PATHOLOGY OF NEOPLASIA (TUMORS)

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- **Definitions**
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- **Epidemiology**
- **Molecular Basis of Cancer**
- **Molecular Basis of Carcinogenesis**
- **Agents (The Usual Suspects)**
- **Host Defense (Tumor Immunity)**
- **Clinical Features of Tumors**

Defnition of Neoplasia

"A neoplasm is an abnormal mass of tissue, the growth of which exceeds and is uncoordinated with that of the normal tissues and persists in the same excessive manner after cessation of the stimuli which evoked the change" - Willis

- Genetic changes
- Autonomous
- Clonal

Nomenclature – Benign Tumors

- -oma = benign neoplasm
- Mesenchymal tumors

- chrondroma: cartilaginous tumor
- fibroma: fibrous tumor
- osteoma: bone tumor

- Epithelial tumor
  - adenoma: tumor forming glands
  - papilloma: tumor with finger like projections
  - papillary cystadenoma: papillalry and cystic tumor forming glands
  - polyp: a tumor that projects above a mucosal surface

Nomenclature – Malignant Tumors

- Sarcomas: mesenchymal tumor
  - chrondrosarcoma: cartilaginous tumor
  - fibrosarcomama: fibrous tumor
  - osteosarcoma: bone tumor
- Carcinomas: epithelial tumors
  - adenocarcinoma: gland forming tumor
  - squamous cell carcinoma: squamous differentiation
  - undifferentiated carcinoma: no differentiation
  - note: carcinomas can arise from ectoderm, mesoderm, or endoderm

- Tumors with mixed differentiation
  - mixed tumors: e.g. pleomorphic adenoma of salivary gland
  - carcinosarcoma
- Teratoma
  - tumor comprised of cells from more than one germ layer
  - arise from totipotent cells (usually gonads)
  - benign cystic teratoma of ovary is the most common teratoma
- Aberrant differentiation (not true neoplasms)
  - Hamartoma: disorganized mass of tissue whose cell types are indiginous to the site of the lesion, e.g., lung
  - Choriostoma: ectopic focus of normal tissue (heterotopia), e.g., pancreas, perhaps endometriosis too
- Misnomers
  - hepatoma: malignant liver tumor
  - melanoma: malignant skin tumor
  - seminoma: malignant testicular tumor
  - lymphoma: malignant tumor of lymphocytes

Natural History Of Malignant Tumors

- Malignant change in the target cell, referred to as transformation
- Growth of the transformed cells
- Local invasion
- Distant metastases.

Differentiation

- Well differentiated neoplasm
  - Resembles mature cells of tissue of origin
- Poorly diffentiated neoplasm
  - Composed of primitive cells with little diffrerentiation
- Undifferentiated or “anaplastic” tumor
- Correlation with biologic behavior
  - Benign tumors are well differentiated
  - Poorly differentiated malignant tumors usually have worse prognosis

"ANAPLASIA" = CANCER

- **Pleomorphism**
  - Size
  - shape
- Abnormal nuclear morphology
  - **Hyperchromasia**
  - **High nuclear cytoplasmic ratio**
  - **Chromatin clumping**
  - **Prominent nucleoli**
- **Mitoses**
  - Mitotic rate
  - Location of mitoses
- **Loss of polarity**

Dysplasia

- **Literally means abnormal growth**
- **Malignant transformation is a multistep process**
- **In dysplasia some but not all of the features of malignancy are present, microscopically**
- **Dysplasia may develop into malignancy**
  - **Uterine cervix**
  - **Colon polyps**
- **Graded as low-grade or high-grade, often prompting different clinical decisions**
- **Dysplasia may NOT develop into malignancy**

- **HIGH grade dysplasia often classified with CIS**

Tumor Growth Rate

- Doubling time of tumor cells
  - Lengthens as tumor grows
  - 30 doublings (10^9 cells) = 1 g **(months to years)**
  - 10 more doublings (1 kg) = lethal burden **(“)**
- Fraction of tumor cells in replicative pool
  - May be only 20% even in rapidly growing tumors
  - Tumor stem cells
- Rate at which tumor cells are shed or lost
  - Apoptosis
  - Maturation
- Implications for therapy

Features of Malignant Tumors

- Cellular features
- Local invasion
  - Capsule
  - Basement membrane
- Metastasis

- Unequivocal sign of malignancy
- Seeding of body cavities
- Lymphatic
- Hematogenous

Significance of Nodal Mets

- Example of breast cancer
  - Halsted radical mastectomy
  - Sentinel node biopsy
- Prognostic
  - Number of involved nodes is an important component of TNM staging system
- Therapeutic
  - Overall risk of recurrence
    - Extent of nodal involvement
    - Histologic grade and other considerations
  - “Adjuvant” chemotherapy

Benign vs Malignant Features

Geographic & Environmental

- Sun exposure
  - Melanomas 6x incidence New Zealand vs Iceland
  - Blacks have low incidence of melanoma, so do normally pigmented areas like areolae on white people
- Smoking and alcohol abuse
- Body mass
  - Overweight = 50% increase in cancer
- Environmental vs racial factors
  - Japanese immigrants to USA
- Viral exposure
  - Human papilloma virus (HPV) and cervical cancer
  - Hepatitis B virus (HBV) and liver cancer (Africa, Asia)
  - Epstein-Barr Virus (EBV) and lymphoma

Predisposing Factors for Cancer

- Age
  - Most cancers occur in persons ≥ 55 years
  - Childhood cancers
    - Leukemias & CNS neoplasms
    - Bone tumors
- Genetic predispostion
  - Familial cancer syndromes

- Early age at onset
- Two or more primary relatives with the cancer
- Multiple or bilateral tumors

- Polymorphisms that metabolize procarcinogens, e.g., nitrites

- Nonhereditary predisposing conditions
  - Chronic inflammation?
  - Precancerous conditions
    - Chronic ulcerative colitis
    - Atrophic gastritis of pernicious anemia
    - Leukoplakia of mucous membranes
    - Immune collapse?

MOLECULAR BASIS of CANCER

- **NON-lethal genetic damage**
- **A tumor is formed by the clonal expansion of a single precursor cell (monoclonal)**
- **Four classes of normal regulatory genes**
  - **PROTO-oncogenes**
  - **Oncogenes→ Oncoproteins**
  - **DNA repair genes**
  - **Apoptosis genes**
- **Carcinogenesis is a multistep process**

TRANSFORMATION & PROGRESSION

- Self-sufficiency in growth signals
- Insensitivity to growth-inhibiting signals
- Evasion of apoptosis
- Defects in DNA repair: “Spell checker”
- Limitless replicative potential: Telomerase
- Angiogenesis
- Invasive ability
- Metastatic ability

Normal CELL CYCLE Phases ONCOGENES

- **Are MUTATIONS of NORMAL genes (PROTO-oncogenes)**
  - **Growth Factors**
  - **Growth Factor Receptors**
  - **Signal Transduction Proteins (RAS)**
  - **Nuclear Regulatory Proteins**
  - **Cell Cycle Regulators**
- **Oncogenes code for → Oncoproteins**

MYC

- **Encodes for transcription factors**

- Also involved with apoptosis

P53 and RAS

p53

- Activates DNA repair proteins
- Sentinel of G1/S transition
- Initiates apoptosis
- Mutated in more than 50% of all human cancers

RAS

- H, N, K, etc., varieties
- Single most common abnormality of dominant oncogenes in human tumors
- Present in about 1/3 of all human cancers

Tumor (really "GROWTH") suppressor genes

- TGF-β → COLON
- E-cadherin → STOMACH
- NF-1,2 → NEURAL TUMORS
- APC/β-cadherin → GI, MELANOMA
- SMADs → GI
- RB → RETINOBLASTOMA
- P53 → EVERYTHING!!
- WT-1 → WILMS TUMOR
- p16 (INK4a) → GI, BREAST (MM if inherited)
- BRCA-1,2 → BREAST
- KLF6 → PROSTATE

Evasion of APOPTOSIS

- BCL-2
- p53
- MYC

DNA REPAIR GENE DEFECTS

- **DNA repair is like a spell checker**
- **HNPCC (Hereditary Non-Polyposis Colon Cancer): TGF-β, β-catenin, BAX**
- **Xeroderma Pigmentosum: UV fixing gene**
- **Ataxia Telangiectasia: ATM gene**
- **Bloom Syndrome: defective helicase**
- **Fanconi anemia**

LIMITLESS REPLICATIVE POTENTIAL

- **TELOMERES determine the limited number of duplications a cell will have, like a cat with nine lives.**
- **TELOMERASE, present in >90% of human cancers, changes telomeres so they will have UNLIMITED replicative potential**

TUMOR ANGIOGENESIS

- **Q: How close to a blood vessel must a cell be?**
- **A: 1-2 mm**

- **Activation of VEGF and FGF-b**

- **Tumor size is regulated (allowed) by angiogenesis/anti-angiogenesis balance**

TRANSFORMATION→
GROWTH→
BM INVASION→
ANGIOGENESIS□
INTRAVASATION→
EMBOLIZATION→
ADHESION→
EXTRAVASATION→
METASTATIC GROWTH→
etc.

Invasion Factors

- **Detachment ("loosening up") of the tumor cells from each other**
- **Attachment to matrix components**
- **Degradation of ECM, e.g., collagenase, etc.**
- **Migration of tumor cells**

METASTATIC GENES?

- NM23
- KAI-1

- KiSS

CHROMOSOME CHANGES in CANCER

- **TRANSLOCATIONS and INVERSIONS**

- **Occur in MOST Lymphomas/Leukemias**
- **Occur in MANY (and growing numbers) of NON-hematologic malignancies also**

Carcinogenesis is "MULTISTEP"

- **NO single oncogene causes cancer**
- **BOTH several oncogenes AND several tumor suppressor genes must be involved**
- **Gatekeeper/Caretaker concept**
  - **Gatekeepers: ONCOGENES and TUMOR SUPPRESSOR GENES**
  - **Caretakers: DNA REPAIR GENES**
- **Tumor "PROGRESSION"**
  - **ANGIOGENESIS**
  - **HETEROGENEITY from original single cell**

Carcinogenesis:

The USUAL (3) Suspects

- Initiation/Promotion concept:
  - BOTH initiators AND promotors are needed
  - NEITHER can cause cancer by itself
  - INITIATORS (carcinogens) cause MUTATIONS
  - PROMOTORS are NOT carcinogenic by themselves, and MUST take effect AFTER initiation, NOT before
  - PROMOTORS enhance the proliferation of initiated cells

Q: WHO are the usual suspects?

- Inflammation?
- Teratogenesis?
- Immune Suppression?
- Neoplasia?
- Mutations?

A: The SAME 3 that are ALWAYS blamed!

- 1) Chemicals
- 2) Radiation
- 3) Infectious Pathogens

CHEMICAL CARCINOGENS: INITIATORS

- **DIRECT**
- **β-Propiolactone**
- **Dimeth. sulfate**
- **Diepoxybutane**
- **Anticancer drugs (cyclophosphamide, chlorambucil, nitrosoureas, and others)**
- **Acylating Agents**
  - **1-Acetyl-imidazole**
  - **Dimethylcarbamyl chloride**
- **"PRO"CARCINOGENS**
- **Polycyclic and Heterocyclic Aromatic Hydrocarbons**
- **Aromatic Amines, Amides, Azo Dyes**
- **Natural Plant and Microbial Products**
  - Aflatoxin B1→ Hepatomas
  - Griseofulvin→ Antifungal
  - Cycasin→ from cycads
  - Safrole→ from sassafras
  - Betel nuts→ Oral SCC

CHEMICAL CARCINOGENS: INITIATORS

- **OTHERS**
- **Nitrosamine and amides (tar, nitrites)**
- **Vinyl chloride→ angiosarcoma in Kentucky**

- Nickel
- Chromium
- Insecticides
- Fungicides
- PolyChlorinated Biphenyls (PCBs)

CHEMICAL CARCINOGENS: PROMOTORS

- HORMONES
- PHORBOL ESTERS (TPA), activate kinase C
- PHENOLS
- DRUGS, many

RADIATION CARCINOGENS

- UV: BCC, SCC, MM (i.e., all 3)
- IONIZING: photons and particulate
  - Hematopoetic and Thyroid (90%/15yrs) tumors in fallout victims
  - Solid tumors either less susceptible or require a longer latency period than LEUK/LYMPH
  - BCCs in Therapeutic Radiation

VIRAL CARCINOGENESIS

- HPV→ SCC
- EBV□Burkitt Lymphoma
- HBV□Hepatocellular Carcinoma (Hepatoma)
- HTLV1□T-Cell Malignancies
- KSHV□Kaposi Sarcoma

H. pylori CARCINOGENESIS

- 100% of gastric lymphomas (i.e., M.A.L.T.-omas)
- Gastric CARCINOMAS also!

HOST DEFENSES

- IMMUNE SURVEILLENCE CONCEPT
- CD8+ T-Cells
- NK cells
- MACROPHAGES
- ANTIBODIES

How do tumor cells escape immune surveillance?

- Mutation, like microbes
- ↓ MHC molecules on tumor cell surface
- Lack of CO-stimulation molecules, e.g., (CD28, ICOS), not just Ag-Ab recognition
- Immunosuppressive agents
- Antigen masking
- Apoptosis of cytotoxic T-Cells (CD8), i.e., the damn tumor cell KILLS the T-cell!

Effects of TUMOR on the HOST

- Location→ anatomic ENCROACHMENT

- HORMONE production
- Bleeding, Infection
- ACUTE symptoms, e.g., rupture, infarction
- METASTASES

CACHEXIA

- Reduced diet: Fat loss>Muscle loss
- Cachexia: Fat loss AND Muscle loss
- TNF (α by default)
- IL-1
- PIF (Proteolysis Inducing Factor)

PARA-Neoplastic Syndromes

- Endocrine
- Nerve/Muscle, e.g., myasthenia w. lung ca.
- Skin: e.g., acanthosis nigricans, dermatomyositis
- Bone/Joint/Soft tissue: HPOA (Hypertrophic Pulmonary OsteoArthropathy)
- Vascular: Trousseau, Endocarditis
- Hematologic: Anemias
- Renal: e.g., Nephrotic Syndrome

ENDOCRINE GRADING/STAGING

- GRADING: HOW "DIFFERENTIATED" ARE THE CELLS?

- **STAGING: HOW MUCH ANATOMIC EXTENSION? TNM**
- **Which one of the above do you think is more important?**

ADENOCARCINOMA GRADING
Let's have some FUN!
LAB DIAGNOSIS

- BIOPSY
- CYTOLOGY: (exfoliative)
- CYTOLOGY: (FNA, Fine Needle Aspirate)

IMMUNOHISTOCHEMISTRY

- **Categorization of undifferentiated tumors**
- **Leukemias/Lymphomas**
- **Site of origin**
- **Receptors, e.g., ERA, PRA**

TUMOR MARKERS

- **HORMONES: (Paraneoplastic Syndromes)**
- **"ONCO"FETAL: AFP, CEA**
- **ISOENZYMES: PAP, NSE**
- **PROTEINS: PSA, PSMA ("M" = "membrane")**
- **GLYCOPROTEINS: CA-125, CA-19-5, CA-15-3**
- **MOLECULAR: p53, RAS**

MICRO-ARRAYS