Carcinogenesis

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

Carcinogenesis

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

Major Principles (cont’d)

4. Principle targets of genetic damage:
   4 classes of normal regulatory genes:
   - 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
Tumor progression and generation of heterogeneity
Steps in normal physiologic cell proliferation

- GF (Growth factor)
- GFR (GF receptor)
- cascade of signal transduction molecules
- kinase pathway
- 2nd messengers
- nuclear regulatory factors
- DNA transcription
- G1-S-G2-M Cell cycle

Self-sufficiency in growth signals

- Evading apoptosis
- Insensitivity to anti-growth signals
GROWTH FACTORS

- glioblastomas ➔ PDGF & express its receptor
  - sarcomas: ➔ TGF-α and its receptor

Cell cycle

nucleus

DNA transcription

nuclear regulatory factors

G1-S-G2-M

cascade of signal transduction molecules

kinase pathway

2nd messengers

signal transducing proteins

- GF (Growth factor)
- GFR (GF receptor)

GFR's

- overexpression (e.g., amplification) ➔ cancer cells hyperrespond to levels of GF's

- ERBB1 (EGF receptor) overexpressed in 80% sq. 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

- GF (Growth factor)
- GFR (GF receptor)
- kinase pathway
- cascade of signal transduction molecules
- nuclear regulatory factors
- DNA transcription
- G1-S-G2-M Cell cycle
- nuclear membrane
- signal transducing proteins
- 2nd messengers
- cell membrane
Freidrich von Recklinghausen

1882
“neurofibromatosis”

1889
“hemochromatosis”
Neurofibroma in T2/T3 intervertebral foramen

Schwann cells
Axons
Fibroblasts
Collagen
Neurofibromin is a 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)

Steps in normal physiologic cell proliferation

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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
Kaposi sarcoma

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)
Burkitt Lymphoma (B cell)

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

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

- HBxAg activates transcription factors & signal transduction.
- Viral integration causes secondary chromosomal rearrangements → deletions.

Estimated Hepatitis B Prevalence, 1997

Proportion of population infected:
- Less than 2 percent
- 2 - 7 percent
- Greater than 7 percent
- No data available
Ongoing inflammation, cell injury, cell division → prone to mutations/viral actions

Acute hepatitis  →  Chronic hepatitis  →  Cirrhosis  →  Carcinoma

Pathogenetic sequence of HCC in chronic HBV and HCV infections