Cancer

Facts & Stats
- folic acid supplementation linked to breast cancer. May be best to use folate
- stress induced cancer initiation…..rate of DNA damage exceeds rate of repair…..repair capacity insufficient to meet demand
- single strand breaks of DNA ae proposed to be necessary in both mutagenesis and carcinogenesis
- glucocorticoids increase the toxicity of ROS generators, and increase the level of ROS produced in cells
- glucocorticoids alter antioxidant enzyme capacity
- levels of superoxide dismutase and glutathione peroxidase are decreased in the presence of glucocorticoids
- telomerase activity has been detected in 85 - 95% of tumors
- progression and long term growth of malignant tumors is associated with activated telomerase
- Benzopyrene in cigarette smoke causes mutations of p53 in lung cells.
- Folate deficiency can lead to DNA strand breaks of p53 gene.
- BRCA1 gene (BReast CAncer 1 gene) and BRCA2, when mutated, prediposes to breast/ovarian cancer.
- BRCA1 gene is a tumor suppressor. Loss of both normal copies plays a major role in breast and ovarian cancer.
- breast cancer patients have higher cortisol levels than non-patients.
- patients metastatic breast cancer have higher cortisols than early stage patients
- when anti-apoptosis members of the Bcl-2 family are overexpressed, neoplasia is greatly enhanced
- some tumor cells express FasL on their membranes, allowing them to kill T-cells by inducing apoptosis via providing binding to Fas on T-cells. These tumors are also able to remove their Fas receptors, thus preventing induction of that form of apoptosis
- indescriminant inhibition of apoptosis (ie.protease inhibitors) will lead to widespread hyperplasia
- When essential fatty acids are oxidized by free radicals, they create an immune response that other fatty acids are incapable of inducing. This immune response inhibits tumor growth, such as in breast cancer.
- Diets that are high in other fatty acids (linoleic acid in corn oil, safflower oil) have been shown to aid tumor growth. Diets that contain high levels of essential fatty acids have been shown to inhibit or suppress tumor growth.
- The measured levels of essential fatty acids in breast tissue has been a good predictor of the metastatic potential and tumor size in breast cancer patients. The greater the levels of essential fatty acids, the lower the potential for metastasis and the smaller the tumor.
- Retinoids reduce levels of Estrogen receptors in breast cancer cells
- Retinoids induce apoptosis in adult T cell luekemia
- Retinoids has antiproliferative effect on Epstein Barr cells
- nitric oxide induces vascular endothelial growth factor (EDGF) expression
- nitric oxide synthase inhibitor can decrease tumor growth via blocking EDGF induced angiogenesis
- sarcoma = malignant cancer of epithelial cells
- carcinoma = malignant cancer of connective tissue/blood
- “oma” = benign tumor
-- folate supplementation in pregnancy reduces the risk of common acute lymphoblastic leukaemia in the child.
- gliomas…..highly malignant brain cancer
- thrombozane synthase……..enzyme activity associated with high malignancy [blocking the enzyme decreases migration]
--- soybean contents……lunasin [polypeptide]
--- lunasin induces apoptosis in malignant cells
--- soybean isoflavone……Genisten
--- Genisten inhibits prostate cancer cell growth……..may induce genetic damage via DNA cleavage
--- isoflavones…….anti-estrogenic….inhibition of angiogenesis
-- alpha-tocopheryl succinate……most effective form of Vitamin E in causing inhibition of proliferation in cancer cells, and causing apoptosis of cancer cells
--- 5 nanograms/ml caused 50% growth inhibition, 10 nanograms/ml caused nearly 100% cell death
--- children who received radiation for leukemia……associated with a second cancer, increased mortality, and unemployment rate later in life.
--- French fries…….at 175 degrees F, the amino acid –asparagine- is converted to acrylamide…….and oxidant that can cause DNA strand breaks
--- IFN-alpha/beta stimulates transcription of p53
--- p53 is in dormant form, must be activated
--- p53 is activated by agents that induce DNA damage or other cell stress [radiation, chemotherapy, aberrant cell growth]
--- EMSY protein…….binds BRCA-2 tumor suppressor protein

Glucose/glycolysis
-- low availability of glucose in tumors negatively affects the activity of tumor-infiltrating T cells
-- loss of T cell function under is mediated by the microRNAs miR-101 and miR-26a
    -- they target expression of the methytransferase EZH2 = diminishes expression of anti-tumor cytokines.
-- cancer cells are dependent on glycolysis
    -- this helps them avoid mitochondria's oxidant related cell death issues
    -- forcing them to use mitochondria creates burst of free radicals
    -- limit sugar intake, increase exercise.....helps

Tumor Necrosis Factor

- soluble TNF Receptor Type 1 = sTNFRT1
- sTNFRT1 is shed from the cancer cell surface by proteolytic cleavage…it retains the ability to bind TNF with high affinity, which antagonizes binding to TNF cell surface receptors.
- TNF directly induces apoptosis
- Vascular endothelial cells are induced to apoptosis by TNF
- IL-2 indirectly stimulates TNF production.
- TNF-Related Apoptosis-Inducing Ligand [TRAIL/Apo2L]
  -- corresponding death receptor…….DR4, DR5
- TNF antagonist = IgG

Fas ligand (FasL, CD95L)
- Fas L is a cytokine that induces apoptosis by binding to its cell surface receptor called Fas. FasL is restricted to certain types of cells, but Fas is expressed on most cells.
- activated T & NK cells produce Fas L.
- FasL can protect tissues from immune system attack.
- neutrophils may not have Fas receptors and can thus avoid destruction by FasL.
- FasL causes peritoneal exudate cells (PEC) to release IL-1-beta that attracts neutrophils
- cell surface molecule belonging to the tumor necrosis factor/nerve growth factor family
- inducibly expressed on T,B, and NK cells during activation of the immune system.
- engagement of Fas by FasL can result in apoptic death of the Fas-bearing cell.
- Fas/FasL interactions downregulate immune responses by inducing T cell apoptosis
- mutations in Fas or FasL.....make one susceptible to auto-immune diseases as a consequence of disrupted T cell homeostasis
- organs that express Fas such as liver, thyroid, pancreas...are susceptible to Fas/FasL mediated organ damage
- FasL expression on tumor cells can prevent immune mediated tumor rejection by triggering apoptosis on the attacking T cells

MUC-1
- member of mucin family….make mucus
- used by epithelial cells
- prevents apoptosis in cancer cells
- overproduction in cancer cells by 50 – 100 times

ErbB2
-- membrane receptor
-- in the epidermal growth factor family of receptors
-- over-expression in cancer predicts tumor aggressiveness

Tumor Suppressors

Tumor Suppressor genes and proteins
- there are at least 30 tumor suppressor genes

p53 protein is called the tumor suppressor. Induction of DNA damage in cells leads to accumulation of p53 and arrest of the cell cycle at G1. In this period of growth arrest, repairs are undertaken or if the damage is too great, the cell may commit suicide by apoptosis. Tumor cells in which p53 is inactivated cannot enter G1 arrest. These cells are therefore proposed to be genetically less stable and more prone to the accumulation of genetic damage at an increasing rate, which leads to the selection of malignant clones with an improved growth advantage. In this way, p53 in proposed to be the guardian of the genome. Loss of p53 is correlated with a loss of blood vessel proliferative inhibition (angiogenic inhibition of the tumor)

- p53 can be activated by UV light
- transforming growth factor beta (potent inhibitor of cellular proliferation....tumor suppressor)
- tumor suppressor genes = p40, p51a, p51b, p53, p73
- anti-apoptosis gene = bcl-2, expressed in cancer cells, but not normal cells
- p53 deficient cells...more resistant to radiation therapy than cells containing normal p53.
- loss of p53 correlates well with tumor aggressiveness
- there are 2 copies of the p53 gene.....Li-Fraumeni syndrome = inherited defect in one of the p53 genes = high development rate of cancer
- p53 induces apoptosis by acting as a transcription factor, activing expression of numerous apoptosis mediating genes
- several p53 induced genes encode proteins that regulate the redox state of cells. DNA damage causes the p53 protein to turn on genes whose products generate free radicals that damage mitochondria, whose contents (ie. cytochrome C) leak out and activate apoptotic caspases.
- p53 can cause an upregulation of Bax, one of the cell death promoting members of the Bcl-2 family
- PTEN switches off cell growth signals by dephosphorylating phospholipids
  - is mutated in breast & prostate cancer
- Fragile Histidine Triad (FHIT).....tumor suppressor gene
- ATM gene.....produces a protein that activates p53
- decreasing cellular polyamines increases expression of the p53 gene.....polyamine depletion leads to cell growth inhibition
- decreasing cellular amine levels inhibit cell renewal
- cellular polyamines.....spermidine, spermine.....their precursor = putrescine

- DCC gene for Deleted Colorectal Carcinomas…..a tumor suppressor gene
-- BRCA1 is a component of the RNA polymerase II
-- BRCA1 tumor suppressor protein affects the transcription process as a RNA polymerase II--bound protein
- p27…..inhibitor of cell cycle……decrease in p27 occurs in at least half of carcinomas…..in some cancers the protein has moved outside the nucleus where it can not affect cell proliferation
- p27 is an inhibitor of cyclin-dependent kinase 2 [cdk2]……cdk2 activates E2F1 transcription factor, promoting DNA reeplication
- TGF-beta mobilizes p27, enabling it to bind and inhibit cdk2
- Akt is a protein kinase that can keep p27 out of the nucleus……..Pten is a tumor suppressor that functions to reverse accumulation of Akt. Pten mutation allows accumulation of Akt, which keeps p27 out of the nucleus

mutated tumor suppressors
--- mutated pro-apoptosis gene [BAX]

p53
- muscle contraction increases phosphorylation

PTEN
-- tumor suppressor
-- loss of function is common in cancer
-- at least 50% of breast cancer patients have mutation of PTEN
-- degree of loss of PTEN predicts tumor stage and grade
-- complete loss of PTEN more common in metastatic cancer than other tumors
-- critical role in antiviral immunity.....production of type I interferon.

Apoptosis
- The sequence of morphological changes in apoptosis can be completed in less than an hour.
- Death commitment signals converge to activate the central executioner...the caspase cascade
- cell surface death receptors such as Fas are activated, their tails that extend into the cell's cytoplasm bind to adaptor proteins such as Fas Associated Death Domain protein (FADD). The Fas-FADD complex thing binds to and activates caspase-8, which initiates the lethal proteolytic cascade of apoptosis execution.
- mechanism by which tumor cells can kill T-cells.....Fas ligand (FasL) is on the surface of T-cells. FasL then binds to Fas, a cell surface receptor (on the tumor cell). This activates Fas, which intiates an intracellular apoptotic signal.
- CED-4 receives a death commitment signal and subsequently binds to CED-3, causing it to release active CED-3. CED-9 is localized to the outer membranes of mitochondria and other intracellular membranes, binds to CED-4 and prevents activation of CED-3. Thus CED 3 & 4 induce apoptosis, and CED-9 prevents it.
- humans have a CED-4 homologue that induces apoptosis, called Apoptotic Protease Activating Factor-1 (Apaf-1). When cytochrome C binds to Apaf-1, Apaf-1 is able to bind to and activate human caspase-3, intiating the caspase cascade. Apaf-1 has a binding site for ATP.....ATP level in an injured cell may play a critical role in deciding whether the cell has sufficient energy to die by apoptosis, or rather by energy independent necrosis. Apaf-1 can also bind to CED-9, which can sequester Apaf-1 away from caspase-3, thus suppressing apoptosis.

The protein products of genes ced-3 and ced-4 are required for the execution of apoptosis. ced-9 prevents apoptosis by inhibiting the activation of ced-3 and ced-4. CED-3, a cysteine aspartly protease (called caspase), when activated it cleaves a variety of cellular proteins, inactivating some and activating others. These death substrates of the CED-3 caspase include;
- DNA repair enzymes (it will inactivate them)
- endonucleases responsible for cleaving the apoptotic cell's DNA (will activate them)

The activation of caspases causes breakdown of normal barriers between cellular compartments, wreaking havoc within the cell but leaving the membrane relatively intact.
- defective regulation of programmed cell death may play a part in the etiology of cancer, AIDS, autoimmune diseases, and degenerative diseases of the central nervous system.
- endonuclease degrades DNA
- Bax, Bad, cell death promoter genes
- Bax is pro-apoptotic……cells lacking Bax are resistant to apoptosis [Bax is member of Bcl-2 family]
  -- half of all colon cancers have mutated Bax gene
- use of d-alpha-tocopherol succinate [alpha-TS] during radiation therapy enhances tumor chromosome damage, and protects normal cells

Cell Death Suppressors
- CED-9 is a bcl-2 family cell death suppressor
- bcl-2 is a family of genes that can suppress or promote apoptosis
- Bcl-2, Bcl-x cell death suppressor genes.....potent inhibitor of microtubule integrity. Upregulation of bcl-2 of hypophosphorylated bcl-2 is cause of the most common lymphoma in the western world. Anti-microtubule agents cause apoptosis by inducing bcl-2 phosphorylation.
- in people with autoimmune disease, their immune cells may have a high concentrations of bcl-2.
- premature or excessive cell loss during aging can lead to organ dysfunction and disease.
- bcl-2 is highly expressed in neurons that are undergoing neurotrophin deprivation
- more than 90% of metastatic tumors overexpress bcl-2

- extract of bark from an East African evergreen tree contains betulinic acid....destroys tumor cells by inducing apoptosis. It interupts the cell cycle in the G0/G1 phase. It is produce by many plants species in small amounts. A related compound, butulin is produced in large amounts in the bark of birch trees.
Survivin is an anti-apoptotic bcl-2 protein expressed in most common human cancers
Retinoids reduce levels of bcl-2 cell death suppressors

Oxidants
- estimation of oxidative damage = 10 to the 4th nucleotides….per cell…..per day
- In humans the number of oxidative hits to the DNA per cell per day is ~10,000. Oxidative lesions of DNA accumulate with age.
- Oxidatively modified proteins are degraded to their constuent amino acids.
- 8-hydroxyde oxyguanosine = by product of DNA oxidative damage [goes out in urine]
- gain of electrons = reduction
- loss of electrons = oxidation
- the tissue losing electrons is being "oxidized".
- there are 3 primary ROS....O2-, H2O2, OH
- excess electrons are donated to oxygen, generating a superoxide anion
- superoxide anion is reduced by the superoxide dismutases to hydrogen peroxide. Hydrogen peroxide is reduced to water by catalase and glutathione peroxidase
- Free radicals can be defined as molecules or ions containing an unpaired electron (called a radical), and capable of existing independently (free).
- Molecular O2 contains two unpaired electrons with parallel spins and is therefore a radical itself.
- In mitochondria, there takes place a reduction of molecular oxygen, one electron at a time. Intermediate steps in this process exist, thus things gradually reduced oxygen during these steps is called an intermediate.
- Intermediates produced in this process are oxygen-derived free radicals. These free radicals, due to their unpaired electron, are highly reactive with tissue proteins and fats, inciting oxidative damage. Some of these reactive intermediaries may escape from the process of complete reduction and react with tissues, and produce other reative oxygen species (ROS).
- ROS represent a broader spectrum of species including nonradical derivatives of oxygen, thus these are not the same as oxygen free radicals.
- In normal phagocytosis, ROS destroy invading microoganisms by a process commonly referred to as respiratory burst.
- ROS are capable of inducing genes which encode transcription factors involved in the induction of cell growth, differentiation, and development.
- Through this mechanism in early inflamation, ROS may contribute to wound healing. ROS are also known to activate nuclear factor-kB, the transcription factor in the cytosol that controls transcription of cytokine genes including interlukin-2 and TNFa. TNFa promotes angiogenesis, a process critical to wound healing.
- Multiple unsaturation points in polyunsaturated fatty acids (PUFA) make them highly susceptible to ROS attack and oxidative damage.
- ROS inhibits calcium ATPase from transporting calcium back into the sarcoplasmic reticulum (possible cause of cramping following damage inducing exercise).
- high external levels of potassium causes membrane depolarization and activation of T-tubule calcium channels and receptors that activate calcium release from the SR (ROS may cause an increase in potassium that increases involuntary contraction)
    - electrons are donated to oxygen during the electron transport process in mitochondria
- programed cell death may be induced by the release of Cytochrome C from the mitochondria
    - Cytochrome C and dATP activates caspase, a protease
- Nitric oxide (NO) is a biological messenger, formed fro arginine by 3 nitric oxide synthases (NOS)
- nitric oxide synthase has a binding site for nitric oxide
- other substances (arginine analogs) can compete for the binding site, thus inhibiting NO production
- arginine analogs = nitro arginine monomethyl ester (NMME), nitro arginine methyl ester (NAME)
- Nitric oxide is short lived

Antioxidants
- The possible mechanisms by which antioxidants protect against oxygen toxicity are these;
    - prevention of ROS formation
    - interception of ROS attack by scavenging the reactive metabolites and converting them to less reactive molecules and/or by enhancing the resistance of sensitive biological targets to ROS attack
    - avoiding the transformation of less reactive ROS to more deleterious forms
    - facilitate the repair of damage caused by ROS
    - triggering the expression of genes that encode antioxidant proteins
    - providing favorable environment for the effective functioning of other antioxidants.
- SOD, catalase, glutathione peroxidase, each has an irreplaceable function, catalysing electron transfer to ROS
- To obtain best results, antioxidant supplementation protocols should consider the requirement of all components of the chain.
- Vitamin E in the absence of adequate amounts of regenerating agents will fail to provide full-strength antioxidant protection.
- Pentane is a possible by product of oxidative lipid damage or lipid peroxidation. It is exhaled, thus it can be used as measure of oxidative stress.
- Oxidative stress is suggested to be implicated in the generation of oxidative muscle fatigue. Free radicals are one of the factors that contribute to oxidative muscle fatigue. It may affect the potassium transport system (affects recovery of K+ during repeated contractions).
- Endogenous antioxidant defenses are modulated by the state of physical training. 5 minute interval high intensity training is superior to continuous exercise in upregulating muscle antioxidant defenses.
- Estrogen (E2) has the ability to inhibit generation of superoxide radical.
- estrogens have been shown to be powerful antioxidants
- estrogens decrease oxidative modification of LDL....this may be the mechanism by which estrogens protect from heart disease.
- the chemical structure of estrogen allows for donation of a hydrogen atom to a peroxly radical. This allows free radical scavenging.
- Red wine, not white wine contains polyphenols -- may be an antioxidant

- ascorbic acid and glutathione are recycled as they are used
    - ascorbic acid is recycled by GSH and dehydroascorbate reductase
    - gluthathione is recycled by GSH reductase

Superoxidide Dismutase (SOD)
- excess electrons are donated to molecular oxygen to generate superoxide anion
- superoxide anion is reduced by superoxide dismutases to hydrogen peroxide.
- Hydrogen peroxide is reduced to water by Catalase (CAT).
- SOD has 3 isoforms.....SOD 1, SOD 2, SOD 3
- SOD1 comprised of copper and zinc
- reacts with superoxide anion
- works by removing one electron and placing it on a second superoxide anion. Together with two protons, the second superoxide is converted into hydrogen peroxide. The hydrogen peroxide is removed by the catalase or glutathione peroxidase enzymes.

Glutathione (GSH)
Spontaneously scavenges a wide variety of ROS. During the course of its antioxidant action, reduced glutathione gets oxidized to glutathione disulfided (GSSG). In the presence of NADPH, GSSG may be reduced to GSH by glutathione reductase (GRD). If the oxidative challenge is severe, the rate of GSSG formation may exceed the capacity of the cell to reduce the disulfide. In this situation, the cell will expel GSSG. GSH modulates activity of redox sensitive transcription factors. The SH pool contributed by glutathione and dihydrolipoate plays a central role in regenerating vitamins C and E from their radical forms. The antioxidant activities of selenium and vitamin B6 are glutathione dependent. Selenium functions as a cofactor of glutathione peroxidase, an enzyme that requires glutathione as its substrate for the scavenging of hydrogen and other peroxides. Vitamin B6 facilitates the availability of selenium for glutathione peroxidase.
- levels elevate within 24 hours post stimulus
- GSH inhibition increases suseptibility of the cochlea to noise induced damage
- replenishing GSH attenuates noice induced cochlear damage

Multi-Drug Resistance gene (MDR 1)
is responsible for failure of chemotherapy in many cancers. It is up-regulated by mutant p53 proteins. The presence or absence of the gene for the protein of MDR is an important prognostic indicator of response to chemotherapy. One mechanism of multi-drug resistance is the expression of mdr1 gene, and its product, P-glycoprotein. P-glycoprotein confers resistance to a wide range of unrelated drugs by functioning as an efflux pump that reduces intracellular drug concentrations.

Metastisis
Membrane-Type Matrix Metalloproteinase (MT-MMP) are a family of proteolytic enzymes contributing to the degredation of the extracellular matrix, a process that enables cell migration, whether for tissue development, repair, or invasion. Gelatinase A is a MT-MMP, and is produced by stomal cells of tumors. It can be activated by tumor cell surfaces, and tumor spread is correlated with increased concentrations of its active form, which degrades molecules such as collagen. MT-MMP may be an important factor triggering tumor cell invasion in that its association with the plasma membrane leads to degradation of the extracellular matrix in the vicinity of the tumor cell.

Angiogenesis In Tumor Growth
Angiostatin suppresses tumor growth by inhibition of angiogenesis. Tumors produce both inhibitors and promoters of angiogenesis. When the tumor is removed/destroyed, the largest source of angiogenesis inhibition is also removed, thus there can be other growths in other portions of the body. Rapid metastatic growth occurs after removal of certain primary tumors, including those in lung, colon, breast, and bone.
- Thrombospondin-1 [TSP-1]……inhibitor of angiogenesis by inducing apoptosis of microvascular endothelial cells that form new blood vessels
- Inhibitors…..angiostatin, endostatin, 2-methoxyestradiol, thrombospondin-1, naspin—protein induced by a tumor suppressior gene
- promoters….vascular endothelial growth factro [VEGF], FGF-1, FGF-2
- Macrophage derived peptide [PR39]….inhibits degredation of [hypoxia-inducible factor-1 alpha] which results in increase of angiogenesis
- hypoxia-inducible factor-1 alpha…regulates production of VEGF receptor-1
- VEGF causes immuno-suppression
- VEGF is associated with early recurrence [within 6 months……and w/short survival]

Prostate Specific Antigen [PSA]

-- 2.5 nanograms per milliliter may be as predictive as 4ng per milliliter or greater
-- prostate cancer is –not—rare in men with PSA at 4ng or less
-- high grade cancers increase from 12% at PSA 0.5ng to 25% at PSA 3.1 – 4ng
-- prevalence of prostate cancer ….
6% w/PSA at 0.5ng
10% w/PSA at 0.6 - 1ng
17% w/PSA at 1.1 - 2ng
24% w/PSA at 2.1 - 3ng
27% w/PSA at 3.1 - 4ng

Brain Cancer

medulloblastoma
-- medulloblastoma is the most common malignant brain tumor in children
-- cerebellum is the target of transformation in medulloblastoma, the most common malignant brain tumor in children.

Glioma
-- gliomas recruit and manipulate microglial function to promote their growth
-- gliomas trigger S-nitrosylation of microglial caspase-3.....which initiates a tumor-promoting phenotype
— miR-370-3p is down-regulated in glioma
— miR-370-3p suppresses glioma cell growth by directly targeting β-catenin
——— β-catenin….protein involved in regulation cell adhesion and gene transcription
———-Mutations and overexpression of β-catenin are associated with many cancers

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Leukemia
4 types.....
1. Acute myeloid leukemia (AML)
2. Chronic myeloid leukemia (CML)
3. Acute lymphocytic leukemia (ALL)
4. Chronic lymphocytic leukemia (CLL)
- adding folate to diet of pregnant women can reduce leukemia in the offspring
- [A.L.L.] acute lymphoblastic leukemia
- stem cells or their progenitors are altered
- p53 not altered, but components of the p53 pathway are altered = p14, p21, p16 tumor suppressor
- also altered is the tumor suppressor retinoblastoma protein [RB]
- some cases originate in utero
- lower leukemia rate in offspring of pregnant women given folate
- B cell Chronic Lymphocytic Luekemia [B-CLL].....expansion of small B lymphocytes….most frequent adult luekemia
- Leukemic CD5 and/or CD23 lymphcytes accumulate in the circulation……have redued ability to undergo apoptosis…..and/or overexpression of BCL2 gene [anti-apoptotic]
- consists of stem cell mutation/transformation…..mutation of B-cell progeninator
- people with mutated V(H) genes…..have average survival of 25 years
- people with unmutate V(H) genes…….have progressive disease with average survival of 8 years
- [purinergic P2X receptors….family of 7 receptors] P2x7 receptor….found on macrophages, dendritic cells, and B-CLL cells…….chemical gated ion channel…….mediates cell death in B-CLL
- long term stimulation of P2x7 can induce apoptosis…..lower stimulation leads to cell proliferation
- human T-cell virus type-1….[HTLV-1]……..causes leukemia by interfering with a tumor suppressor
- DCC gene expression [a tumor suppressor] is reduced or absent in leukemias
- Myeloid leukemia = 2 cell abnormalities
---- abnormal capacity for self-replication
---- abnormal capacity for autocrine stimulation
- hemopoietic growth factors can inhibit leukemic stem cells from self-regeneration
- predisposition to juvenile leukemia = mutations in NF1 gene [neurofibromatosis type 1]
- NF-1 gene codes for tumor suppressor protein that negatively regulates Ras proteins
- both alleles of NF-1 are inactivated in leukemic cells in some patients with neurofibromatosis type 1
- in B-cell leukemia, IL-6 receptor concentration is elevated, and is highest in people who are non-responders to treatment
- there is positive correlation between IL-6 receptors concentration and lymphocyte count in B-cell leukemia patients
- Leukimia Inhibitory Factor (LIF)……
- decreases binding to IL-6 receptors, by decreasing the number of receptors on the cell surface, by down regulating mRNA
- causes activation of transcription factors Stat-1, Stat-3, and Stat-5a
- these factors are members of the IL-6 family of cytokines
- produced by activated monocytes and T lymphocytes.....and by stimulated osteoblasts

- induces growth arrest of myeloid leukemic cells through the LIF receptor
- causes activation of stat-1, stat-3, and stat-5...signal transducers and activators of transcription...can lead to cell growth arrest
- potent bone remodeling agents
- stimulates myoblasts.....increases muscle mass by stimulating hypertrophy
- neurotrophic for motor neurons
- induces differentiation of macrophages
- folate supplementation in pregnancy reduces the risk of common acute lymphoblastic leukaemia in the child

[acute] Lymphoblastic leukaemia [childhood]
- malignant disorder of lymphoid progenitor cells
- origin may be in haemopoietic stem cell that has multilineage development ability
- location = genes for immunoglobulin receptors or T-cell receptors
- less than 5% inherited, only 10% co-occurance in twins
- industrialized, affluent, modern societies.....have higher incidence
- clusters in new towns
- children cure rate 80%
- adult cure rate is low
- high birth weight associated with childhood leukaemia
- children....exposure to environmental toxins [inhibitors of topisomerases, and reduced ability to detoxify them]
- prenatal origin highly likely in children [maternal occupation, tobacco/alchol use]
- reduction in Smad-3 production and loss of p27….together promote leukemogenesis
- Smad-3 is a part of Transforming Growth Factor-beta cytoplasm signaling for tumor suppression
- TGF-beta binds to its receptor, that activates Smad-3 function

Chronic lymphocytic Leukemia
--- commonest form in Europe and north America
-- mainly older adults
-- balance between proliferation and apoptosis
-- nearly all patients relapse
-- early detection makes no difference in outcome
-- about 4 of every 100,000 Americans develop leukemia
-- rare in people younger than 50, averge age at death = 70 - 74
-- In Asian Americans incidence = 5 times lower than non-Asian Americans
-- Jewish Americans incidence = 2 times higher than non-Jewish Americans
-- most frequent deletion on chromosome 13q [55%], deletion of chromosome 17p's p53 gene = 7%
-- deletion of 17p or 11p = poor prognosis.....this seen in advanced stages
-- 13q deletions may cause missing microRNA that affects BCL2, preventing apoptosis.....affecting the balance between proliferation and apoptosis
-- patients may share a common mechanism of cell transformation or

Chronic myeloid leukemia
-- mutation of a chromosome....results in production of a protein kinase that chronically activates production of immune cells, rather than normal start Nd stop of cell production.
-- tumour cells implement induction of T-cell exhaustion
--- T-cell exhaustion = state of hypo-responsiveness from continuous antigenic stimulus
--- myeloid leukaemia-derived co-stimulatory signals on CD4+ T helper (Th) cell exhaustion
----- limits anti-tumour immunity
-- co-stimulatory molecules found on myeloid leukaemia cells = CD86 and inducible T-cell co-stimulator ligand
--- supports CD4+ T helper cell activation and proliferation
--- under continuous stimulation they become functionally exhausted
--- defined by up-regulation of.....
----- programmed cell death 1 (PD-1)
----- cytotoxic T-lymphocyte antigen 4 (CTLA-4)
----- lymphocyte activation gene 3 (LAG3)
----- T-cell immunoglobulin and mucin domain-containing protein 3 (TIM-3) inhibitory receptors

Lymphoid cells
-- population of innate lymphoid cells in the tumor microenvironment.....
--- limits T cell expansion and cytokine production
--- associates with early recurrence in patients with cancer
-- depletion of this regulatory immunosuppressive cell population overcomes this effect

Pancreatic cancer

— arise from microscopic non-invasive epithelial proliferations within the pancreatic ducts [pancreatic intraepithelial neoplasia]
— 4 major driver genes for pancreatic cancer.....
    —— KRAS
    —— CDKN2A
    —— TP53
    —— SMAD4
— KRAS mutation and alterations in CDKN2A are early events in pancreatic tumorigenesis

Breast Cancer
- when breast cancer cells reach the axillary lymph nodes, they can continue to grow, often causing swelling of the lymph nodes in the underarm area. If breast cancer cells have grown in the axillary lymph nodes, they are more likely to have spread to other organs of the body as well.
- Infiltrating (invasive) ductal carcinoma.....starting in the milk passage or duct, of the breast, this cancer breaks through the wall of the duct and invades the fatty tissue of the breast.
- infilatrating ductal carcinoma accounts for about 80% of breast cancers
- Infiltrating (invasive) lobular carcinoma.....starts in the milk producing glands. 10 - 15% of invasive breast cancers are invasive lobular carcinomas
- estrogen and xenoestrogens stimulate growth-arrested breast cancer cells to enter the growth cycle
- aromatase is present in high concentrations in the ovaries of pre-menopausal women
- post-menopausal women have decreased aromatase in ovary……have some in breast, body fat
- aromatase has estrogen producing stimulatory affect on estrogen receptors
- aromatase inhibitors decrease estrogen receptor activation…..may work better than tamoxifen
- 2 estrogen receptors……ER-alpha…..ER-beta…..role of ER beta in breast cancer may be unclear

Ovarian Cancer
- women who have T-cells in the tumor have better outcomes [live 3 – 4 times as long]
- about 50% of patients w/advanced cancer have intra-tumor T-cells
- Women who have lower VEGF levels [live 3 times less long]

Prostate Cancer
- androgen receptors can mutate to accept cortisol…result in tumor growth
- prostate cancers progress from androgen dependent growth, to androgen independent growth
- androgen receptors are involved in prostate tumor growth and development…..80% of androgen independent tumors have high expression of androgen receptors…….in some there is overexpression, in others the receptors are mutated

Skin Cancer
- Oxybenzone in sunscreens is absorbed through the skin. Oxybenzone is a benzophenone derivative. 1 - 2% is absorbed over a 10 hour period.
- Benzopyrene is in cigarette smoke, causes damage to p53 gene of lung cells.
-- Ultraviolet radiation (UV) represents one of the most important environmental factors affecting human health, especially with regard to its hazardous effects on the suppression of the….immune system…
-- Epidermal Langerhans cells (LC) are considered as the main targets of UV, as UV inhibits their antigen-presenting activity and their capacity to stimulate allogeneic type 1 T cells.
-- In human skin, IL-10 is mainly produced by dermis CD11b + macrophages and neutrophils that infiltrate epidermis after intense UV.

Colon Cancer

- DCC gene for Deleted Colorectal Carcinomas…..a tumor suppressor gene
- DCC gene located on chromosome band 18q21 is deleted in at least 88% of cases, reduced or absent in leukemias
- the DCC protein in similar to neural adhesion molecules and other cell surface glycoproteins