Carcinogenesis

1. Basic principles
2. 6 hallmark features
3. Abnormal cell proliferation: mechanisms
4. Carcinogens: examples

Major Principles:
1. Nonlethal genetic damage is central to carcinogenesis
2. Tumor mass arises from CLONAL expansion of a single progenitor cell that has incurred genetic damage
3. X-linked markers can be used to assess clonality

Carcinogenesis

Major Principles (cont’d)
4. Principle targets of genetic damage:
   - growth promoting proto-oncogenes
   - growth-inhibiting tumor suppressor genes
   - genes regulating programmed cell death (apoptosis)
   - genes involved in DNA repair
5. Mutant alleles of proto-oncogenes = oncogenes—DOMINANT (mutation of single allele → cell transformation)

Major principles (cont’d)
6. Disabled DNA repair genes (caretaker genes) predispose cells to genome mutations—“mutator phenotype”
7. CARCINOGENESIS is a MULTISTEP PROCESS--both phenotypically & genotypically

Clonality of tumors: assess in women heterozygous for polymorphic X-linked isoenzyme/molecular markers (e.g. glucose-6-phosphate dehydrogenase)
Tumor progression and generation of heterogeneity

GROWTH FACTORS
- Glioblastomas → PDGF & express its receptor
- Sarcomas: → TGF-α and its receptor

Steps in normal physiologic cell proliferation

GFR’s
- Overexpression (e.g., amplification) → cancer cells hyperrespond to levels of GF’s
- ERBB1 (EGF receptor) overexpressed in 80% squ. cell Ca’s lung
- HER2/NEU (ERBB2) amplified in 25%-30% breast Ca’s → bad prognosis
  (Rx: role of anti-HER2/NEU antibodies)
**Signal Transducing Proteins**

**RAS**: the most commonly mutated proto-oncogene in human tumors

**ABL**: in chronic myelogenous leukemia

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**Freidrich von Recklinghausen**

1882

“neurofibromatosis”

1889

“hemochromatosis”

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**NORMAL CHROMOSOMES**

- BCR locus
- ABL oncogene

**CHRONIC MYELOGENOUS LEUKEMIA**

- BCR locus
- BCR-ABL hybrid gene
- Tyrosine kinase
Schwann cells
Axons
Fibroblasts
Collagen

Neurofibroma
Neurofibroma in T2/T3 intervertebral foramen

Neurofibromin is a GAP prot.

Neurofibromin (GAP prot.)

Neurofibromin
17q11.2

NF1 gene

Neurofibromin (GAP prot.)
Neurofibromatosis 1 (NF1)

1. Inherited as autosomal dominant
2. Incidence of NF1: 1 in 2500-3000
3. NF1 gene localized to chromosome 17
4. Gene product = neurofibromin, a GAP (GTPase-activating protein)—inhibits cell prolif.
5. Mutation in NF1 → neurofibromatosis
6. Neurofibromatosis phenotype:
   - Neurofibromas:
     - cutaneous
     - peripheral nerves
   - Café-au-lait spots (hyperpigmentation)

Carcinogenic agents

- Chemicals
- Radiation
- Oncogenic RNA viruses
- Oncogenic DNA viruses

Sir Percival Pott, London surgeon
> 200 yrs. ago: scrotal skin cancer in chimney sweeps
Thorotrast (X-rays: used until 1956)

Thorotrast: ThO2: alpha particles, half-life 30 yrs.

Oncogenic Viruses
High Risk HPV’s: HPV 16 and 18

Oncogenic properties:
Products of 2 early viral genes: E6 & E7

E7: binds to Rb protein → displaces E2F transcription factors that are normally sequestered by Rb → progression thru cell cycle

EBV (Epstein-Barr Virus)

- acts as oncogene
- activates signaling
- activates cyclin D
- t(8;14) translocation activates MYC (nuclear transcription factor regulating growth promoting genes such as cyclins)

HHV8
Kaposi sarcoma

“Starry Sky” lymph node appearance (Van Gogh painting)

Burkitt Lymphoma (B cell)

Hepatitis C Virus (HCV)
(RNA virus, but definite risk for hepatocellular carcinoma)
Hepatitis B Virus (HBV)

Viral integration causes secondary chromos. rearrangements→deletions
activate transcription factors & signal transduction

Acute hepatitis → Chronic hepatitis → Cirrhosis → Carcinoma

Ongoing inflammation, cell injury, cell division-prone to mutations/viral actions

Pathogenetic sequence of HCC in chronic HBV and HCV infections