Lecture 7: Cell Division and Cancer

Objectives:
- Understand basic concepts of cancer
- Understand cell division
- Understand how cell division is regulated
- Understand programmed cell death

Key Terms: Mitosis, interphase, tumor, metastasis, angiogenesis, neoplasm, benign, malignant, adenoma, carcinoma, tumor suppressor, growth factor, check point, oncogene, programmed cell death

Leading Causes of Death

<table>
<thead>
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<tbody>
<tr>
<td>Heart Disease</td>
<td>Accidents</td>
</tr>
<tr>
<td>Cancer</td>
<td>Homicide</td>
</tr>
<tr>
<td>Stroke</td>
<td>Suicide</td>
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<tr>
<td>Lung diseases</td>
<td>Cancer</td>
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<tr>
<td>Accidents</td>
<td>Heart disease</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Genetic Disease</td>
</tr>
<tr>
<td>Flu and Pneumonia</td>
<td>HIV (AIDS)</td>
</tr>
<tr>
<td>Alzheimer’s disease</td>
<td>Stroke</td>
</tr>
<tr>
<td>Kidney Disease</td>
<td>Flu and Pneumonia</td>
</tr>
<tr>
<td>Infections</td>
<td>Diabetes</td>
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(Most current data available are for U.S. in 2001: www.cdc.gov/nchs/fastats/lcod.htm)

Leading Sites of New Cancer and Deaths 2003 estimates

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<thead>
<tr>
<th>Male</th>
<th>New cases</th>
<th>Deaths</th>
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<tbody>
<tr>
<td>Prostate</td>
<td>220,900</td>
<td>28,900</td>
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<tr>
<td>Lung</td>
<td>91,800</td>
<td>88,400</td>
</tr>
<tr>
<td>Colon</td>
<td>72,800</td>
<td>28,300</td>
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<tr>
<td>Bladder</td>
<td>42,200</td>
<td>8,600</td>
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<tr>
<td>Melanoma (skin)</td>
<td>29,900</td>
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<table>
<thead>
<tr>
<th>Female</th>
<th>New cases</th>
<th>Deaths</th>
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<tbody>
<tr>
<td>Breast</td>
<td>211,300</td>
<td>39,800</td>
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<tr>
<td>Lung</td>
<td>80,100</td>
<td>68,800</td>
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<tr>
<td>Colon</td>
<td>74,700</td>
<td>28,800</td>
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<tr>
<td>Uterine</td>
<td>40,100</td>
<td>6,800</td>
</tr>
<tr>
<td>Ovary</td>
<td>24,400</td>
<td>14,300</td>
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Cancer

Features of Cancer Cells
1. Make their own growth signals
2. Insensitive to growth stopping signals
3. Insensitive to self destruct signals
4. Immortal ! : unlimited replication
5. Stimulate new blood vessel growth
6. Invasive : move out of tumor

How does Cancer Start?
Cellular Damage Control

Normal cells protect their DNA Information

Damage control system
1. Detect DNA and cellular damage
2. Stop cell division (prevent replication of damage)
3. Activate damage repair systems
4. Activate self destruct system

[Diagram of Damage Event and Repair Process]

Damage Accumulation
Leads to Cancer
Programmed Cell Death
Tumor
- An abnormal mass of undifferentiated cells
- It often interferes with body functions
- It can absorb nutrients needed elsewhere
- It can be **benign**, grow slowly and stay in one area.
- It can be **malignant**, grow rapidly and spread to other parts of the body

Cancer Terminology
- **Neoplasm** - Cells that have no potential to spread to and grow in another location in the body
- **Benign** - Non-cancerous growth that does not invade nearby tissue or spread
- **Malignant** - Growth no longer under normal growth control
- **Metastasis** - Spread of cancer from its original site to another part of the body
- **Adenoma** - A benign tumor that develops from glandular tissue
- **Carcinoma** - A tumor that develops from epithelial cells, such as the inside of the cheek or the lining of the intestine

Understanding Cancer
To understand cancer, you must understand three fundamental cellular processes

1. Cell Division
2. Gene Regulation
3. Programmed Cell Death

Cell Division

**Key concepts of Cell Division**
1. Cell Cycle
2. DNA Replication
3. Chromosome Division
4. Cell Division

Cell Division

**Key Concept:**
There are two types of cell division

- **Mitosis** – for growing, results in two identical cells.
- **Meiosis** – for sexual reproduction, results in four cells with only one copy of chromosomes
Cell Cycle

- Cycle starts when a new cell forms
- During cycle, cell increases in mass and duplicates its chromosomes
- Cycle ends when the new cell divides

Key Terms:
Cell Cycle, Chromosomes, Cell Division

What do they Mean?

Interphase

- Phase between division and starting division again.

Three parts of Interphase

1. G_1
   - 1st Growth phase- cell makes parts, and does normal things

2. S
   - Synthesis phase- DNA replication

3. G_2
   - 2nd Growth phase- making parts for cell division

4. G_0
   - Zero Growth phase
     - Like getting stuck in park
     - Terminal development

Key Concept:
At each step, the cell must be in order

Longest part of the cycle
Cell mass increases
Cytoplasmic components double
DNA is duplicated

Decoding the Cell Cycle

Control of the Cycle

- Once S begins, the cycle automatically runs through G2 and mitosis
- The cycle has a built-in molecular brake in G1 (p53 tumor suppressor)
- Cancer involves a loss of control over the cycle, malfunction of the “brakes”

Cell Division

DNA Replication Summary

Enzymes
- Topoisomerase unwinds strands
- DNA Polymerase attaches new complementary nucleotides
- DNA Ligase connects the bonds between phosphate sugar backbone of the new nucleotides

Chemical Bonds
- Break hydrogen bonds with Topoisomerase
- Make Hydrogen bonds with DNA Polymerase
- Make covalent bonds with DNA Ligase

Final Products
- The strand being replicated is the template
- Start with one copy of a DNA molecule and end with two copies
  - New copies have one new strand and one old strand
  - Both copies are “identical” to the original
Mitosis

Definition:
• Period of nuclear division
• Followed by cytoplasmic division

Multi-step process

Cell at Interphase
Early Prophase
Late Prophase
Fig. 8.7a, p. 132

The cell duplicates its DNA, prepares for nuclear division. Mitosis begins. The DNA and its associated proteins have started to condense. The two chromosomes, color coded purple, were inherited from the female parent. The other two (blue) are their counterparts, inherited from the male parent.

Chromosomes continue to condense. New microtubules become assembled. They move one of the two pairs of centrioles to the opposite end of the cell. The nuclear envelope starts to break up.

Now microtubules penetrate the nuclear region. Collectively, they form a bipolar spindle apparatus. Many of the spindle microtubules become attached to the two sister chromatids of each chromosome.

Cell Division

Mitosis

Key Concept:
• During mitosis each cell gets a high fidelity copy of each chromosome
• Multiple checkpoints prevent run-away cycling

Cancer cells are in run-away mode, the checkpoints are broken or ignored

Stupmer

also… Key Concept:
• Each chromosome has two strands of DNA
• Each chromosome has one copy of each gene*
• Each somatic cell has two of each chromosome
• Each somatic cell has two copies of each gene*

*assume single copy genes

Chromosomes

DNA and proteins arranged as cylindrical fiber
Nucleosome

Chromosome: A double stranded DNA molecule & attached proteins
Chromosome (unduplicated)

Almost no naked DNA
Chromosome (duplicated)
Cancer and Genetics
- Genetic disease
- Meiosis
- Sexual reproduction

Focus on mechanism
(Genetic Disease etc. after Exam #1)

Understanding Cancer
To understand cancer, you must understand three fundamental cellular processes
1. Cell Division
2. Gene Regulation
3. Programmed Cell Death

Gene Regulation
Oncogenes
Genes who’s products transform normal cells into cancer cells.
- Required for normal cell cycling
- Products of these genes are no longer regulated
- “gain of function”

Tumor suppressors
Proteins that prevent the progression of the cell cycle
- P53 is a DNA binding protein that recognizes damaged DNA and stops DNA replication
- “loss of function”

Gene Regulation
Growth Factors
- Signaling molecules that enhance cell division
- Activate “cascade” of signaling inside cell
- Hyperactive cascade members can trigger cell division by turning genes on at the wrong time
- Hyperactivity lets cells ignore regulatory signals

Anchorage dependent cell cycle arrest
Adhesion is required for normal cell division rates
Cancer cells loose cell adhesion molecules
Cancer cells don’t respond to limiting signals

Gene Regulation
Imortalization
- Normal cells only divide about 50 times in a petri dish (if you can get them to divide)
- Cancer cells just keep dividing (HeLa and MCF-7 cells)
- Telomers (ends of chromosomes) usually spell the end for normal cells, but they don’t wear out

Angiogenesis
Blood vessel formation
Cancer cells trick blood vessels into supplying nutrients
Cancer cells secrete the growth factors that they are using

Cancer and Smoking
- The smoke emerging from a cigarette contains about $10^{16}$ particles/ml and 4800 chemical compounds
- There are over 60 carcinogens in cigarette smoke that have been evaluated for which there is ‘sufficient evidence for carcinogenicity’ in either laboratory animals or humans
- These compounds damage DNA in the cells of the lung. The mechanism behind the damage is unknown.
- Damage leads to mutations
Smoking and Cancer

• The kicker
  – Somehow p53 gets more mutations than other randomly selected sites
  – The mutations keep p53 from binding to DNA
  – This means that p53 can no longer prevent DNA replication when there is other damage

Understanding Cancer

To understand cancer, you must understand three fundamental cellular processes

1. Cell Division
2. Gene Regulation
3. Programmed Cell Death

Programmed Cell Death

Key Concepts

• Cells are caused to die on purpose
  – Two examples: Epithelial cells, Damaged cells
• Based on a balance of protecting proteins and killing proteins.
• Cancer cells often have high levels of protecting proteins.

AKA: Apoptosis

Programmed Cell Death

Colon Cancer

• Crypt
• Polyp
• Malignant polyp

Programmed Cell Death

The cell death program
1. Activated by cell surface receptors
2. Makes pores in Mitochondria
3. DNA is chopped up
4. Blebbing (not popping)
5. Adsorption by neighbors

Nematodes, frog tails, webbed fingers, and HIV
The Cancer has Spread

- Two linked processes
  - Metastasis
  - Angiogenesis
- Key concept
  - Metastasized cancer cells require angiogenesis to produce another malignant tumor
  - Angiogenesis- formation of new blood vessels
  - Metastasis- migration of cancer cells to a new location

Metastasis

Cancer cells leave the tumor and establish new colonies in other tissues

Angiogenesis

- Depends on growth factors released by the invading cancer cells
Markers for Cancer

- Markers are proteins found in blood
- Levels markers correlates with certain cancer types
- Some tumor markers are antigens, others are enzymes.
- Example: prostate-specific antigen (PSA) is a marker for prostate cancer in males

HeLa Cells

- Line of human cancer cells that can be grown in culture
- Descendents of tumor cells from a woman named Henrietta Lacks
- Lacks died at 31, but her cells continue to live and divide in labs around the world

Review

Thursday in class review
Normal time and place

Thursday evening review
Anthony Hall 1279
7:00 pm to 9:00 pm

Review Outline Available on Website
Wednesday at about 4:00 pm
EXTRA CREDIT #1
- Please stay after class for topic assignments

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<th>Question #1</th>
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<tr>
<td>Energy for metabolic processes only comes from Sugar</td>
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<td>A. True 19%</td>
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<td>B. False 81%</td>
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<th>Question #2</th>
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<tr>
<td>Cells burn insulin to make ATP</td>
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<td>A. True 50%</td>
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<td>B. False 50%</td>
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<td>More ATP is produced by the electron transport system than is produced by glycolysis</td>
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<td>A. True 58%</td>
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<td>B. False 42%</td>
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<td>Is Insulin a:</td>
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<td>A. Carbohydrate 20%</td>
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<td>B. Protein 33%</td>
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<tr>
<td>C. Lipid 18%</td>
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<td>D. Organophosphate 29%</td>
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<td>Carbon Dioxide Gas is used to build energy storage molecules in the liver</td>
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<td>A. True 30%</td>
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<td>B. False 70%</td>
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