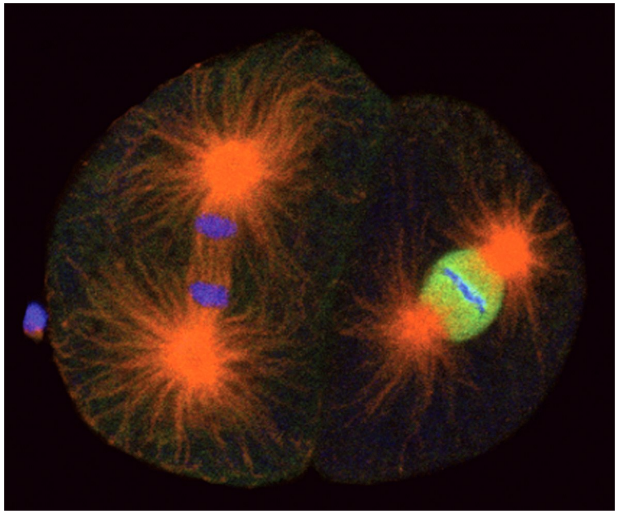
General Biology

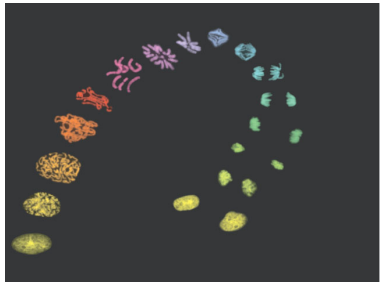
Course No: BNG2003
Credits: 3.00

8. The Cell Cycle

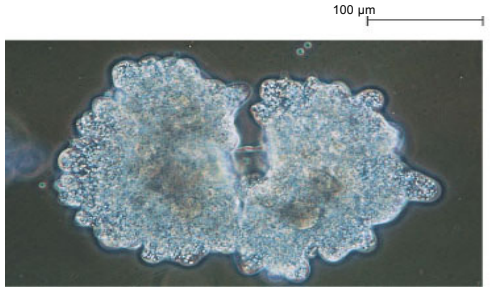
Prof. Dr. Klaus Heese



- **Overview: The Key Roles of Cell Division**
- The continuity of life is based upon the reproduction of cells, or cell division

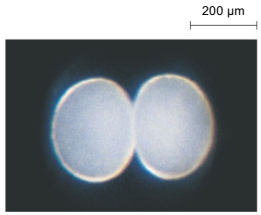


- Unicellular organisms
  - Reproduce by cell division

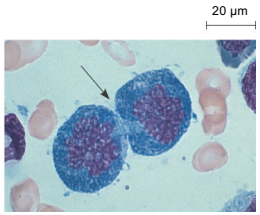


(a) Reproduction. An amoeba, a single-celled eukaryote, is dividing into two cells. Each new cell will be an individual organism (LM).

- Multicellular organisms depend on cell division for
  - development from a fertilized cell
  - growth
  - repair



(b) Growth and development. This micrograph shows a sand dollar embryo shortly after the fertilized egg divided, forming two cells (LM).

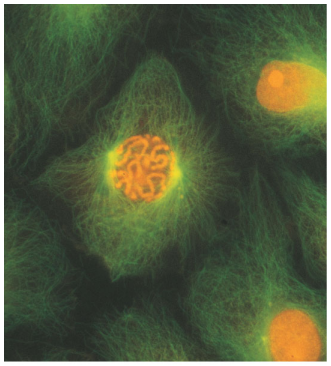


(c) Tissue renewal. These dividing bone marrow cells (arrow) will give rise to new blood cells (LM).

- The cell division process is an integral part of the cell cycle
- Cell division results in genetically identical daughter cells
- Cells duplicate their genetic material
  - before they divide, ensuring that each daughter cell receives an exact copy of the genetic material, DNA

Cellular Organization of the Genetic Material

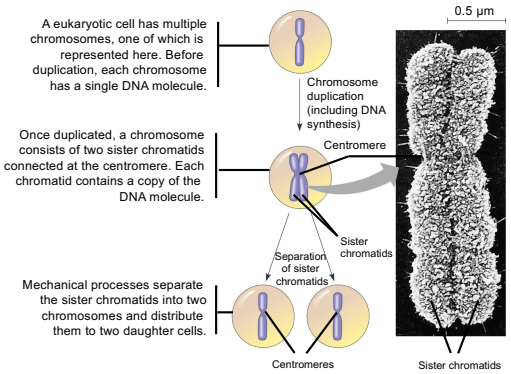
- A cell's endowment of DNA, its genetic information
  - is called its genome
- The DNA molecules in a cell
  - are packaged into chromosomes



- Eukaryotic chromosomes
  - consist of chromatin, a complex of DNA and protein that condenses during cell division
- In animals
  - somatic (body) cells have two sets of chromosomes
  - gametes have one set of chromosomes

Distribution of Chromosomes During Cell Division

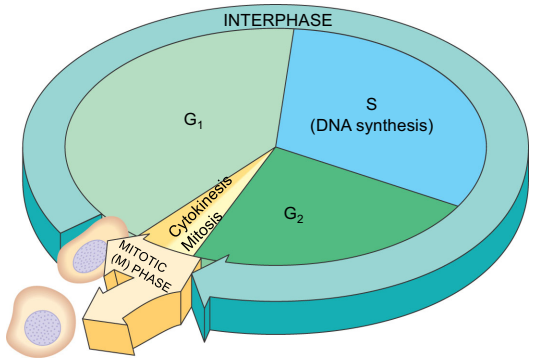
- In preparation for cell division DNA is replicated and the chromosomes condense
- Each duplicated chromosome has two sister chromatids, which separate during cell division



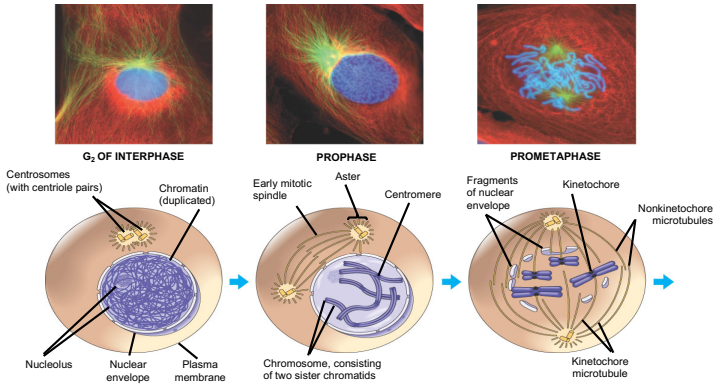
- Eukaryotic cell division consists of
  - Mitosis, the division of the nucleus
  - Cytokinesis, the division of the cytoplasm
- In meiosis
  - sex cells are produced after a reduction in chromosome number
- The mitotic phase **alternates** with interphase in the cell cycle
- A labeled probe can reveal patterns of gene expression in different kinds of cells

Phases of the Cell Cycle

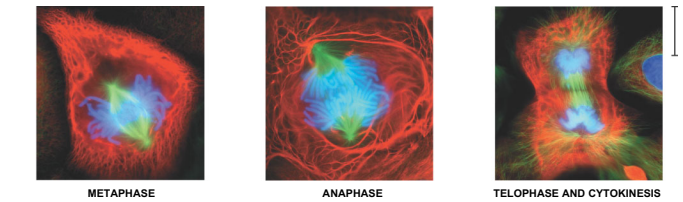
- The cell cycle consists of
  - the Mitotic phase (M)
  - Interphase (G1, S, G2)
- Interphase can be divided into sub-phases
  - G_1 phase
  - S phase
  - G_2 phase
- The mitotic phase
  - is made up of mitosis and cytokinesis

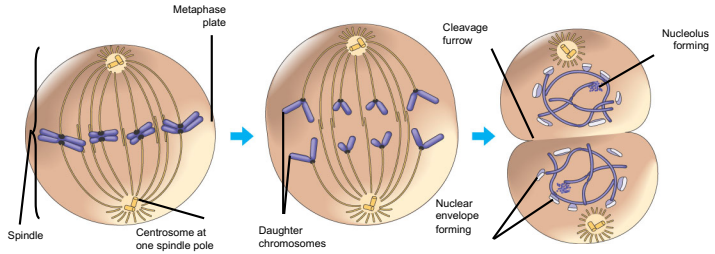


- Mitosis consists of five distinct phases
  - Prophase Prometaphase



- Metaphase, - Anaphase, - Telophase

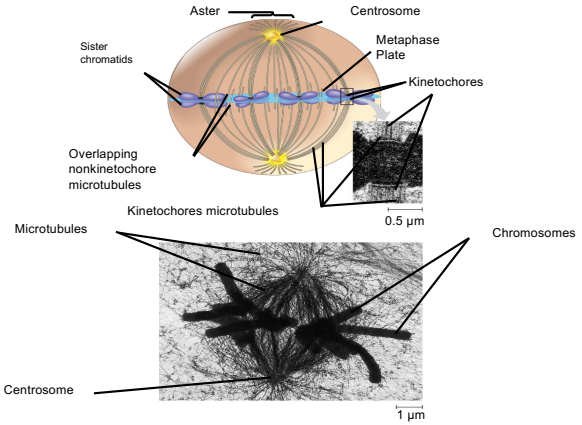




The Mitotic Spindle: *A Closer Look*

- The mitotic spindle
  - is an apparatus of microtubules that controls chromosome movement during mitosis
- The spindle arises from the centrosomes
  - and includes spindle microtubules and asters

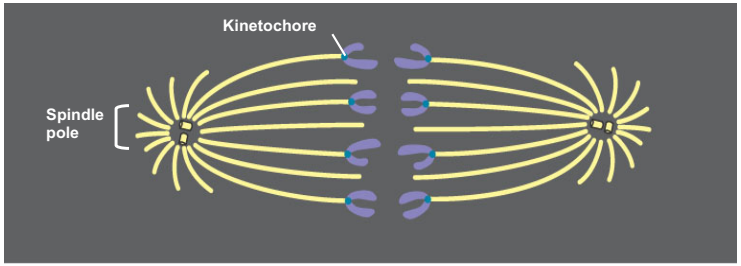
- Some spindle microtubules
  - attach to the kinetochores of chromosomes and move the chromosomes to the metaphase plate



- In **anaphase**, sister chromatids separate
  - And move along the kinetochore microtubules toward opposite ends of the cell

EXPERIMENT

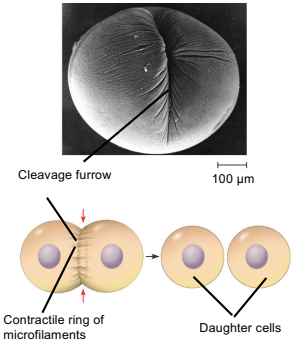
1 The microtubules of a cell in early anaphase were labeled with a fluorescent dye that glows in the microscope (yellow).



- Nonkinetechore microtubules from opposite poles - overlap and push against each other, elongating the cell
- In **telophase** - genetically identical daughter nuclei form at opposite ends of the cell

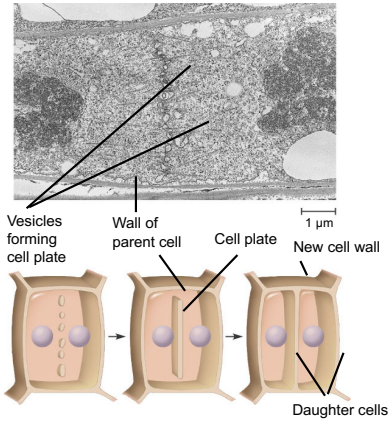
Cytokinesis: *A Closer Look*

- In animal cells
  - Cytokinesis occurs by a process known as cleavage, forming a cleavage furrow



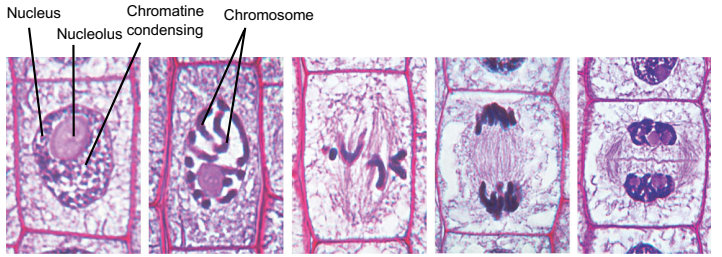
(a) Cleavage of an animal cell (SEM)

- In plant cells, during cytokinesis
  - a cell plate forms



(b) Cell plate formation in a plant cell (SEM)

- Mitosis in a plant cell



1 **Prophase.** The chromatin is condensing. The nucleolus is beginning to disappear. Although not yet visible in the micrograph, the mitotic spindle is starting to form.

2 **Prometaphase.** We now see discrete chromosomes; each consists of two identical sister chromatids. Later in prometaphase, the nuclear envelop will fragment.

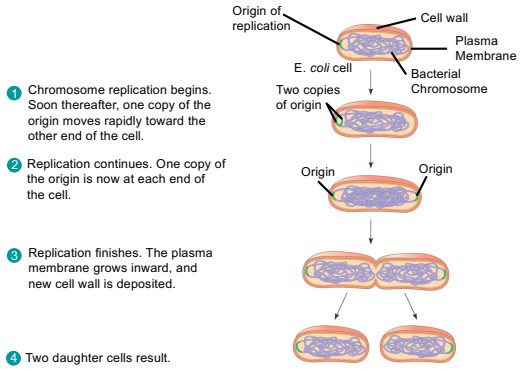
3 **Metaphase.** The spindle is complete, and the chromosomes, attached to microtubules at their kinetochores, are all at the metaphase plate.

4 **Anaphase.** The chromatids of each chromosome have separated, and the daughter chromosomes are moving to the ends of the cell as their kinetochore microtubles shorten.

5 **Telophase.** Daughter nuclei are forming. Meanwhile, cytokinesis has started: The cell plate, which will divided the cytoplasm in two, is growing toward the perimeter of the parent cell.

Binary Fission

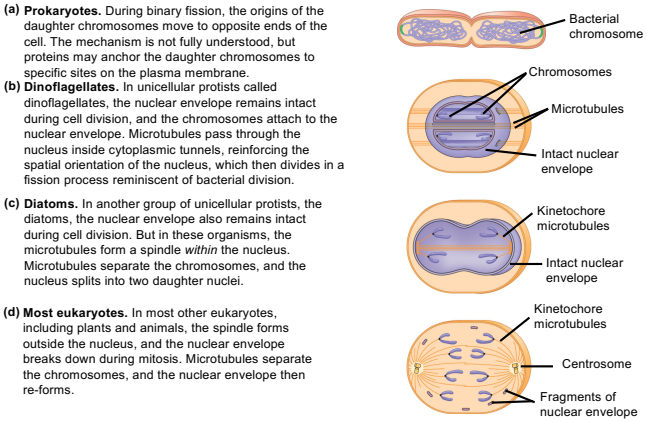
- Prokaryotes (bacteria) reproduce by a type of cell division called binary fission
- In binary fission the bacterial chromosome replicates and the two daughter chromosomes actively move apart



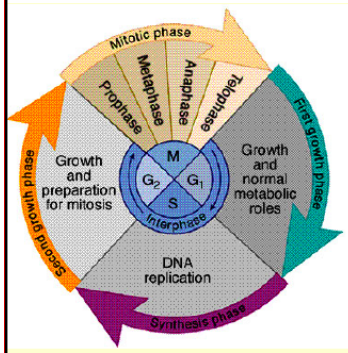
The theory of evolution of Mitosis

- **In** the **evolution** theory **the prokaryotes preceded eukaryotes by billions of years** and concluded that
  - it is likely that mitosis evolved from bacterial cell division
- Certain **protists**
  - exhibit types of cell division that seem intermediate between binary fission and mitosis carried out by most eukaryotic cells

- **A hypothetical sequence for the evolution of mitosis**



- **The cell cycle is regulated by a molecular control system**
- The frequency of cell division
  - varies with the type of cell
- These cell cycle differences
  - result from regulation at the molecular level



Interphase: G1, G2, and S.

G1 and G2 (gap 1 and gap 2) are characterized by protein and RNA synthesis, but no DNA synthesis. S is the period of DNA synthesis.

Mitosis:

Mitosis followed by cell division is the period when the nucleus and then the rest of the cell divides.

Mitosis is traditionally divided into four phases:

Prophase when chromosome condense into visible structures,
Metaphase when sister chromatids line up at the center of the cell,
Anaphase when sister chromatids start to separate, and
Telophase when sister chromatids are pulled to opposite sides of the cell.

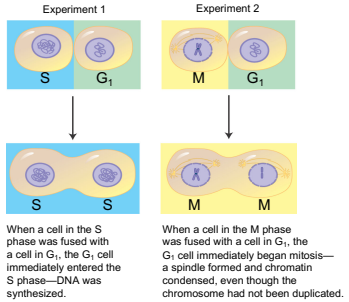
Evidence for Cytoplasmic Signals

- Molecules present in the cytoplasm
  - regulate progress through the cell cycle

EXPERIMENTS

In each experiment, cultured mammalian cells at two different phases of the cell cycle were induced to fuse.

RESULTS



When a cell in the S phase was fused with a cell in G_1, the G_1 cell immediately entered the S phase—DNA was synthesized.

When a cell in the M phase was fused with a cell in G_1, the G_1 cell immediately began mitosis—a spindle formed and chromatin condensed, even though the chromosome had not been duplicated.

CONCLUSION

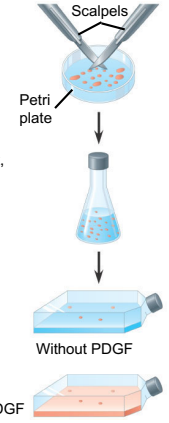
The results of fusing cells at two different phases of the cell cycle suggest that molecules present in the cytoplasm of cells in the S or M phase control the progression of phases.

Stop and Go Signs: Internal and External Signals at the Checkpoints

- Both internal and external signals control the cell cycle checkpoints
  - Growth factors stimulate other cells to divide

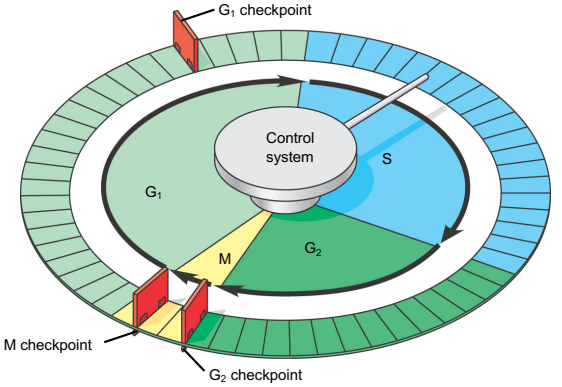
EXPERIMENT

1. A sample of connective tissue was cut up into small pieces.
2. Enzymes were used to digest the extracellular matrix, resulting in a suspension of free fibroblast cells.
3. Cells were transferred to sterile culture vessels containing a basic growth medium consisting of glucose, amino acids, salts, and antibiotics (as a precaution against bacterial growth). PDGF was added to half the vessels. The culture vessels were incubated at 37° C.

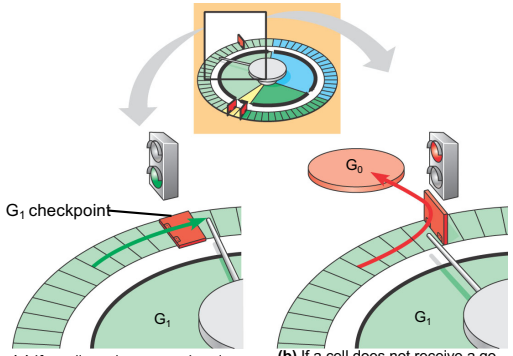


The Cell Cycle Control System

- The sequential events of the cell cycle
  - are directed by a distinct cell cycle control system, which is similar to a clock



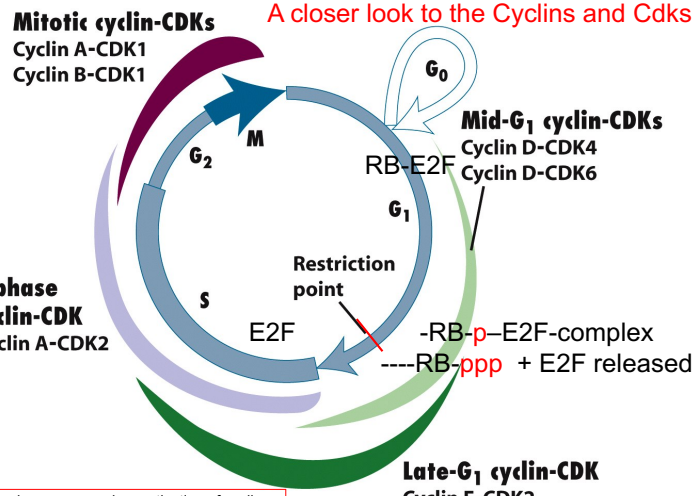
- The clock has specific checkpoints
  - where the cell cycle stops until a go-ahead signal is received



(a) If a cell receives a go-ahead signal at the G_1 checkpoint, the cell continues on in the cell cycle.

(b) If a cell does not receive a go-ahead signal at the G_1checkpoint, the cell exits the cell cycle and goes into G_0, a non-dividing state.

A closer look to the Cyclins and Cdks



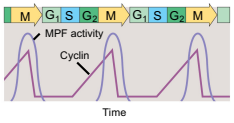
During G_1 phase progression, activation of cyclin D/cdk4 and cyclin E/cdk2 complexes by cyclin activating kinase (CAK) leads to sequential phosphorylation of the transcription factor RB.

The Cell Cycle Clock: Cyclins and Cyclin-Dependent Kinases

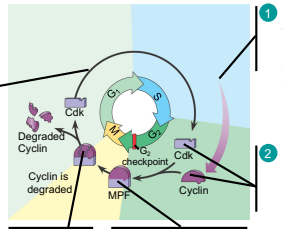
- two types of regulatory proteins are involved in cell cycle control: cyclins **and** cyclin-dependent kinases (Cdks)

the **activity of cyclins and Cdks fluctuates during the cell cycle**

(a) Fluctuation of MPF (Mitosis Promoting Factor, MPF) activity and cyclin concentration during the cell cycle



(b) Molecular mechanisms that help regulate the cell cycle



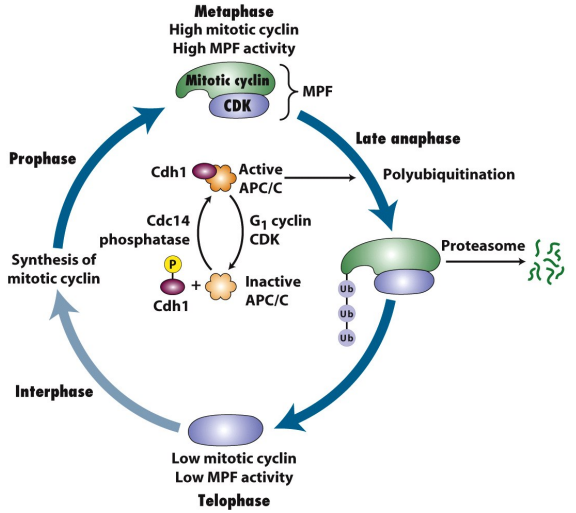
5 During G_1, conditions in the cell favor degradation of cyclin, and the Cdk component of MPF is recycled.

1 Synthesis of cyclin begins in late S phase and continues through G_2. Because cyclin is protected from degradation during this stage, it accumulates.

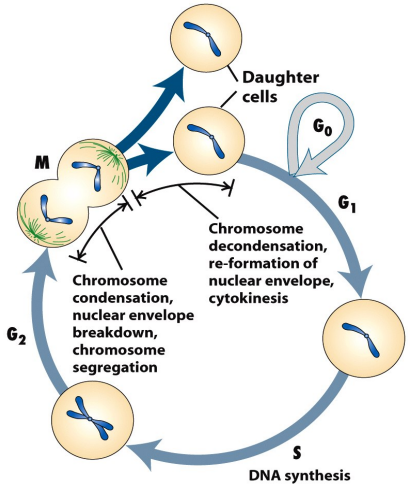
2 Accumulated cyclin molecules combine with recycled Cdk molecules, producing enough molecules of MPF to pass the G_2 checkpoint and initiate the events of mitosis.

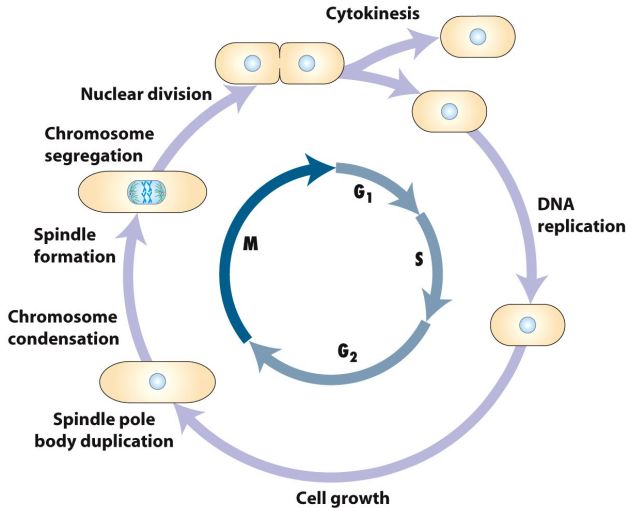
3 MPF promotes mitosis by phosphorylating various proteins. MPF 's activity peaks during metaphase.

4 During anaphase, the cyclin component of MPF is degraded, terminating the M phase. The cell enters the G_1 phase.



A closer look to the Cyclins and Cdks

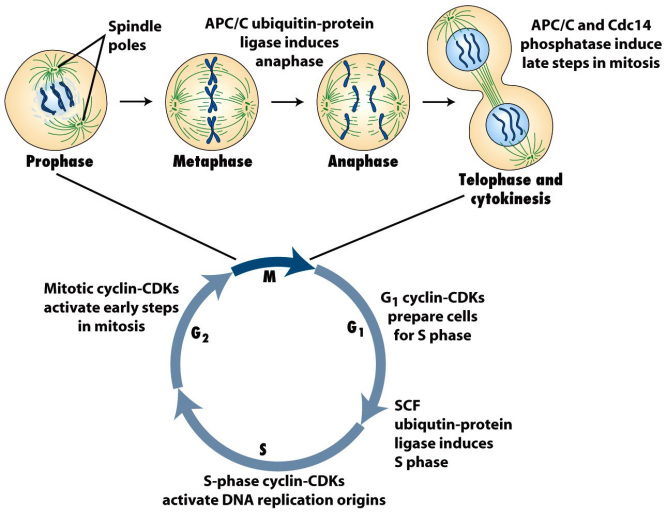


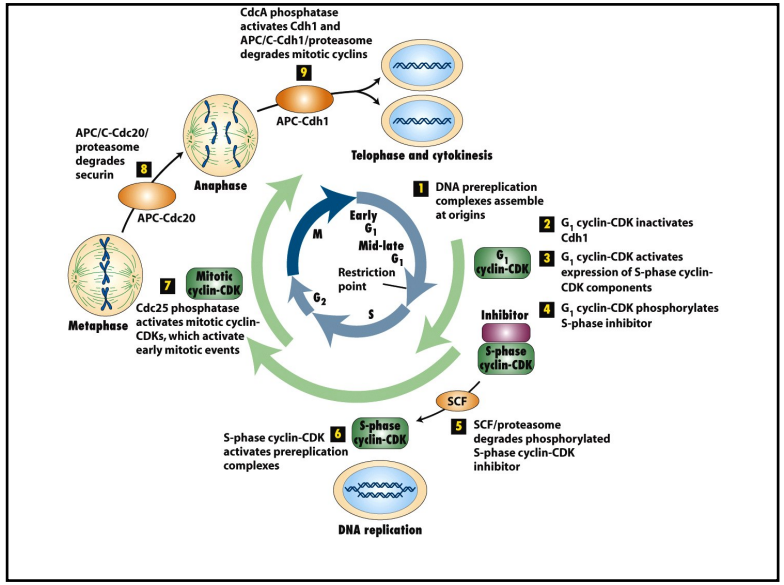


Selected Cyclins and Cyclin-Dependent Kinases (CDKs)

ORGANISM /PROTEIN	NAME
VERTEBRATES	
Mid-G_1 CDKs	CDK4, CDK6
Late-G_1 and S-phase CDK	CDK2
Mitotic CDKs	CDK1, CDK2
Mid-G_1 cyclins	D-type cyclins
Late-G_1 and S-phase cyclin	Cyclin E
S-phase and mitotic cyclin	Cyclin A
Mitotic cyclins	Cyclin A, Cyclin B

NOTE: Those cyclins and CDKs discussed in this chapter are listed and classified by the period in the cell cycle in which they function. A heterodimer composed of a mitotic cyclin and CDK is commonly referred to as a *mitosis-promoting factor (MPF)*.





Regulators of Cyclin-CDK Activity

TYPE OF REGULATOR	FUNCTION
KINASES AND PHOSPHATASES	
CAK kinase	Activates cyclin-CDKs
Wee1 kinase	Inhibits cyclin-CDKs
Cdc25 phosphatase	Activates cyclin-CDKs
Cdc14 phosphatase	Activates Cdh1 to inhibit mitotic cyclin-CDK
Cdc25A phosphatase	Activates vertebrate S-phase cyclin-CDK
Cdc25C phosphatase	Activates vertebrate mitotic cyclin-CDK
ATM/ATR kinases	Checkpoint controls, activate Chk1/Chk2 kinases
Chk1/Chk2 kinases	Checkpoint controls, inactivate Cdc25C and Cdc25A phosphatases to induce cell-cycle arrest
INHIBITORY PROTEINS	
Sic1	Binds and inhibits S-phase cyclin-CDKs
CKIs $p27^{KIP1}$, $p57^{KIP2}$, and $p21^{CIP}$	Bind and inhibit cyclin-CDKs
INK4	Binds and inhibits mid-G_1 CDKs
Mad2	Spindle-assembly checkpoint control, binds Cdc20 and prevents onset of anaphase and inactivation of B-type cyclin-CDKs
Rb	Binds E2Fs, preventing transcription of multiple cell cycle genes
UBIQUITIN-PROTEIN LIGASES	
SCF	Degradation of phosphorylated Sic1 or $p27^{KIP1}$ to activate S-phase cyclin-CDKs
APC/C + Cdc20	Induces degradation of Securin, initiating anaphase. Induces partial degradation of B-type cyclins
APC/C + Cdh1	Induces complete degradation of B-type cyclins to initiate telophase, and geminin in metazoans to allow formation of prereplication complexes on DNA replication origins

Regulators of Cyclin-CDK Activity

TYPE OF REGULATOR	FUNCTION
KINASES AND PHOSPHATASES	
CAK kinase	Activates cyclin-CDKs
Wee1 kinase	Inhibits cyclin-CDKs
Cdc25 phosphatase	Activates cyclin-CDKs
Cdc14 phosphatase	Activates Cdh1 to inhibit mitotic cyclin-CDK
Cdc25A phosphatase	Activates vertebrate S-phase cyclin-CDK
Cdc25C phosphatase	Activates vertebrate mitotic cyclin-CDK
ATM/ATR kinases	Checkpoint controls, activate Chk1/Chk2 kinases
Chk1/Chk2 kinases	Checkpoint controls, inactivate Cdc25C and Cdc25A phosphatases to induce cell-cycle arrest
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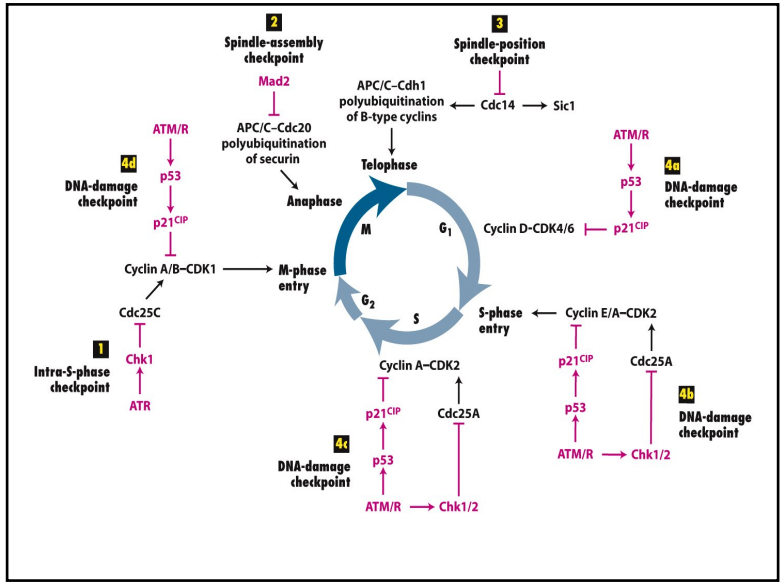
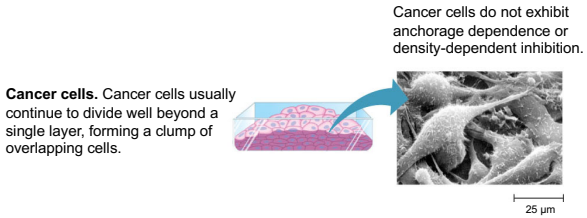
APC/C + Cdh1	Induces complete degradation of B-type cyclins to initiate telophase, and geminin in metazoans to allow formation of prereplication complexes on DNA replication origins



Checkpoint Proteins

CHECKPOINT	PURPOSE	SENSOR	ACTION
Intra-S phase checkpoint	Ensures all DNA replication is complete before entering M-phase	ATR detects replication forks	Inhibition of Cdc25C to prevent activation of mitotic cyclin-CDKs, blocking early mitotic events
Spindle-assembly checkpoint	Ensures all chromosome kinetochores are attached to spindle microtubules before anaphase	Mad2 detects kinetochores unattached to microtubules	Inhibition of Cdc20 to prevent activation of separase and onset of anaphase
Spindle-position checkpoint	Ensures all chromosomes are properly segregated to daughter cells before telophase and cytokinesis	*(S. cerevisiae)* Tem-1 detects proper position of spindle pole body in bud	Prevention of Cdc14 activation and degradation of mitotic cyclins, blocking late mitotic events
DNA-damage checkpoint	Detects damage to DNA throughout the cell cycle	ATM, ATR detect DNA damage	Inhibition of Cdc25A to prevent entry into S phase; $p21^{CIP}$ inhibition of all cyclin-CDK complexes to induce cell cycle arrest

- **Cancer cells**
  - exhibit neither density-dependent inhibition nor anchorage dependence

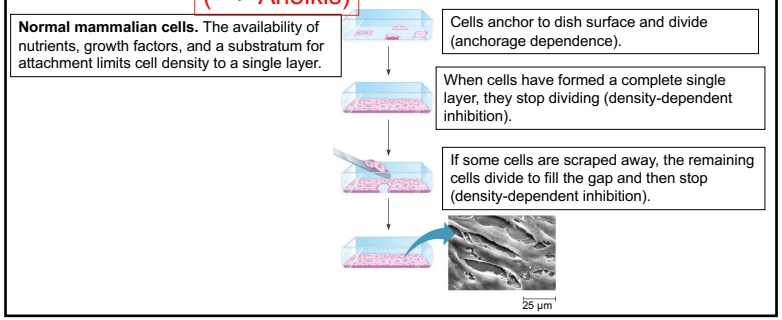


Loss of Cell Cycle Controls in Cancer Cells

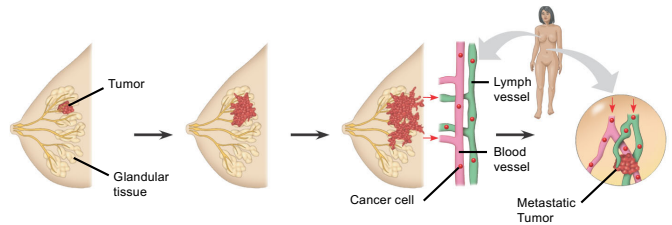
- Cancer cells
  - do not respond normally to the body's control mechanisms
  - form tumors

Cancer cells exhibit neither density-dependent inhibition nor anchorage dependence (loss of cell cycle control)

- In density-dependent inhibition
  - crowded cells stop dividing
- Most animal cells exhibit anchorage dependence
  - in which they must be attached to a substratum to divide (---> Anoikis)



- **Malignant tumors invade surrounding tissues and can metastasize**
  - exporting cancer cells to other parts of the body where they may form secondary tumors



(angiogenesis)

Growth factors over-expressed or mutated in gliomas:
EGF, PDGF (A, B), IGF-1, TGF-α