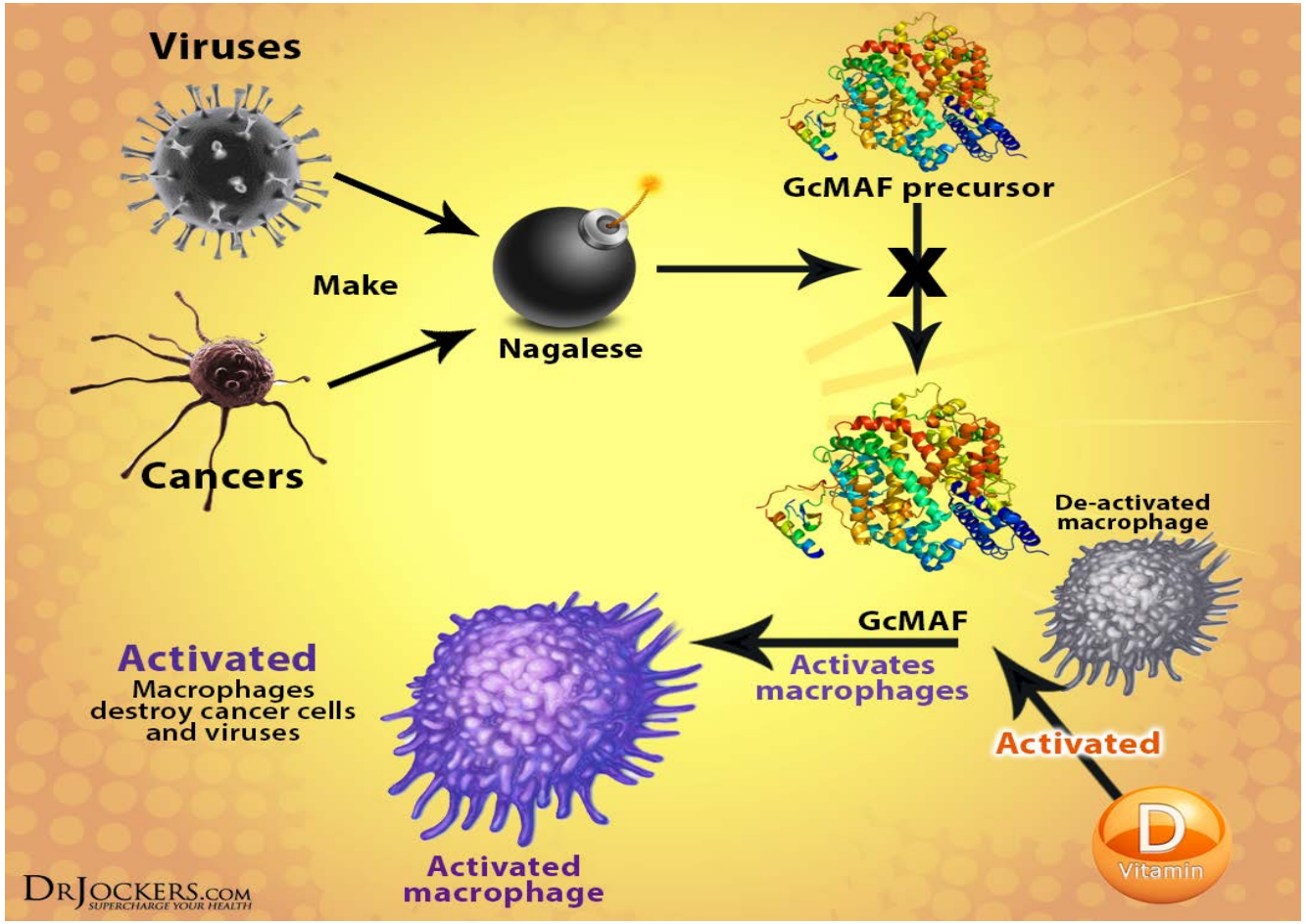
GcMAF and Nagalese in Cancer



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Unique Acidity-Killing Mechanism Of Protocol:

Enzymes/pumps/transporters involved in the excretion of acid, as well as the acidification of the cancer tissue extracellular milieu, include:

- Carbonic Anhydrase (CA)
- Monocarboxylate transporter
- Vacuolar H+ ATPase Pump (proton pump)

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pH Manipulation Method

- Patients take 360 mg per day of omeprazole (Prilosec); 2 weeks on and one week off and repeat cycle indefinitely (breaks are necessary when taking omeprazole). **This will block the pumping of protons (acid) out of the cancer cell.**

- **Patients take methazolamide (carbonic anhydrase inhibitor**) daily with doses up to 400 mg per day.

- Patients periodically (1-2 times per week) present for the following infusion:
  - A liter of sterile water, containing at least **150 grams of glucose** and at least **175 mEq of sodium lactate.**
  - The goal is to achieve a blood-glucose concentration of at least 400 mg/dl.
  - Regular insulin is then injected intravenously to drop the blood-glucose concentration to less than 100 mg/dl.

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How It Works

The theory behind this process is that artificially-induced hyperglycemia (high blood-sugar) followed by insulin administration will preferentially increase glucose in the cancer cells (studies reveal that glycolytic tumors express from 7-16 times the number of insulin receptors as normal tissue).

Because of the chronic ingestion of proton pump inhibitor and CA inhibitor, these **cells will quickly become very acidic.**

In addition, elevated lactate in the blood will be bound by the bidirectional transporter MCT, which can **inhibit the cell's ability to efflux lactic acid.**

Also, for the MCT to effectively efflux lactic acid, it requires a gradient of high intracellular to low extracellular lactate. **Administering high lactate will reverse this gradient, thereby inhibiting efflux of lactic acid**.

- http://cancerres.aacrjournals.org/content/62/18/5218.full.pdf+html
- http://informahealthcare.com/doi/abs/10.3109/02656739609023527

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pH manipulation cont-d

- Following this infusion, the cancer cells are extremely acidic, and are very susceptible to apoptosis.

- The patient may then receive any type of cytotoxic therapy, such as chemotherapy, radiation therapy, hyperthermia, or intravenous vitamin C.

- Also works well with Cancer-Specific Ketogenic Diet I will explain in next section

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Other Integrative Treatments:

1. **Hyperbaric oxygen** – oxygenated cancer cell is happy and tends not to metastasize to start new colony

2. **Hyperthermia,** used as the sole treatment of cancer, does not kill or damage cancer cells directly, unless the temperature reaches 42 degrees centigrade (107.6 Fahrenheit). On the other hand, mild hyperthermia (up to 40 degrees centigrade; 104 degrees Fahrenheit), in conjunction with other cancer treatment modalities, has demonstrated efficacy.

- Recommended unit is German-made hyperthermia unit called the **Heckel-HT 2000.** This unit will reach a maximum temperature of 40 degrees centigrade.

- **Treatment duration – approx 2 – 6 hours**

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Off-Label Drug Use In Cancer:

1. **DCA (Dichloroacetate)** – inhibits glycolysis

- Typical doses are in the range of 20-25mg/kg/day for adults and 25-50mg/kg/day for children, in a 2 week on and 1 week off cycle.

DCA may be purchased online:

- www.Pharma-dca.com; pureDCA.com

2. Celecoxib (Celebrex) -Typical dose used to treat cancer is 400 mg 2 times per day.

3. Cimetedine (Tagamet) - Doses used in the treatment of cancer are up to 1200 mg per day, with the most common dose used being 800 mg per day in 2 divided doses.

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4. Metformin - Metformin selectively kills cancer stem cells, as well as p-53 deficient cells (p-53 is a tumor suppressor gene).

Metformin has shown to inhibit the growth of breast, prostate, colon, and pancreatic cancer cells through the activation of AMP activated protein kinase (AMPK).

Studies on diabetics show better response to cancer treatment with concurrent metformin administration

Dosage: up to 1000 mg, twice daily

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5. Ammonium Tetrathiomolybdate (ATTM) - sequesters copper preventing angiogenesis

Dosage: typically 20-60 mg per day, with the goal being to decrease the ceruloplasmin level to 20% of baseline.

Achieving this ceruloplasmin level is often limited by anemia, which can be exacerbated by ATTM (copper required to make RBC's)

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6. Doxycycline (Antibiotic)

- inhibits the release of matrix metalloproteinase (MMP) from cancer cells
- inhibits the expression and phosphorylation of focal adhesion kinase (FAK), a protein tyrosine kinase involved in the regulation of cell adhesion and migration of cancer cells
- inhibits prostate cancer cells in vitro and decreases tumor burden in a bone metastasis model of human breast cancer.
- It is also synergistic with Cox-2 inhibitors in inhibiting colorectal cancer cells in vitro

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Doxycycline Continued

- induces apoptosis in pancreatic cancer cells and glioblastoma cells.

Dosage: at 200 mg 2 times per day yields blood levels that were found to be cytotoxic to cancer cells in vitro.

This doctor also places patients on supplements and provides dietary advice

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Part 7

Cancer Specific Treatment Diet, Diet For Cancer Survivors, Exercise Protocol and Approach to Nutrition and Supplement Recommendations

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Cancer-Specific Treatment Diet: Classified as Restrictive Ketogenic Diet

Physiology of How Diet Works:

- Cancer cells primarily dependent upon glucose for energy, which they generate anaerobically

- Anaerobic metabolism is very inefficient, and thus, large amounts of glucose are constantly required to keep cancer cells alive, and to allow them to proliferate. 95% of normal metabolism driven aerobically by comparison.

- Cancer cells, unlike other body cells including brain cells, cannot use free fatty acids or ketones as an energy source

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- Consuming a diet that keeps glucose very low deprives cancer cells of energy while normal cells switch to burning fat and ketones.

- Robbing cancer cells of glucose starves cancer cells to death, which undergo apoptosis in an energy restricted environment and/or cannot replicate as easily (slowing tumor growth)

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- In some cases a low glucose state is sufficient to reverse tumors. In most cases a low glucose state renders cancer cells more susceptible to cancer killing effects of other conventional (e.g. chemotherapy) and integrative (e.g. hyperthermia, pH manipulation) cancer treatments

- As cancer cells can convert glutamine in glucose, glutamine must also be restricted

- As the liver can convert protein into glucose (gluconeogenesis) when the body is in a hypoglycemic state, protein must also be limited to keep glucose in ideal range for cancer killing effect

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- Certain drugs can block the ability of cancer cells from converting glucose into pyruvic acid (block glycolysis). This further deprives cancer cells of ATP energy.

- Certain drugs block the proton pumps that normally pump acid by-products of anaerobic metabolism out of the cell. In this case, acidity builds up in cancer cell, which induces apoptosis as pH levels drop to critical point.

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Macronutrient Intake Specifics and Blood Urine Criteria

In order to rob cancer cells of glucose the following objectives are critical:

- Maintain total CHO calories no higher than 100 calories per day (25 gms)
- Maintain total protein intake between 55-65 gm
- Blood monitoring of glucose and ketone levels should be performed three times daily (before breakfast, two hours after lunch, and two hours after dinner).
- Blood glucose should be kept within the following range - 55-70 mg/dL (3.1-3.8 mmol/L) – this is hard to do and takes great discipline
- Blood ketones should be maintained within the range of 4-7 mmol/L – this requires the use of the Medisense Precision Xtra blood glucose and ketone monitor (Abbott Laboratories).

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- Ketones should be present in all urine samples

- If the patient is in good health and medical monitoring available – beginning the program with a 3-day water fast is most ideal

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Dr Meschino's Ketogenic Menu Plan: Featuring Healthy Fats – See Additional Course Notes

Daily Calorie Summary Of Cancer–Specific Ketogenic Diet

- Total Daily Calories - approximately 2045 calories
- CHO – 22.5 gm or 90 calories
- Protein – 63.2 gm or 252.8 calories
- Fat – 190.1 gm or 1710.9 calories – mostly medium chain triglycerides, which are highly ketogenic and not atherogenic

- **Percentage Breakdown Of Calories From all Food, Shakes And Supplements):**
- 83.2% Calories From Fat
- 4.4 % Calories From Carbohydrate
- 12.4% Calories From Protein

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Breakfast:

Skake Mix:

- KetoCal Shake: add 20 gm of KetoCal powder to approximately 200 ml of water (or desired thickness)
- Protein – 6 gm
- CHO – 1.2 gm
- Fat – 29.2 gm

Add ½ Scoop Whey Factors Shake Mix to 200 ml of KetoCal Shake – choice of vanilla, chocolate or strawberry (Natural Factors)

- Protein – 8.5 gm
- CHO – 1 gm
- Fat – 0.75 gm

Add 1 tablespoon of MCT oil (example Alpha's Supreme MCT Oil) to 200 ml of KetoCal Shake

- Fat – 14 gm

Take 2 Essential Fatty Acid Supplement Capsules (e.g. Adeeva Nature's Essential Oils)

- Protein – 3 gm (12 calories)
- CHO - .6 gms (2.4 calories)
- Fat – 23.5 gms (211.5 calories)

Take 2 High Potency Multivitamin and Mineral Caplets (i.e. Adeeva Multiple Vitamin and Mineral)

Breakfast Calories Summarized:

- *CHO= 2.8gms (11.2 calories)*
- *Protein= 17.5 (70 calories)*
- *Fat = 67.5 gms (607 calories)*
- *Total Calories – approx. 688.2 calories*

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Mid Morning Snack: ½ cup of strawberries: (23 calories) or other fruit, but no more than 23 calories allowed

- ***Mid Moring Snack Calories Summarized:***

- *CHO – 4 gm (16 calories)*
- *Fat – 0.5 gm (4.5 calories)*
- *Protein 0.6 (2.4 calories)*
- *Total Calories – 23 calories*

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Lunch:

Skake Mix:

- KetoCal Shake: add 20 gm of KetoCal powder to approximately 200 ml of water (or desired thickness)

Add 1 tablespoon of MCT oil to 200 ml of KetoCal Shake

1 tablespoon Fry's Premium Cocoa to 200 ml of KetoCal Shake

- CHO – 2 gm
- Protein – 1 gam
- Fat- 0.5 gm

Add artificial sweetener Sucralose (Splenda) to 200 ml of KetoCal Shake – to achieve desired level of sweetness if necessary

- **Take 2 Essential Fatty Acid Capsules (i.e. Adeeva Nature's Essential Oils)**

- **Take 2 High Potency Multivitamin and Mineral Caplets (i.e. Adeeva Multiple Vitamin and Mineral)**

Lunch Calories Summarized:

- *CHO= 3.8 gms (15.2 calories)*
- *Protein= 10 gms (40 calories)*
- *Fat = 67.2 gms (604.8 calories)*
- *Total Calories – approx.660 calories*

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Dinner:

Salmon (4 ounces) or other fatty fish choices limited to halibut, sardines, herring or cod:

- *CHO – 0 gms (0 calories)*
- *Protein – 22.6 gms (90.4 calories)*
- *Fat – 7.2 gms (64.8 calories)*

1 cup of chopped vegetables from using any combination of the following non-starchy vegetables:

- broccoli, cauliflower, Brussels sprouts, kale, chard, spinach, dandelion greens, endive, asparagus, cabbage, cucumber (skinned and deseeded), collard greens, any lettuce

Steam, boil or have them raw. You may add olive oil, lemon, and/or non-sweet vinegar to add flavour

Vegetable Calories:

- *CHO – 8 gms (32 calories)*
- *Protein – 4 gm (16 calories)*
- *Fat – 0 gms (0 calories)*

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Evening Snack If Necessary (active patients and patients weighing more than 175 pounds)

Mixed Nut Combo:

- Brazil Nuts – 12 nuts
- Pecans – 1 oz or 20 halves

- *CHO – 4.7 gm (18.8 calories)*
- *Protein – 8.6 gm (34.4 calories)*
- *Fat – 47.6 gm (428.4 calories)*

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By Removing Nuts The Nutrient Count Changes as per the following:

- Total Calories - 470 fewer cals with no nuts (new calorie total – 1575 calories vs 2045
- 47.6 gm fewer fat (428.40 calories) (new total 142.5 gm or 1282.5) – 81% calories from fat in total daily intake
- 8.6 gm fewer protein (34.4 calories) (new total protein 54.6 gm) – this is perfect number to shoot for
- 4.7 gm fewer carbs (18.8 calories) (new total CHO 17.8 gm) – this is well under 25 gms of CHO

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Where To Obtain Products:

- KetoCal – online from Nutricia (http://www.nutricia-na.com/pages/ketocal.htm)

- MCT oil (health food store)

- Natural Factors - Whey Factors Protein Formula – most health food stores in Canada

- Adeeva Supplements (www.adeeva.com)

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High Animal Fat Ketogenic Diet Version

Breakfast:

- 40 gm 36% Heavy Cream
- 32 gm - Sausage link
- 24 gm Avocado – Hass
- 5 gm Canola oil

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Lunch

40 gm 36% Heavy Cream

18 gm Sliced turkey breast

22 gm Raw cucumber slices & celery sticks

22 gm Mayonnaise

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Dinner:

- 40 gm 36% Heavy Cream
- 20 gm Baked cod
- 43 gm Roasted cauliflower
- 23 gm Butter

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Snack: 10 g Sliced strawberries

28 g - 36% Whipped heavy cream

In your notes see 12-day High Animal Fat Ketogenic Menu Plan

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Suggested Drugs And Supplements To Enhance Efficacy of Ketogenic Diet In Cancer Patients:

Drugs:

- **2-deoxyglucose (2DG)** – 30-40 mg/kg (restricts glycolysis in tumor cells)

- **Phenylbutyrate** – 3-5 gm per day (this drug is metabolized to phenylacetate, which binds glutamine for elimination in urine. This prevents cancer cells from fermenting glutamine into a fuel for energy production, as a substitute for glucose.

- **Dichloroacetate (DCA)** – Typical doses are in the range of 20-25mg/kg/day for adults and 25-50mg/kg/day for children, in a 2 week on and 1 week off cycle. (inhibits glycolysis)

- **Omeprazole** (Prilosec in US and Losec in Canada) - 360 mg per day, Take it 2 weeks on and one week off and repeat cycle indefinitely. This will block the pumping of protons (acid) out of the cancer cell.

- **Methazolamide** (carbonic annhydrase inhibitor) – take up to 400 mg per day. Take this on the days the patients is also taking omeprazole

- **Allopurinol** – required only if uric acid rises due to ketogenic diet

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Supplement Considerations:

- High Potency Multiple Vitamin and Mineral (i.e. Adeeva Multiple Vitamin and Mineral – 4 caplets per day - mandatory to prevent serious nutrient deficiencies on ketogenic diet)

- Essential Fatty Acids (i.e. Adeeva Nature's Essential Oils – 4 capsules per day)

- Natural Anti-inflammatory (Curcumin-Boswellia, Ginger, White Willow Extract (i.e. Adeeva Nature's Relief – 3-4 caps/3 times per day)

- Immune and Detox Boost Supplement (i.e. Adeeva Immuno-Detox Prime – 4 capsules, three times daily)- Reishi m extr, Astragalus, Indole-3-carbinol, Milk thistle-Silymarin)

- **Other Individual Nutrients to Consider in Foundation Program**
- Vitamin E Succinate – 2000 IU
- Vitamin C – 2000-4000 mg
- Selenium – 400-500 mcg
- Vitamin D – 5000 – 20,000 IU
- Quercetin – 1000 mg, twice daily
- CoQ10 – 300 – 400 mg per day
- 14 Mushroom Blend – www.mushroomharvest.com

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Cancer Patient Survivor Diet

General Principles:

Low glycemic, but not necessarily ketogenic

Sufficient protein

Low animal fat, transfats, fried foods. Monounsaturated fats and omega-3 fats preferred.

Include fish twice per week if desirable

Rich in phytonutrients, vitamins and minerals

No alcohol

Moderate exercise

Snacks must be low fat and moderate glycemic or nuts

Achieve and maintain Ideal weight

Best example of diet found in the following book:

- *Anticancer*: A New Way Of Life - David Servan-Schreiber

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Whole Food Anticancer Broth

Servan-Schreiber M.D., Ph.D. The specific brewed cocktail given to these mice closely matched what would be attainable for humans to mirror and included:

- Cabbage – example 4 ounces (100 gms)
- Blueberries – example 2 ounces (50 gms)
- Brussels sprouts
- Broccoli
- Garlic
- Scallions
- Turmeric
- Black Pepper
- Cranberries
- Grapefruit
- Green tea

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Exercise Section

Do any of the following statements apply to you:

- Your doctor has informed you that you have heart trouble or a heart condition of some kind
- You frequently have pain in your chest or have had chest pain recently
- You often feel faint or have spells of severe dizziness that are not caused by an innner ear condition
- You have been informed that you have high blood pressure
- You are over the age of 65 and are unaccustomed to vigorous exercise

Describe Your Present Exercise Routine as well As Physical Activity At Work and Leisure and Sports Activities_____

_____

_____

_____

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Physical Activity and Survival After Breast Cancer Diagnosis

Reference: Michelle D. Holmes, MD, DrPH; Wendy Y. Chen, MD; Diane Feskanich, ScD; Candyce H. Kroenke, ScD; Graham A. Colditz, MD, DrPH

JAMA. 2005;293:2479-2486.

Conclusions:

1. Physical activity after a breast cancer diagnosis may reduce the risk of death from this disease.

2. The greatest benefit occurred in women who performed the equivalent of walking 3 to 5 hours per week at an average pace, with little evidence of a correlation between increased benefit and greater energy expenditure.

3. Women with breast cancer who follow US physical activity recommendations may improve their survival.

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Physical Activity and Survival After Colorectal Cancer Diagnosis

Reference

Jeffrey A. Meyerhardt, Edward L. Giovannucci, Michelle D. Holmes, Andrew T. Chan, Jennifer A. Chan, Graham A. Colditz, Charles S. Fuchs

Journal of Clinical Oncology, Vol 24, No 22 (August 1), 2006: pp. 3527-3534.

PATIENTS AND METHODS:

By a prospective, observational study of 573 women with stage I to III colorectal cancer, we studied colorectal cancer–specific and overall mortality according to predefined physical activity categories before and after diagnosis and by change in activity after diagnosis. To minimize bias by occult recurrences, we excluded women who died within 6 months of their postdiagnosis physical activity assessment.

- ***Women who increased their activity (when comparing prediagnosis to postdiagnosis values) had a hazard ratio of 0.48 for colorectal cancer deaths and a hazard ratio of 0.51 for any-cause death, compared with those with no change in activity.***

CONCLUSION: Recreational physical activity after the diagnosis of stages I to III colorectal cancer may reduce the risk

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Exercise Prescription – depends on functional ability of patient, but a 30 minute walking program should be encouraged at least 5 times per week as a minimum standard, if patient is capable

This may also help reduce body fat, improve glucose tolerance and tone down insulin and IGF-1 Receptors (Increase IGF-1BP)

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Supplementation Protocol Considerations

1. General Meschino Supplementation Scheme For Cancer– but look for any general contra-indications (e.g. hyperparathyroidism and vitamin D)

2. Fine tune according to Type Of Cancer (e.g. colon cancer – add calcium and wheat bran to prevent recurrence; no high dose beta-carotene in lung cancer patients or smokers)

3. Fine tune according to genomic and immune panel testing (e.g. no glutathione precursors in conjunction with over expression of GCS gene, which produces excess glutathione to protect against alkylating agents; very underactive NK cells then provide maximum boost with mushrooms and astragalus etc)

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3. Fine tune according to contra-indications based on Cancer drugs being applied (or radiation treatment) (e.g. methotrexate and folic acid; no antioxidants with radiation, but use immune modulators and anti-angiogenesis, pro-apoptotic supplements)

4. Fine tune according to synergistic action of supplements with cancer drug (e.g. over expression of egfr-2 and vitamin E succinate, vitamin D, curcumin, working synergistically with certain drugs like Herceptin etc.)

5. Fine tune according to upcoming Surgery (e.g. Modified citrus pectin, AHCC, but nothing else)

6. Fine tune according to any other cancer-specific altered metabolism (e.g. hypercalcemia of malignancy and Vitamin A and vitamin D; extensive liver involvement, compromised kidney function)

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Overall Feedback To Patient

1. Anthropometric Findings – and relationship to disease risk – Ideal Weight
2. Recommended Dietary Modifications
3. Supplementation Recommendations – and how to access them (brand names, internet, stores, MLM etc)
4. Contra-indications they should know
5. Exercise Protocol
6. Stress-Reduction Protocol and/or Resources

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Various Levels Of MD and Nutritional Consultant Involvement In Cancer

1. Nutrition and Supplementation Advisor

2. Nutrition Advisor ***Plus In-office IV practices*** that are synergistic to treatment (Vitamin C, Hydrogen Peroxide, Sodium Bicarbonate, **IV Ozone Therapy,** etc.) and off label use or synergistic drugs.

3. Nutrition Advisor, ***Further Testing*** (Chemo Sensitivity, Immune Panel, Genomic Testing Of Cancer Cells) to help fine tune cancer treatment approach (advising oncologist of your findings), and/or In-office IV practices,

4. **Take over management of entire case** (e.g. Assessment and monitoring panels and imaging, IPT, IV practices, drug prescribing, Nutrition and Supplementation advice etc.)

At each level of involvement may refer patient for further assistance:

- Radiation Treatment
- Stem Cell (Dr Maharaj)
- Thermal Therapy (local or systemic)
- Radio Frequency Therapy
- Hyperthermia
- Photodynamic Therapy

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Customized Diet and Supplement Plan: Criteria

An individualized diet and supplementation program is provided to patient based on:

1. Type of cancer
2. Stage of cancer
3. Chemo cocktail
4. Immune panel
5. Genomic testing of tumor cells
6. Patient's constitution (liver, kidney fnct, extent of metastasis, cachexia etc.)
7. Is patient fighting cancer or cancer survivor?

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Additional Notes Provided for this Subject:

1. Ancillary Reading – lengthy, referenced, detailed review of many oncogenes, receptors, tumor suppressor genes and anti-cancer effects of individual nutrients
2. Ketogenetic Diet – Original Research Papers (Glioblastoma)
3. Ketogenic Diet – My Version – Healthy Fats
4. Ketogenic Diet- Traditional version
5. Other Key Reference Material (Antioxidants, Angiogenesis)