NEOPLASIA 3: CONCLUSION

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DIFFERENTIATION

Melanocytoma, with differentiated cells capable of melanin production
Malignant Melanoma: Minimal Differentiation
TUMOR PROGRESSION

• Colorectal cancer model system
• Very common form
  – 60,000 deaths per year (11%)
  – 90% diagnosed after age 55
  – 10-35 year transition from benign polyp to malignancy
  – Larger polyps more likely to become malignant

LARGE COLON POLYP
PROGRESSION

• 3 Key Genes
  – **APC** (in familial form, FAP)
    • APC protein antagonizes epithelial growth
    • 1st mutation
    • ↑ cell proliferation
  – **K-ras**
    • Point mutation creates oncogene
    • Cells proliferate w/o external signals
  – **p53**
    • Inactivated or deleted
    • Occurs late in development of carcinoma
    • ↑ resistance to apoptosis
    • ↑ chance of additional mutations

<table>
<thead>
<tr>
<th>GENE</th>
<th>CLASS</th>
<th>PATHWAY</th>
<th>TUMORS WITH MUTATIONS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>K-Ras</td>
<td>oncogene</td>
<td>receptor tyrosine-kinase signaling</td>
<td>40</td>
</tr>
<tr>
<td>β-catenin</td>
<td>oncogene</td>
<td>Wnt signaling</td>
<td>5–10</td>
</tr>
<tr>
<td>p53</td>
<td>tumor suppressor</td>
<td>stress/genetic-damage response</td>
<td>60</td>
</tr>
<tr>
<td>APC</td>
<td>tumor suppressor</td>
<td>Wnt signaling</td>
<td>&gt; 60</td>
</tr>
<tr>
<td>Smad4</td>
<td>tumor suppressor</td>
<td>TGFβ signaling</td>
<td>30</td>
</tr>
<tr>
<td>TGFβ receptor II</td>
<td>tumor suppressor</td>
<td>TGFβ signaling</td>
<td>10</td>
</tr>
<tr>
<td>MLH1 and other DNA mismatch repair genes</td>
<td>tumor suppressor</td>
<td>DNA mismatch repair</td>
<td>15 (often silenced by methylation)</td>
</tr>
</tbody>
</table>

- Normal colon cells
- Loss of APC tumor-suppressor gene (chromosome 5)
- Activation of K-ras oncogene (chromosome 12)
- Loss of DCC tumor-suppressor gene (chromosome 18)
- Loss of p53 tumor-suppressor gene (chromosome 17)

Other changes

- Invasive tumor cells
- Normal colon epithelial cells
- Blood vessel
- Basal lamina
- Tumor cells invade blood vessels, allowing metastasis to occur
- The cancer metastasizes (spreads to other tissues)
POLYP TO CANCER
VIRAL INITIATION OF NEOPLASIA

- About 15% of cancers are of viral origin
  - Principally due to DNA viruses
    - HPV
    - Epstein-Barr
    - Hepatitis B
  - Some RNA viruses
    - HIV
    - HTLV-1
- Viruses act in conjunction with other factors
- Infections >> than cancers
  - Viruses may act "secondarily" or directly
  - May be decades of latency
DNA TUMOR VIRUSES

- Block key tumor suppressor genes
  - Interfere with cell cycle controls
- Co-opts cellular machinery
  - May remove restraints on DNA replication
    - Cell dies
  - May act as a “passenger” capsid, permit normal cycles
  - May switch modes
- May be “accidental” tumorigenesis
  - Instead of its own replication may initiate uncontrolled cell replication
INFECTION WITH HPV

- **Widespread**
  - Up to 75% of sexually active women
    - 10% develop dysplasia
    - 1600 invasive cervical cancers per 1,000,000 infections
  - Types 16 & 18 often associated with CC
  - Often asymptomatic
  - May cause genital warts
VIRAL ACTIVATION

- Viral proteins E6 & E7
  - Inhibitors of p53 & Rb
- P53 destroyed by cell machinery

← Cervical carcinoma in situ
EPSTEIN-BARR VIRUS

- A herpes virus
  - Very common
  - In USA causes mononucleosis
  - Implicated in
    - Burkitt’s lymphoma (Africa)
    - B-cell lymphomas in patients with HIV/immune suppression
    - Hodgkin’s lymphoma
    - Nasopharyngeal carcinoma
- Forms episomes in B cells
  - Infected cells are “immortalized”

Epstein–Barr virus (EBV) infection in normal healthy virus carriers
6 Latent Genes
- LMP-1 mimics signal of CD-40 receptor of B cells
- Signals NFkB and JAK/STAT signalling cascade
- Mimics natural survival pathway
- EBER2 activates cyclin genes
  - Promotes cell through G1 phase
  - Also ↑ expression of LMP-1

BL also requires other mutations
- MYC oncogene

EBV facilitates transformation becoming “immortalized”

100% of all nasopharyngeal cancers are + for EBV
- Role in NPC unclear
HEPATITIS B

- **Strong association with liver cancer**
  - Virus integrated into genome inconsistently

- **Putative mechanism is chronic liver damage**
  - ↑ repair hyperplasia
  - ↑ pool of mutation-prone cells
  - Exogenous toxins may opportunistically trigger neoplasia
  - Viral HbX protein regulates transcription of host growth genes & binds p53
Incidence of liver cancer coincides with distribution of HBV:

Lowest in Canada
Highest in China

<table>
<thead>
<tr>
<th>HBsAg Prevalence</th>
<th>Color</th>
</tr>
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<tbody>
<tr>
<td>≥8% - High</td>
<td>Red</td>
</tr>
<tr>
<td>2-7% - Intermediate</td>
<td>Yellow</td>
</tr>
<tr>
<td>&lt;2% - Low</td>
<td>Green</td>
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IMMUNE SURVEILLANCE

• Tumor cells are not “self”
  – Recognition signals may be skewed
    • Immune system may destroy cells
    • Evasion of detection is key to survival
• Ag’s may be tumor-specific
  – Found only on tumor cells
• Ag’s may be tumor-associated
  – Present on normal and tumor cells
  – Represent “camouflage” for tumor cells
• Cytotoxic T-cells are main removal mechanism
TUMOR ANTIGENS

• Genetic instability promotes synthesis of numerous proteins with no known function
  – Mutation is a random event
  – Mutant proteins may be processed and displayed on surface via normal MHC system
  – May become tumor-specific markers
• Marker may be overexpressed normal protein
  – Tyrosinase
• Marker may be a viral component
• Marker may be a fetal protein
  – AFP & CEA

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AVOIDING IMMUNE RECOGNITION

• Cancer incidence ↑ in immunodeficiency
  – AIDS
  – Transplant recipients

• Tumor cells can evade detection
  – Selection of marker-negative clones
  – Loss of MHC proteins
  – No expression of co-stimulatory molecules
  – Masking of antigens by glycocalyx
THERAPEUTIC STRATEGIES

• Taking advantage of what is known
  – Prevention campaigns
    • Anti-smoking
    • Breast cancer awareness
  • Screening exams
    – Mammography, colonoscopy
    – Genetic analysis
• Exploits sensitivity of dividing cells to DNA damage
  – A two-edged sword
  – Thin therapeutic margin in some cases
  – Drug resistance may develop
PATHWAY BLOCKING

- Interference with signal reception, transduction or internal transmission
  - Herceptin
    - Block HER 2/Neu protein
  - Tamoxifen, aromatase inhibitors
    - Interfere with estrogen-sensitive pathways
TARGETED KILLING

- Uses specificity of immune system to “mark” the tumor cells
  - Depends on complete understanding of the tumor markers
  - Requires specific Abs to them
  - Linkage of Ab to a killing system
    - Monoclonal Ab
    - Some chemicals
    - Photo-sensitization therapies
MONOCLONAL Ab

- Activation of complement cascade at specific cells
- In theory can kill 100% of tumor cells
RESOURCES

Chapter 7, pp. 269-339

Chapter 23, pp. 1313-1361