DEND 211
NEOPLASIA (Carcinogenesis)

Neoplasia (new form)
The irreversible loss of responsiveness to normal growth controls.

Neoplasm
An abnormal mass of cells not responsive to the normal mechanisms for the control of growth.

Tumor
Any tissue swelling. Includes both neoplastic and non-neoplastic causes.

Oncology
The study of tumors (neoplasms).

Classification of Neoplasms
- Benign
- Malignant (cancers)

Types of Malignant Neoplasms
- Carcinomas (epithelial)
- Sarcomas (mesenchymal)
- Carcinosarcomas & teratomas (mixed)

Carcinogenesis
The molecular basis for cancer.

Fundamental Principals of

Carcinogenesis

- Nonlethal genetic damage lies at the heart of carcinogenesis
- Growth promoting protooncogenes, growth suppressor antioncogenes & apoptosis genes are the principal targets of damage

Fundamental Principals of Carcinogenesis

- DNA repair genes affect proliferation, survival and therefore, transformation
- Multistep process (tumor progression) phenotype of excessive growth, invasion, metastasis & genotype of oncogenes, repair genes, apoptosis, etc.

Transformation

The point at which cells no longer respond to the normal controls for growth and which cannot be reversed. The acquisition of the neoplastic state.

Metastasis

The ability of a neoplasm to disseminate and establish a remote colony of cells.

Hallmarks of Cancers

- Self sufficiency in growth signals
- Insensitivity to anti-growth signals
- Evading apoptosis
- Sustained angiogenesis
- Limitless replicative potential
- Tissue invasion & metastasis

Self-sufficiency in Growth Signals

- Autocrine production of growth factors (RAS)
- Over expression of growth factor receptors (HER2)

- Mutation in signaling protein genes (ABL)
- Mutation of transcription genes (MYC)
- Mutations of cyclins and cyclin-dependent kinase genes (cyclin D)

Insensitivity to Growth-inhibitory Signals

- RB gene mutation removes “brake” from cell cycle (RB)
- Transforming growth factor-β mutation
- Adenomatous polyposis coli-β-catenin pathway mutation (APC)
- Mutation of antiproliferative and apoptosis gene (TP53)

Evasion of Apoptosis

- CD95 (Fas) receptor
- Caspase enzymes that cleave DNA

Limitless Replicative Potential

- Activation of telomerase (CDKN2A)
- Inactivation of RB and TP53

Development of Sustained Angiogenesis

- Vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (BFGF)
- Development of resistance to, or lack of production of antiangiogenesis factor thrombospondin-1
- Hypoxia induced factor (HIF-1) (RAS)

Ability to Invade and Metastasize

- Invasion of extracellular matrix (detachment from tumor cells, attachment to ECM degradation & migration)
- Vascular dissemination and homing (endothelial adhesion, emigration and chemokine receptor homing)

Genomic Instability Enables Malignancy

Inherited mutations in DNA repair:

- Hereditary nonpolyposis colon carcinoma syndrome (HNPCC) (BAX)
- Xeroderma pigmentosum, Bloom syndrome, ataxia-telangiectasia &

Fanconi anemia (TP53)
- Some breast cancers (BRCA1, BRCA2)

Molecular Basis of Multistep Carcinogenesis

- DNA damage
- DNA repair
- Mutation
- Transformation
- Clonal expansion
- Invasion
- Metastasis

Development of the Malignant State

- Activation of one or more growth promoting oncogenes
- Loss of two or more growth suppressor antioncogenes

Karyotype Changes

- Point mutation (RAS common cancers)
- Balanced translocation (Ph chromosome chronic myelogenous leukemia)
- Deletion (17p colon, 3p lung)
- Gene amplification N-MCY neuroblastoma, HER-2 breast)

Carcinogenic Agents

- Chemical
- Radiation
- Microbial

Carcinogen

Any agent that can induce malignancy (“cause cancer”).

Oncogenic

Giving rise to a neoplasm. Causing transformation of cells.

Chemical Carcinogenesis

- Direct acting carcinogens (initiator)

- Indirect acting carcinogens (conversion of procarcinogen to ultimate carcinogen)
- Promoters augment carcinogens
- Co-carcinogens act together

Promoters

Induction of cell proliferation is a *sine qua non* of tumor promotion.

Radiation Carcinogenesis

Interaction of tissue with high energy species that produce free-radicals capable of causing mutogenic events leading to transformation.

Oncogenic Microbes

- HTLV-1 associated with T-cell leukemia/lymphoma
- HPV associated with cervical, perianal and oropharyngeal cancers
- Epstein-Barr associated with Burkitt lymphoma, brain lymphoma , nasopharyngeal carcinoma
- HBV & HCV associated with liver cancer
- *Helicobacter pylori* gastric carcinoma & lymphoma

Tumor Antigens

- Cancer-testis antigens (MAGE-1)
- Tissue-specific antigens (MART-1)
- Antigens (proteins)from mutations (RAS)
- Over expressed antigens (HER2)
- Viral antigens (EBV)
- Mucin antigens MUC-1)
- Oncofetal antigens (CEA)

- Differentiation-specific antigens (PSA)

Antitumor Effector Mechanisms

- Cytotoxic T lymphocytes (respond to tumor antigens)
- NK lymphocytes (respond to stress-induced antigens)
- Activated macrophages (produce free radicals/TNF)
- Activation of complement and anti-body dependent cell cytotoxicity

Loss of (evasion of) Imunosurveillance

- Antigen-negative variants
- Reduced expression of MCH antigens
- Lack of co-stimulation
- Immunosuppression