Review of Normal Cells

- During its life span, each cell follows the basic cell cycle of growth and reproduction called **mitosis**
- The timing of each event varies with the specific cell type.

- Epithelial cells that reproduce rapidly may complete the cycle in hours
- Other cells may spend months completing one cycle.
- Genetic control over growth and reproduction is exerted through DNA:
  - Daughter cells are identical to parent cell
  - If the DNA is altered, the mutation is passed to the daughter cells
Social Control Genes

- Cells of a multicellular organism form a society.
- Goal of cellular society is survival of the entire organism, not just the individual cells.
- Therefore, some cells must refrain from dividing even when nutrients are plentiful.
- Cell division and differentiation are strictly regulated under normal conditions.
- Cell birth rate is balanced with cell death rate.

- When a need arises in an organ or tissue, as in repair for damage, non-dividing cells are rapidly triggered to re-enter the division cycle and then stopped from dividing after repair is complete.
- Cellular control mechanisms that regulate cell birth and death are referred to as social controls and require **social control genes**.
- Abnormal cells that disobey the social control mechanisms of normal cell division, proliferation and differentiation develop into tumors in the body.
- Virtually every cell in the body, if mutated, has the potential of forming tumors.

- Two mutational routes result in uncontrolled cell proliferation that is characteristic of cancer:
  - Stimulation of a gene causing hyperactivity.
  - Inhibition of a gene causing inactivity.
- Altered genes that stimulate overproduction of a growth stimulating product are called **oncogenes** (normal allele called **proto-oncogene**).
- Loss or alteration of a gene that normally inhibits cell division and leads to cancer is called a **tumor suppressor gene**.
- In addition to ordinary mutation mechanisms, tumor viruses can cause DNA changes leading to cancer.
Tumor formation by social control gene mutation

Proto-oncogene → regulates normal rate of mitosis for growth and repair.
Proto-oncogene → dominant mutation → stimulates hyperactive cell division → tumor

Tumor suppressor gene → suppresses excessive cell division
Tumor suppressor gene → mutation or deletion resulting in an inability to prevent excessive cell division → tumor

Differentiation of Cells

- Body cells vary in the degree of differentiation and specialization related to its particular function.
- Normally, cells are organized in an orderly arrangement in a tissue and differentiated to fulfill that tissue’s purpose.
- When cells become disorganized or undifferentiated or their growth becomes uncontrolled, their specialized function is lost.

Life span of different cell types

- Different cell types experience different life spans:
  - Erythrocytes live about 120 days
  - Some leucocytes survive only a few days
  - Highly specialized cells like neurons and muscle cells cannot undergo mitosis and have a life span of many years
  - Some cells can increase their reproductive rate on demand for purposes of repair
Cell reproduction always requires an adequate blood supply to the area and sufficient supplies of essential nutrients.

Normally, cell growth and reproduction are also subject to stimuli such as hormones or to inhibition by contact with nearby cells.

Cellular aging occurs naturally over time and results in an altered structure of the cell, decreased function and ultimately, cell death.

**Causes of DNA changes**

- Changes in DNA can alter cell structure and function or cause cell death.
- Changes in DNA can occur due to:
  - Spontaneous mutation
  - Exposure to chemicals (*mutagens*)
  - Viruses
  - Radiation
  - Other environmental hazards
- Mutant cells may lose or change function or lose control of mitosis.

**Benign and Malignant Tumors**

- A *neoplasm* or *tumor* is a cellular growth that is no longer responding to normal body controls.
- Cells continue to reproduce when there is no need.
- The excessive growth deprives other cells of nutrients.
- Characteristics of each tumor depend on the specific type of cell from which the tumor arises.
Characteristics of specific tumors vary considerably depending on the cell of origin

**Benign** tumors usually:
- Consist of differentiated cells that reproduce at a higher rate than normal
- Are typically encapsulated and expand but do not spread
- Tissue damage results from compression of adjacent structures like blood vessels
- Is not life-threatening unless it is in an area like the brain, where pressure can become critical

**Malignant** tumors usually are made up of undifferentiated, nonfunctional cells

The cells tend to:
- Reproduce more rapidly than normal
- **Infiltrate** or spread into surrounding tissue
- Easily break away to spread to other organs and tissues

**Oncology** is the study of malignant tumors, also called **cancer**

### Nomenclature and Characteristics of Tumors

<table>
<thead>
<tr>
<th>Benign Tumors</th>
<th>Malignant Tumors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consist of differentiated cells that reproduce at a higher rate than normal</td>
<td>Consist of undifferentiated, nonfunctional cells</td>
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<td>Typically encapsulated and expand but do not spread</td>
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</tr>
</tbody>
</table>

In addition, there are lymphomas and gliomas. Some neoplastic disorders have names that have persisted in spite of newer systematic naming, e.g. Hodgkin's Disease, leukemia
Benign vs. Malignant Tumors

Malignant breast tumor showing infiltration into surrounding tissue

Encapsulated Benign breast tumor

Malignant Tumors-Cancer
Pathophysiology

- The tumor manifests as an enlarging, space-occupying mass
- The expanding mass compresses nearby blood vessels leading to necrosis and an area of inflammation around the tumor
- Infection may develop
- Malignant cells do not adhere to each other but often break loose from the growing mass, infiltrating adjacent tissue

- Some neoplasms develop very rapidly; others remain in situ for a long time
- In situ refers to neoplastic cells in a preinvasive stage of cancer that may persist for months or years, offering the opportunity for early diagnosis and treatment, e.g. cervical cancer and some oral cancers
As tumors grow, inner cells may die and lead to inflammation and infection.

Some tumor cells secrete enzymes, like collagenase, which breaks down proteins or cells, adding to the tissue destruction and spreading of the tumor.

Inflammation and loss of normal cells leads to progressive reduction in organ function.

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Clicker Questions 1-4

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Grading of Tumors

Tumor grading is based on the degree of differentiation of malignant cells:

- Grade I tumor has well-differentiated cells similar to the original cells,
- Grade IV tumor is undifferentiated with cells varying in size and shape (anaplasia); this type tumor is considered highly malignant and likely to progress quickly.
Warning signs of Cancer

1. Unusual bleeding or discharge anywhere in the body
2. Change in bowel or bladder habits (e.g., prolonged diarrhea or discomfort)
3. A change in a wart or mole (i.e., color, size, or shape)
4. A sore that does not heal (on the skin or in the mouth, anywhere)
5. Unexplained weight loss
6. Anemia or low hemoglobin, and persistent fatigue
7. Persistent cough or hoarseness without reason
8. A solid lump, often painless, in the breast or testes or anywhere on the body

Local Effects of Tumors

- Pain is
  - NOT usually an early symptom of cancer, but occurs when the tumor is well advanced
  - Severity of pain depends on the type of tumor and its location

- Obstruction
  - Can occur if the tumor compresses a duct or passageway; e.g., blood vessel, intestine, respiratory passageway, nerve compression
  - Obstructions can cause serious complications even in the early stage

- Tissue necrosis and ulceration may lead to:
  - Infection around the tumor especially where normal flora may become opportunistic, e.g., cancer of oral cavity
  - Host resistance to microbial invasion is often reduced in cancer patients
Systemic Effects of Cancer

- Weight loss or cachexia (severe tissue wasting)
- Anemia
- Infections like pneumonia
- Bleeding
- Paraneoplastic syndromes; e.g. bronchogenic cancers may secrete ACTH, leading to manifestations of Cushing's syndrome (high levels of glucocorticoids) in the patient

Cancer in the U.S.

- More than 500,000 people in the United States died in 2005 of some form of cancer.
- Early detection could significantly reduce the number of deaths by allowing treatment to begin before more advanced and difficult to treat stages are reached.

Spread of Malignant Tumors

- Tumors may spread by one or more methods depending on the characteristics of the specific tumor cells
- They produce secondary tumors that consist of cells identical to the primary tumor.
- Many cancers are spread prior to diagnosis, an important fact to identify before treatment begins
There are three basic mechanisms for the spread of cancer:

- **Invasion** refers to local spread where the tumor cells grow into adjacent tissue.
- **Metastasis** means spread to distant sites by blood or lymphatics.
- **Seeding** refers to the spread of cancer cells in body fluids or along membranes, usually in body cavities.

Note early *in situ* pre-cancer condition with cells contained within the epithelium.

Later, cells become invasive, breaking through the basement lamina and invading deeper tissues.
Staging of Cancer

- Staging of cancer is a classification process applied to a specific malignant tumor at the time of diagnosis
- It may be repeated at critical times
- Staging describes the extent of the disease at the time and is useful in providing:
  - A basis for treatment
  - Prognosis
Staging systems are based on:
- Size of the primary tumor (T)
- Extent of involvement of regional lymph nodes (N)
- Spread (invasion or metastasis) of the tumor (M)

Generally, stage I tumors are small, well localized, easy to treat and have a good prognosis; stage IV tumors are well advanced, difficult to treat at multiple sites and have a poorer prognosis.

### Table 5-3
**Example of Staging—Breast Cancer**

<table>
<thead>
<tr>
<th>T</th>
<th>Size of tumor</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>Involvement of lymph nodes</td>
</tr>
<tr>
<td>M</td>
<td>Presence of metastasis</td>
</tr>
</tbody>
</table>

**Breast cancer**
- **Stage I**: T₁—tumor 2 cm or less in diameter; N₀—no lymph nodes involved; M₀—no metastasis
- **Stage II**: T₂ to T₃—tumor less than 5 cm in diameter; N₁—nodes involved; M₀—no metastasis
- **Stage III**: T₄—tumor larger than 5 cm in diameter; N₁ or N₂—nodes involved; tumor may be fixed; M₀—no metastasis
- **Stage IV**: T₄—tumor any size but fixed to chest wall or skin; N₀—clavicular nodes involved (spread); Mₑ—metastasis present

### Carcinogenesis
- Current research is examining various genes responsible for cell growth and replication and the mechanisms that stimulate or inhibit the activity of these genes.
- Genes have been discovered that:
  - Repair DNA (code for DNA repair enzymes)
  - Program cell death (apoptotic genes)
  - Cause cancer (oncogenes)
  - Suppress tumor growth (tumor-suppressor genes)
- Changes in cell DNA are at the root of malignant transformation
Is cancer genetic?

- The causes of "common" cancers include environmental factors.
- Environmental agents seem to cause cancer by increasing the frequency of mutations in somatic cells.
- Most carcinogens are mutagens.

Two lines of evidence support the idea that exposure to environmental agents increase the risk of cancer

- Identification of environment agents that have carcinogenic properties:
  - Cigarette smoke → lung cancer
  - Chemical carcinogens, UV and X-rays → certain types of cancer
- Comparisons of populations with different lifestyles.

Breast cancer is prevalent in northern Europe and United States but rare in Japan

Question is, are these differences due to genetic differences or lifestyle differences?

- In Japan, colon cancer is rare but stomach cancer is common; in U.S. colon cancer is common and stomach cancer is rare.
- Descendants of Japanese who emigrated to U.S. after WWII and adopted American eating habits have stomach and colon rates similar to U. S. averages.
Most cancers appear to arise spontaneously, without any known prior exposure to a carcinogenic agent.

There are cancer oncogenes that can be introduced (by mutation) into individuals or inherited within some families.

If mutations occur in somatic cells they are NOT passed on, but if the mutations occur in germ cells, they are inherited into every cell of the individual.

Examples of inherited human cancers include:
- Wilms tumor (a childhood cancer of the kidney)
- Retinoblastoma (a childhood cancer of the eye)
- Familial cancer of the breast
- Adenomas of the colon

Carcinogenesis is the process by which normal cells are transformed into cancer cells.

Malignant tumors develop from a sequence of changes that take place over a relatively long time.

A combination of factors, or repeated exposure to a single factor predisposes the person to neoplastic changes in cells.
Stages in Carcinogenesis

- **Initiating** factors cause the first irreversible changes in cell DNA
  - Genetic damage or exposure to environmental risk may cause first mutation
  - This initial change does not cause active neoplasm
- Exposure to **promoters** later causes further changes in DNA resulting in less differentiation and an increased rate of cell division.
  - This leads to development of the tumor
  - Promoters can include hormones or chemicals

**Risk Factors and Prevention**

<table>
<thead>
<tr>
<th>Risk Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Smoking</strong></td>
</tr>
<tr>
<td><strong>Radiation</strong></td>
</tr>
<tr>
<td><strong>Genetic predisposition</strong></td>
</tr>
</tbody>
</table>

**Table 3-4**

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>Formula</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast cancer: high tumor incidence, retinoblastoma, inherited susceptibility</td>
<td>Monosomy of chromosome 17</td>
</tr>
<tr>
<td>Prostate cancer: increase in incidence, late onset</td>
<td>Promoter activation</td>
</tr>
<tr>
<td>Colorectal cancer: adenomatous polyps</td>
<td>Adenomatous polyps</td>
</tr>
<tr>
<td>Skin cancer: sun exposure, ultraviolet light</td>
<td>Ultraviolet light exposure</td>
</tr>
<tr>
<td>Laryngeal cancer: smoking, alcohol</td>
<td>Smoker, heavy drinker</td>
</tr>
</tbody>
</table>

**Risk Factors and Prevention**

- **Chronic lower respiratory conditions** with increased risk of cancer
  - Age, increasing
  - Dark, neutral, or protective colors, and protective methods avoided
  - Colon cancer: ulcerative colitis, cancer associated cancer-associated familial adenomatous polyposis syndrome
  - Many cancers more common in older persons
  - Colon cancer: high-fat diet, gastric cancer: inherited breast/ovarian cancer, etiology
Host Defenses

- Immune system offers protection by reacting to nonself antigens on tumor cells
- Immune system response includes both cell mediated and humoral immunity
- Cytotoxic T-cells, macrophages and NK cells all help in destruction of abnormal cancer cells
- Immunodeficiency increases risk of cancer

Treatment for cancer

- Basic treatment involves:
  - Surgery
  - Chemotherapy
  - Radiation
  - Combination
- Treatment may be:
  - Curative
  - Palliative

Prognosis

- “Cure” for cancer is generally defined as a 5-year survival without recurrence after diagnosis and treatment
- Sometimes periods of remission may occur before the disease becomes terminal
- Death rates for specific cancers vary
  - Some cancer types (lung) show no improvement in outcome even with aggression treatment
  - For others (certain childhood leukemias) effective treatments have been developed and survival rates have improved
Clicker Questions 9-11