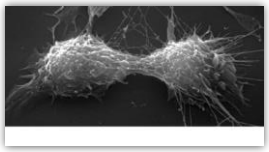
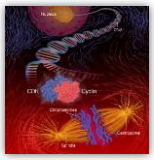
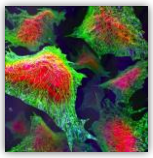



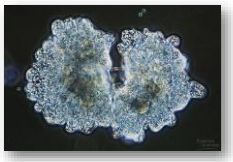
Chapter 11.1, 11.2, 11.7

Regulation of Cell Division




Getting from there to here…

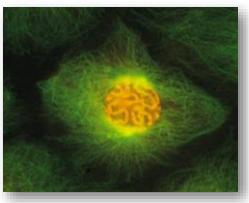
- Cell division
  - continuity of life = reproduction of cells
    - reproduction
      - unicellular life
    - growth and repair
      - multicellular life
- Cell cycle
  - life of a cell from origin to division into 2 new daughter cells




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

chromosomes (stained orange) in kangaroo rat epithelial cell

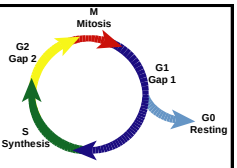


Copying DNA

- 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

G_1, S, G_2, M

liver cells

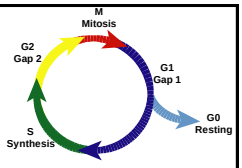
G_0

epithelial cells, blood cells, stem cells

brain, nerve cells

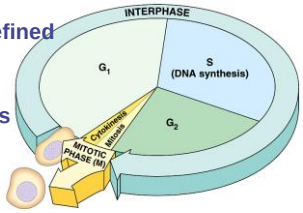
Cell Cycle

- 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



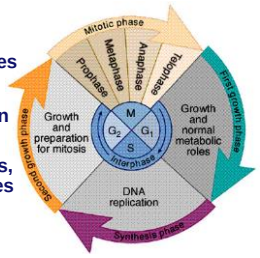
Interphase

- 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



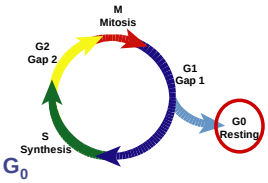
Interphase

- Divided into 3 phases:
  - G_1 = 1st Gap
    - cell doing its "everyday job"
    - cell grows
  - S = DNA Synthesis
    - copies chromosomes
  - G_2 = 2nd Gap
    - prepares for division
    - cell grows
    - produces organelles, proteins, membranes



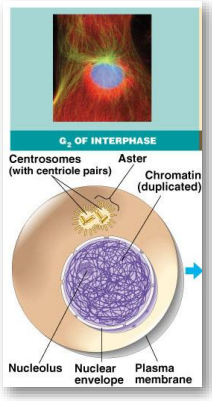
G_0 phase

- G_0 phase
  - non-dividing, differentiated state
  - most human cells in G_0 phase
    - nerve & muscle cells
      - highly specialized; arrested in G_0 and can never divide!
    - liver cells
      - in G_0, but can be "called back" to cell cycle by external cues



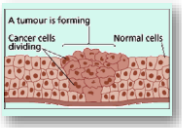
Interphase G2

- 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?

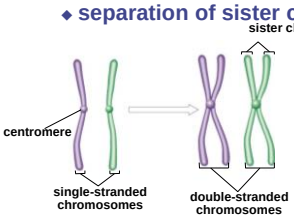


Frequency of Cell Cycle

- 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

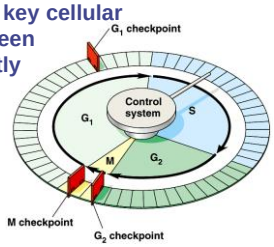
Cell Cycle Control

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



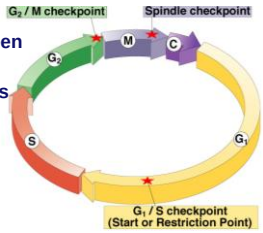
Checkpoint control system

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



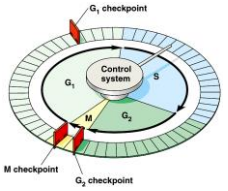
Checkpoint control system

- 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?



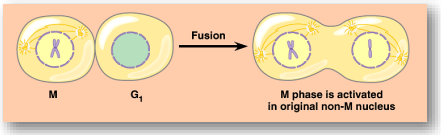
G_1 checkpoint

- G_1 checkpoint is critical
  - primary decision point
    - "restriction point"
  - if cell receives "go" signal, it divides
  - if does not receive "go" signal, cell exits cycle & switches to G_0 phase
    - non-dividing state



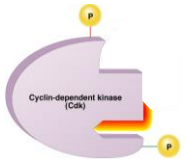
Activation of cell division

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



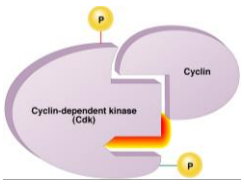
"Go-ahead" signals

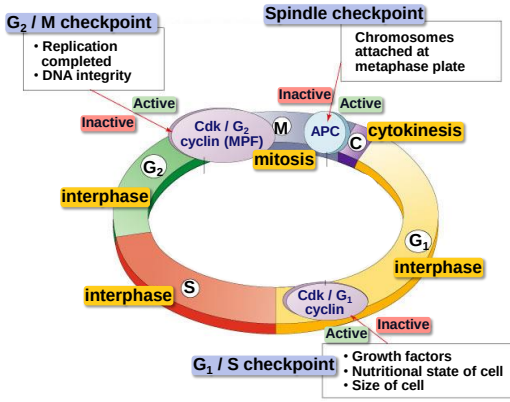
- Signals that promote cell growth & division
  - internal signals
    - "promoting factors"
  - external signals
    - "growth factors"
- Primary mechanism of control
  - phosphorylation
    - kinase enzymes



Protein signals

- Promoting factors
  - Cyclins
    - regulatory proteins
    - levels cycle in the cell
  - Cdks
    - cyclin-dependent kinases
    - enzyme activates cellular proteins
  - MPF (for G2 checkpoint): maturation/mitosis promoting factor
  - APC (for M checkpoint): anaphase promoting complex

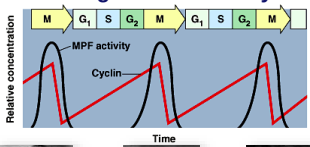




Cyclins & Cdks

1970s-'80s | 2001

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



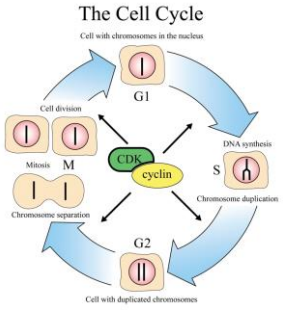
Leland H. Hartwell checkpoints

Tim Hunt Cdks

Sir Paul Nurse cyclins

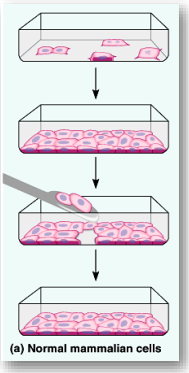
Internal Signals

- 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

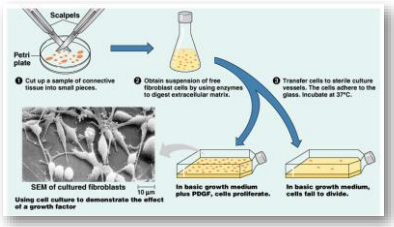
- Growth factors
  - external signals
  - protein signals released by body cells that stimulate other cells to divide
    - density-dependent inhibition
      - crowded cells stop dividing
      - mass of cells use up growth factors
      - not enough left to trigger cell division
    - anchorage dependence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



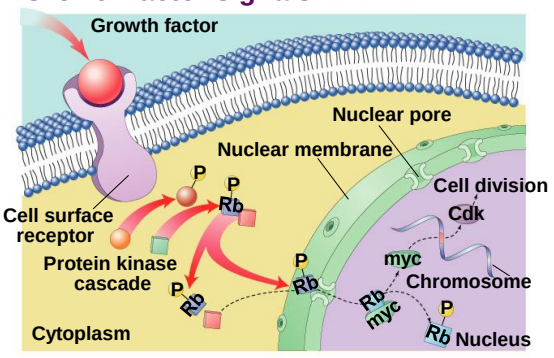
Example of a Growth Factor

- 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!



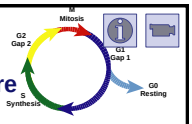
Growth factor signals



Growth Factors and Cancer

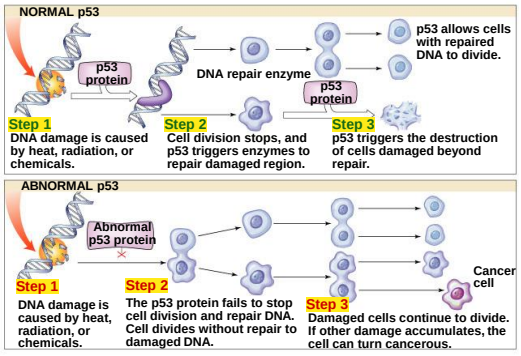
- Growth factors influence cell cycle
  - proto-oncogenes
    - normal genes that become oncogenes (cancer-causing) when mutated
    - stimulates cell growth
    - if switched on can cause cancer
    - example: RAS (activates cyclins)
  - tumor-suppressor genes
    - inhibits cell division
    - if switched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

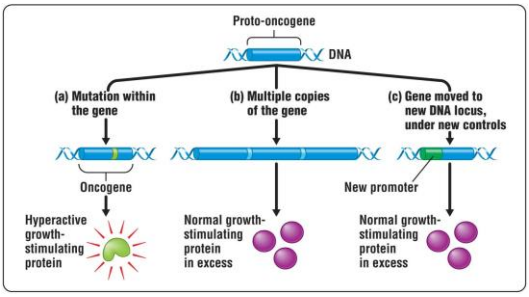
Cancer & Cell Growth

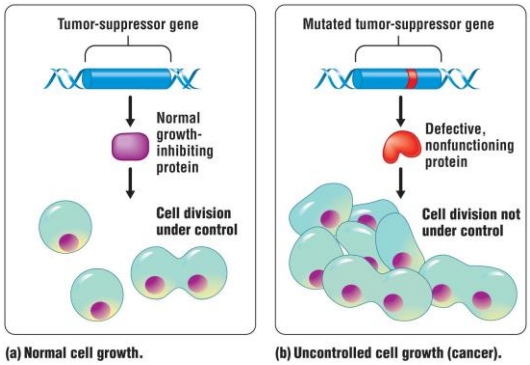


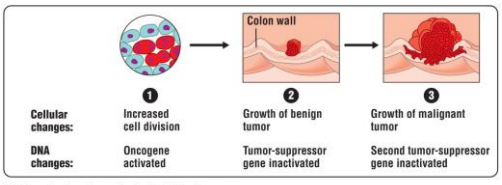
- Cancer is essentially a failure of cell division control
  - unrestrained, uncontrolled cell growth
- What control is lost?
  - checkpoint stops
  - gene p53 plays a key role in G_1 checkpoint
    - p53 protein halts cell division if it detects damaged DNA
      - stimulates repair enzymes to fix DNA
      - forces and keeps cell in G_0 resting stage
      - causes apoptosis of severely damaged cell
    - ALL cancers have to shut down p53 activity

p53 — Master Regulator Gene

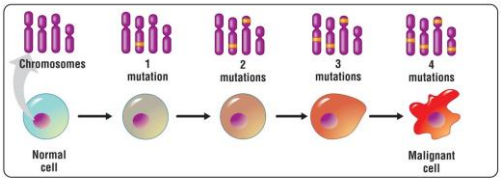








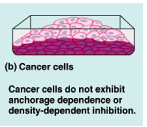
(a) Stepwise development of a typical colon cancer.



(b) Accumulation of mutations in the development of a 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 sensor" gene

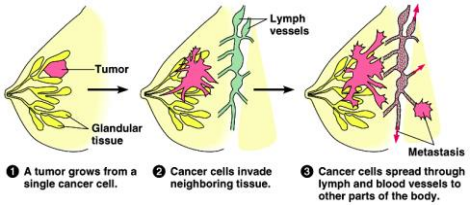


(b) Cancer cells

Cancer cells do not exhibit anchorage dependence or density-dependent inhibition.

What causes these "hits"?

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

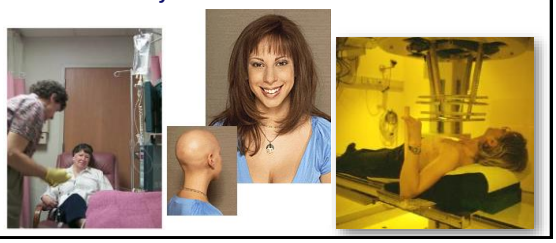


Tumors

- Mass of abnormal cells
  - Benign tumor (not totally safe…)
    - abnormal cells remain at original site as a lump
      - p53 has halted cell divisions
    - 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 at expense of healthy 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