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 & muscle cells**
    - do not divide at all after maturity
    - permanently in $G_0$
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

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:
  - $G_1/S$
    - can DNA synthesis begin?
  - $G_2/M$
    - 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
**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

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

- Primary mechanism of control
  - phosphorylation
    - kinase enzymes
    - either activates or inactivates cell signals
Cell cycle signals

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

- Interaction of Cdk's & different cyclins triggers the stages of the cell cycle.
G₂ / M checkpoint
- Replication completed
- DNA integrity

Spindle checkpoint
- Chromosomes attached at metaphase plate

MPF = Mitosis Promoting Factor
APC = Anaphase Promoting Complex

G₁ / S checkpoint
- Growth factors
- Nutritional state of cell
- Size of cell

Cdk / G₂ cyclin (MPF)
Active
Inactive

Cdk / G₁ cyclin
Active
Inactive
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

- Growth factor
- Cell surface receptor
- Protein kinase cascade
- Nuclear membrane
- Nuclear pore
- Cell division
- Chromosome
- Cdk
- Rb
- E2F
- Cytoplasm
- Nucleus
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 fibroblast (connective tissue)
  - heal wounds

Don’t forget to mention **erythropoietin**! (EPO)
Growth Factors and Cancer

- Growth factors can create cancers
  - **proto-oncogenes**
    - normal growth factor 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?
  - lose checkpoint stops
  - gene p53 plays a key role in G\(_1\)/S restriction point
    - p53 protein halts cell division if it detects damaged DNA
      - options:
        - stimulates repair enzymes to fix DNA
        - forces cell into G\(_0\) resting stage
        - keeps cell in G\(_1\) arrest
        - causes apoptosis of damaged cell
- **ALL** cancers have to shut down p53 activity

p53 discovered at Stony Brook by Dr. Arnold Levine
**p53 — master regulator gene**

### NORMAL p53

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

**Step 2**
DNA repair enzyme is activated to repair damaged DNA.

**Step 3**
p53 allows cells with repaired DNA to divide.

### ABNORMAL p53

**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.
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

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
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
    - 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

Novartes

Gleevec: HOW IT WORKS

without Gleevec

- CML Enzyme
- ATP
- Cancer Protein
- CML

with Gleevec

- CML Enzyme
- Gleevec
- ATP
- Cancer Protein
- CML