CH 12 NOTES, part 2: Regulation of the Cell Cycle (12.3)
12.3 - The eukaryotic cell cycle is regulated by a molecular control system

- The frequency of cell division varies with the type of cell:
  - human skin cell: every 24-28 hrs
  - human nerve cell: never after maturity
  - frog embryo cell: every hour

- These cell cycle differences result from regulation at the molecular level
Evidence for Cytoplasmic Signals

- The cell cycle appears to be driven by specific chemical signals present in the cytoplasm.
- Some evidence for this hypothesis comes from experiments in which cultured mammalian cells at different phases of the cell cycle were fused to form a single cell with two nuclei.
When a cell in the S phase was fused with a cell in G₁, the G₁ cell immediately entered the S phase—DNA was synthesized.

When a cell in the M phase was fused with a cell in G₁, the G₁ cell immediately began mitosis—a spindle formed and chromatin condensed, even though the chromosome had not been duplicated.
The Cell Cycle Control System

- The sequential events of the cell cycle are directed by a distinct cell cycle control system, which is similar to a built-in clock.
- The clock has specific **checkpoints** where the cell cycle stops until a go-ahead signal is received.
• For many cells, the **G₁ checkpoint** seems to be the most important one

• If a cell receives a go-ahead signal at the G₁ checkpoint, it will usually **complete the S, G₂, and M phases and divide**

• If the cell does not receive the go-ahead signal, it will exit the cycle, switching into a **nondividing state called the G₀ phase**
If a cell receives a go-ahead signal at the G₁ checkpoint, the cell continues on in the cell cycle.

If a cell does not receive a go-ahead signal at the G₁ checkpoint, the cell exits the cell cycle and goes into G₀, a nondividing state.
Researchers have identified several factors that can influence cell division:

1) **Chemical factors**
2) **Physical Factors**

![Diagram of cell division and factors leading to cancer]
External CHEMICAL FACTORS – Nutrients & Growth Factors:

- if essential **NUTRIENTS** are left out of the culture medium, **cells will not divide**.

- **GROWTH FACTORS** = specific regulatory proteins released by certain body cells that stimulate other cells to divide

  ➔ **PDGF** (platelet derived growth factor) binds to cell membrane receptors and stimulates cell division in fibroblasts (i.e. as a response to heal wounds)
1. A sample of connective tissue was cut up into small pieces.

2. Enzymes were used to digest the extracellular matrix, resulting in a suspension of free fibroblast cells.

3. Cells were transferred to sterile culture vessels containing a basic growth medium consisting of glucose, amino acids, salts, and antibiotics (as a precaution against bacterial growth). PDGF was added to half the vessels. The culture vessels were incubated at 37°C.

   (a) In a basic growth medium without PDGF (the control), cells failed to divide.

   (b) In a basic growth medium plus PDGF, cells proliferated. The SEM shows cultured fibroblasts.
Internal CHEMICAL FACTORS
- Cyclins & Cdk

● Two types of regulatory proteins are involved in cell cycle control: CYCLINS and CYCLIN-DEPENDENT KINASES (Cdk)

● The activity of cyclins and Cdk fluctuates during the cell cycle
The Cell Cycle

- Cell with chromosomes in the nucleus
- Cell division
- DNA synthesis
- Chromosome duplication
- Mitosis
- Chromosome separation
- G1
- G2

CDK and cyclin regulate the cell cycle.
Fluctuation of MPF activity and cyclin concentration during the cell cycle
(b) Molecular mechanisms that help regulate the cell cycle
Stop and Go Signs: Internal and External Signals at the Checkpoints

- **EX. of internal signal:** kinetochores not attached to spindle microtubules send a molecular signal that delays anaphase (by keeping an anaphase-promoting complex (APC) in an inactive state)

- **EX. of external signal:** PDGF released by damaged/injured body cells stimulates fibroblast growth to heal injury
The platelet-derived growth factor (PDGF) mitogenic signalling pathway in hepatic stellate cells

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PHYSICAL FACTORS:

- crowding inhibits cell division in what is called **DENSITY-DEPENDENT INHIBITION**.

Normal sheet (upper, left) and "cell crowding" in three grades of expression
many animal cells exhibit **ANCHORAGE DEPENDENCE** (cells must adhere to a substratum, such as the surface of a culture dish or the extracellular matrix of a tissue)

**Cancer cells are abnormal and do not exhibit density-dependent inhibition or anchorage-dependent inhibition.**
Cells anchor to dish surface and divide (anchorage dependence).

When cells have formed a complete single layer, they stop dividing (density-dependent inhibition).

If some cells are scraped away, the remaining cells divide to fill the gap and then stop (density-dependent inhibition).

(a) Normal mammalian cells
Cancer cells do not exhibit anchorage dependence or density-dependent inhibition.
CANCER:

- Cancer cells do not respond to body’s control mechanisms.
- Cancer cells divide excessively, invade other tissues, and can kill the organism if left unchecked.
**HOW do they do this?**

- some cancer cells may make their own **growth factors**;

- cancer cells may have an **abnormal growth factor signaling system**;

- cancer cells **divide indefinitely** (as opposed to normal cells, which typically divide about 20-50 times before they stop).
• Normally, the immune system recognizes and destroys transformed or mutated cells which are growing abnormally.
• If abnormal cells evade the immune system, they may form a TUMOR.
Cancer - a problem of cell proliferation and differentiation

(A) NORMAL PATHWAY

self-renewing stem cell

daughter cell with limited proliferation capacity

terminal differentiation

nondividing cells eventually discarded

(B) STEM CELL FAILS TO PRODUCE ONE NON-STEM-CELL DAUGHTER IN EACH DIVISION AND THEREBY PROLIFERATES TO FORM A TUMOR

(C) DAUGHTER CELLS FAIL TO DIFFERENTIATE NORMALLY AND THEREBY PROLIFERATE TO FORM A TUMOR
• if the cells remain at the original site, the mass is called a **BENIGN TUMOR** and can be completely removed by surgery.

• if the tumor cells have invaded other tissues / organs, it is a **MALIGNANT TUMOR**.
Malignant versus Benign Tumors

Benign (not cancer) tumor cells grow only locally and cannot spread by invasion or metastasis.

Malignant (cancer) cells invade neighboring tissues, enter blood vessels, and metastasize to different sites.

Time
Properties of malignant tumors:

- excessive cell proliferation
- may have unusual numbers of chromosomes
- may have abnormal metabolism
- abnormal cell surface changes (i.e. lost attachments to neighboring cells)
- they cease to function in any constructive way
• if cancer cells separate from the original tumor and spread into other tissues, entering the blood and lymph vessels, they may invade other parts of the body and develop into new tumors…this is called… **METASTASIS**.
A tumor grows from a single cancer cell.

Cancer cells invade neighboring tissue.

Cancer cells spread through lymph and blood vessels to other parts of the body.
Cancer is the 2\textsuperscript{nd} leading cause of death in the U.S.

- It can affect any tissue, but the most commonly affected are:
  - lung
  - colon
  - breast
  - prostate
Healthy Human Lung

Tobacco Smoker's Lung

There are 60 known cancer-causing substances in tobacco.

These harmful chemicals include:

Nicotine – a powerful, fast-acting and addictive drug which reaches your brain in seven seconds. It increases heart rate and raises blood pressure.

Carbon monoxide – a colourless poisonous gas found in high concentrations in tobacco smoke. When you inhale it enters your bloodstream and interferes with the working of your heart and blood vessels.

Tar – a sticky brown substance that forms when tobacco cools and thickens. It collects in your lungs and can cause cancer.
Treatments

- **surgery** (for benign tumors)
- **radiation**
- **chemotherapy**
Although we do not fully understand how a normal cell is transformed into a cancerous cell, it seems clear that there is an alteration of genes that somehow influence the cell-cycle control system.
**Factors which can cause an “alteration of genes”** *(a.k.a. MUTAGENS)* include:

1) Chemicals
2) Radiation

![Chemical Symbol](image1.png)

![Radiation Symbol](image2.png)

![Toxic Symbol](image3.png)
Examples of Chemical Mutagens:
- cigarette smoke
- DDT
- chewing tobacco
- pollution
- chromium-6
Healthy Human Lung

Tobacco Smoker’s Lung
• Examples of Radiation Mutagens:
  – sun (UV rays)
  – nuclear waste
  – x-rays

spots: sun damage

skin cancer caused by too much sun
HHMI Website: Biointeractive.org

- CELL CYCLE “Click & Learn”