Cell Division and Cancer

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The Cell Cycle

- Interphase: $G_1$, $S$, $G_2$, ($G_0$)
- Cell division and cytokinesis
  - prophase
  - metaphase
  - anaphase
  - telophase
Interphase
DNA replication

- Occurs during S phase
- Semi-conservative
- New nucleotides added in 5’ to 3’ direction
- Precedes cell division
Steps of DNA Replication

- Double helix uncoils with help of DNA helicase
- H bonds break between N bases
- Bi-directional synthesis only in 5’3’ direction
- DNA polymerase directs joining of DNA nucleotides to 3’ hydroxyl group
- Leading strand builds toward replication fork
- Lagging strand builds away from fork
  - Okazaki fragments
  - joined by DNA ligase
- Each new strand = 1/2 old & 1/2 new
- chromatin recoils
- condenses to form chromosomes
- Prophase begins
Origin of replication

Parental strand

Daughter strand

Bubble

Two daughter DNA molecules

Daughter strand synthesized continuously

DNA polymerase molecule

Parental DNA

3' 5'

3' 5'

Daughter strand synthesized in pieces

5' 3'

5' 3'

DNA ligase

Overall direction of replication
Mitosis

- **Goal:** to produce **identical** cells
- occurs in somatic cells
  - growth
  - tissue repair
  - tissue replacement
Steps of mitosis (1)

- Prophase: chromosomes become visible
- nuclear envelope disappears
- centrioles to opposite poles
- spindle fibers form
Steps of mitosis (2)

- **Metaphase**: chromosomes line up in center
- chromatids still attached at the centromeres
Steps of mitosis (3)

- Anaphase: centromeres split
- chromosomes to opposite poles
Steps of mitosis (4)

- Telophase: nuclear envelope reforms from ER
- Chromosomes form chromatin
- Nucleoli reappear
- Cytokinesis - division of the cytoplasm
Can you tell which phase of mitosis?
Meiosis

- Production of gametes
- Goal: to produce cells that
  - Are genetically different
  - Have only one complete set of DNA (n)
Meiosis I

• Prophase I
  - homologous chromosome attach the nuclear envelope forming tetrads
  - crossing over at chiasma
  - nuclear membrane breaks down
  - spindle fibers form and catch each chromosome at the centromere
Crossing over

Tetrads = 4 chromatids
Meiosis I (2)

• Metaphase I
  - random arrangement of chromosomes at the equator
Meiosis I (3)

- **Anaphase I**
  - homologous chromosomes separate and move toward opposite poles
Meiosis I (4)

• Telophase I
  - cytokinesis and production of 2 genetically different haploid cells
Meiosis II

- Similar to mitosis
  - Prophase II
  - Metaphase II
  - Anaphase II
  - Telophase II
Mitosis vs. Meiosis

Mitosis:
1. **Diploid (2n)**
   - **Division**
   - Result: 2 diploid cells (2n)

Meiosis:
1. **Diploid (2n)**
   - **Division**
   - Result: 4 haploid cells (1n)

2. **Diploid (2n)**
   - **Division**
   - Result: 2 diploid cells (2n)

3. **Diploid (2n)**
   - **Division**
   - Result: 4 haploid cells (1n)

4. **Haploid (1n)**
   - **Division**
   - Result: 8 haploid cells (1n)
Oogenesis vs. spermatogenesis

• Spermatogenesis = production of sperm
  - for each spermatogonium dividing, four sperm are produced

• Oogenesis = production of oocytes
  - uneven cytoplasmic division
  - for each oogonium dividing, one viable oocyte is produced (and three polar bodies)
  - Meiosis II occurs in females only if the oocyte is fertilized
Spermatogenesis

Production of sperm cells in seminiferous tubules
Control of Cell Division

- Surface-to-volume ratio of cells
- Chemical signals such as growth factors and hormones
- Contact inhibition
- Cyclins and cyclin-dependent kinases (Cdks) complexes
Telomeres and Cell Division

• Decreased ability of cells to divide is an indicator of senescence (aging).
  - May be related to the loss of DNA sequences at the ends of chromosomes (regions called telomeres).
    • Telomeres serve as caps on the ends of DNA.
    • DNA polymerase does not fully copy the DNA at end-regions.
      - Each time a chromosome replicates it loses 50-100 base pairs in its telomeres.
  - Germinal cells can divide indefinitely due to the enzyme telomerase.
    • Duplicates telomere DNA.
Cell Death

• Pathologically:
  - Cells deprived of blood supply swell, the membrane ruptures, and the cell bursts (necrosis).

• Apoptosis:
  - Cells shrink, membranes become bubbled, nuclei condense.
  - Capsases ("executioner enzymes"):  
    • Mitochondria membranes become permeable to proteins and other products.
  - Programmed cell death  
    • Physiological process responsible for remodeling of tissues during embryonic development and tissue turnover in the adult.
"The two mice on the left were fed small amounts of watermelon. The two mice on the right were fed tons of watermelon. Since the two mice on the right developed cancer, it has now been determined that watermelon is hazardous to your health."
Cancer

- Cell Division
- Growth
- Cell Differentiation
Regulation of Cellular Division and Growth

• Cyclins promote different phases of the cell cycle.
  - During $G_1$ phase an increase in cyclin D proteins activates enzymes to move the cell quickly through the $G_1$ phase.
    • Overactivity of a gene that codes for cyclin D might cause uncontrolled cell division (cancer).

• Mutations alter genes that control growth-related cell division
  - Proto-oncogenes to oncogenes
    • Overexpression of certain proteins leads to tumor formation
  - Tumor suppressor genes
    • Inactivated or deleted gene releases controls that inhibit growth
  - Oncogenic virus
    • Insert RNA or DNA into genome transforming cells

Result: Overgrowth of mutated cells and loss of contact inhibition.
Cell differentiation

- **Anaplasia** = loss of differentiation
- **Differentiation** = Irreversible specialization as cells mature
- **Grading tumors**

<table>
<thead>
<tr>
<th>Grade</th>
<th>Differentiation</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Good</td>
<td>Resemble tissue of origin</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Retains some specialized function</td>
</tr>
<tr>
<td>II</td>
<td>Moderate</td>
<td>Less resemblance to tissues</td>
</tr>
<tr>
<td></td>
<td></td>
<td>More variation, increased mitosis</td>
</tr>
<tr>
<td>III</td>
<td>Poor</td>
<td>Little resemblance to tissues</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Increased variation, and mitosis</td>
</tr>
<tr>
<td>IV</td>
<td>Very poor</td>
<td>No resemblance to tissues</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Great variation</td>
</tr>
</tbody>
</table>
(A) Normal cell layers

(B) Early stage of abnormal growth

(C) Later stage of abnormal growth

(D) Cancerous tumor spreading to new locations

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Skin cancer
Basal Cell Carcinoma

• Least malignant
• Most common skin cancer
• Pathology
  - Stratum basale cells proliferate
  - invade the dermis and hypodermis
  - Slow growing
  - do not often metastasize
• Can be cured by surgical excision in 99% of the cases
Basal Cell Carcinoma
Squamous Cell Carcinoma

- **Pathology**
  - Arises from keratinocytes of stratum spinosum
  - Occurs most often on scalp, ears, and lower lip
  - Grows rapidly
  - Metastasizes if not removed

- **Prognosis** is good if treated by radiation therapy or surgical excision
Squamous Cell Carcinoma
Melanoma

- Most dangerous type of skin cancer
- Pathology
  - Cancer of melanocytes
  - Highly metastatic
  - Resistant to chemotherapy
<table>
<thead>
<tr>
<th>Normal Mole</th>
<th>Melanoma</th>
<th>Sign</th>
<th>Characteristic</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1.png" alt="Normal Mole Image" /></td>
<td><img src="image2.png" alt="Melanoma Image" /></td>
<td>Asymmetry</td>
<td>when half of the mole does not match the other half</td>
</tr>
<tr>
<td><img src="image3.png" alt="Normal Mole Image" /></td>
<td><img src="image4.png" alt="Melanoma Image" /></td>
<td>Border</td>
<td>when the border (edges) of the mole are ragged or irregular</td>
</tr>
<tr>
<td><img src="image5.png" alt="Normal Mole Image" /></td>
<td><img src="image6.png" alt="Melanoma Image" /></td>
<td>Color</td>
<td>when the color of the mole varies throughout</td>
</tr>
<tr>
<td><img src="image7.png" alt="Normal Mole Image" /></td>
<td><img src="image8.png" alt="Melanoma Image" /></td>
<td>Diameter</td>
<td>if the mole’s diameter is larger than a pencil’s eraser</td>
</tr>
</tbody>
</table>

*Photographs Used By Permission: National Cancer Institute*
Melanoma

- Treated by wide surgical excision accompanied by immunotherapy
- Chance of survival is poor if the lesion is over 4 mm thick
Evaluating skin lesions

• Here is a great website that will help you distinguish benign skin lesions from those that are malignant!

Table 24-1 Cancer Incidence and Cancer Mortality in the United States, 1993

<table>
<thead>
<tr>
<th>Type of Cancer</th>
<th>New Cases per Year</th>
<th>Deaths per Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cancers</td>
<td>1,170,000</td>
<td>528,300</td>
</tr>
<tr>
<td>Cancers of epithelia: carcinomas</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral cavity and pharynx</td>
<td>29,800 (3%)</td>
<td>7,700 (1%)</td>
</tr>
<tr>
<td>Digestive organs (total)</td>
<td>236,900 (20%)</td>
<td>120,325 (23%)</td>
</tr>
<tr>
<td>Colon and rectum</td>
<td>152,000 (13%)</td>
<td>57,000 (11%)</td>
</tr>
<tr>
<td>Pancreas</td>
<td>27,700 (2%)</td>
<td>25,000 (5%)</td>
</tr>
<tr>
<td>Stomach</td>
<td>24,000 (2%)</td>
<td>13,600 (3%)</td>
</tr>
<tr>
<td>Liver and biliary system</td>
<td>15,800 (1%)</td>
<td>12,600 (2%)</td>
</tr>
<tr>
<td>Respiratory system (total)</td>
<td>187,100 (16%)</td>
<td>154,200 (29%)</td>
</tr>
<tr>
<td>Lung</td>
<td>170,000 (15%)</td>
<td>149,000 (28%)</td>
</tr>
<tr>
<td>Breast</td>
<td>183,000 (16%)</td>
<td>46,300 (9%)</td>
</tr>
<tr>
<td>Skin (total)</td>
<td>(&gt;700,000)</td>
<td>9,100 (2%)</td>
</tr>
<tr>
<td>Malignant melanoma</td>
<td>32,000 (3%)</td>
<td>6,800 (1%)</td>
</tr>
<tr>
<td>Reproductive tract (total)</td>
<td>244,400 (21%)</td>
<td>59,950 (11%)</td>
</tr>
<tr>
<td>Prostate gland</td>
<td>166,000 (14%)</td>
<td>35,000 (7%)</td>
</tr>
<tr>
<td>Ovary</td>
<td>22,000 (2%)</td>
<td>13,300 (3%)</td>
</tr>
<tr>
<td>Uterine cervix</td>
<td>13,500 (1%)</td>
<td>4,400 (1%)</td>
</tr>
<tr>
<td>Uterus (endometrium)</td>
<td>31,000 (3%)</td>
<td>5,700 (1%)</td>
</tr>
<tr>
<td>Urinary organs (total)</td>
<td>79,500 (7%)</td>
<td>20,800 (4%)</td>
</tr>
<tr>
<td>Bladder</td>
<td>52,300 (4%)</td>
<td>9,900 (2%)</td>
</tr>
<tr>
<td>Cancers of the hemopoietic and immune system: leukemias and lymphomas</td>
<td>93,000 (8%)</td>
<td>50,000 (9%)</td>
</tr>
<tr>
<td>Cancers of central nervous system and eye: gliomas, retinoblastoma, etc.</td>
<td>18,250 (2%)</td>
<td>12,350 (2%)</td>
</tr>
<tr>
<td>Cancers of connective tissues, muscles, and vasculature: sarcomas</td>
<td>8,000 (1%)</td>
<td>4,150 (1%)</td>
</tr>
<tr>
<td>All other cancers + unspecified sites</td>
<td>57,050 (5%)</td>
<td>43,425 (8%)</td>
</tr>
</tbody>
</table>

*Nonmelanoma skin cancers are not included in total of all cancers, since almost all are cured easily and many go unrecorded.

In the world as a whole, the five most common cancers are those of the lung, stomach, breast, colon/rectum, and uterine cervix, and the total number of new cancer cases per year is just over 6 million. Note that only about half the number of people who develop cancer die of it. (Data for USA from American Cancer Society, Cancer Facts and Figures, 1993.)
<table>
<thead>
<tr>
<th>Site of Origin of Cancer</th>
<th>High-Incidence Population</th>
<th>Low-Incidence Population</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Location</td>
<td>Incidence*</td>
</tr>
<tr>
<td>Lung</td>
<td>USA (New Orleans, blacks)</td>
<td>110</td>
</tr>
<tr>
<td>Breast</td>
<td>Hawaii (Hawaiians)</td>
<td>94</td>
</tr>
<tr>
<td>Prostate</td>
<td>USA (Atlanta, blacks)</td>
<td>91</td>
</tr>
<tr>
<td>Uterine cervix</td>
<td>Brazil (Recife)</td>
<td>83</td>
</tr>
<tr>
<td>Stomach</td>
<td>Japan (Nagasaki)</td>
<td>82</td>
</tr>
<tr>
<td>Liver</td>
<td>China (Shanghai)</td>
<td>34</td>
</tr>
<tr>
<td>Colon</td>
<td>USA (Connecticut, whites)</td>
<td>34</td>
</tr>
<tr>
<td>Melanoma</td>
<td>Australia (Queensland)</td>
<td>31</td>
</tr>
<tr>
<td>Nasopharynx</td>
<td>Hong Kong</td>
<td>30</td>
</tr>
<tr>
<td>Esophagus</td>
<td>France (Calvados)</td>
<td>30</td>
</tr>
<tr>
<td>Bladder</td>
<td>Switzerland (Basel)</td>
<td>28</td>
</tr>
<tr>
<td>Uterus</td>
<td>USA (San Francisco Bay Area, whites)</td>
<td>26</td>
</tr>
<tr>
<td>Ovary</td>
<td>New Zealand (Polynesian Islanders)</td>
<td>26</td>
</tr>
<tr>
<td>Rectum</td>
<td>Israel (European and USA born)</td>
<td>23</td>
</tr>
<tr>
<td>Larynx</td>
<td>Brazil (São Paulo)</td>
<td>18</td>
</tr>
<tr>
<td>Pancreas</td>
<td>USA (Los Angeles, Koreans)</td>
<td>16</td>
</tr>
<tr>
<td>Lip</td>
<td>Canada (Newfoundland)</td>
<td>15</td>
</tr>
<tr>
<td>Kidney</td>
<td>Canada (NWT and Yukon)</td>
<td>15</td>
</tr>
<tr>
<td>Oral cavity</td>
<td>France (Bas-Rhin)</td>
<td>14</td>
</tr>
<tr>
<td>Leukemia</td>
<td>Canada (Ontario)</td>
<td>12</td>
</tr>
<tr>
<td>Testis</td>
<td>Switzerland (urban Vaud)</td>
<td>10</td>
</tr>
</tbody>
</table>

*Incidence = number of new cases per year per 100,000 population, adjusted for a standardized population age distribution (so as to eliminate effects due merely to differences of population age distribution). Figures for cancers of breast, uterine cervix, uterus, and ovary are for women; other figures are for men.
