Chapter 11.1, 11.2, 11.7
Regulation of Cell Division

Getting from there to here...

- Cell division
  - continuity of life = reproduction of cells
    - reproduction
    - unicellular life
    - growth and repair
    - multicellular life
- Cell cycle
  - life of a cell from origin to division into 2 new daughter cells

Getting the right stuff

- What is passed to daughter cells?
  - exact copy of genetic material = DNA
    - this division step = mitosis
  - assortment of organelles & cytoplasm
    - this division step = cytokinesis

Copying DNA

- Dividing cell duplicates DNA
  - separates each copy to opposite ends of cell
  - splits into 2 daughter cells
    - each human cell duplicates ~2 meters DNA
    - separates 2 copies so each daughter cell has complete identical copy
    - error rate = ~1 per 100 million bases
      - 3 billion base pairs
      - mammalian genome
      - ~30 errors per cell cycle
      - mutations

Cell Cycle

- Cell has a “life cycle”
  - cell is formed from a mitotic division
    - cell grows & matures to divide again
    - cell grows & matures to never divide again

- Phases of a dividing cell’s life
  - interphase
    - cell grows
    - replicates chromosomes
    - produces new organelles & biomolecules
  - mitotic phase
    - cell separates & divides chromosomes
      - mitosis
    - cell divides cytoplasm & organelles
      - cytokinesis
Interphase
- 90+% of cell life cycle
  - cell doing its “everyday job”
    - produce RNA, synthesize proteins
  - prepares for duplication if triggered
- Characteristics
  - nucleus well-defined
  - DNA loosely packed in long chromatin fibers

Interphase
- Divided into 3 phases:
  - G1 = 1st Gap
    - cell doing its “everyday job”
    - cell grows
  - S = DNA Synthesis
    - copies chromosomes
  - G2 = 2nd Gap
    - prepares for division
    - cell grows
    - produces organelles, proteins, membranes

G0 phase
- G0 phase
  - non-dividing, differentiated state
  - most human cells in G0 phase
    - nerve & muscle cells
      - highly specialized; arrested in G0 and can never divide!
    - liver cells
      - in G0, but can be “called back” to cell cycle by external cues

Interphase G2
- Nucleus well-defined
  - chromosome duplication complete
  - DNA loosely packed (more or less) in long chromatin fibers
- Prepares for mitosis
  - produces proteins & organelles

Coordination of Cell Cycle
- 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?
Frequency of Cell Cycle
- 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
- Cell cycle can be put on hold at specific checkpoints
- Irreversible points in cell cycle
  - replication of genetic material
  - separation of sister chromatids

“Go-ahead” signals
- Signals that promote cell growth & division
  - intracellular signals: “promoting factors”
  - extracellular signals: “growth factors”
- Primary mechanism of control
  - phosphorylation
    - kinase enzymes

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

G₁ checkpoint
- G₁ checkpoint is critical
  - primary decision point
    - “restriction point”
  - if cell receives “go” signal, it continues on...
  - if does not receive “go” signal, cell exits cycle & switches to G₀ phase
    - non-dividing state
Intracellular signals

- **Promoting factors**
  - Cyclins
    - regulatory proteins
    - levels cycle in the cell
  - Cdns
    - cyclin-dependent kinases
    - enzyme activates cellular proteins

- **MPF (for G2 checkpoint):**
  - maturation/mitosis promoting factor
- **APC (for M checkpoint):**
  - anaphase promoting complex

Cyclins & Cdns

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

Extracellular 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

Example of a Growth Factor

- **Platelet Derived Growth Factor (PDGF)**
  - made by platelets (blood cells)
  - binding of PDGF to cell receptors stimulates fibroblast cell division
  - **Growth of fibroblast cells (connective tissue cells) helps heal wounds!**
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 and keeps cell in **G₂** resting stage
      - causes apoptosis of severely damaged cell
    - **MOST** cancers have to shut down p53 activity

Growth Factors, Genes, and Cancer

- Cancer is a “genetic” disease...
  - **proto-oncogenes**
    - normal genes that become oncogenes (cancer-causing) when mutated
    - stimulates cell growth
    - if switched on or **increased expression** can cause cancer
      - example: RAS (activates cyclin production)
  - **tumor-suppressor genes**
    - inhibits cell division
    - if switched off can cause cancer
      - example: p53

**p53 — Master Regulator Gene**

- normal p53
  - DNA repair enzyme
    - p53 allows cells with repaired DNA to divide.
- **abnormal** p53
  - DNA damage is caused by heat, radiation, or chemicals.
  - p53 fails to stop cell division and repair DNA.
  - Cell divides without repair to damaged DNA.
  - Damaged cells continue to divide. If other damage accumulates, the cell can turn cancerous.
Development of Cancer

- Cancer develops only after a cell line experiences ~6 key mutations ("hits")
  - unlimited growth
    - turn on oncogenes
  - ignore checkpoints
    - turn off tumor suppressor genes
  - escape apoptosis
    - turn off programmed cell death 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 sensor" gene

What causes these "hits"?
- Mutations in cells can be triggered by:
  - UV radiation
  - chemical exposure
  - radiation exposure
  - heat
  - cigarette smoke
  - pollution
  - age
  - genetics

Tumors
- Mass of abnormal cells
  - Benign tumor (not totally safe...)
    - abnormal cells remain at original site as a lump
      - p53 has halted cell divisions
      - still have properties of ‘original’ tissue
      - 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
    - no longer resembles ‘original’ tissue
    - 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 at expense of healthy cells

New “miracle drugs”
- Drugs targeting proteins (enzymes) found only in SPECIFIC tumor cells
  - Gleevec
    - treatment for adult leukemia (CML)
    - stomach cancer (GIST)
    - 1st successful targeted drug