Definitions

- **Neoplasia** - new growth
  - Abnormal mass of tissue with growth that exceeds and is uncoordinated with that of the surrounding normal tissues; autonomous

- **Tumor** - synonymous with neoplasm

- **Cancer** - common term for malignant neoplasm

- Neoplasms have **parenchyma** and **stroma**

- Benign and malignant tumors each have their own nomenclature
Benign tumors

- Based on parenchymal component
- **Mesenchymal tumors** add -oma to cell of origin
  - Fibroblasts = fibroma
  - Cartilage = chondroma
  - Osteoblasts = osteoma
- **Epithelial tumors** can be named for cell of origin, microscopic architecture, or macroscopic appearance
  - **Adenoma** = glandular appearance OR from glandular tissue
Malignant tumors

- **Mesenchymal tumors usually called sarcomas**
  - Fibrosarcoma, liposarcoma, leiomyosarcoma, rhabdomyosarcoma
- **Epithelial tumors usually called carcinomas**
  - Adenocarcinoma = glandular growth pattern
  - Squamous cell carcinoma = squamous pattern
  - Can either be named for organ of origin, or “poorly differentiated” or “undifferentiated”
- **Many exceptions**
Liver tumors

- Focal nodular hyperplasia - spontaneous
- Nodular regenerative hyperplasia - portal hypertension
- Hemangiomas - benign blood vessel tumors
- Liver cell adenomas - rarely become malignant
- Hepatocellular carcinoma (HCC) - common
- Cholangiocarcinoma - much less common
Biology of tumor growth

1) Malignant change in target cell (transformation)
2) Growth of the transformed cells
3) Local invasion
4) Distant metastases
   • Generally, morphologic criteria can be used to distinguish benign and malignant tumors, but not always
Differentiation and anaplasia

- Differentiation = extent to which neoplastic cells resemble normal cells
- Anaplasia = lack of differentiation
  - Hallmark of transformation
  - But cancer is not “reverse differentiation”
- In general, benign tumors are well differentiated
- Malignant tumors range from well differentiated to undifferentiated
Features of anaplasia

• Pleomorphism
• Abnormal cell morphology (atypia)
• Abundant and/or atypical mitoses
• Loss of polarity
• Dysplasia = “disordered growth”
  - In epithelia, represents a state between hyperplasia and carcinoma in situ (preinvasive neoplasia)
  - Does not necessarily progress to cancer
Rates of tumor cell growth

- From 1 transformed cell to smallest clinically detectable mass (1 gm) of $10^9$ cells = 30 doublings
- To reach $10^{12}$ cells (1 kg) requires only 10 additional doublings
  - Doubling time of tumor cells
  - Fraction of tumor cells replicating
  - Rate at which cells are shed/lost
- Total cell cell-cycle time is typically normal
Figure removed for copyright reasons.

Source: Figure 7-12 in [RC]
Local invasion and metastasis

• Growth of cancer is usually accompanied by progressive infiltration, invasion, and destruction of surrounding tissue
• Next to metastasis, invasiveness is the most reliable feature that distinguishes malignant tumors from benign tumors
• Metastasis (tumor mass discontinuous with the primary tumor) unequivocally marks a tumor as malignant
Figure removed for copyright reasons.

Source: Figure 7-22 in [RC]
Molecular basis of cancer

- Nonlethal genetic damage
- Clonal expansion of a precursor cell
- Main classes of genes involved
  1) Oncogenes
  2) Tumor suppressor genes
  3) Genes regulating apoptosis
  4) DNA repair genes
- Carcinogenesis is a multistep process

Figure by MIT OCW.
Figure removed for copyright reasons.

Source: Figure 7-31 in [RC]
Oncogenes

- First recognized in acute transforming retroviruses (v-onc)
- Most known oncogenes do not have viral counterparts
- Function as growth factors, receptors, signal transducers, transcription factors, and cell-cycle components
- Have similar functions as protooncogenes, but lack regulation/are constitutive
Figure removed for copyright reasons.

Source: Figure 7-32 in [RC]
RAS oncogene

- 15-20% of all human cancers have a RAS mutation
- Normally, RAS is activated by receptors to exchange GDP for GTP
- Activated RAS returns to ground state by its intrinsic GTPase activity
- GTPase activating proteins (GAPs) augment this process
- Mutant forms of RAS bind GAP but their GTPase activity is not augmented
Tumor suppressor genes

• Normally serve to inhibit cell proliferation
• First recognized in retinoblastoma, rare pediatric tumor of the eye
• RB tumor suppressor gene is a nuclear phosphoprotein that regulates cell cycle
  - Active, hypophosphorylated state in non-dividing cells
  - Inactive, hyperphosphorylated in G1/S transition
• Many cancers have mutations in the RB pathway (i.e. INK4a, Cyclin D, CDK4)
PATHOGENESIS OF RETINOBLASTOMA

FAMILIAL FORM

- Normal gene
- Mutant Rb gene
- Somatic cells of parents
- Germ cells
- Zygote
- Retinal Cells
- Retinoblastoma

SPORADIC FORM

- Normal gene
- Mutant Rb gene
- Somatic cells of parents
- Germ cells
- Zygote
- Somatic cells of child
- Retinal Cells
- Retinoblastoma

Figure by MIT OCW.
Metastasis

- Invasion of ECM
  - Detachment from cells
  - Attachment to ECM
  - Degradation of ECM
  - Migration of tumor cells
- Vascular dissemination
  - Adhesion molecules
  - Chemokines

Figure removed for copyright reasons.

Source: Figure 7-42 in [RC]
Tumor immunity

• Immune surveillance
  - Cancer immunoediting
• Tumor-specific antigens
• Tumor-associated antigens
• Anti-tumor effector mechanisms
  - CTL
  - NK cell
  - Macrophages
  - Antibodies
<table>
<thead>
<tr>
<th>Normal host cell displaying multiple MHC-associated self antigens</th>
<th>Tumor cells expressing different types of tumor antigens</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Normal self proteins</strong></td>
<td><strong>Product of oncogene or mutated tumor suppressor gene</strong></td>
</tr>
<tr>
<td><img src="image" alt="Normal host cell" /></td>
<td><img src="image" alt="Tumor cells" /></td>
</tr>
<tr>
<td>MHC Class I</td>
<td>CD8+ CTL</td>
</tr>
<tr>
<td><strong>No T cell response</strong></td>
<td><strong>Mutated self protein</strong></td>
</tr>
<tr>
<td>T cell</td>
<td>T cell</td>
</tr>
<tr>
<td><strong>Overexpressed or aberrantly expressed self protein</strong></td>
<td><strong>Oncogenic virus</strong></td>
</tr>
<tr>
<td>T cell</td>
<td>T cell</td>
</tr>
<tr>
<td>CD8+ CTL</td>
<td>Virus antigen-specific CD8+ CTL</td>
</tr>
</tbody>
</table>

**Examples**

<table>
<thead>
<tr>
<th>Oncogene products: mutated RAS, Bcr/Abl fusion proteins</th>
<th>Various mutant proteins in carcinogen, or radiation, induced animal tumors; various mutated proteins in melanomas</th>
<th>Overexpressed: tyrosinase, gp100, MART in melanomas</th>
<th>Human papilloma virus E6, E7 proteins in cervical carcinoma: EBNA proteins in EBV induced lymphoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor suppressor gene products: mutated p53 protein</td>
<td>Aberrantly expressed: cancer-testis antigens (MAGE, BAGE)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Figure by MIT OCW.
<table>
<thead>
<tr>
<th>Anti-tumor immunity</th>
<th>Immune evasion by tumors</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MHC molecule</strong></td>
<td><strong>Failure to produce tumor antigen</strong></td>
</tr>
<tr>
<td>Tumor antigen</td>
<td>Antigen-loss variant of tumor cell</td>
</tr>
<tr>
<td>Tumor cell</td>
<td>Class I MHC-deficient tumor cell</td>
</tr>
<tr>
<td>T cell specific for tumor antigen</td>
<td></td>
</tr>
</tbody>
</table>

| | **Mutations in MHC genes or genes needed for antigen processing** |
| | |
| | |
| | |
| | |

| | **Production of immuno-suppressive protein** |
| | |
| | |
| | |

- **T cell recognition of tumor antigen leading to T cell activation**
- **Lack of T cell recognition of tumor**
- **Lack of T cell recognition of tumor**
- **Inhibition of T cell activation**

Figure by MIT OCW.
Special topics

- Epidemiology
- p53
- Epigenetic changes
- Chemical carcinogenesis
- Microbial carcinogenesis
- Molecular profiling
  - Genomic
  - Proteomic