PRINCIPLES OF NEOPLASIA

NEOPLASIA STARTING POINTS

1. Cancer-Greek word for crab “karkinoma”
    a. Tumor-swelling
2. Genetic disorder caused by DNA mutations
3. Neoplastic cells are either benign or malignant
4. Tumor nomenclature
    a. based on lineage of differentiation (type of tissue produced and whether benign or tumor)
5. Mutations & epigenetic alterations

HALLMARKS OF NEOPLASIA

1. Unregulated

2. Irreversible

3. Monoclonal
    a. From single mother cell

CANCER SCREENING

1. Begins as 1 mutated cell >> takes approx. 30 cell divisions before earliest clinical sx are detectable
2. Each cell division results in increased mutations
3. Screening seeks to catch dysplasia (pre-cancerous) before carcinoma or carcinoma before symptoms
    a. Detected late=poor prognosis (usually Mets before detection)
    b. Low sx producing cancers
4. Screening includes:
    a. CIN >> cervical dysplasia before carcinoma
    b. Mammography >> in situ breast cancer before invasive or clinically palpable
    c. PSA and DRE >> detects before it spreads
    d. Occult testing and colonoscopy >> detect colonic adenoma before carcinoma

FEATURES OF MALIGNANT VS BENIGN GROWTHS

Benign	Malignant
Grow slowly	Grow rapidly
Well defined capsule	Not encapsulated
Not invasive	Invade local structures
Well-differentiated	Poorly differentiated
Low mitotic index	High mitotic index
Do not metastasize	Metastasize

CARCINOMA IN SITU

1. group of abnormal cells that remain in the place where they first formed (have not penetrated basement membrane)
2. They have not spread
3. may become cancer and spread into nearby normal tissue
4. Called stage 0 disease
5. breast, cervix, skin, oral cavity, esophagus, and bronchus

6. 3 fates:
    a. Can remain stable for a long time
    b. Can progress to metastatic dz
    c. Can regress and disappear

TUMOR NOMENCLATURE

Linage	Benign	Malignant
Parenchymal tissues Epithelium/skin Glands	Squamous cell papilloma adenoma or papilloma	Squamous cell carcinoma adenocarcinoma
Mesenchymal connective tissue, BV, lymphatic sys	lipoma Fibroma Chondroma Lymphangioma	liposarcoma Fibrosarcoma Chondrosarcoma Lymphangiosarcoma
Lymphocyte		lymphoma or leukemia
Melanocyte	nevus	melanoma
Neuronal tissue	Glioma Meningioma	Meningeal sarcoma

CANCER EPIDEMIOLOGY – 2ND LEADING CAUSE OF DEATH IN BOTH ADULTS AND CHILDREN

Adults most common cancers**

1. Breast/prostate
2. Lung
3. Colorectal

Mortality rate in cancers

1. Lung
2. Breast/prostate
3. Colorectal

Children

1. Accidents
2. Cancer
3. Congenital

*** skin cancer top of list but non-fatal most of time***

CANCER EPIDEMIOLOGY

LIFESTYLE & ENVIRONMENTAL RISKS

1. Nutritional intake, ETOH, smoking
2. Environmental – UVB/UVA, natural and medical radiation, workplace exposures, involuntary and unknown exposures
3. Lack of exercise, obesity/overweight
4. Sexual practices
5. Prescribed and illicit drugs
6. Socioeconomic factors
7. Carcinogenic exposure- water, air, soil

CHRONIC INFLAMMATION

1. Microenvironment participates in complex signaling, this facilitates tumor proliferation and metastasis
2. Infiltration of immune complexes and inflammation creates a permissive tumor enrichening environment

TOBACCO

1. CARCINOGENIC AND MOST IMPORTANT CAUSE OF CANCER!!!

2. ACCOUNTS FOR 1 out of 5 DEATHS
    a. AND YET IS SINGLE MOST PREVENTABLE RISK
        i. 80% MALE LUNG CANCER DEATH BURDEN
        ii. 50% FEMALE LUNG CANCER DEATH BURDEN
    b. Besides lung, also increases risk for lip, throat, nasal cavity, sinus, esophagus, pancreas, kidney, colon, uterus, cervix, and acute leukemia

Key DIET risks ??

1. NO NO's??
    a. cooking techniques (no/limited grilling, curing/smoking meats/charring)
    b. Heterocyclic amines
    c. N-nitroso compounds (NOCs)
    d. naturally occurring carcinogens in molds and alkaloid products
    e. Nitrates and nitrites
    f. Alcohol

2. Yeah yeah' s??
    a. modulators of methylation –b vitamins, folate, betaine serine, methionyl, and choline
    b. resveratrol (red wine) and grape juice
    c. garlic and cruciferous vegetables
    d. antioxidants
    e. tea (green)

OBESITY AND CANCER

1. OBESITY
    a. increased risk of
    b. endometrium, colorectal, kidney, esophagus, breast (post meno), and pancreas
    c. emerging is thyroid, gallbladder, liver, ovary, prostate, and nhl
    d. also a poor prognostic factor for several cancers
    e. based on bmi
    f. hyperinsulinemia and sex steroids also have stimulatory effects

2. Energy Balance
    a. energy expenditure/balance
    b. resting metabolic rate + thermic effect of food + energy needed to digest+ physical activity (does not include lean body mass)

***Further studies needed to evaluate whether obesity drives cancer or whether the energy balance has a greater effect on cancer

ETIOLOGY OF CANCER

1. 3 classes of carcinogenic agents
    a. Chemicals
    b. Radiant energy
    c. Microbial products
2. DIRECT: Do not require any metabolic conversion to become carcinogenic
    a. Alkylating agents
    b. Anti-cancer drugs
3. INDIRECT: Require metabolic conversion to carcinogen
    a. Hydrocarbons

COMMON CARCINOGENS

Carcinogen	**Types of cancer**
Arsenic Asbestos Aflatoxins	Lung cancer Mesothelioma Liver cancer
Benzene	Leukemia
Nickle Cadmium Vinyl Chloride	Lung cancer, nasal sinus cancer Lung Cancer Liver cancer/hepatoangiosarcoma
Alcohol and smoking	Many different types of cancer
HPV, EBV, HCV, HBV, HHV-8	Liver, Cervical, Uterine, vaginal/vulva
Alkylating agents	Leukemia

CARCINOGENESIS STARTING POINTS

1. Formation is initiated by damage to stem cell DNA
    a. Initial damage overcomes repair but is not lethal caused by carcinogens; inheritance patterns, or be spontaneous and random
    b. Important carcinogens include but not limited to chemicals, oncogenic viruses, radiation, toxins (environmental)
2. mutations will eventually disrupt 4 key regulatory systems allowing for tumor promotion (growth) and progression (spread)
    a. Proto-oncogenes, tumor-suppression genes, genes responsible for DNA repair and regulation of apoptosis

3. Accumulation of complimentary mutations in a step wise fashion over time

BIOLOGY OF CANCER CELLS

1. Complex genetic disease
2. Cumulative genetic changes during aging
3. Mutational or epigenetic
    a. Point mutations
    b. Chromosomal translocations
    c. Gene amplification
    d. Driver mutations
    e. Epigenetics
    f. Malignant transformation
4. Once established, tumors “evolve” genetically over time
    a. Darwinian survival of the fittest

PROTO-ONCOGENES /ONCOGENES

1. Proto-oncogenes (non-mutant) are necessary for cell growth and differentiation
    a. Mutations of proto-oncogenes lead to oncogenes and unregulated cellular growth (increased proliferation)
    b. GF, GFr, signal transducers, nuclear regulators, and cell cycle regulators
    c. Oncogenes are mutant
2. 3 main mechanisms
    a. Deletion or point mutation hyperactive or loss of regulation and gene is overexpressed
    b. Gene amplification normal protein mRNA overexpressed
    c. Chromosomal rearrangement hyperactive or overexpressed fusion

GENOMIC HALLMARKS

1. Uncontrolled cellular proliferation
    a. Normal cells only enter proliferation if growth factors are present via TKR receptors
    b. RAS, D cyclins
    c. GAPS apply brakes to RAS activation
2. Proto-oncogenes
3. Oncogenes
    a. Mutated genes that cause excessive cellular growth

SELECTED ONCOGENES AND TARGETS

1. FGF3= amplification/overexpression
    a. Osteosarcoma, stomach cancer, breast cancer, melanoma
2. KRAS =GDP and phosphate =Growth factor stimulation –on/off switch

    a. Melanomas, leukemias, colin carcinoma, others
3. MYC transcript factor activators=Translocation
    a. Burkitt's Lymphoma
4. CDK4 =amplification or point mutation
    a. Glioblastoma, melanoma, sarcoma

TUMOR SUPPRESSOR GENES

1. Regulate cell growth and hence "suppress" the risk of tumor growth
    a. Rb and p53
2. These are inactive and allow uncontrolled growth
3. In response to DNA damage p53 (guardian of the genome) slows the cell cycle and upregulates DNA repair enzymes if not possible, then apoptosis is started
    a. Both copies of p53 must be blocked to allow tumor formation
    b. Loss is seen in >50% all cancers
4. Example: Rb gene if mutated = retinoblastoma
    a. Retinoblastoma

THE WARBURG EFFECT

1. Cancer cells demonstrate a distinctive form of cellular metabolism
2. High levels of glucose uptake
    a. Increased conversion of glucose to lactose (fermentation) via glycolytic pathway
    b. Aerobic glycolysis (2 ATPs)
    c. "glucose hunger" is what the PET scans look for in tumor cells when injected with glucose solution Warburg effect
    d. Reprogrammed metabolism is produced by signaling cascades of growth factor receptors (same pathways deregulated by mutations in oncogenes and tumor suppressor genes)

EVASION OF CELL DEATH: REGULATORS OF APOPTOSIS

1. Individual cells have programmed cell death under certain circumstances
    a. 2 pathways- intrinsic and extrinsic
    b. Pathways are dysregulated in cancers
    c. Evade and suppress apoptotic pathways=no cell death
2. Evade senescence
3. Evasion of mitotic crisis
4. Self-renewal
5. Example: BCL2=Normally blocks cytochrome C (stopping release from mitochondria) and inactivating apoptosis is lost therefore allowing for no apoptosis
    a. BCL2 is overexpressed in follicular lymphoma

b. B cells normally undergo apoptosis during somatic hypermutation accumulate and cause lymphoma

CANCER METABOLISM AND ENVIRONMENT

1. Hypoxic and acidotic
2. Parasites
    a. use what they need from nearby cells
3. Use glycolysis instead of OXPHOS
    a. which allows for more efficient and rapid growth (many oncogenes promote the switch to this)
4. Telomerase is necessary for cell immortality
    a. Normally they shorten with serial cell division, resulting in cellular senescence-in cancer these are upregulated which preserves them
5. Angiogenesis
    a. Production of new blood vessels is necessary for growth and survival
6. Avoiding immune surveillance
    a. Usually result production of abnormal proteins, but are downregulated (MHC1) in cancer and then are not destroyed by T cells (under surveilled)
    b. Immunodeficiency increases risk of cancer (less surveilled)
7. Autocrine stimulation –secrete their own growth factors

FUNDAMENTAL CHANGES W/ CANCER

TUMOR PROGRESSION

INVASION AND SPREAD

1. Accumulations of mutations eventually lead to invasion and spreading epithelial tumor cells are attached to one-another by cellular adhesions (E-cadherin) , this is downregulated, leads to dissociation of the cells, and less adherence, the cells attach to laminin and destroy the basement membrane also attach to fibronectin in the EC matrix and spread locally
2. Entrance into the lymphatic system and vascular spaces= metastasis

METASTASIS

1. Significant cause of pain and suffering with cancer, also major cause of mortality
2. Invasion and local spread is prerequisite for Mets, eventually the spreading cells with travel by invasion into blood and lymph system and must be able to attach to new environment
3. Lymphatic spread common with carcinomas
4. Hematogenous spread common with sarcomas
5. Seeding in cavities common with ovarian carcinomas

CLINICAL ASPECTS OF NEOPLASIA

1. Cachexia: progressive loss of body fat and lean body mass, accompanied by profound weakness, anorexia, and anemia, that is caused by release of factors by the tumor or host immune cells.
2. Paraneoplastic syndromes: symptom complexes in individuals with cancer that cannot be explained by tumor spread or release of hormones that are indigenous to the tumor "cell of origin."
    a. Endocrinopathies (Cushing syndrome, hypercalcemia)
    b. Neuropathic syndromes (polymyopathy, peripheral neuropathies, encephalopathy, neural degeneration, myasthenic syndromes)
    c. Skin disorders (acanthosis nigricans)
    d. Skeletal and joint abnormalities (hypertrophic osteoarthritis)
    e. Hypercoagulability (migratory thrombophlebitis, disseminated intravascular coagulation, nonbacterial thrombotic endocarditis)

GRADING OF CANCER

1. Grading: determined by cytologic appearance; based on the idea that behavior and differentiation are related, with poorly differentiated tumors having more aggressive behavior.
2. Microscopic assessment of differentiation
    a. Well differentiated >> Low grade- resembles parent tissue (GOOD)
    b. Poorly differentiated >> high grade not resembling parent (BAD)
3. Important in determining prognosis

STAGING OF CANCER

1. Staging: determined by surgical exploration or imaging
2. Assessment of size and spread
3. Key prognostic factor, more important than grade
4. Determined after final surgical resection of the tumor
5. TNM staging system
    a. T= tumor size and depth of invasion
    b. N= spread to regional lymph nodes
    c. M =Metastasis most important prognostic factor

CLASSIFICATION OF TUMORS

1. Now involves genetic testing and termed "personalized medicine"
2. Example
    a. Breast cancer- tumor expressing genes such as BRCA, EGF, HER2
    b. Tumor expresses? Estrogen receptor, progesterone receptor?
3. Subdivides cancer further for therapeutic and prognostic treatment
4. Breast, colorectal, GI, kidney, lung, melanoma, MM, some leukemia and lymphomas, some childhood

LABORATORY DIAGNOSIS OF CANCER

- Morphological Methods
    - Biopsy
    - Excision
    - FNA
    - Cytological
    - Immunochemistry
    - Flow cytometry
- Tumor markers
- Molecular diagnosis
    - Polymerase chain reaction (PCR)
    - Germline detection

TUMOR MARKERS

1. substances that are produced by cancer or by other cells of the body in response to cancer or certain benign (noncancerous) conditions
2. Most tumor markers are proteins but also include hormones, enzymes, antigens and antibodies
3. patterns of gene expression and changes to DNA have also begun to be used as tumor markers
4. Examples include:
    a. Estrogen receptor/progesterone receptor >>breast
    b. HER2/neu gene amplification or protein overexpression >>breast
    c. Prostate specific antigen (PSA)>> prostate cancer
    d. Thyroglobulin >>thyroid cancer

CANCER IN CHILDREN STARTING POINTS

1. Rare, but major cause of death in this age group
2. Most cancers originate from the mesodermal germ layer and embryonal tumors
3. Birth to 14 y/o
    a. Leukemia's and brain tumors account for >60% of cancers
    b. Neuroblastoma, sarcomas, and bone cancers less common
4. 15-19 y/o
    a. Hodgkin's' lymphoma, leukemia, germ cell tumors (testicular) CNS tumors, non-Hodgkin's, colon, thyroid, melanoma, sarcomas and breast/cervical

ETIOLOGY

1. Largely unknown
2. Tumor suppressor genes and oncogenes associated with childhood cancers
3. Chromosomal aberrations
4. Ionizing radiation
5. Drugs

6. Viruses

CANCER ETIOLOGY-CHILDHOOD CANCERS

1. Pre-natal exposure
    a. ??ETOH, smoking
2. Environmental (limited data and causation in studies)
    a. Radiation??
    b. Radon??
    c. Viral – EBV??
3. Prescribed medication
    a. DES; anabolic steroids, chemotherapy??

PROGNOSIS

1. More than 85% are cured
2. Mortality rates have significantly declined over the past 45 years
3. Advances in treatments and clinical trials are responsible
4. Young children particularly susceptible to long term sequela from treatment

NEOPLASTIC DISORDERS
SELECTED DISORDERS

LEUKEMIAS

Acute	Chronic
Characterized by undifferentiated or immature Quick/rapid onset Short survival time	More differentiated leukocyte but doesn't not function 100% normal Slower progression

ACUTE LEUKEMIAS

1. Starting points
    a. Neoplastic proliferation of blasts
    b. Defined as >20% in bone marrow
    c. Blast crowds out nml hematopoiesis resulting in acute phase
    d. AML or ALL

ACUTE LYMPHOBLASTIC LEUKEMIA

1. Starting points
    a. Neoplastic accumulation of lymphoblast's
    b. Diagnosed by
    c. >20% in bone marrow

    d. +nuclear staining for TdT (a DNA polymerase)
    e. TdT is absent in myeloid blasts and mature lymphocytes
    f. B-or T ALL based on surface markers
    g. Most commonly arises in children
    h. Down syndrome assoc
        a. after the 5 yr mark

2. Clinical presentation
    a. Fevers
    b. Anemia
    c. Bleeding
    d. Clotting/DIC
    e. palp lymphadenopathy
    f. Bone pain
    g. LUQ fullness
    h. Mediastinal mass

ACUTE MYELOID LEUKEMIA

1. Neoplastic accumulation of immature myeloid cells
2. Commonly seen in older adults (50-60 yrs)
3. Subclasses on cytogenic abnormalities; lineage of immature myeloid cells and surface markers
    a. Acute promyeloytic
    b. Acute monocytic
    c. Acute megakaroyoblasts
4. May also arise from pre-existing myelodysplastic disorders
5. Diagnosis/Laboratory
    a. >20% in bone marrow
    b. +staining for cytoplasmic staining for myeloperoxidase (MPO)

CHRONIC LEUKEMIAS

1. Neoplastic proliferation of mature circulating lymphocytes characterized by high WBC count
2. 2 main types
    a. CLL
    b. CML
3. Insidious onset seen in older adults
4. progressive accumulation of functionally incompetent lymphocytes, which are usually monoclonal in origin
5. "active disease" =therapy is initiated
    a. advanced stage

b. high tumor burden
c. anemia, thrombocytopenia
d. severe disease-related "B" symptoms

CHRONIC LYMPHOCYTIC LEUKEMIA

1. Proliferation of naïve B cells
2. Most common leukemia
3. Involvement of lymph nodes lead to generalized lymphadenopathy
4. Increased lymphocytes and smudge cells on smear
5. is called small lymphocytic lymphoma
6. Complications include:
    a. hypogammaglobulinemia- infection is the most common cause of death
    b. autoimmune hemolytic anemia; thrombocytopenia
    c. transformation to diffuse large B-cell lymphoma
        i. Richter transformation (Richter syndrome) marked clinically by enlarging lymph node or spleen

CHRONIC MYELOID LEUKEMIA

1. Neoplastic proliferation of mature myeloid cells
2. Driven by Philadelphia chromosome
    a. t (9,22)⍰ BRC-ABL fusion protein =inc kinase
    b. Presence of Philadelphia chromosome = pathognomic
    c. Massive myeloid hyperplasia of the bone marrow
    d. BCR-ABL fusion ⍰ causes abnormal expansion of myeloid cells
3. Splenomegaly is common
4. CML vs leukemoid reaction
5. No genetic or environmental links, only known etiology is related to ionizing radiation
6. Slight male preponderance; median age 65 yr

LYMPHOMA

1. Neoplastic proliferation of lymphoid cells that form a mass
2. Divided in Non-Hodgkin or Hodgkin
3. Some NHLs behave indolently with lymphadenopathy waxing and waning over years.
4. Others are highly aggressive, resulting in death within weeks if left untreated.
5. Further based on cell type B vs T; cell size, pattern of growth , surface marker expression, cytogenic translocations
6. Systemic “B” symptoms

HODGKIN'S LYMPHOMA STARTING POINTS

1. arises from germinal center or post-germinal center B cells
    a. Neoplastic proliferation of REED-Sternberg cells (RS)
    b. B cells w/ multi-lobed nuclei and prominent nucleoli
    c. RS secrete cytokines
    d. Reactive inflammatory cells make up bulk of tumor
2. divided into two major sub-groups, based on the appearance and immuno-phenotype of the tumor cells
    a. Classical HL (HL)
    b. Nodular lymphocyte predominate HL (LDHL)
3. increased risk of HL in patients with a history of infectious mononucleosis caused by EBV
4. Clinical presentation
    a. Asymptomatic lymphadenopathy
    b. Palpable painless cervical, axillae, or inguinal areas
    c. Constitutional symptoms
        i. Weight loss, fevers, night sweats =B symptoms
    d. Chest pain, SOB
    e. Pruritis
    f. Pain (lymph nodes, bone or back)
    g. Splenomegaly or hepatomegaly
    h. SVC syndrome
    i. Paraneoplastic syndromes

MGUS STARTING POINTS

1. Monoclonal gammopathy of undetermined significance
2. clinically asymptomatic premalignant clonal plasma cell or lymphoplasmacytic proliferative disorder
    a. M spike on serum electrophoresis –usually incidentally found when getting serum electrophoresis for another cause
3. Increased serum protein without the other features of MM
4. Common in elderly
5. Can progress to MM 1% per year
6. Etiology/Epidemiology
    a. ??familial component
        i. 2-3-fold increased risk in first* relative
    b. Population based studies may represent personal HX of autoimmune dz or infection precluding diagnosis
    c. 2-3% of white population age 50 and older
        i. Prevalence increases w/ age
    d. 2-3x AA>Caucasian

e. Men >> women
f. Pesticides? Inc risk

MULTIPLE MYELOMA STARTING POINTS

1. Malignant proliferation of the plasma cells in the bone marrow
2. Most common primary malignancy of the bone
3. High serum IL-6 may be present an stimulates the plasma cell growth and immunoglobulin production
4. Etiology/Epidemiology
    a. US incidence 7/100,000
    b. Median age 65-75
        i. Only 10% <50
        ii. Only 2%<40
    c. M>F slight preponderance
    d. AA>>Cauc>>Asian(japan)>>Mexican
5. No clear etiological agent has been identified
    a. ? inheritance
    b. Environmental Ionizing radiation and petroleum products
6. Clinical features of MM
    a. #1-bone pain with hypercalcemia neoplastic cells activate the RANK receptor on osteoclasts leading to bone destruction
        i. LYTIC or punched out skeletal lesions are seen on xray especially on the vertebrae and skull (increased risk of fracture)
    b. #2-elevated serum protein neoplastic cells produce immunoglobulin
        i. M spike on serum electrophoresis usually due to monoclonal IgG or IgA
    c. #3-increased risk of infections monoclonal antibodies lack antigenic diversity infection is most common cause of death in MM
    d. #4-Rouleax formation on RBCs on blood smear increased serum proteins decreases charge between RBCs
    e. #5-primary AL amyloidosis free light chains circulate and deposit in tissues
    f. #6-proteinuria free light chains excreted in urine as Bence jones protein =deposit in kidney tubules and increased risk of kidney failure
    g. Diagnostics
        i. serum/urine electrophoresis
        ii. serum free light-chain assay
        iii. CBC
        iv. CMP: creatinine, BUN, calcium, albumin
        v. bone marrow aspirate and biopsy
        vi. PET scans
        vii. skeletal survey

viii. whole-body, low-dose computed tomography (WBLD-CT)

h. Differential
    i. MGUS
    ii. Waldenstrom macroglobulinemia
    iii. Amyloidosis
    iv. Heavy chain disease

CANCER INTERVENTIONS

1. Chemotherapy
    a. Take advantage of certain vulnerabilities of the cancer cell
        i. Antimetabolites- block normal growth pathways in ALL cells but leukemia and some other cancers are extremely sensitive to folic acid and asparagine deprivation
            1. Methotrexate and L-asparaginase
        ii. DNA- damaging agents –undergo mitotic catastrophe
    b. Single agents often shrink but alone are not enough to destroy cancer cells, many offered in combinations
    c. Newest agents are using molecular analysis in addition
2. Radiation
    a. Ionizing radiation used to kill cancer cells directly by imparting molecular damage by energy
        i. Lethal cell killed
        ii. potentially-lethal – wounded and will eventually die
        iii. Sub-lethal- cell can repair itself
    b. Rapidly renewing cells are more sensitive to radiation
    c. Well suited for nonsurgical locations such as brain, prostate (seeds)
3. Surgery
    a. Definitive treatment when cancer has not spread
    b. In selected high-risk diseases, surgery can be preventative
        i. APC germline mutation have ~100% risk of cancer, so prophylactic colectomy may be performed
        ii. BRCA 1&2 have markedly increased risk of breast and ovarian cancer