General Pathology
VPM 152

Disorders of Cell Growth & Neoplasia

Lecture 3
Rate of growth, local invasion, and metastasis. Molecular basis of cancer (normal cell-cycle and cellular proliferation).

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Rate of Growth (Tumor Cell Kinetics)

- in general, growth rates of neoplasms correlate with their level of differentiation / anaplasia.

  i) doubling time of tumor cells
  
  - after clinical detection, doubling times can range from 1-12 months (average 2-3 months)

Robbin's fig 7-12. Biology of tumor growth. Minimal estimates of tumor cell doublings that precede the formation of a clinically detectable tumor mass. By the time a solid tumor is detected, it has already completed a major portion of its life cycle as measured by cell doublings.
ii) fraction of tumor cells in the replicative pool ("growth fraction")

- tumors with low growth fraction are more refractory to treatment.

iii) rate of cell loss from the tumor

- for tumor growth, cell production must exceed cell loss (apoptosis, shedding, etc).
Malignant Local Invasion of Tissue

- cancer growth is characterized by progressive infiltration (invasion) and destruction of surrounding tissues.

Osteosarcoma of the nasal cavity, dog. The neoplasm has invaded the adjacent nasal sinuses and the hard palate (white arrows), and also the calvarium / brain (black arrow)
Malignant

Local Invasion of Tissue

Osteosarcoma, distal region of the right femur. dog. This tumor has destroyed the femoral head (h) and has extensively invaded the adjacent bone and surrounding soft tissues. Hemorrhages within the neoplastic mass are also consistent with a malignant process.
Malignant Metastasis

- metastasis refers to tumor implants discontinuous with the primary tumor.
- unequivocally indicates malignancy & what kills the majority of cancer patients.

i) Lymphatic spread

Metastatic osteosarcoma, axillary lymph node, dog. Several metastatic foci of osteosarcoma (arrows) are scattered throughout a local lymph node.
Mammary gland carcinoma, dog (c), with lymphatic dissemination and pitting edema of the right hind limb (arrow). Note the presence (permeation) of tumor cells within a lymphatic vessel (top right) and neoplastic tissue partially effacing a local lymph node (bottom right, arrows).
Mammary gland carcinoma, dog. Hematogenous dissemination involving the liver and spleen.

Metastasis ii) Hematogenous spread

Same liver, cut surface
ii) Hematogenous spread

Hemangiosarcoma of the right atrium (left, arrow) with metastases to the lungs (right). These tumors contain irregular vascular channels filled with blood which explains its dark red color. They are very common in the heart, friable and prone to rupture. Hemopericardium and dissemination to the lungs are common complications.
iii) Seeding of Body Cavities and Surfaces (“exfoliation and implantation”)

Peritoneal carcinomatosis, renal adenocarcinoma, dog. Note multiple, white-yellow, raised nodules scattered throughout the serosal surface of the abdominal viscera. These metastatic sites are the result of numerous individual neoplastic cells that have exfoliated from the surface of the primary tumor and after random movement through the peritoneal cavity fluid have implanted on the peritoneal surface and grown into individual tumor masses.

Renal adenocarcinoma (cystadenocarcinoma), dog.
iii) Seeding of Body Cavities and Surfaces

**Splenic hemangiosarcoma**, dog. The primary tumor is in spleen (large arrow) with numerous tumor implants attached to the omentum (top, right) and diaphragm (bottom, right).
Molecular Basis of Cancer

i) **Nonlethal genetic damage is central to neoplastic transformation**
   - damage may be inherited or acquired (radiation, chemical, viral, spontaneous).

ii) **Tumors formed from clonal expansion of single, genetically damaged cell.**
   - progressively more heterogeneous with respect to genotypic & phenotypic features
   - clones can vary with respect to morphology, karyotype, metastatic capacity, etc.

iii) **Normal regulatory genes are the principle targets of genetic damage**
   - activation of the growth-promoting protooncogenes.
   - inactivation of the growth-inhibiting tumor suppressor genes.
   - alteration of the genes that regulate apoptosis.
   - alteration of the genes involved in DNA repair.

iv) **Cells with mutations in DNA repair genes are said to have developed a mutator phenotype**
Molecular Basis of Cancer

v) **Neoplastic transformation is a multistep process**

- at both the genetic and phenotypic levels.

Emergence of a cancer cell from a normal one (tan) is thought to occur through a process known as clonal evolution. First, one daughter cell (pink) inherits or acquires a cancer-promoting mutation and passes the defect to its progeny and all future generations. At some point, one of the descendants (red) acquires a second mutation, and later a third mutation (grey), and so on. Eventually, some cell (purple) accumulates enough mutations to cross the threshold to cancer.

Robbin’s 7-12. Clonal evolution of tumors and generation of tumor cell heterogeneity. New subclones arise from the descendants of the original transformed cell, and with progressive growth the tumor mass becomes enriched for those variants that are more adept at evading host defenses & are likely to be more aggressive.
The Normal Cell Cycle

The Cell-Cycle and Cellular Proliferation

- cell division is achieved by a highly controlled sequence called the cell-cycle.
- mostly stimulated by growth factors or ECM components.
- cell-cycle phases =  \( G_0 \) (quiescent),  
  \( G_1 \) (presynthetic),  
  \( S \) (DNA synthesis),  
  \( G_2 \) (premitotic)  
  \( M \) (mitotic)  
- each phase is dependant on proper activation and completion of the previous one.
- C-C has multiple controls (stimulatory & inhibitory) as well as checkpoint mechanisms.
Robbin’s Fig 3-3. Cell-cycle landmarks: cell-cycle phases (G0, G1, G2, S, and M), the location of the G1 restriction point, and the G1/S and G2/M cell-cycle checkpoints. Cells from labile tissues such as the epidermis and the gastrointestinal tract may cycle continuously; stable cells such as hepatocytes are quiescent but can enter the cell cycle; permanent cells such as neurons and cardiac myocytes have lost the capacity to proliferate.
The Normal Cell Cycle

1. The Cell-Cycle and Cellular Proliferation

- to enter cycle, quiescent cells must go from G\(_0\) to G\(_1\) (*transcription of many genes*).
- must pass G\(_1\)/S restriction point, beyond which cells committed to DNA replication.
- checkpoints present to monitor for DNA damage (elimination by apoptosis if damaged)
- progression through the cycle regulated by proteins called cyclins & CDK’s.
- activity of cyclin-CDK complexes tightly regulated by inhibitors.
- GF’s stimulate proliferation by upregulating cyclins or downregulating inhibitors.
The Normal Cell Cycle

Robbin’s Fig 7-28. Expression of cyclin-cyclin-dependent kinase (CDK) complexes during the various stages of the cell cycle.

Robbin’s fig 7-29 Schematic illustration of the role of cyclins, CDKs, and cyclin-dependent kinase inhibitors in regulating the G1/S cell-cycle transition.
The Normal Cell Cycle

- phosphorylation of RB by cyclin D-CDK4 complex is a molecular ON-OFF switch.

Robbin’s fig 7-30. Mechanism of cell-cycle regulation by RB. In a resting cell, RB is a component of the E2F/DP1/RB complex, which represses gene transcription through the recruitment of histone deacetylase, an enzyme that alters the conformation of chromatin, making it more compact. Phosphorylation of RB by cyclin D-CDK4 removes histone deacetylase from chromatin, allowing the activation of E2F transcriptional activity. E2F-mediated transcription of cyclins E & A, and of genes required for DNA replication, permit the passage through the G1 restriction point.
The Normal Cell Cycle

2 Growth Factors

- extracellular polypeptide signal molecules that stimulate a cell to grow or proliferate.

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<tr>
<th>Growth factor</th>
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<tbody>
<tr>
<td>Epidermal growth factor</td>
<td>EGF</td>
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<tr>
<td>Transforming growth factor alpha</td>
<td>TGF-α</td>
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<td>Hepatocyte growth factor</td>
<td>HGF</td>
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<td>Vascular endothelial cell growth factor</td>
<td>VEGF</td>
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<td>Platelet-derived growth factor</td>
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<td>Insulin-like growth factor</td>
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<table>
<thead>
<tr>
<th>Cytokine</th>
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<tr>
<td>Interleukins</td>
<td>IL-1, etc</td>
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<tr>
<td>Interferons</td>
<td>IFN-α, etc</td>
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Signaling Mechanisms in Cell Proliferation

- GF-receptor binding ➔ “receptor-initiated signal transduction” ➔ gene transcription

Robbin’s Fig 3-9 Examples of signal transduction systems that require cell-surface receptors. Shown are receptors with intrinsic tyrosine kinase activity, seven transmembrane G-protein-coupled receptors, and receptors without intrinsic tyrosine kinase activity. The figure also shows important signaling pathways transduced by the activation of these receptors through ligand binding.
Ligands for steroid receptors diffuse through the cell membrane and bind to receptors in the nucleus or receptors in the cytoplasm which then move into the nucleus. These steroid receptors are transcription factors that lead to the transcription of specific genes.