Chapter 12.

Regulation of Cell Division
Coordination of cell division

- **Multicellular organism**
  - need to coordinate across different parts of organism
    - timing of cell division
    - rates of cell division
  - crucial for normal growth, development & maintenance
    - do all cells have same cell cycle?

**Why is this such a hot topic right now?**
Frequency of cell division

- Frequency of cell division varies with cell type
  - Skin cells: divide frequently throughout life
  - Liver cells: retain ability to divide, but keep it in reserve
  - Mature nerve cells & muscle cells: do not divide at all after maturity
Cell Cycle Control

- Two irreversible points in cell cycle
  - replication of genetic material
  - separation of sister chromatids
- Cell can be put on hold at specific checkpoints

![Diagram showing centromere, single-stranded chromosomes, double-stranded chromosomes, and sister chromatids.]

There’s no turning back, now!
Checkpoint control system

- **Checkpoints**
  - cell cycle controlled by **STOP & GO** chemical signals at critical points
  - signals indicate if key cellular processes have been completed correctly
Checkpoint control system

- 3 major checkpoints:
  - $G_1$
    - can DNA synthesis begin?
  - $G_2$
    - has DNA synthesis been completed correctly?
    - commitment to mitosis
  - M phases
    - spindle checkpoint
    - can sister chromatids separate correctly?

G1 / S checkpoint (Start or Restriction Point)

G2 / M checkpoint
Spindle checkpoint

S
M
C
G1
G2

2005-2006
G₁ checkpoint

- G₁ checkpoint is most critical
  - primary decision point
    - “restriction point”
  - if cell receives **“go” signal**, it divides
  - if does **not** receive “go” signal, cell exits cycle & switches to G₀ phase
    - non-dividing state
G₀ phase

- G₀ phase
  - non-dividing, differentiated state
  - most human cells in G₀ phase

- liver cells
  - in G₀, but can be “called back” to cell cycle by external cues

- nerve & muscle cells
  - highly specialized; arrested in G₀ & can never divide
Activation of cell division

- How do cells know when to divide?
  - cell communication = signals
    - chemical signals in cytoplasm give cue
    - signals usually mean proteins
      - activators
      - inhibitors

Experimental evidence: Can you explain this?
“Go-ahead” signals

- Signals that promote cell growth & division
  - proteins
  - internal signals
    - “promoting factors”
  - external signals
    - “growth factors”

- Primary mechanism of control
  - phosphorylation
    - kinase enzymes
Protein signals

- Promoting factors
  - Cyclins
    - regulatory proteins
    - levels cycle in the cell
  - Cdks
    - cyclin-dependent kinases
    - enzyme activates cellular proteins
    - MPF
      - maturation (mitosis) promoting factor
  - APC
    - anaphase promoting complex
Cyclins & Cdks

- Interaction of Cdks & different Cyclins triggers the stages of the cell cycle.

Leland H. Hartwell
checkpoints

Tim Hunt
Cdks

Sir Paul Nurse
cyclins

1970s-'80s | 2001
Chromosomes attached at metaphase plate

- Replication completed
- DNA integrity

- Growth factors
- Nutritional state of cell
- Size of cell

G_{2} / M checkpoint

Spindle checkpoint

G_{1} / S checkpoint

- Cdk / G_{2} cyclin (MPF)
- APC Active
- G_{2}/M checkpoint

- Cdk / G_{1} cyclin
- APC Inactive
- G_{1}/S checkpoint

- Mitosis
Cyclin & Cyclin dependent kinases

- CDKs & cyclin drive cell from one phase to next in cell cycle
  - proper regulation of cell cycle is so key to life that the genes for these regulatory proteins have been highly conserved through evolution
  - the genes are basically the same in yeast, insects, plants & animals (including humans)

The Cell Cycle

- G1
- S
- G2
- M

Cell with chromosomes in the nucleus

Cell division

Mitosis

Chromosome separation

DNA synthesis

Chromosome duplication

Cell with duplicated chromosomes
External signals

- Growth factors
  - external signals
  - protein signals released by body cells that stimulate other cells to divide
    - density-dependent inhibition
      - crowded cells stop dividing
      - mass of cells use up growth factors
        - not enough left to trigger cell division
    - anchorage dependence
      - to divide cells must be attached to a substrate
Growth factor signals

Growth factor

Cell surface receptor

Protein kinase cascade

Nuclear membrane

Nuclear pore

Cytoplasm

Cell division

Cdk

Chromosome

E2F

Rb

Nucleus
Example of a Growth Factor

- Platelet Derived Growth Factor (PDGF)
  - made by platelets (blood cells)
  - binding of PDGF to cell receptors stimulates fibroblast (connective tissue) cell division
    - wound repair

growth of fibroblast cells (connective tissue cells) helps heal wounds
Growth Factors and Cancer

- Growth factors influence cell cycle
  - proto-oncogenes
    - normal genes that become oncogenes (cancer-causing) when mutated
    - stimulates cell growth
    - if switched **on** can cause cancer
    - example: RAS (activates cyclins)
  - tumor-suppressor genes
    - inhibits cell division
    - if switched **off** can cause cancer
    - example: p53
Cancer & Cell Growth

- Cancer is essentially a failure of cell division control
  - unrestrained, uncontrolled cell growth

- What control is lost?
  - checkpoint stops
  - gene **p53** plays a key role in G₁ checkpoint
    - p53 protein halts cell division if it detects damaged DNA
      - stimulates repair enzymes to fix DNA
      - forces cell into G₀ resting stage
      - keeps cell in G₁ arrest
      - causes apoptosis of damaged cell
    - **ALL** cancers have to shut down p53 activity

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**p53 discovered at Stony Brook by Dr. Arnold Levine**
DNA damage is caused by heat, radiation, or chemicals.

**Step 1**
DNA damage is caused by heat, radiation, or chemicals.

**Step 2**
Cell division stops, and p53 triggers enzymes to repair damaged region.

**Step 3**
p53 triggers the destruction of cells damaged beyond repair.

**NORMAL p53**
- p53 allows cells with repaired DNA to divide.

**ABNORMAL p53**
- Abnormal p53 protein

**Step 1**
DNA damage is caused by heat, radiation, or chemicals.

**Step 2**
The p53 protein fails to stop cell division and repair DNA. Cell divides without repair to damaged DNA.

**Step 3**
Damaged cells continue to divide. If other damage accumulates, the cell can turn cancerous.

**Cancer cell**
Development of Cancer

- Cancer develops only after a cell experiences ~6 key mutations (“hits”)
  - unlimited growth
    - turn on growth promoter genes
  - ignore checkpoints
    - turn off tumor suppressor genes
  - escape apoptosis
    - turn off suicide genes
  - immortality = unlimited divisions
    - turn on chromosome maintenance genes
  - promotes blood vessel growth
    - turn on blood vessel growth genes
  - overcome anchor & density dependence
    - turn off touch censor gene

It’s like an out of control car!
What causes these “hits”? 

- Mutations in cells can be triggered by 
  - UV radiation 
  - chemical exposure 
  - radiation exposure 
  - heat 
  - cigarette smoke 
  - pollution 
  - age 
  - genetics

1. A tumor grows from a single cancer cell. 
2. Cancer cells invade neighboring tissue. 
3. Cancer cells spread through lymph and blood vessels to other parts of the body.
Tumors

- **Mass of abnormal cells**
  - **Benign tumor**
    - abnormal cells remain at original site as a lump
      - p53 has halted cell divisions
    - most do not cause serious problems & can be removed by surgery
  - **Malignant tumors**
    - cells leave original site
      - lose attachment to nearby cells
      - carried by blood & lymph system to other tissues
      - start more tumors = **metastasis**
    - impair functions of organs throughout body
Traditional treatments for cancers

- Treatments target rapidly dividing cells
  - high-energy radiation & chemotherapy with toxic drugs
    - kill rapidly dividing cells
New “miracle drugs”

- Drugs targeting proteins (enzymes) found only in tumor cells
  - Gleevec
    - treatment for adult leukemia (CML) & stomach cancer (GIST)
    - 1st successful targeted drug

Gleevec: HOW IT WORKS
Any Questions??