The Cell Cycle: 
Cell Growth, Cell Division

Why do cells divide?

- **For reproduction**
  - asexual reproduction
  - one-celled organisms
- **For growth**
  - from fertilized egg to multi-celled organism
- **For repair & renewal**
  - replace cells that die from normal wear & tear or from injury

Making new cells

- **Nucleus**
  - chromosomes
  - DNA
- **Cytoskeleton**
  - centrioles
  - in animals
  - microtubule spindle fibers
Getting the right stuff

• What is passed on to daughter cells?
  – exact copy of genetic material = DNA
    • mitosis
  – organelles, cytoplasm, cell membrane, enzymes
    • cytokinesis

chromosomes (stained orange)
in kangaroo rat epithelial cell
→ notice cytoskeleton fibers

Overview of mitosis

Interphase

• 90% of cell life cycle
  – cell doing its “everyday job”
    • produce RNA, synthesize proteins/enzymes
  – prepares for duplication if triggered
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
  - G0, S, G2, M

- Liver cells
- Brain / nerve cells
- Skin cells, blood cells, stem cells

Interphase

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

- G0

Interphase

- Nucleus well-defined
  - DNA loosely packed in long chromatin fibers
- Prepares for mitosis
  - replicates chromosome
    - DNA & proteins
  - produces proteins & organelles
S phase: Copying / Replicating DNA

- **Synthesis phase of Interphase**
  - dividing cell replicates DNA
  - must separate DNA copies correctly to 2 daughter cells
    - human cell duplicates ~3 meters DNA
    - each daughter cell gets complete identical copy
  - error rate = ~1 per 100 million bases
    - ~3 billion base pairs in mammalian genome
    - ~30 errors per cell cycle
      - mutations (to somatic (body) cells)

Organizing DNA

- DNA is organized in chromosomes
  - double helix DNA molecule
  - wrapped around histone proteins
    - like thread on spools
  - DNA-protein complex = chromatin
    - organized into long thin fiber
  - condensed further during mitosis

Copying DNA & packaging it...

- After DNA duplication, chromatin condenses
  - coiling & folding to make a smaller package
Mitotic Chromosome

- **Duplicated chromosome**
  - 2 *sister chromatids*
  - narrow at *centromeres*
  - contain identical copies of original DNA

- *homologous chromosomes*

- *single-stranded*

- *double-stranded*

Mitosis

- Dividing cell's DNA between 2 daughter nuclei
- 4 phases
  - prophase
  - metaphase
  - anaphase
  - telophase
Prophase

- Chromatin condenses
  - visible chromosomes
    - chromatids
- Centrioles move to opposite poles of cell
  - animal cell
- Protein fibers cross cell to form mitotic spindle
  - microtubules
    - actin, myosin
  - coordinates movement of chromosomes
- Nucleolus disappears
- Nuclear membrane breaks down

Transition to Metaphase

- Prometaphase
  - spindle fibers attach to centromeres
    - creating kinetochores
  - microtubules attach at kinetochores
    - connect centromeres to centrioles
  - chromosomes begin moving

Metaphase

- Chromosomes align along middle of cell
  - metaphase plate
    - meta = middle
  - spindle fibers coordinate movement
  - helps to ensure chromosomes separate properly
    - so each new nucleus receives only 1 copy of each chromosome
Anaphase

- Sister chromatids separate at kinetochores
  - move to opposite poles
  - pulled at centromeres
  - pulled by motor proteins "walking" along microtubules
    - actin, myosin
    - increased production of ATP by mitochondria
- Poles move farther apart
  - polar microtubules lengthen

Separation of chromatids

- In anaphase, proteins holding together sister chromatids are inactivated
  - separate to become individual chromosomes

Chromosome movement

- Kinetochores use motor proteins that "walk" chromosome along attached microtubule
  - microtubule shortens by dismantling at kinetochore (chromosome) end
Telophase

- Chromosomes arrive at opposite poles
  - daughter nuclei form
  - nucleoli form
  - chromosomes disperse
    - no longer visible under light microscope
- Spindle fibers disperse
- Cytokinesis begins
  - cell division

Cytokinesis

- Animals
  - constriction belt of actin microfilaments around equator of cell
    - cleavage furrow forms
    - splits cell in two
    - like tightening a draw string

Cytokinesis in Animals
Mitosis in animal cells

Cytokinesis in Plants

• Plants
  — cell plate forms
    • vesicles line up at equator
      — derived from Golgi
    • vesicles fuse to form 2 cell membranes
  — new cell wall laid down between membranes
    • new cell wall fuses with existing cell wall

Cytokinesis in plant cell
Regulation of Cell Division

Coordination of cell division

• A multicellular organism needs to coordinate cell division across different tissues & organs
  – critical for normal growth, development & maintenance
    • coordinate timing of cell division
    • coordinate rates of cell division
    • not all cells can have the same cell cycle

Frequency of cell division

• Frequency of cell division varies by cell type
  – embryo
    • cell cycle < 20 minute
  – skin cells
    • divide frequently throughout life
    • 12-24 hours cycle
  – liver cells
    • retain ability to divide, but keep it in reserve
    • divide once every year or two
  – mature nerve cells
    • do not divide at all after maturity
    • permanently in G0
Overview of Cell Cycle Control

- Two irreversible points in cell cycle
  - replication of genetic material
  - separation of sister chromatids
- Checkpoints
  - process is assessed & possibly halted

![Diagram of cell cycle checkpoints](image)

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

![Diagram of checkpoint control system](image)

Checkpoint control system

- 3 major checkpoints:
  - G1/S
    - can DNA synthesis begin?
  - G2/M
    - has DNA synthesis been completed correctly?
    - commitment to mitosis
  - spindle checkpoint
    - are all chromosomes attached to spindle?
    - can sister chromatids separate correctly?
G1/S checkpoint

• G1/S checkpoint is most critical
  – primary decision point
    • “restriction point”
  – if cell receives “GO” signal, it divides
    • internal signals: cell growth (size), cell nutrition
    • external signals: “growth factors”
  – if cell does not receive signal, it exits cycle & switches to G0 phase
    • non-dividing, working state

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

Cell cycle signals

• Cell cycle controls
  – cyclins
    • regulatory proteins
    • levels cycle in the cell
  – Cdns
    • cyclin-dependent kinases
    • phosphorylates cellular proteins
      – activates or inactivates proteins
  – Cdk-cyclin complex
    • triggers passage through different stages of cell cycle
Cyclins & Cdks

- Interaction of Cdk’s & different cyclins triggers the stages of the cell cycle

1970s-80s | 2001

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)
External signals

- **Growth factors**
  - coordination between cells
  - protein signals released by body cells that stimulate other cells to divide
    - density-dependent inhibition
      - crowded cells stop dividing
      - each cell binds a bit of growth factor
      » not enough activator left to trigger division in any one cell
    - anchorage dependence
      - to divide cells must be attached to a substrate
      » "touch sensor" receptors

Growth factor signals

Example of a Growth Factor

- **Platelet Derived Growth Factor (PDGF)**
  - made by platelets in blood clots
  - binding of PDGF to cell receptors stimulates cell division in connective tissue
    - heal wounds
**Growth Factors and Cancer**

- Growth factors can create cancers
  - proto-oncogenes
    - normally activates cell division
    - become oncogenes (cancer-causing) when mutated
  - if switched "ON" can cause cancer
    - example: RAS (activates cyclins)
  - tumor-suppressor genes
    - normally 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?
  - lose checkpoint stops
    - gene p53 plays a key role in G1/S restriction point
      - p53 protein halts cell division if it detects damaged DNA
        - options:
          - stimulates repair enzymes to fix DNA
          - forces cell into G0 resting stage
          - keeps cell in G1 arrest
          - causes apoptosis of damaged cell
    - cancers have to shut down p53 activity

**p53 — master regulator gene**

- DNA damage is caused by heat, radiation, or chemicals.
- p53 triggers the destruction of cells damaged beyond repair.
  - Damaged cells continue to divide. If further damage accumulates, the cell can turn cancerous.
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 (p53)
  – 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-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
    • abnormal cells remain at original site as a lump
    • most do not cause serious problems & can be removed by surgery
  – Malignant tumor
    • 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
    • kills rapidly dividing cells
  – chemotherapy
    • stop DNA replication
    • stop mitosis & cytokinesis
    • stop blood vessel growth

New “miracle drugs”

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