

The Cell Cycle: Cell Growth, Cell Division



Why do cells divide?

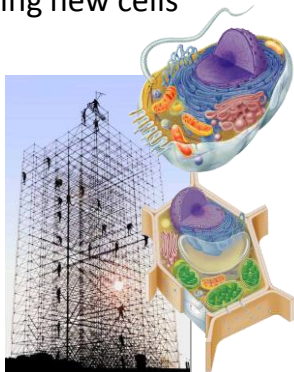
- **For reproduction**
 - asexual reproduction
 - one-celled organisms
- **For growth**
 - from fertilized egg to multi-celled organism
- **For repair & renewal**
 - replace cells that die from normal wear & tear or from injury





Making new cells

- **Nucleus**
 - chromosomes
 - DNA
- **Cytoskeleton**
 - centrioles
 - in animals
 - microtubule spindle fibers

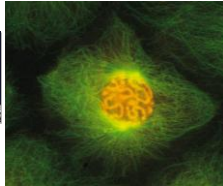


Getting the right stuff

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

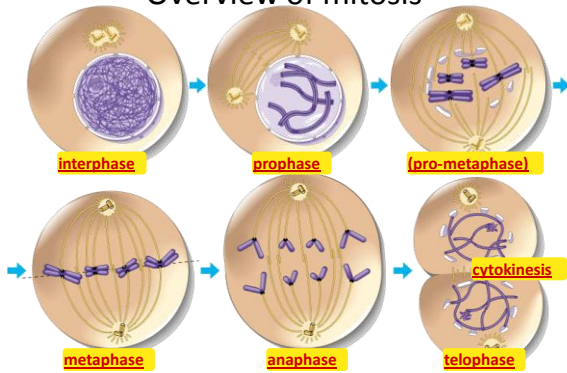


chromosomes (stained orange) in kangaroo rat epithelial cell
→notice cytoskeleton fibers



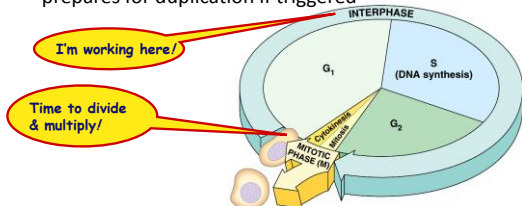
Overview of mitosis

I.P.M.A.T.



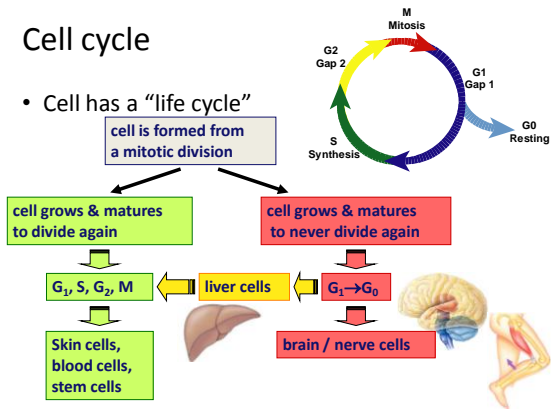
Interphase

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



Cell cycle

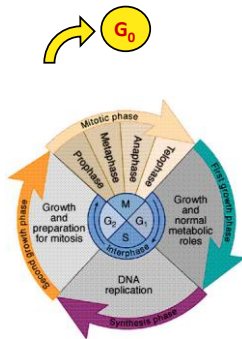
- Cell has a "life cycle"



Interphase

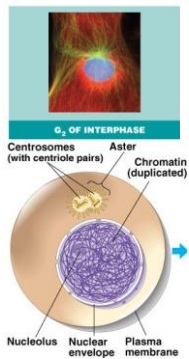
- Divided into 3 phases:
 - G₁ = 1st Gap (Growth)
 - cell doing its "everyday job"
 - cell grows
 - S = DNA Synthesis
 - copies chromosomes
 - G₂ = 2nd Gap (Growth)
 - prepares for division
 - cell grows (more)
 - produces organelles, proteins, membranes

signal to divide



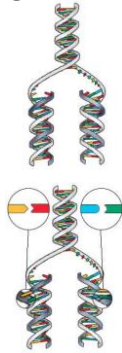
Interphase

- Nucleus well-defined
 - DNA loosely packed in long chromatin fibers
- Prepares for mitosis
 - replicates chromosome
 - DNA & proteins
 - produces proteins & organelles



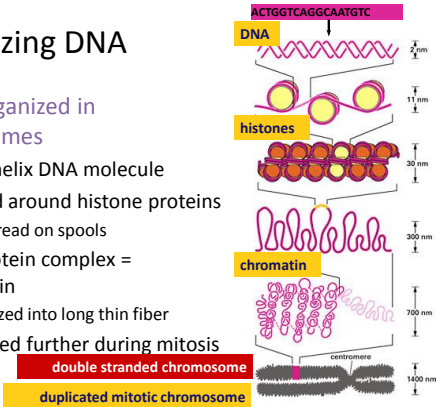
S phase: Copying / Replicating DNA

- 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)



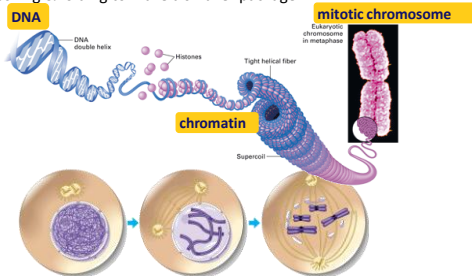
Organizing DNA

- 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

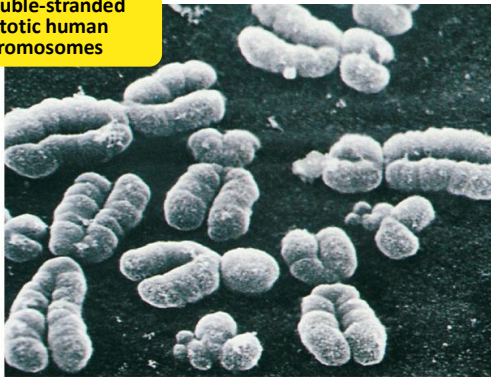


Copying DNA & packaging it...

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



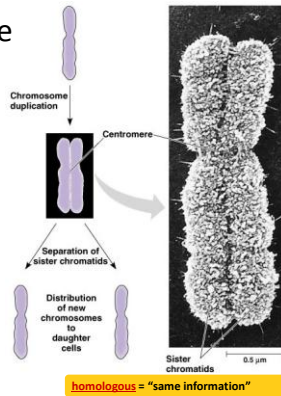
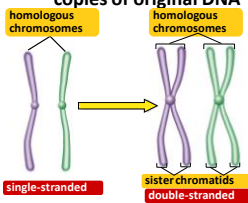
double-stranded mitotic human chromosomes



Mitotic Chromosome

▪ Duplicated chromosome

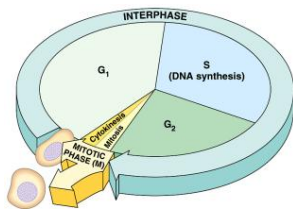
- ◆ 2 **sister chromatids**
- ◆ narrow at **centromeres**
- ◆ contain identical copies of original DNA



Mitosis

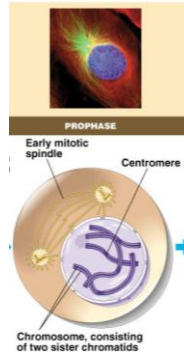


- Dividing cell's DNA between 2 daughter nuclei
- 4 phases
 - prophase
 - metaphase
 - anaphase
 - telophase



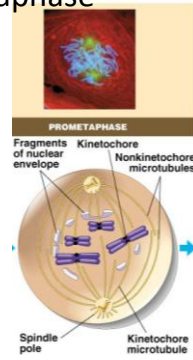
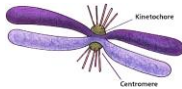
Prophase

- 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



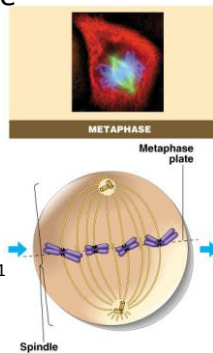
Transition to Metaphase

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



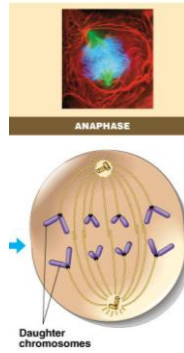
Metaphase

- 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



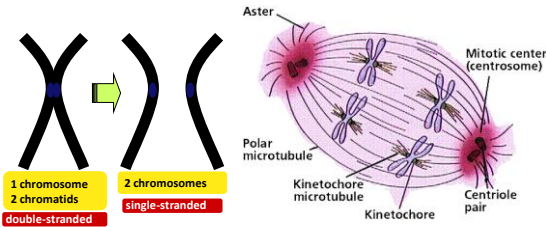
Anaphase

- 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



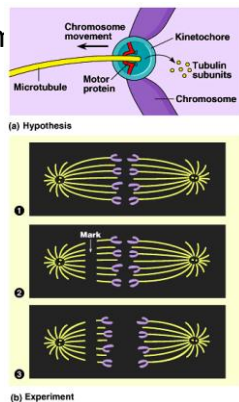
Separation of chromatids

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



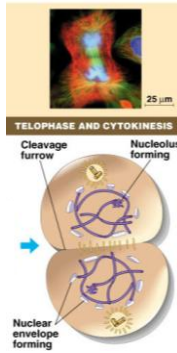
Chromosome n

- Kinetochores use motor proteins that “walk” chromosome along attached microtubule
 - microtubule shortens by dismantling at kinetochole (chromosome) end



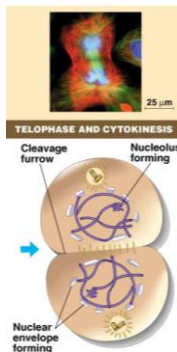
Telophase

- 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

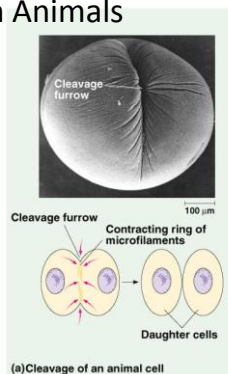
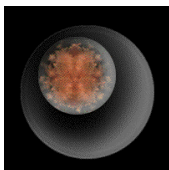


Cytokinesis

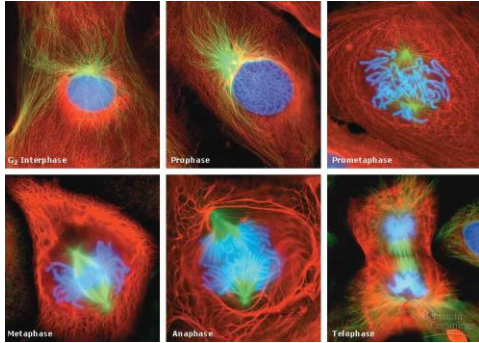
- Animals
 - constriction belt of actin microfilaments around equator of cell
 - cleavage furrow forms
 - splits cell in two
 - like tightening a draw string



Cytokinesis in Animals



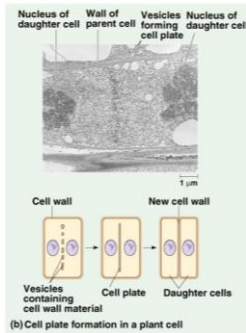
Mitosis in animal cells



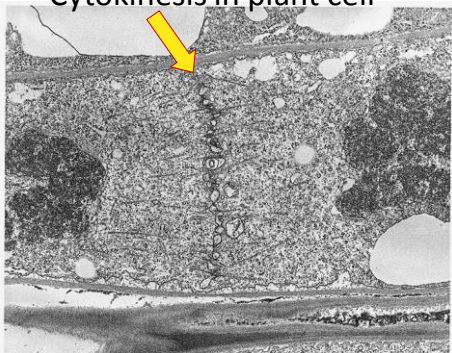
Cytokinesis in Plants

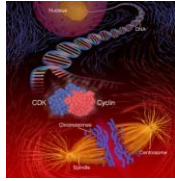
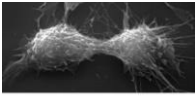
• Plants

- 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

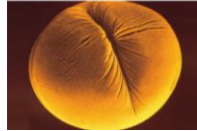
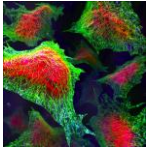


Cytokinesis in plant cell





Regulation of Cell Division



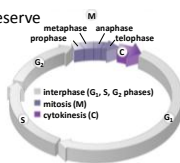
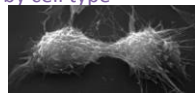
Coordination of cell division

- 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



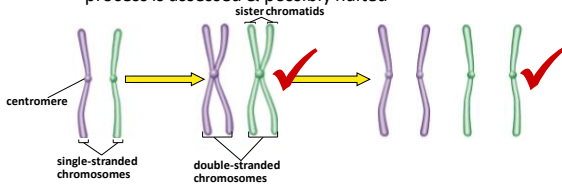
Frequency of cell division

- 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



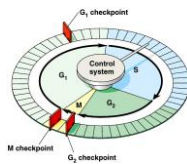
Overview of Cell Cycle Control

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



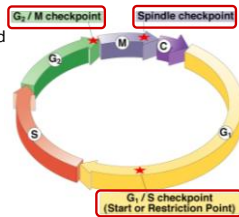
Checkpoint control system

- 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

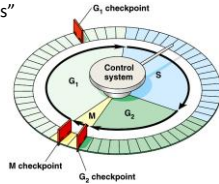
- 3 major checkpoints:
 - G₁/S
 - can DNA synthesis begin?
 - G₂/M
 - has DNA synthesis been completed correctly?
 - commitment to mitosis
 - spindle checkpoint
 - are all chromosomes attached to spindle?
 - can sister chromatids separate correctly?



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

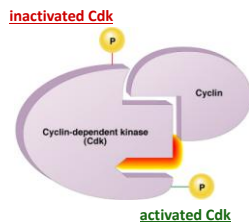


Activation of cell division

- 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

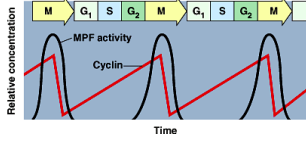
- Cell cycle controls
 - cyclins
 - regulatory proteins
 - levels cycle in the cell
 - Cdks
 - cyclin-dependent kinases
 - phosphorylates cellular proteins
 - activates or inactivates proteins
 - Cdk-cyclin complex
 - triggers passage through different stages of cell cycle



1970s-80s | 2001

Cyclins & Cdks

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



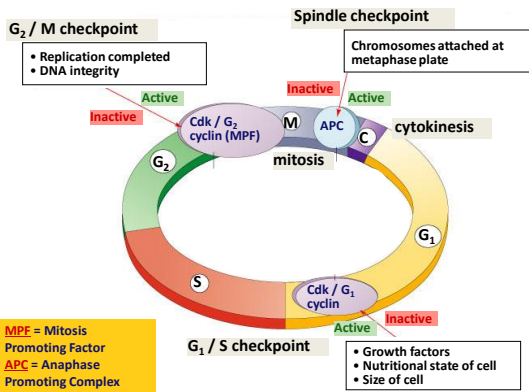
Leland H. Hartwell
checkpoints



Tim Hunt
Cdks

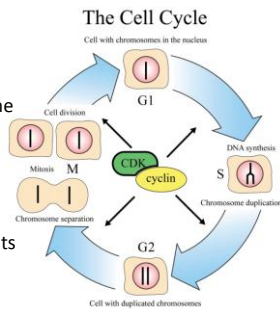


Sir Paul Nurse
cyclins



Cyclin & Cyclin-dependent kinases

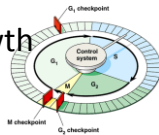
- CDKs & cyclin drive cell from one phase to next in cell cycle
 - proper regulation of cell cycle is so key to life that the genes for these regulatory proteins have been highly conserved through evolution
 - the genes are basically the same in yeast, insects, plants & animals (including humans)



Growth Factors and Cancer

- Growth factors can create cancers
 - proto-oncogenes
 - normally activates cell division
 - growth factor genes
 - 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

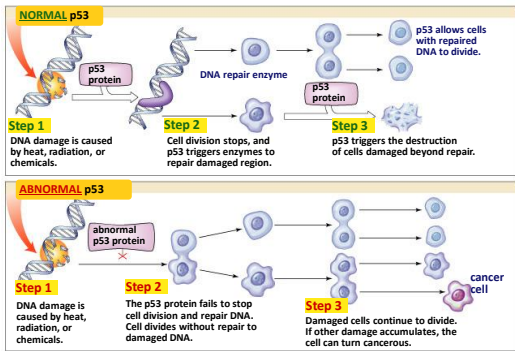
Cancer & Cell Growth



- 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

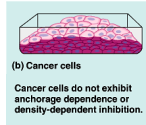
p53 is the Cell Cycle Enforcer

p53 — master regulator gene



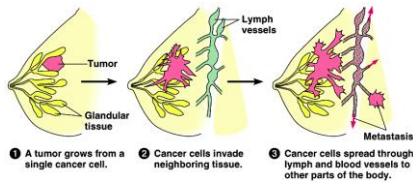
Development of Cancer

- 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



Novartis

