

Molecular and Cellular Biology (MCB)

BB101

LECTURE-2

9/ 1/ 2018

Cell & Cell Cycle

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Associate Professor

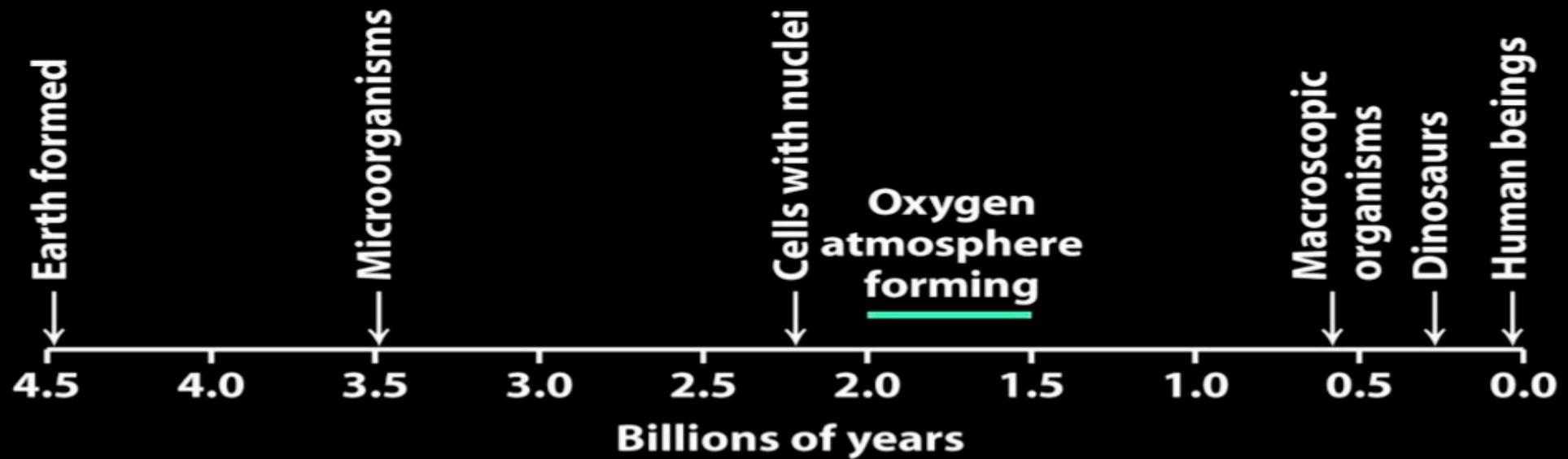
Biosciences and Bioengineering, IIT Bombay

Outline

1. Cell and its properties
2. Cell cycle
3. Cell cycle dysregulation & Cancer

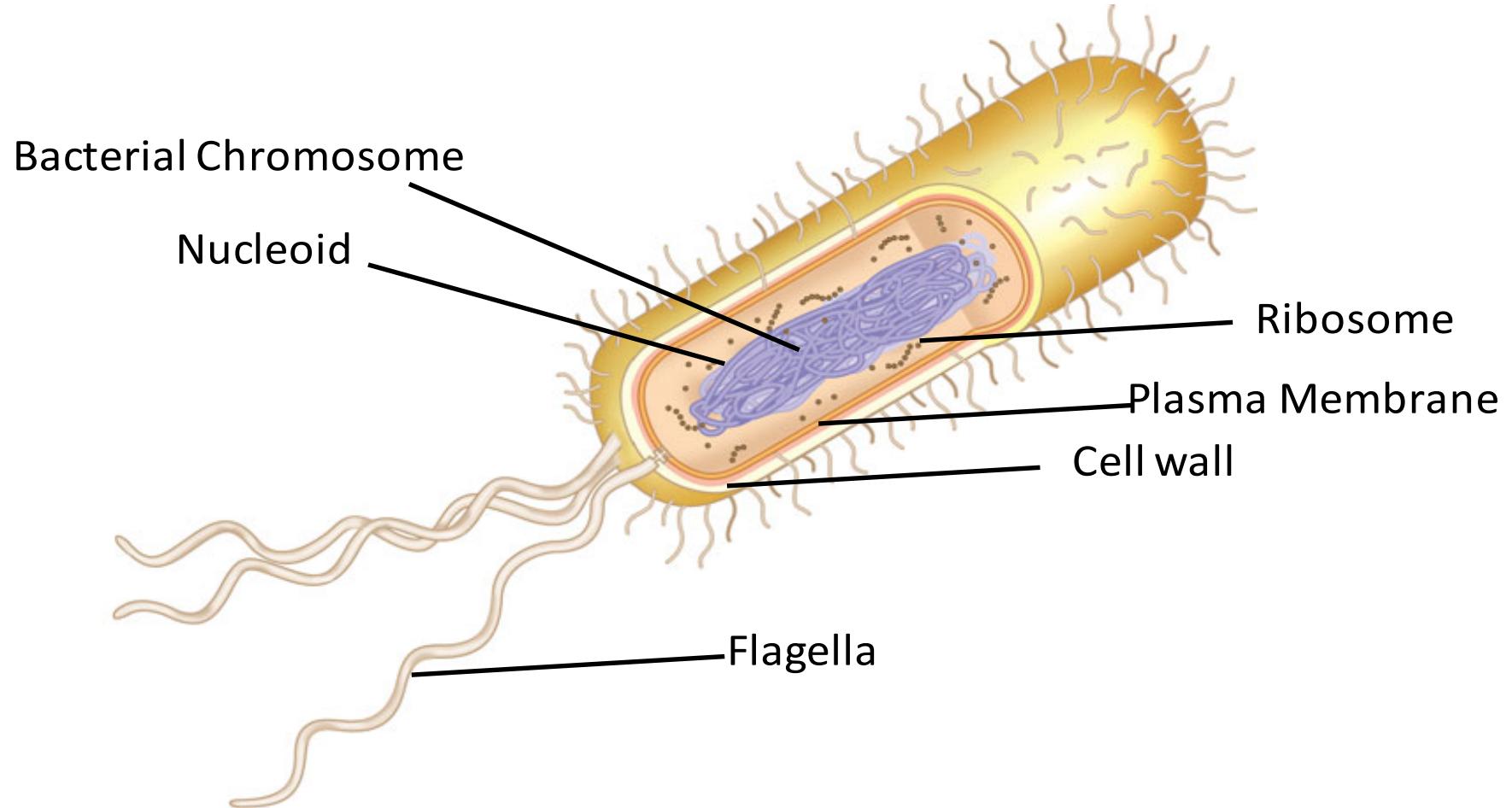
- Cell and its Properties
- Cell cycle
- Cell cycle & Cancer

Cell and its Properties



Prokaryotic Cell

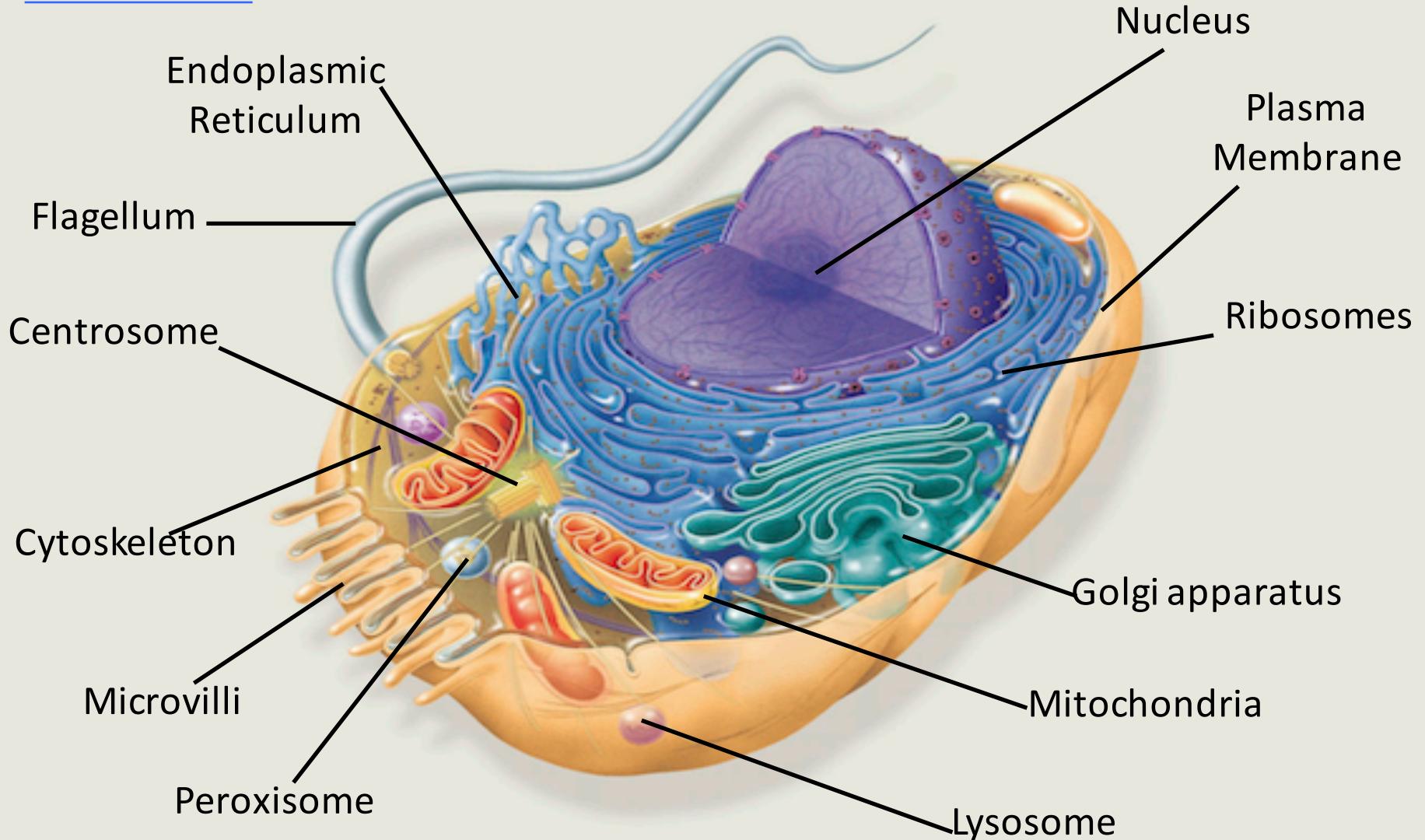
Pro = before, Eu = true, Karyon = nucleus



- Nucleoid - consist of bacterial DNA not enclosed in a membrane

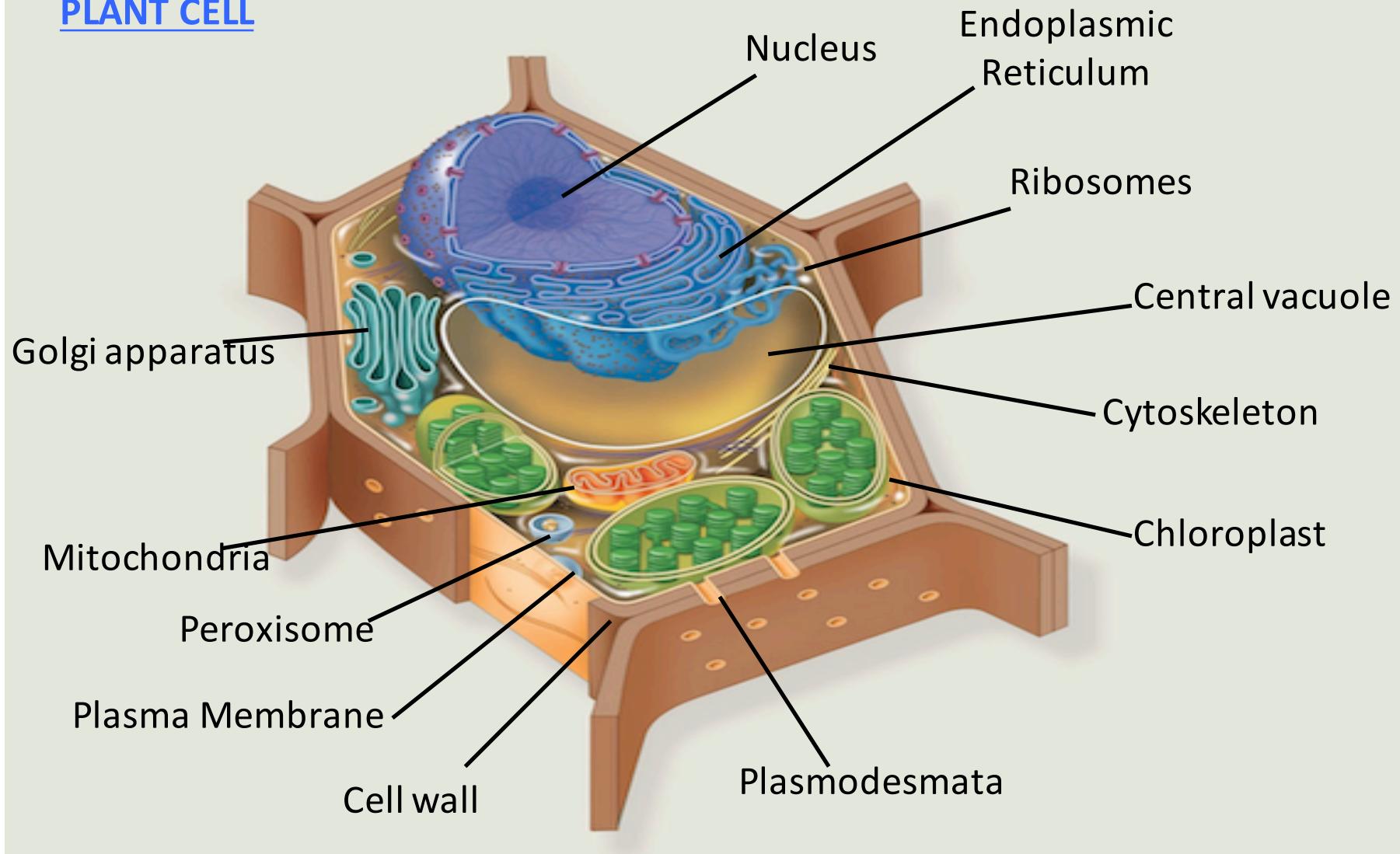
Eukaryotic Cell

ANIMAL CELL



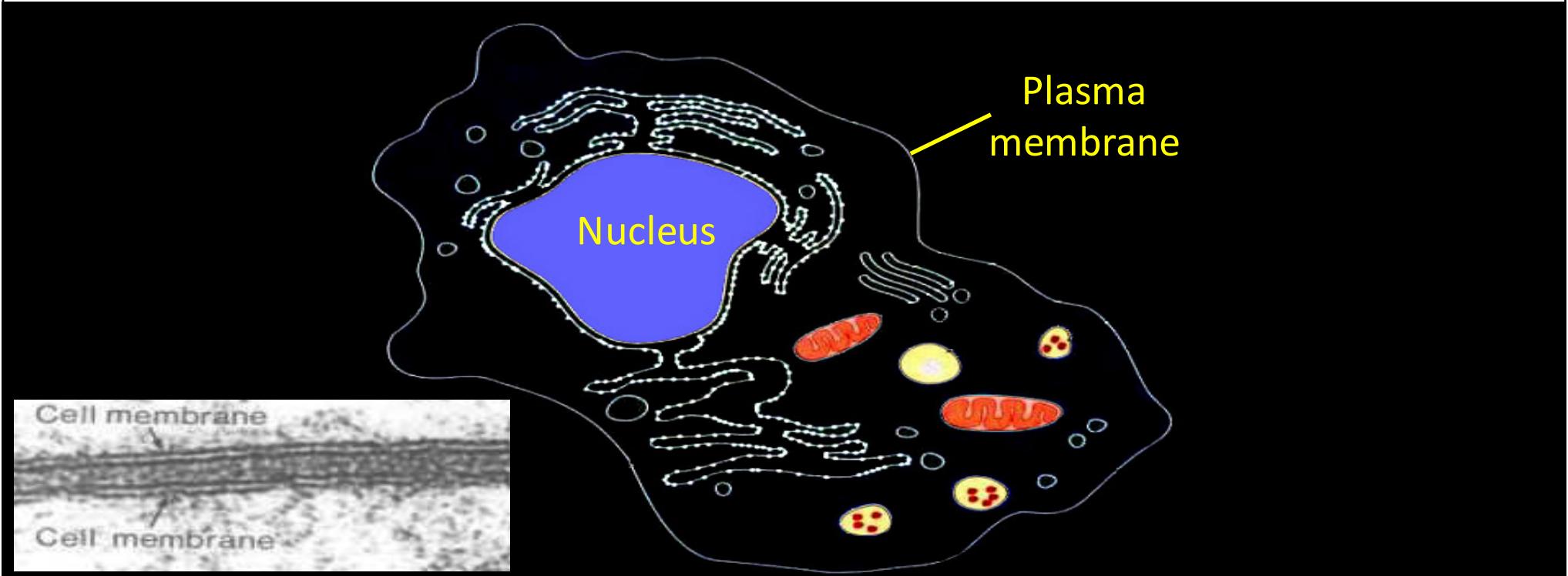
Eukaryotic Cell

PLANT CELL



Eukaryotic Cell Properties

Eukaryotic Cell: Plasma Membrane



- Functional separation between cell & external environment
- Molecular transport, receipt of cell signals

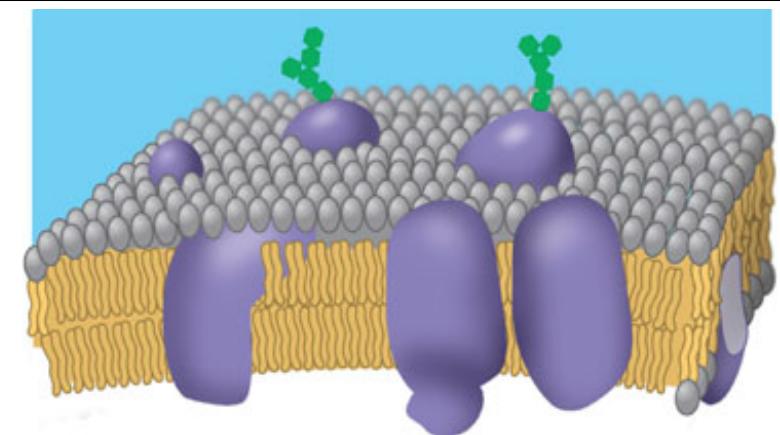
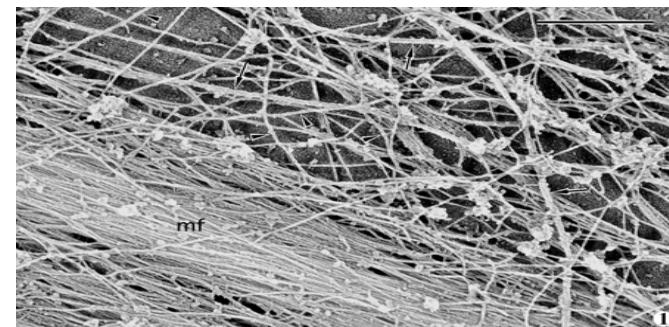
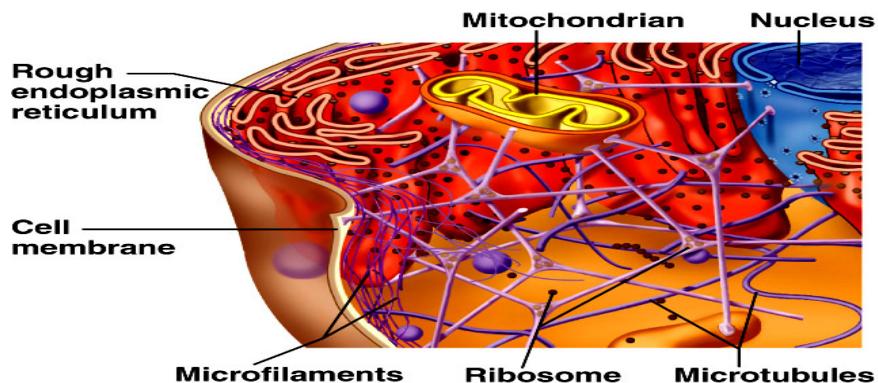


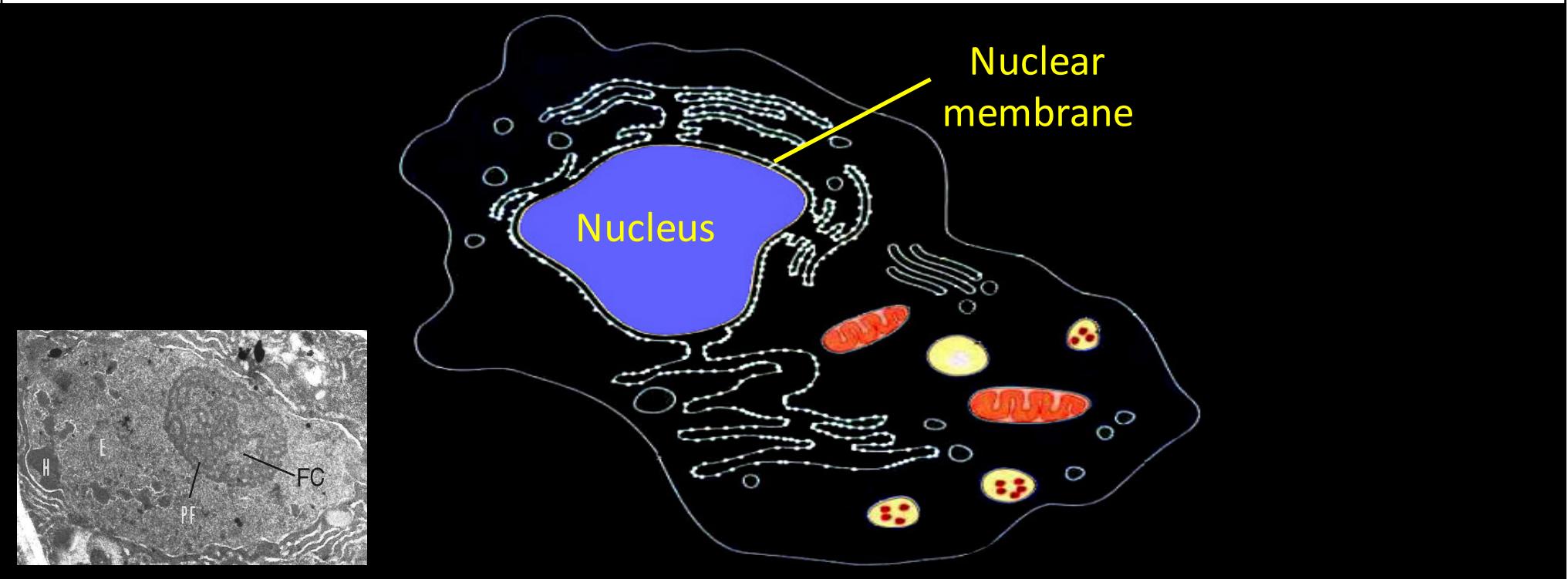
Figure 6.6

Eukaryotic Cell

- **Cytoplasm**
 - Region between plasma membrane and nucleus
 - Refers to the cytosol (aqueous phase) plus protein complexes such as ribosome and cytoskeleton
- **Cytoskeleton**
 - Structural framework of cell, positioning organelles
 - Intracellular transport, chromosome movement
- **Vacuole**
 - Digestion of macromolecules
 - Storage of waste products & nutrients



Eukaryotic Cell: Nucleus



- Most prominent organelle in eukaryotic cell
- Contains genetic information of cell
- Site of DNA replication, RNA synthesis

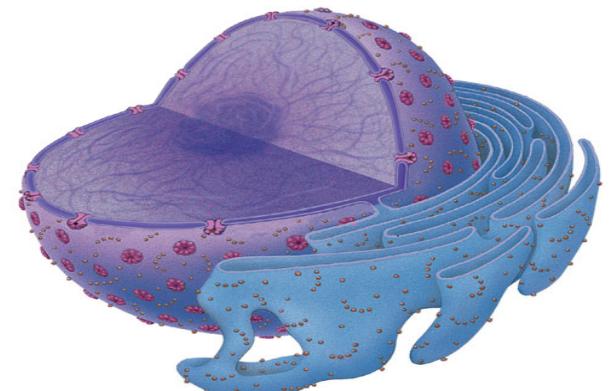
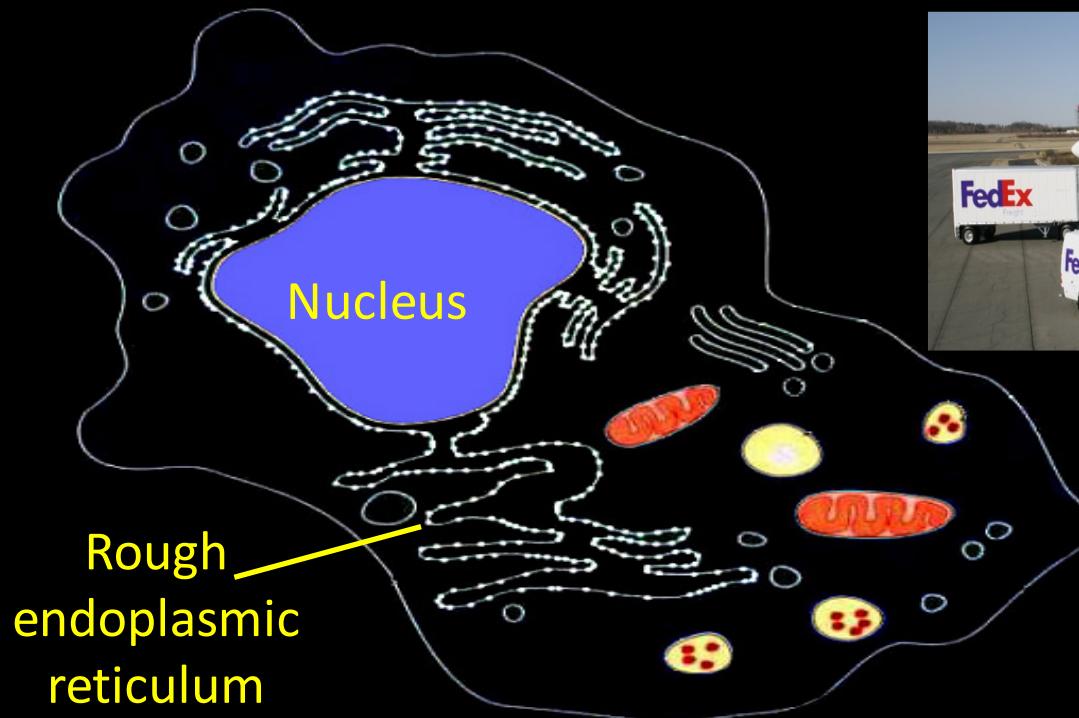


Figure 6.9

10

Eukaryotic Cell: Endoplasmic Reticulum



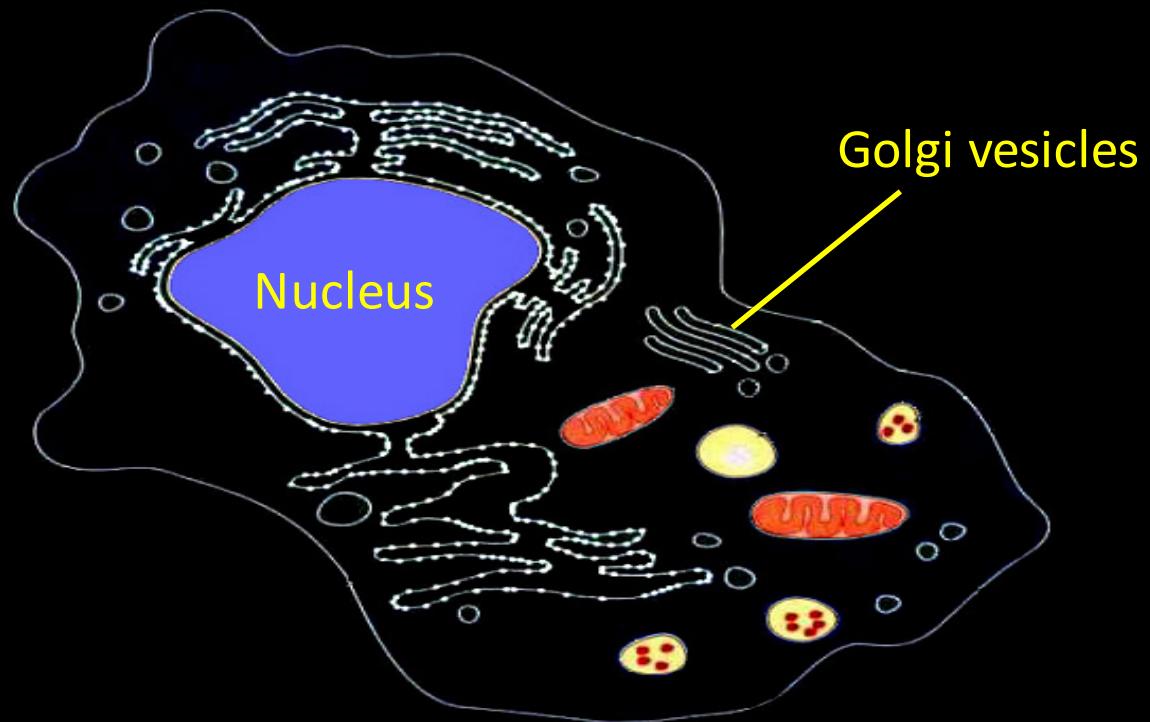
ER has its own FedEx system!

- Processing and transport of protein
- Rough ER: contains ribosome (site of protein synthesis)
- Smooth ER: no ribosome, processes & packages proteins into vesicles, transport to Golgi vesicles

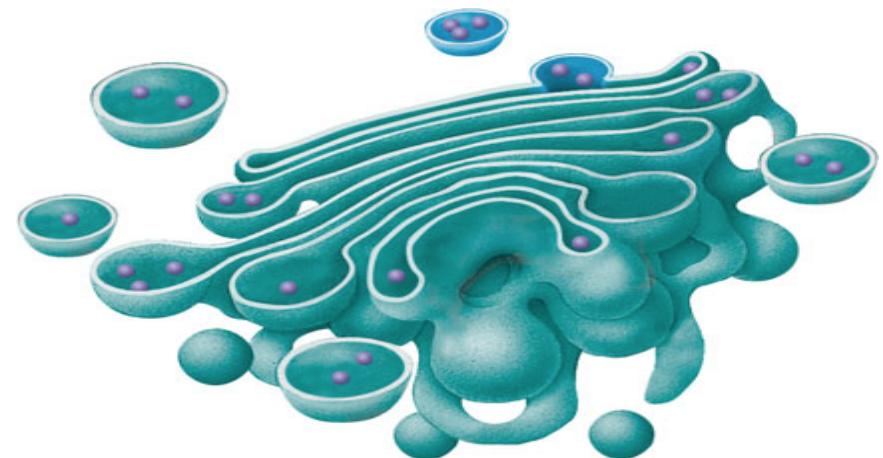


Figure 6.11

Eukaryotic Cell: Golgi Apparatus

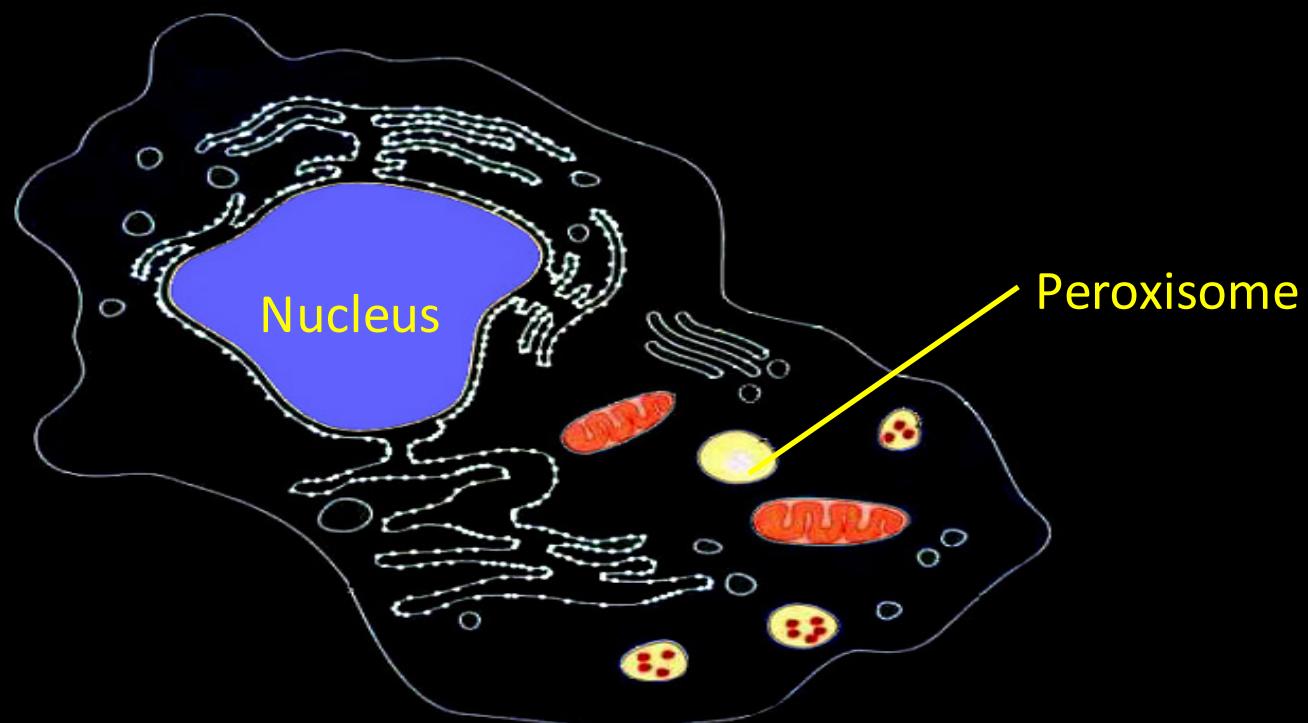


- Membranous, flattened structures
- Protein transport
- Exocytosis = post-office



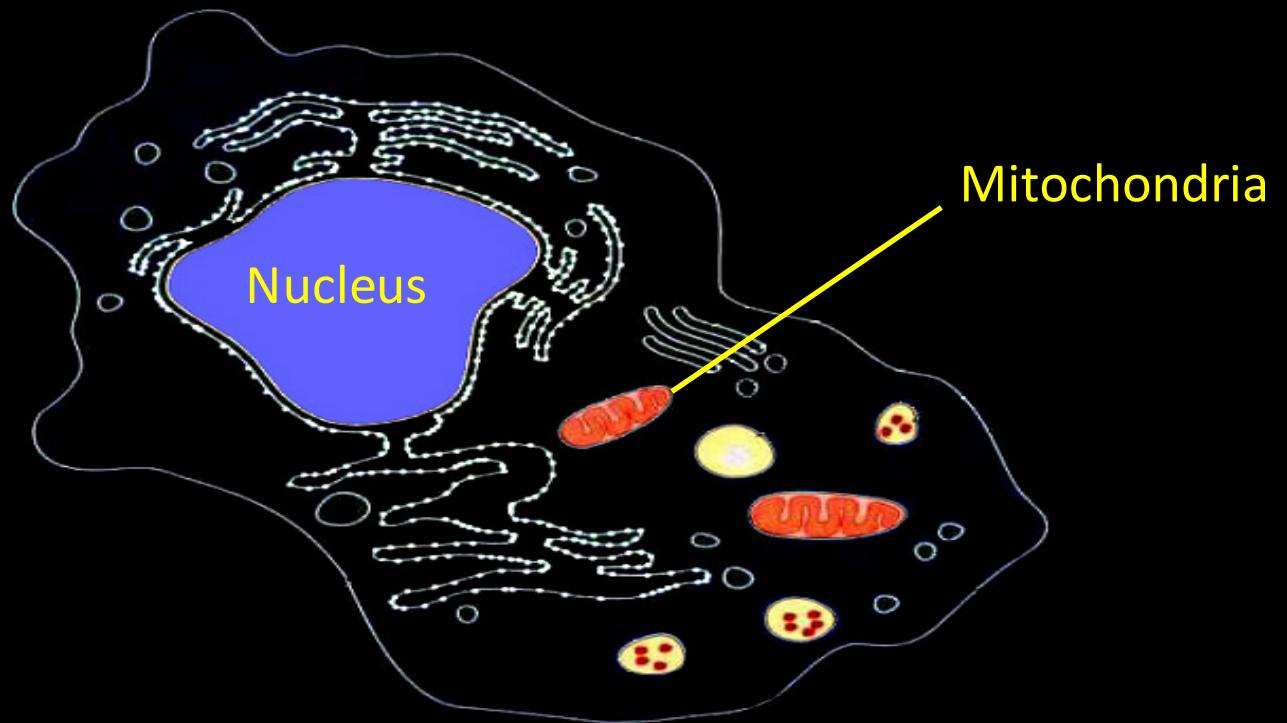
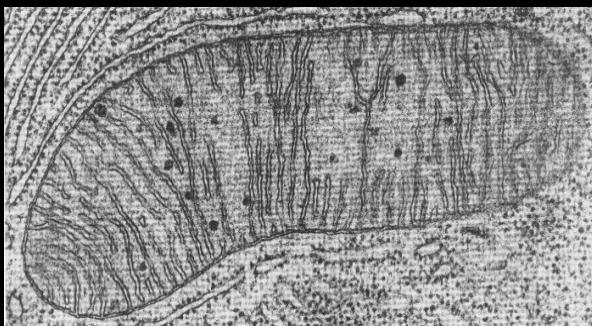
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Eukaryotic Cell: Peroxisome

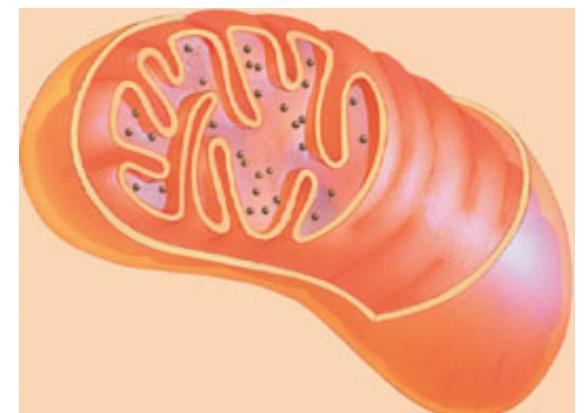


- Contain oxidative enzymes (e.g. catalase) that degrade H_2O_2
- Breakdown of fatty acid molecules
- Single membrane, no genetic system

Eukaryotic Cell: Mitochondria



- Double membranes, own circular DNA molecule
- Site of oxidative metabolism
- Inner membrane is site of ATP synthesis



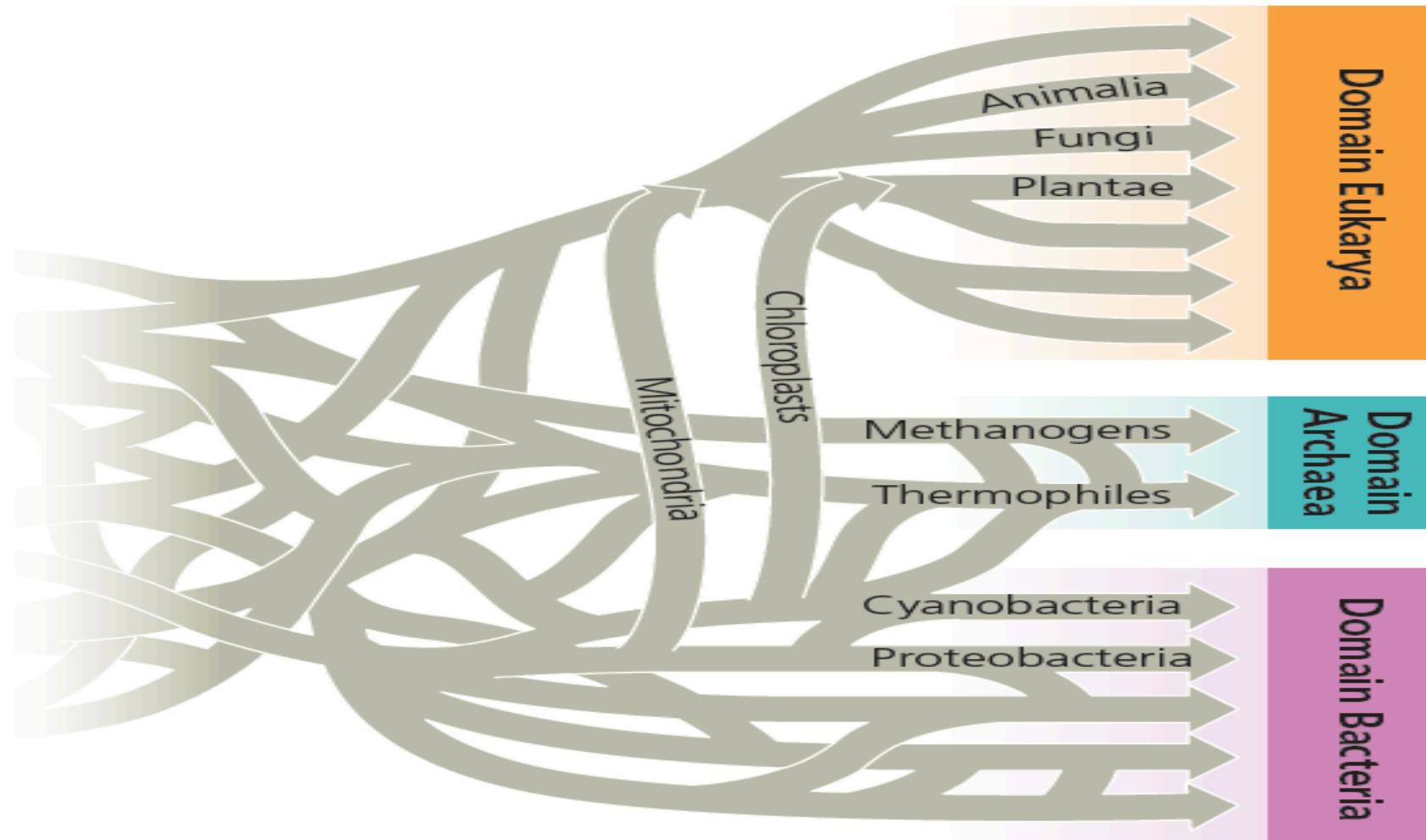
14

Different domains of life

A Tangled Web of Life

- Diverse organisms divided into three fundamental groups
 - **Bacteria** (formerly Eubacteria), **Archaea** (formerly Archaebacteria) and **Eukarya** (Eukaryotes)
 - *on the basis of biochemical characteristics*
 - *fundamental groups known as “domains”*
- Carl Woese suggested to group organisms into 3 domains
 - on the basis of 16S ribosomal RNA

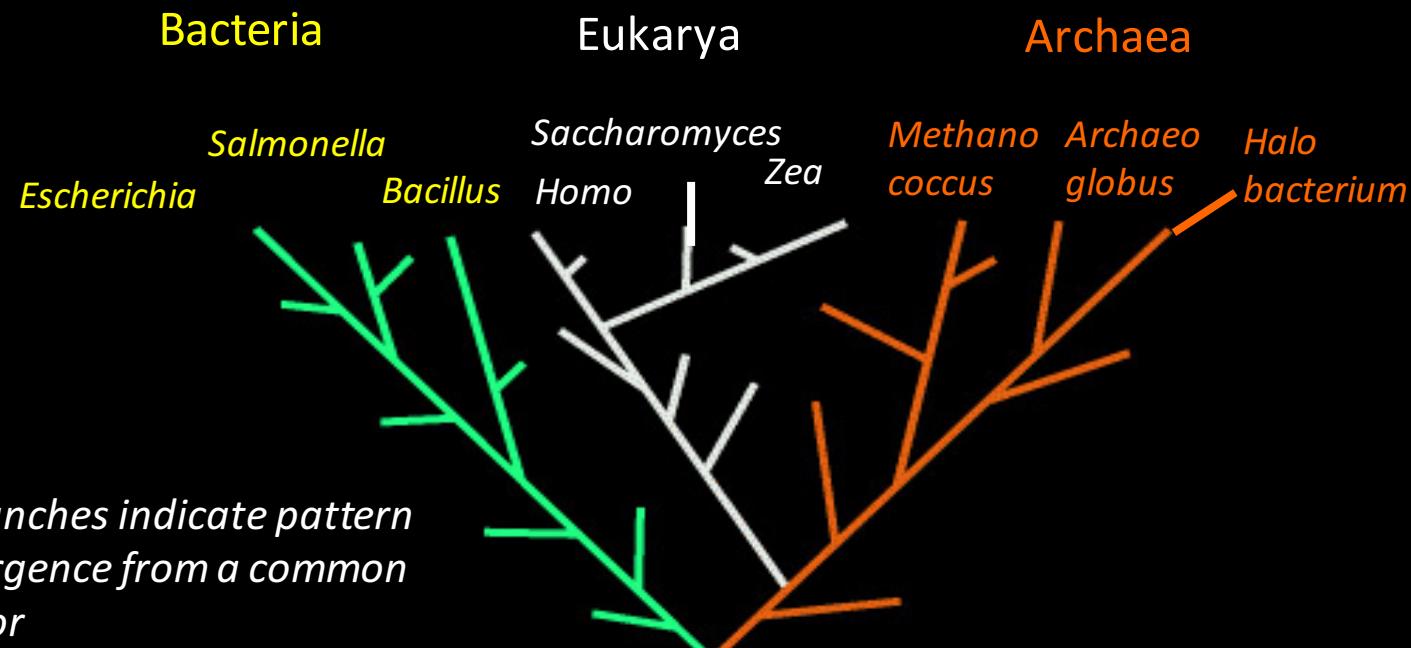
A Tangled Web of Life



Horizontal gene transfer was common in early history of life

Figure 26.23

Three Domains of Life



- DNA sequence distinction defines three groups of organisms
- Evolutionary paths can be analyzed based on biochemical information

Archaea: Are they Super-creatures?



Halophiles



Thermophiles



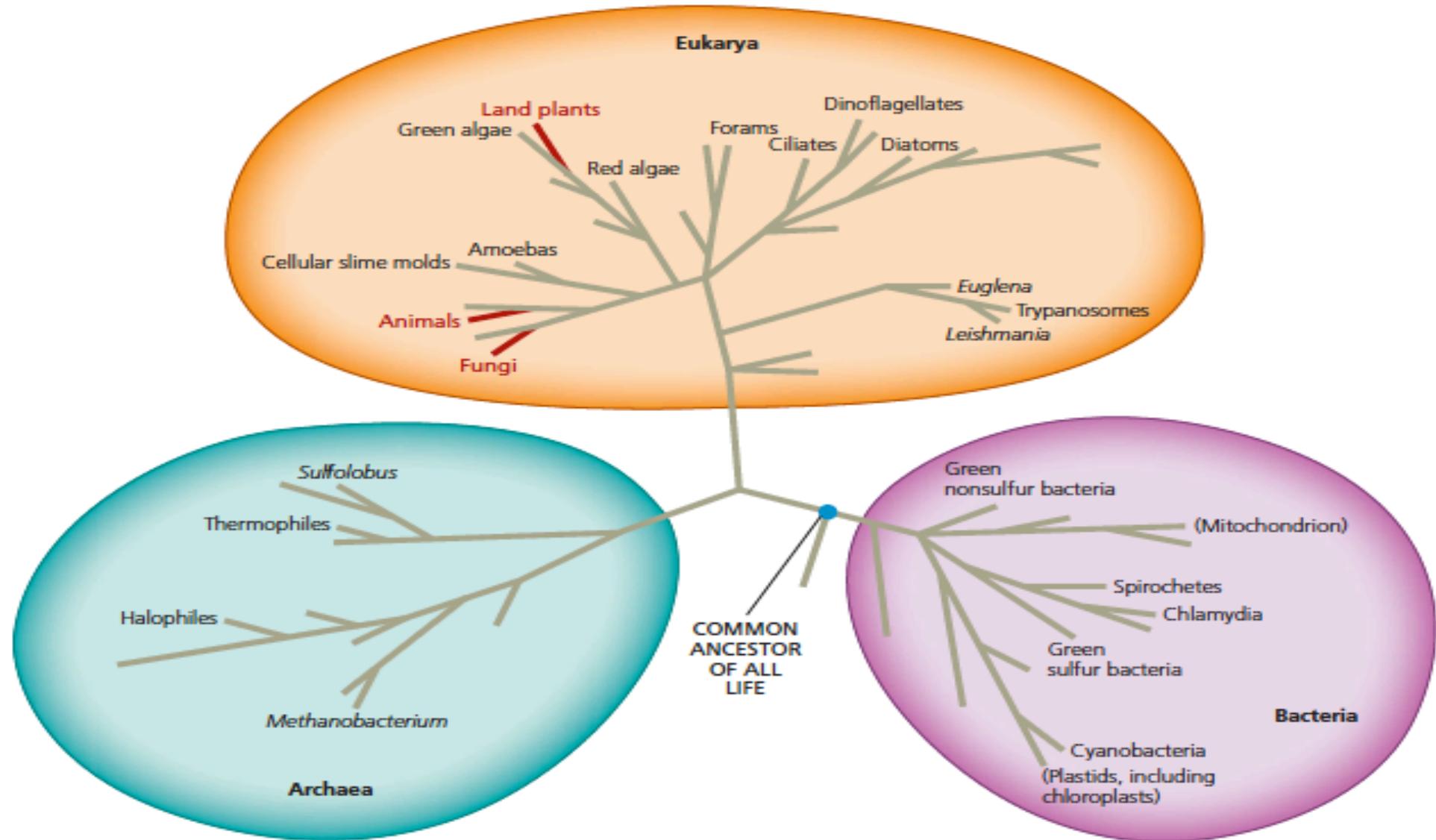
Methanogens

- Archaea: prokaryotes distantly related to bacteria-like organisms
- Archaea cell membranes have chemical properties that differ from bacteria & eukaryotes - cell membranes don't contain fatty acids but instead use branched molecules called isoprenes

Archaea are More Similar to Eukaryotes!

- Archaea are prokaryotes; however, more similar to eukaryotes than bacteria
- Archaea & eukaryotic genomes encode homologous histone proteins, which is associated with DNA
 - In contrast, bacteria lack histones
 - RNA & protein components of archaean ribosome are more similar to eukaryotes than bacteria

The Tree of Life



Evolution of Cells

- Who are the progenitors of ancestral eukaryotic cells?

Evolution of Cells

Prokaryote

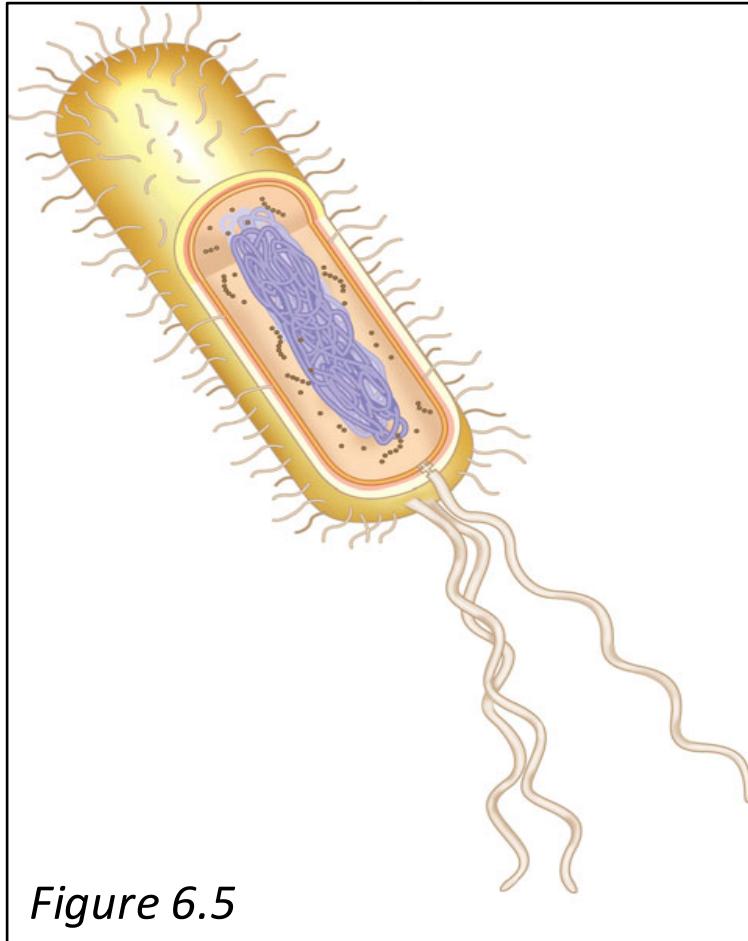


Figure 6.5

Eukaryote

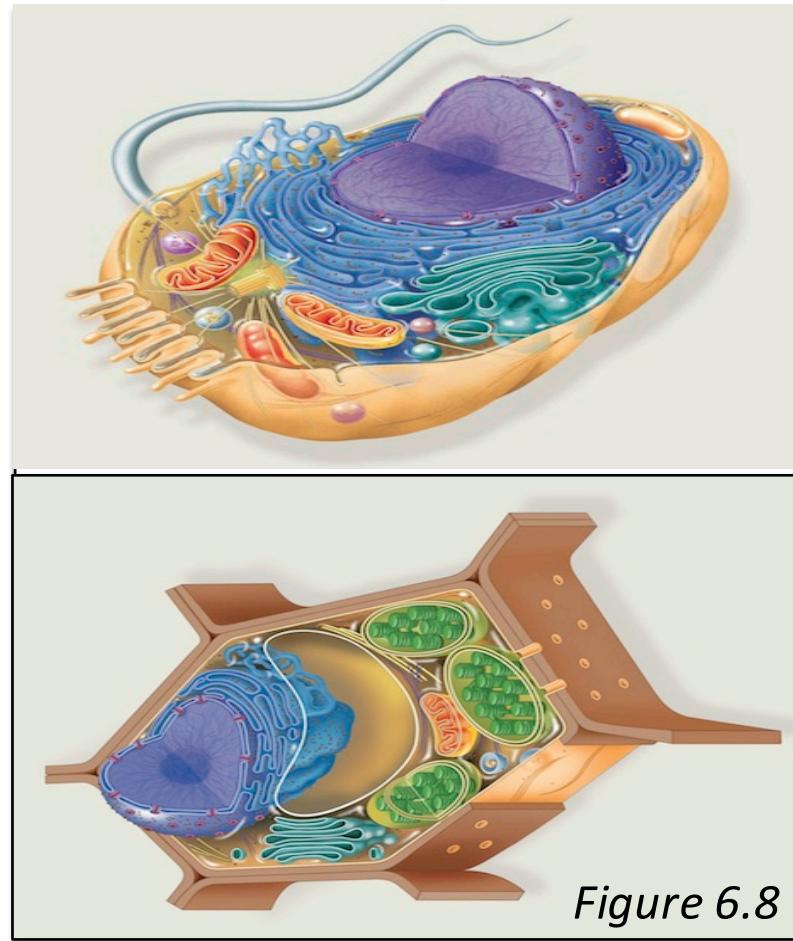
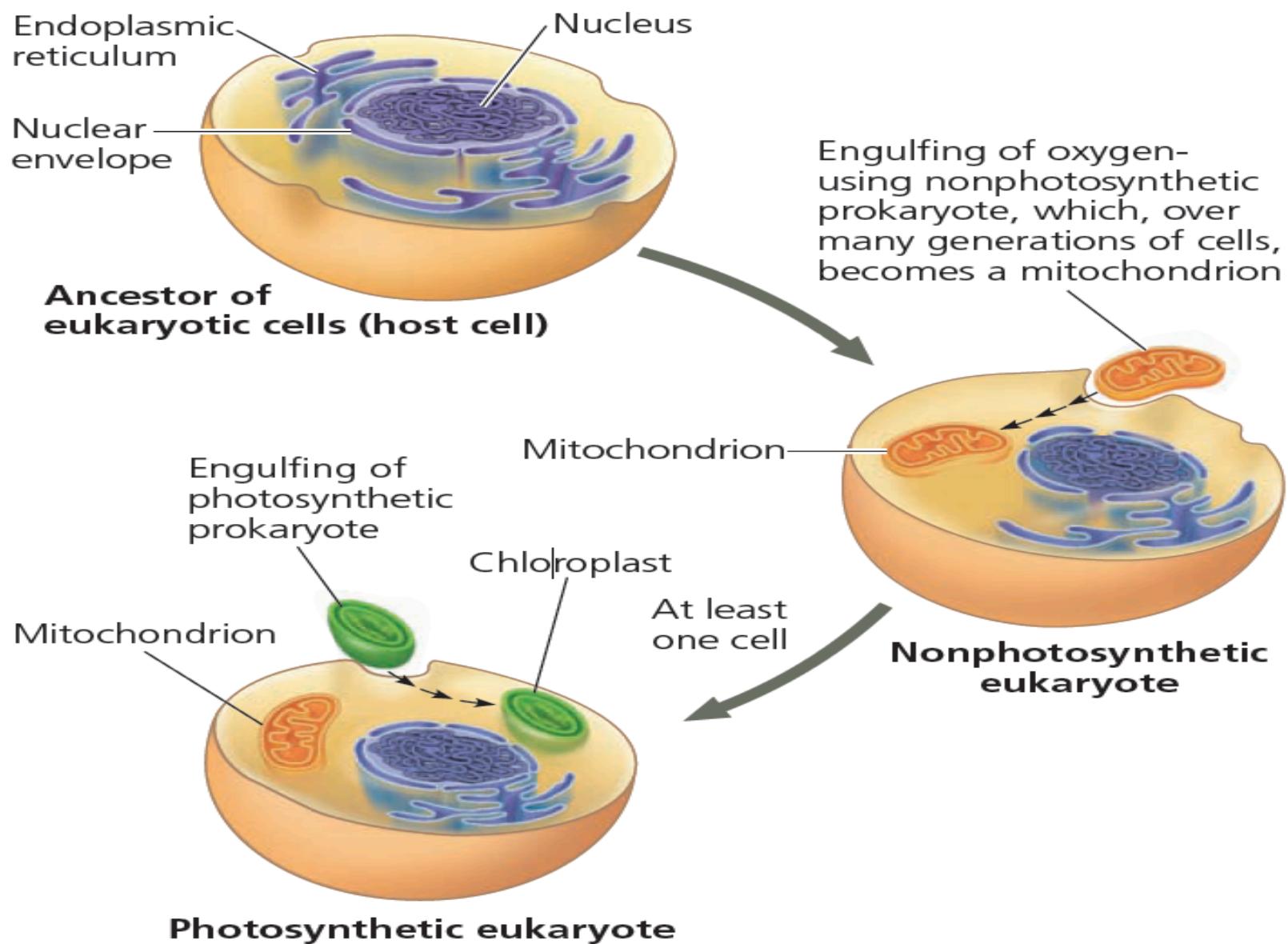


Figure 6.8

- How did present-day eukaryotic cells originate?

Model for Endosymbiotic Origin



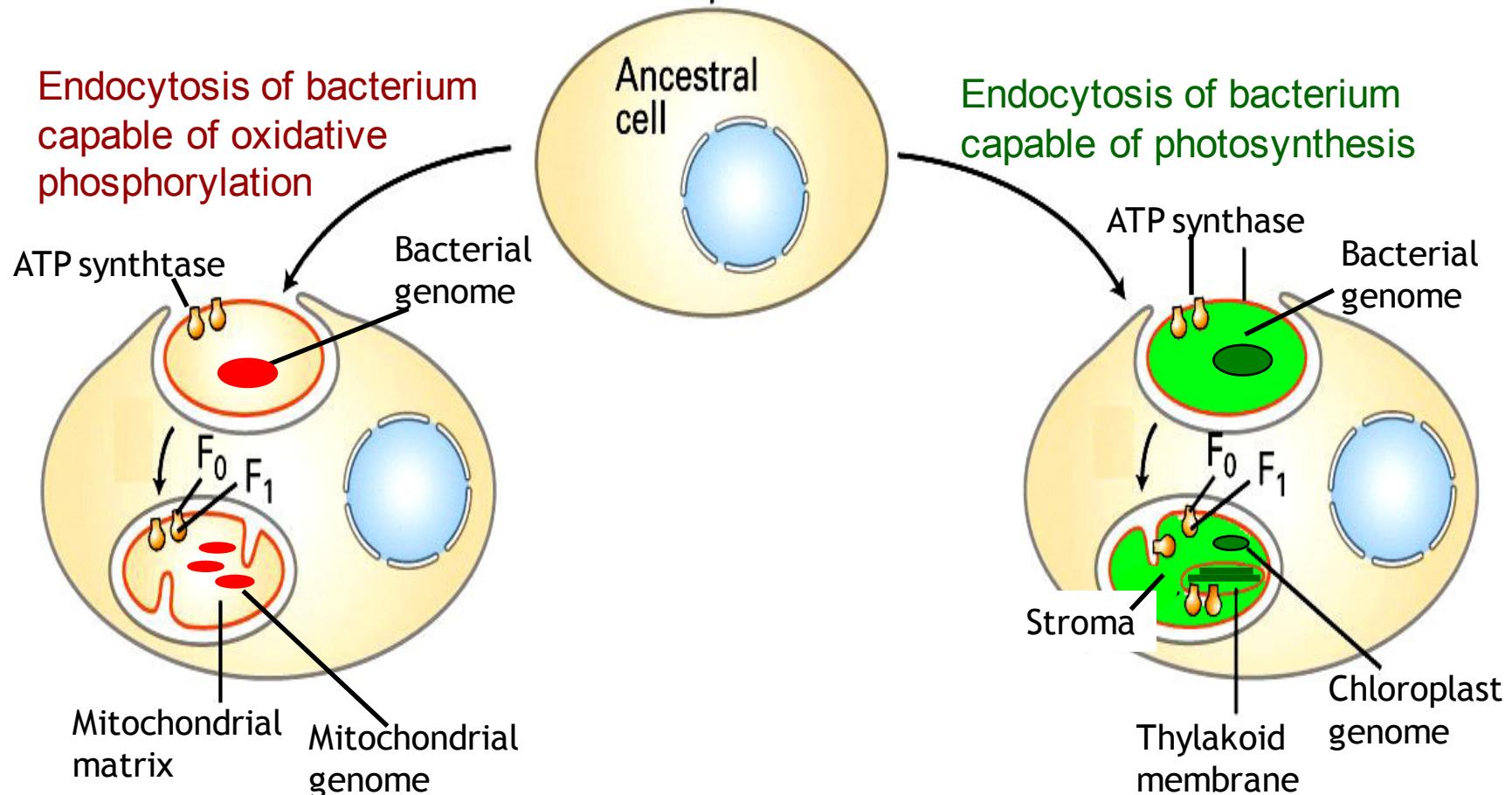
Endosymbiotic Theory

- Mitochondria and chloroplasts evolved from free-living bacteria that formed symbiotic relationships with primordial eukaryotic cell
- Mitochondria and chloroplasts have own
 - Genetic material
 - Protein synthetic machinery
- Over evolutionary time, most of the bacterial genes were lost from organellar DNAs



Lynn Margulis (1981)

Model for Endosymbiotic Origin



- Generation of double membrane organelle
 - Outer membrane from eukaryotic plasma membrane
 - Inner membrane from bacterial plasma membrane

Cells: Two Major Classification

- Cell: morphological and functional unit of all living organisms

	Prokaryotes	Eukaryotes
Examples	<ul style="list-style-type: none">• Various types of bacteria• Almost all unicellular Cyanobacteria	<ul style="list-style-type: none">• All members of plant and animal kingdoms• Fungi (unicellular e.g. yeast, multicellular e.g. molds)• Protozoan (unicellular)
Cell diameter	1-10 μm	10 – 100 μm
Nucleus	Lacks nucleus	Defined membrane bound nucleus

Cells: Two Major Classification (2)

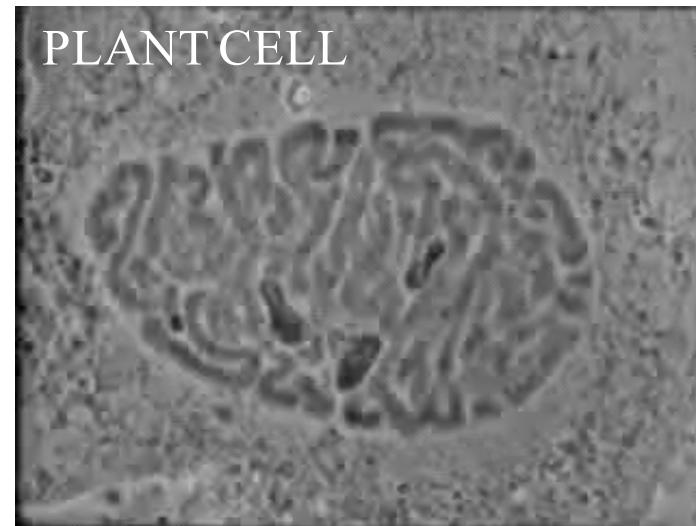
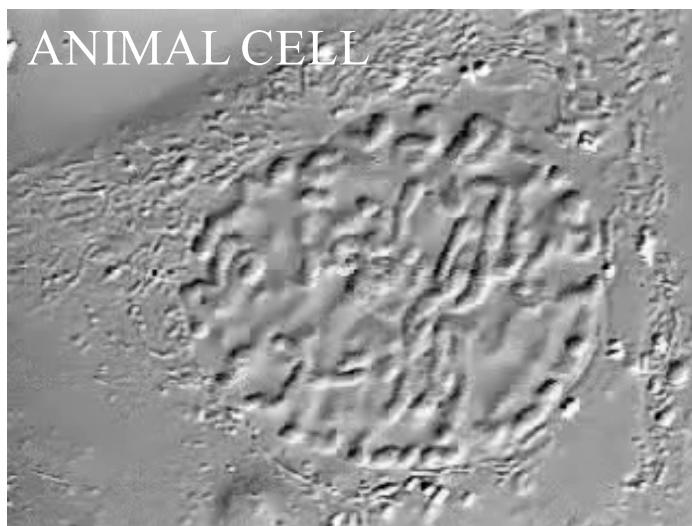
	Prokaryotes	Eukaryotes
Internal organization	Lacks membrane-bound compartments but many proteins are localized in cytosol	Extensive internal membranes enclose other compartments known as organelles
Cytoskeleton	Absent	Present
Cytoplasmic organelles	Absent	Present

Cells: Two Major Classification (3)

	Prokaryotes	Eukaryotes
Chromosome	Single circular DNA molecule	Multiple linear DNA molecules
DNA content	1×10^6 to 5×10^6 base pairs	1.5×10^7 to 5×10^9
mRNA	<ul style="list-style-type: none">mRNA transcript is mature, directly used for translationTranscription & translation are coupled	<ul style="list-style-type: none">mRNA transcript is processed (not mature)Transcription & translation are separate

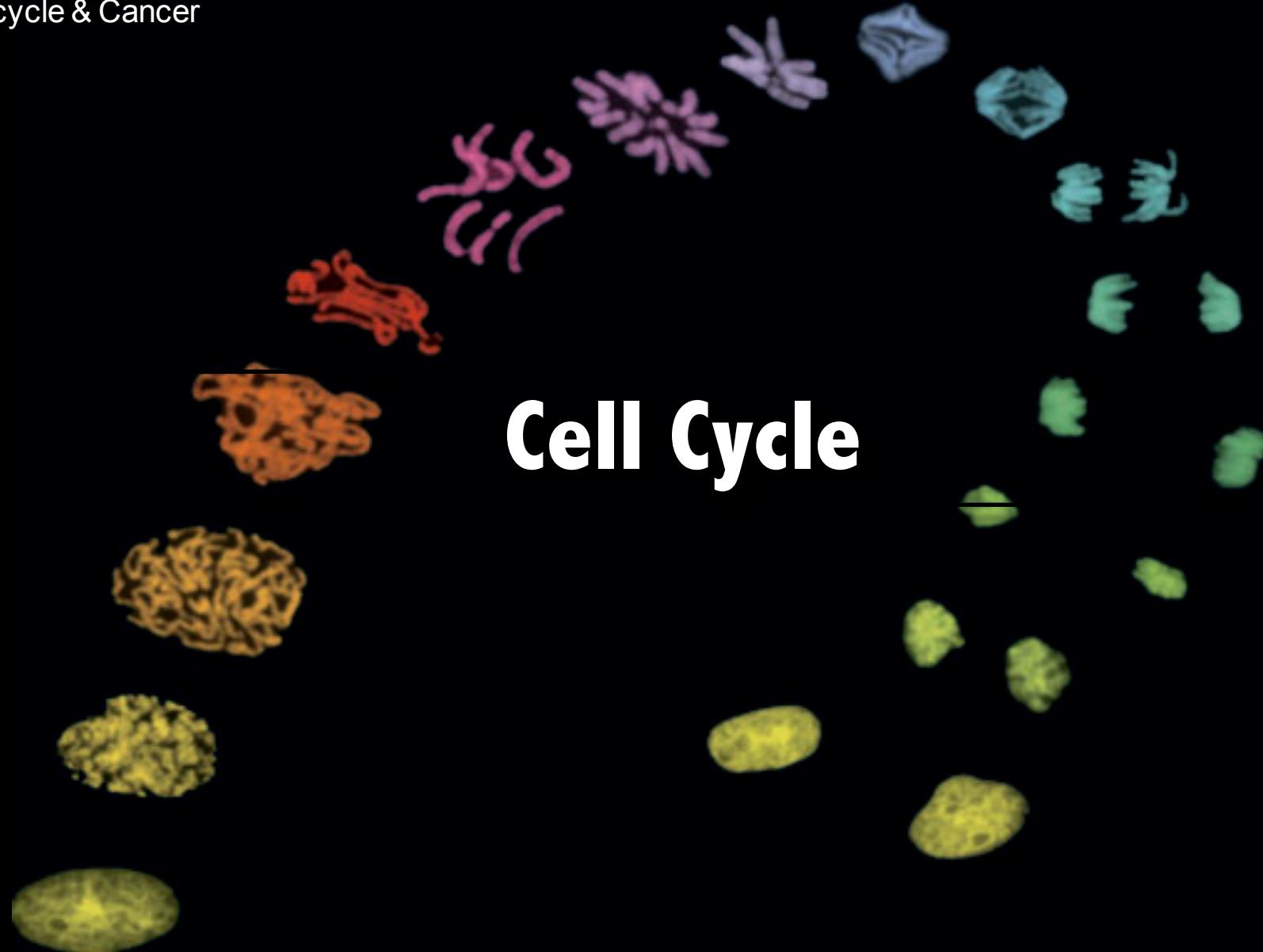
Distinguishing Features of Plant and Animal Cells

	Plant cell	Animal cell
Cell wall	Present	Absent
Vacuole	Large	Small
Plastid	Present	Absent
Glyoxysome	Present	Absent
Lysosome	Absent	Present
Centrosome	Absent	Present



- Cell and its Properties ✓
- Cell cycle
- Cell cycle & Cancer

Cell Cycle



Role of Cell Division

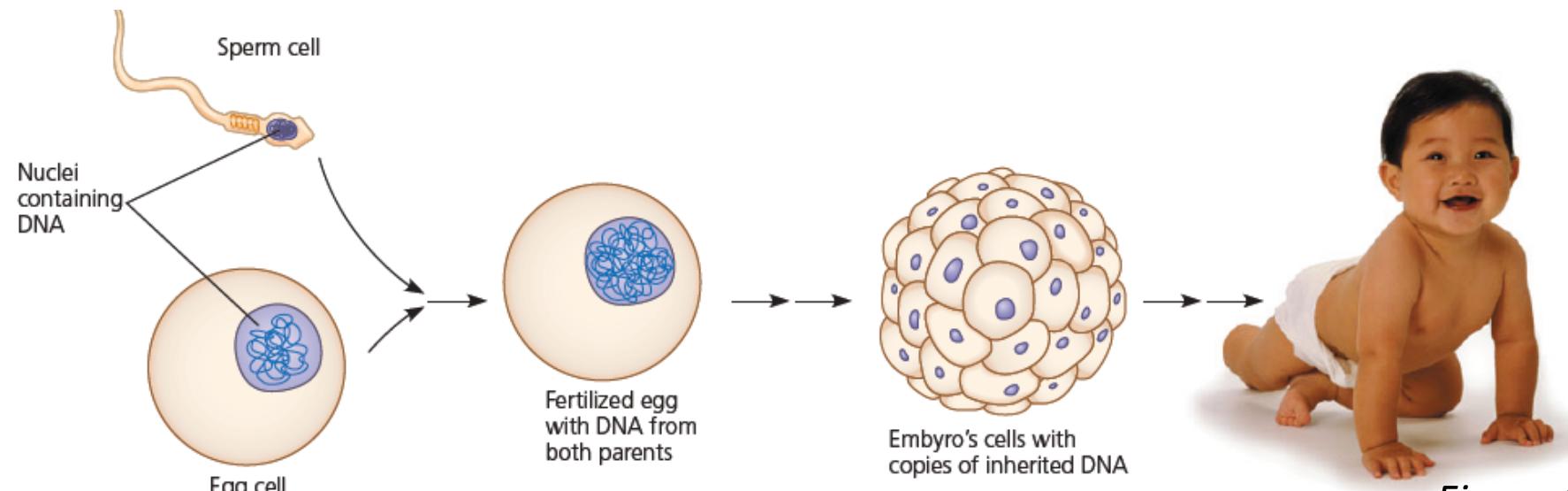


Figure 1.6

Life begins from a Single Cell: Continues with Regulated Cell Division

- Cell division distributes DNA (chromosomes) of a mother cell equally between two daughter cells thereby allowing a cell to proliferate
- Cell proliferation is essential for growth, repair & reproduction

Cellular Organization of the Genetic Material

- A genome consist of a number of DNA molecules (eukaryotic cells) or a single DNA molecule (prokaryotic cells)
- **Somatic cells:** Non-reproductive cells - two sets of chromosomes
- **Gametes:** Reproductive cells: sperm & egg - have half as many chromosomes as somatic cells

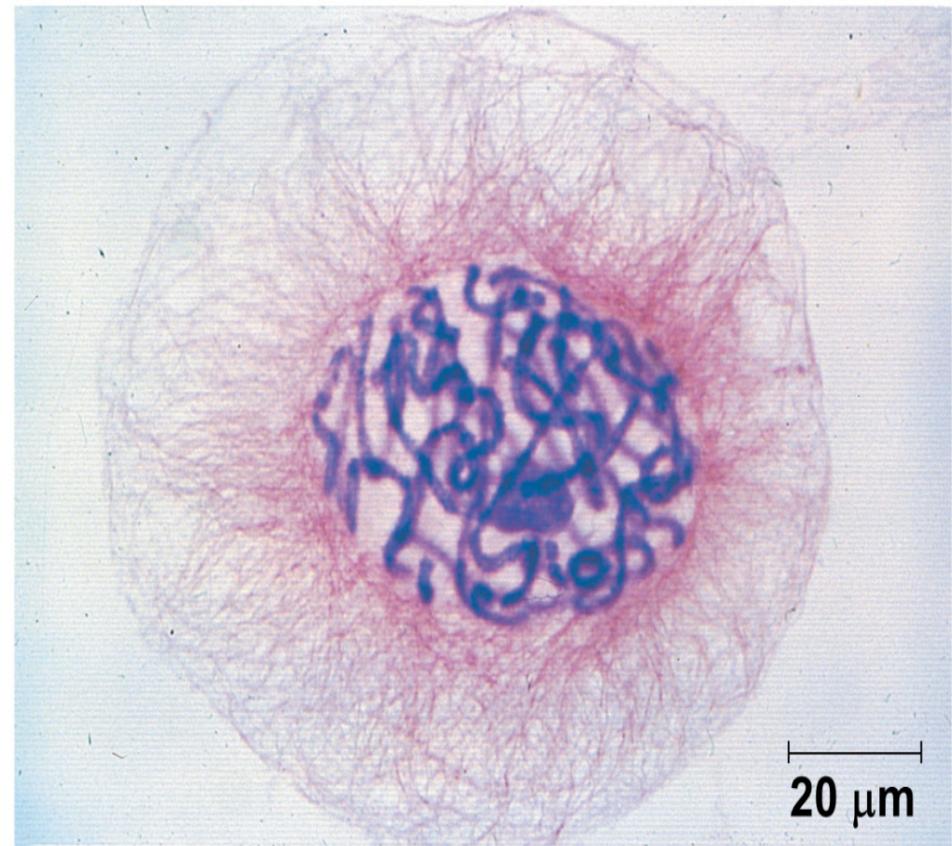


Figure 12.3

The Cell cycle

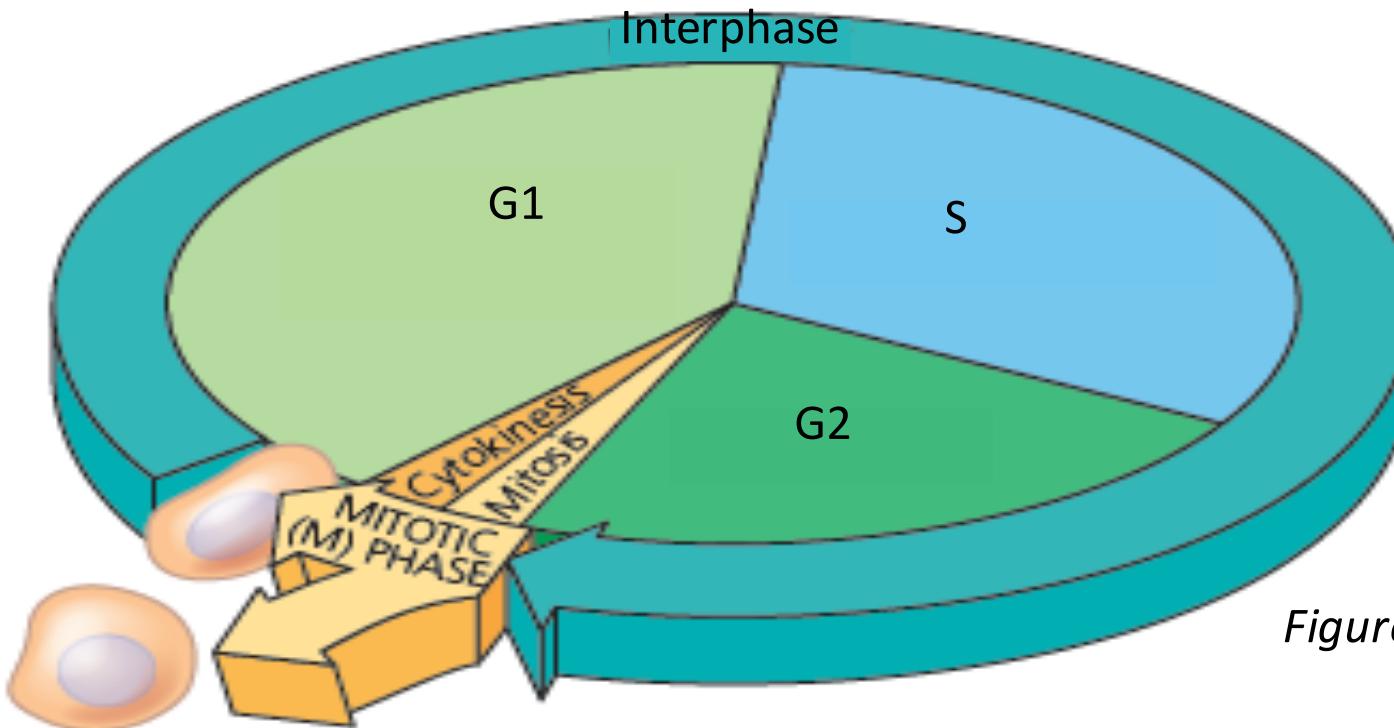
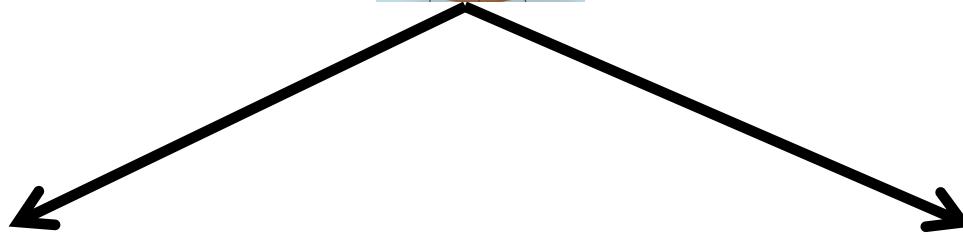
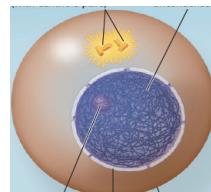


Figure 12.6

- Mitotic (M) phase alternates with interphase (growth period)
- **G1 phase** – first part of interphase
- **S phase** - chromosomes duplicate
- **G2 phase** - last part of interphase
- **M phase** - mitosis distributes chromosomes to daughter nuclei
- **Cytokinesis** - divides cytoplasm and produces two daughter cells

The Cell Cycle



- Division of somatic cells
- Two daughter cells are produced with *same amount of DNA* as mother cell

- Division of gamete cells (Sperm and ovum)
- Four daughter cells are produced with *half the amount of DNA* as mother cell

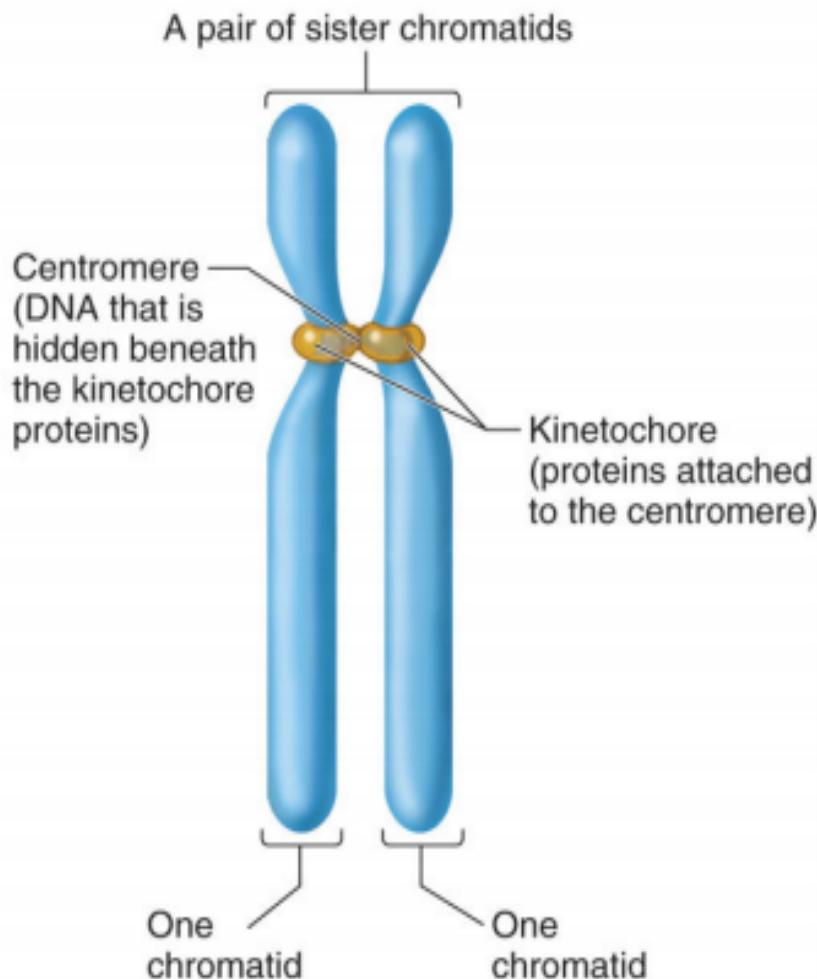


Figure 12.1

Mitosis produces new cells, and replaces cells that are old, lost or damaged.

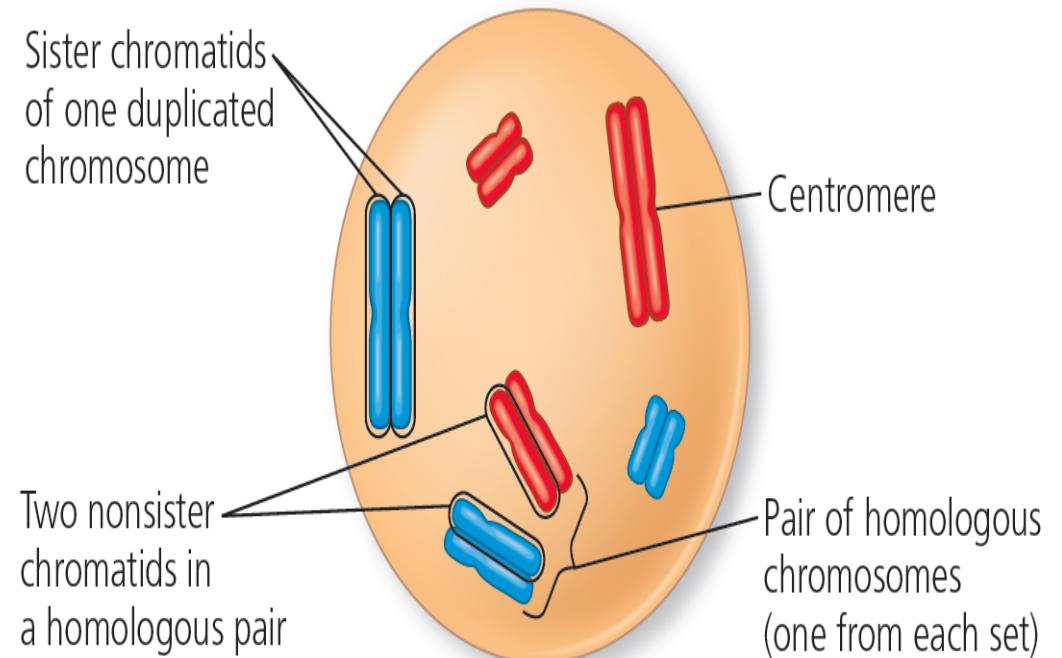
In mitosis a cell divides to form two identical daughter cells.

Few Basics & Terminology



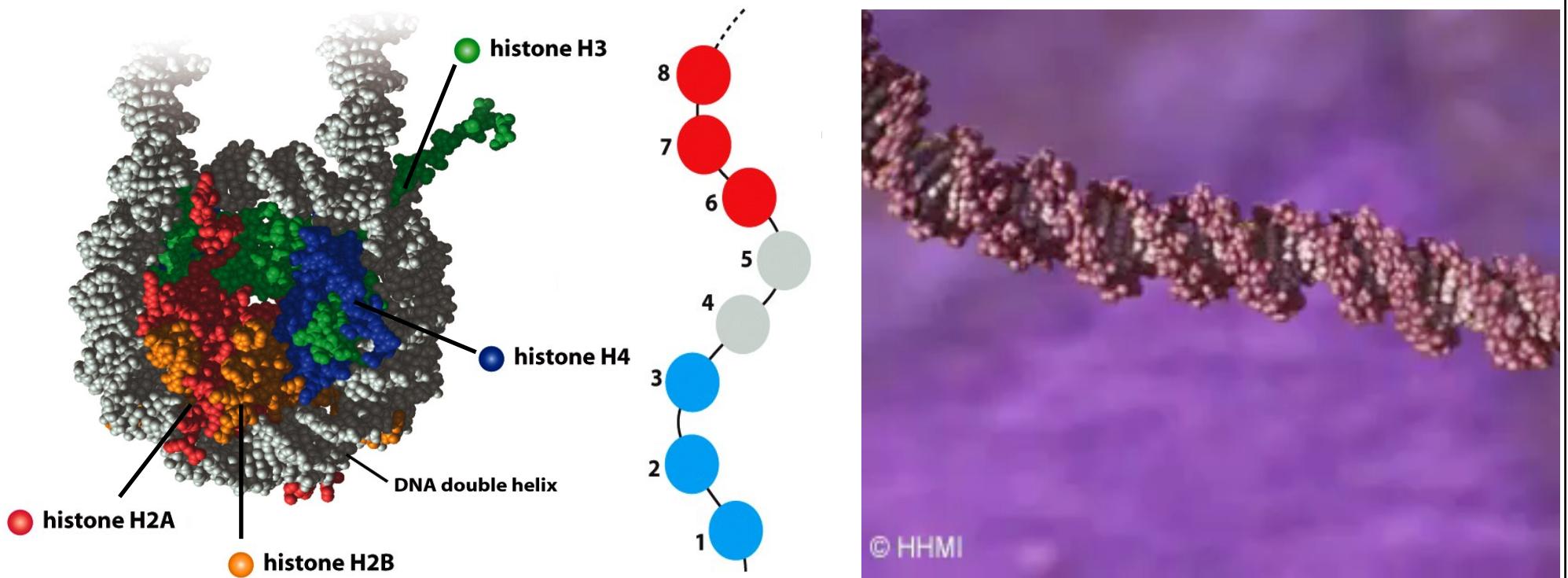
$2n = 6$

- Maternal set of chromosomes ($n = 3$)
- Paternal set of chromosomes ($n = 3$)

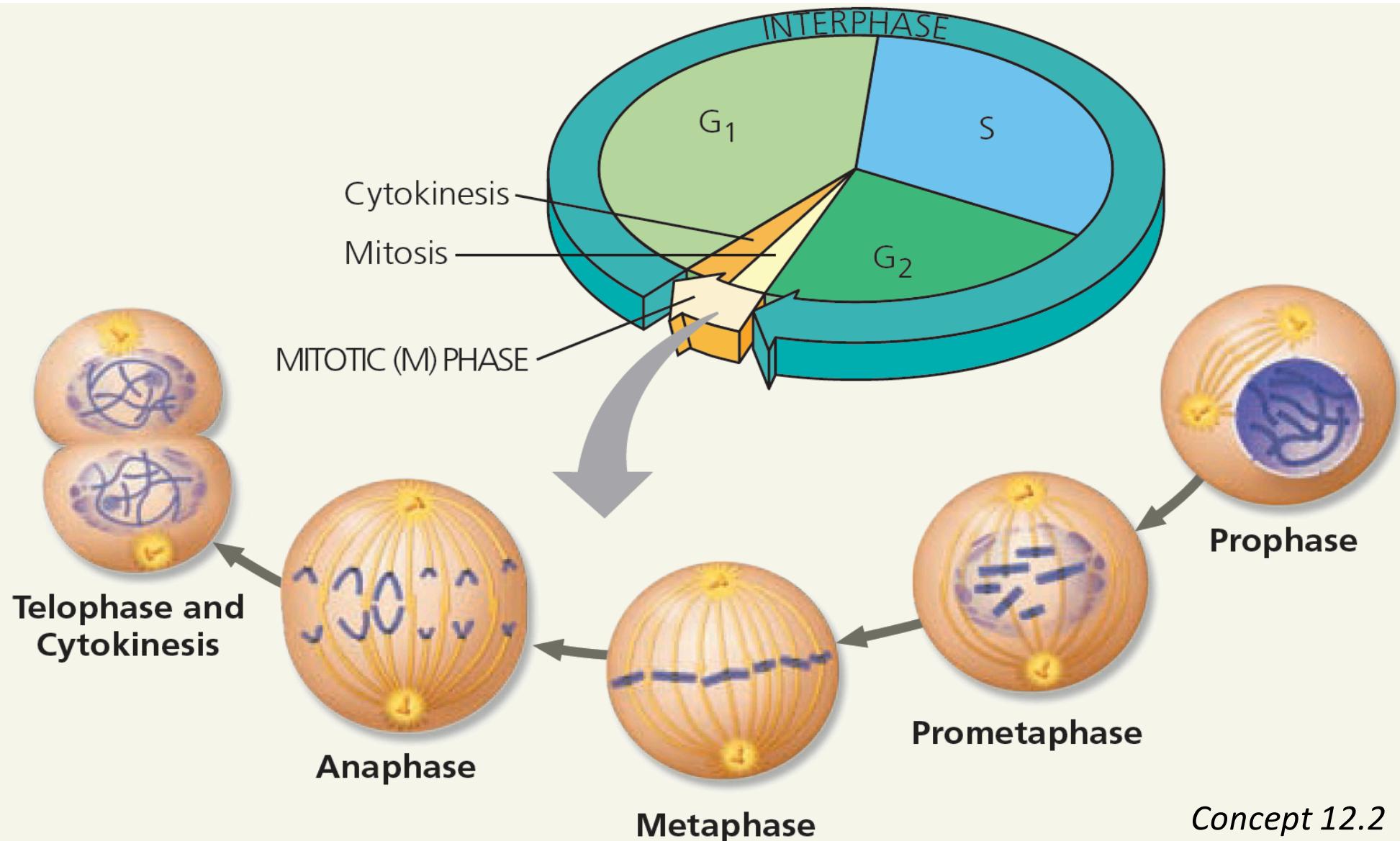


DNA is tightly packed in nucleus of every cell - how?

- 8 separate histone proteins attach to the DNA molecule and form nucleosome
- Fiber of packed nucleosome is known as chromatin



The Cell Cycle: Mitosis



Concept 12.2

Mitosis: Prophase

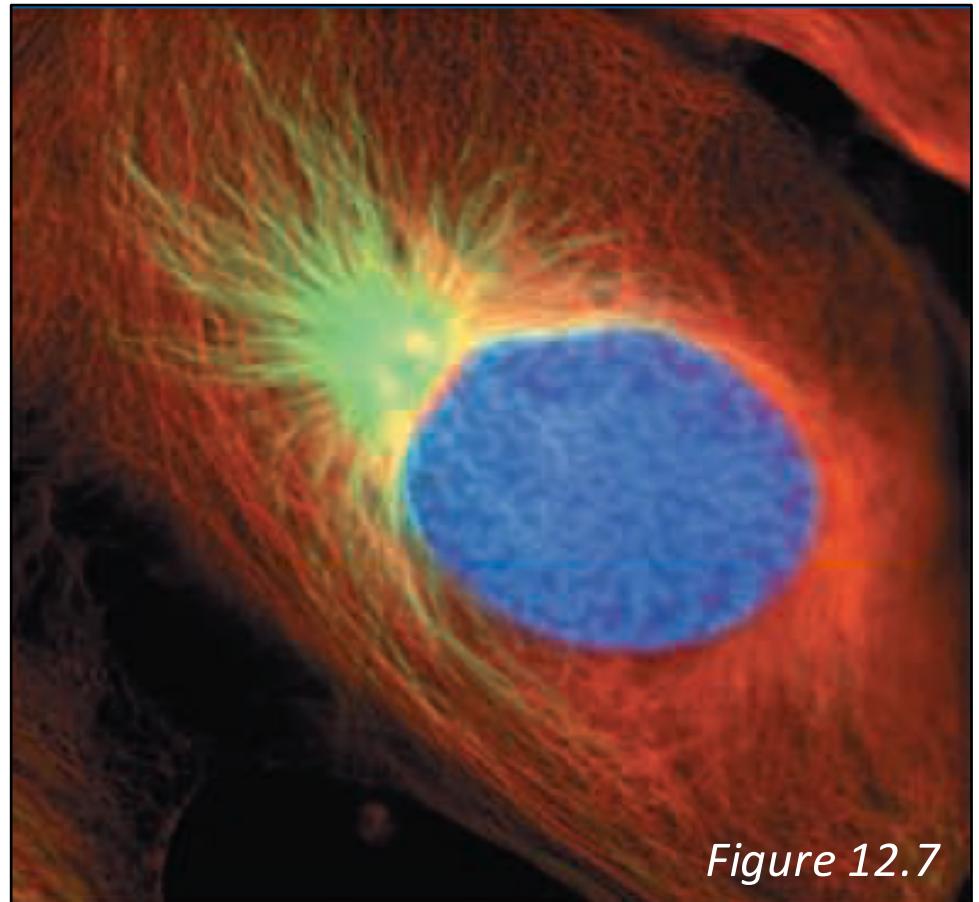
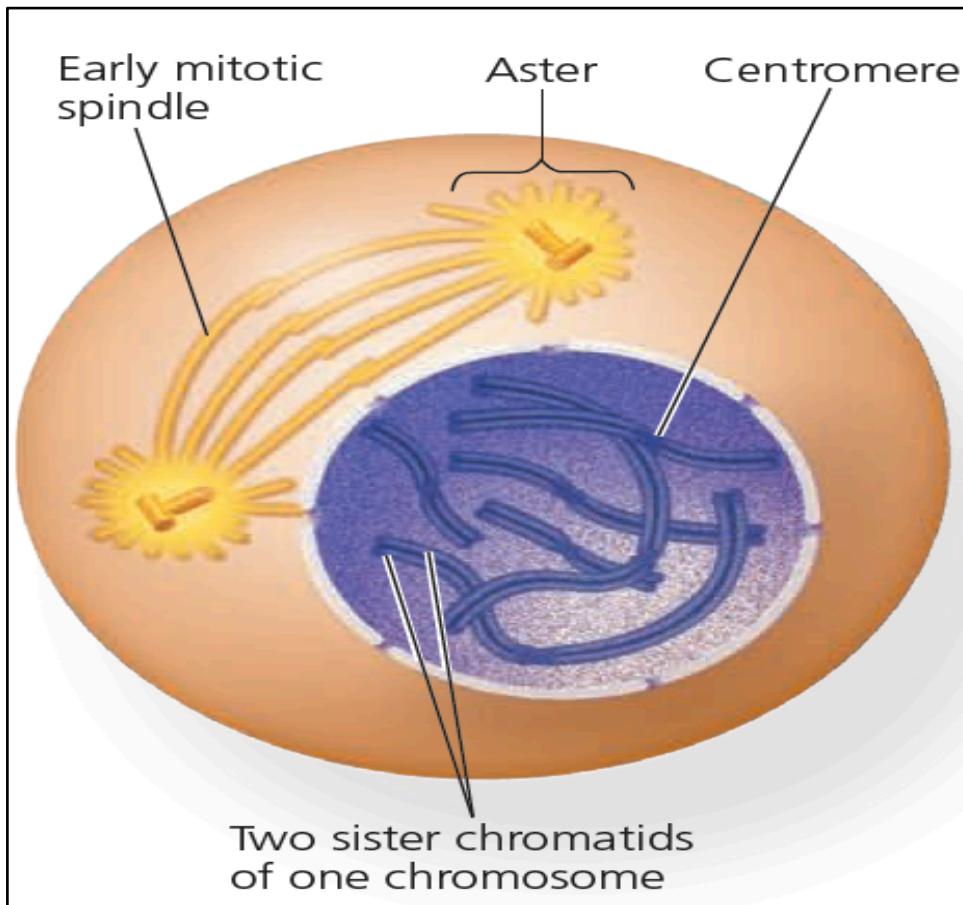
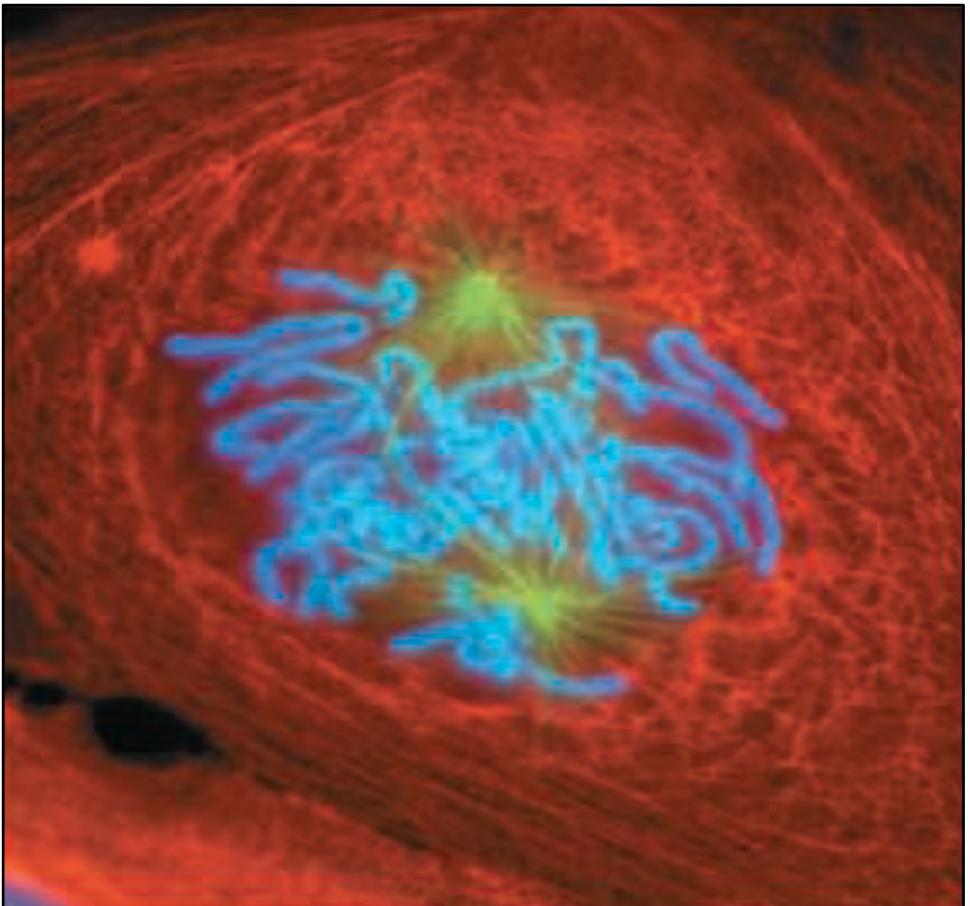
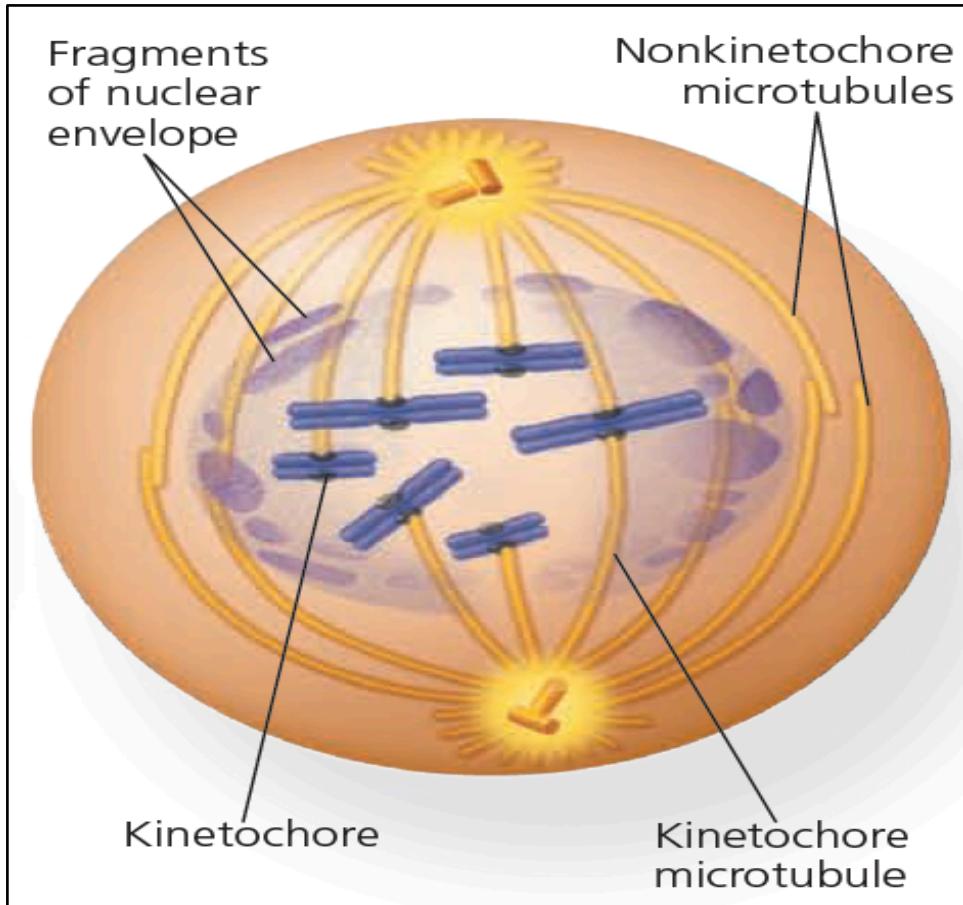


Figure 12.7

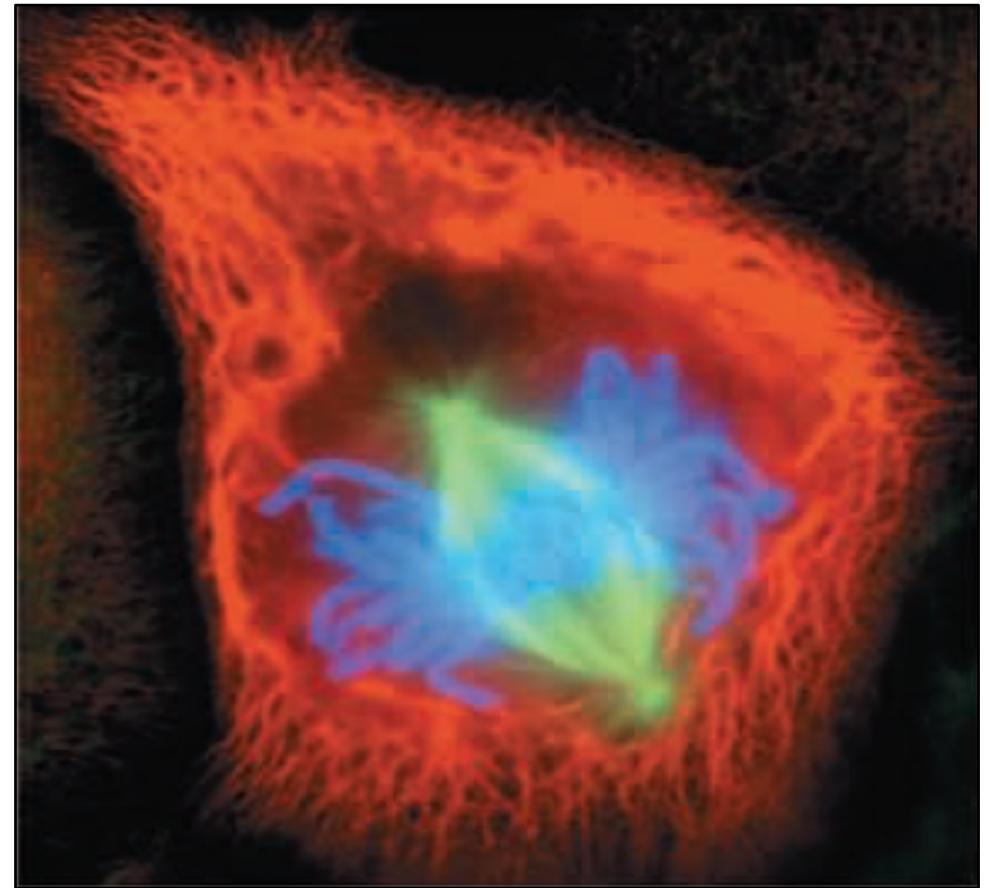
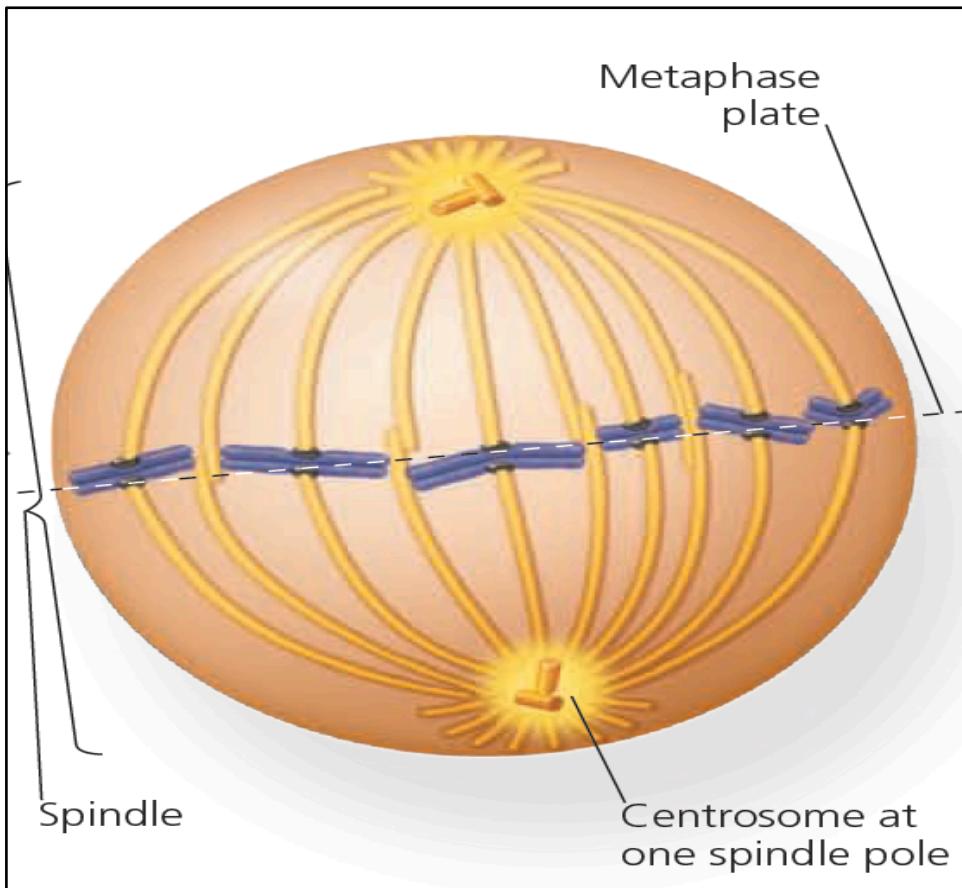
- Chromatins condense into discrete chromosomes and nucleoli disappear
- Each chromosome appears as two sister chromatids, joined at centromere
- Centrosomes move apart and mitotic spindle begins to form

Mitosis: Prometaphase



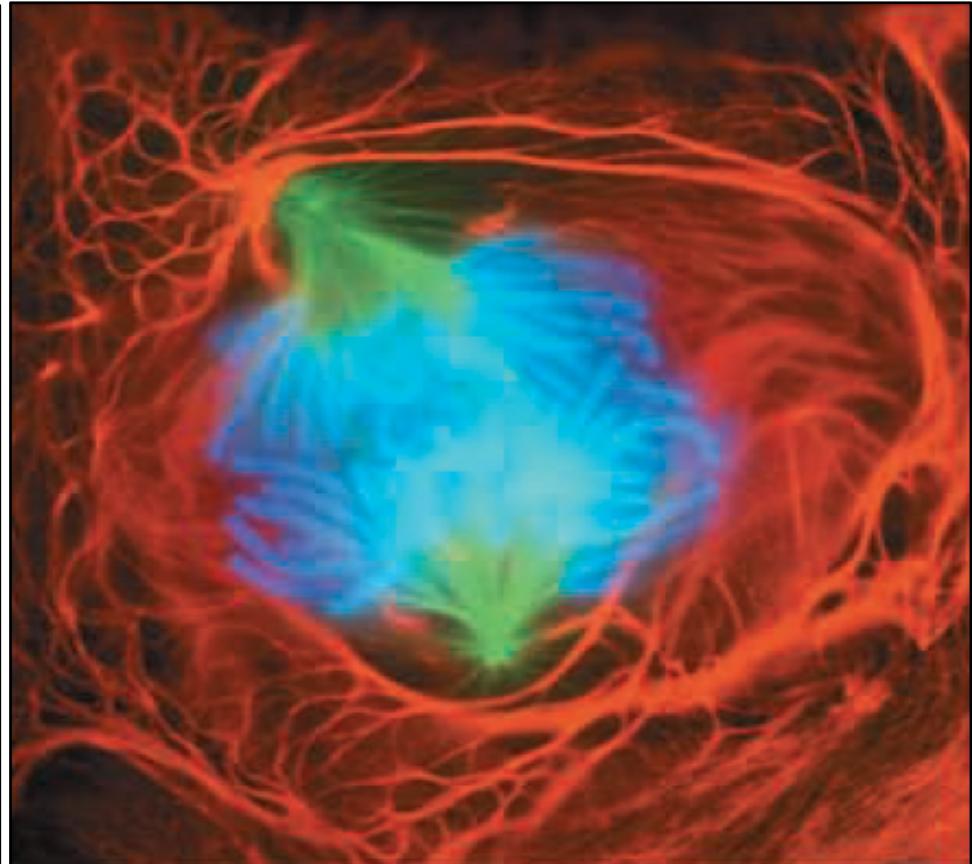
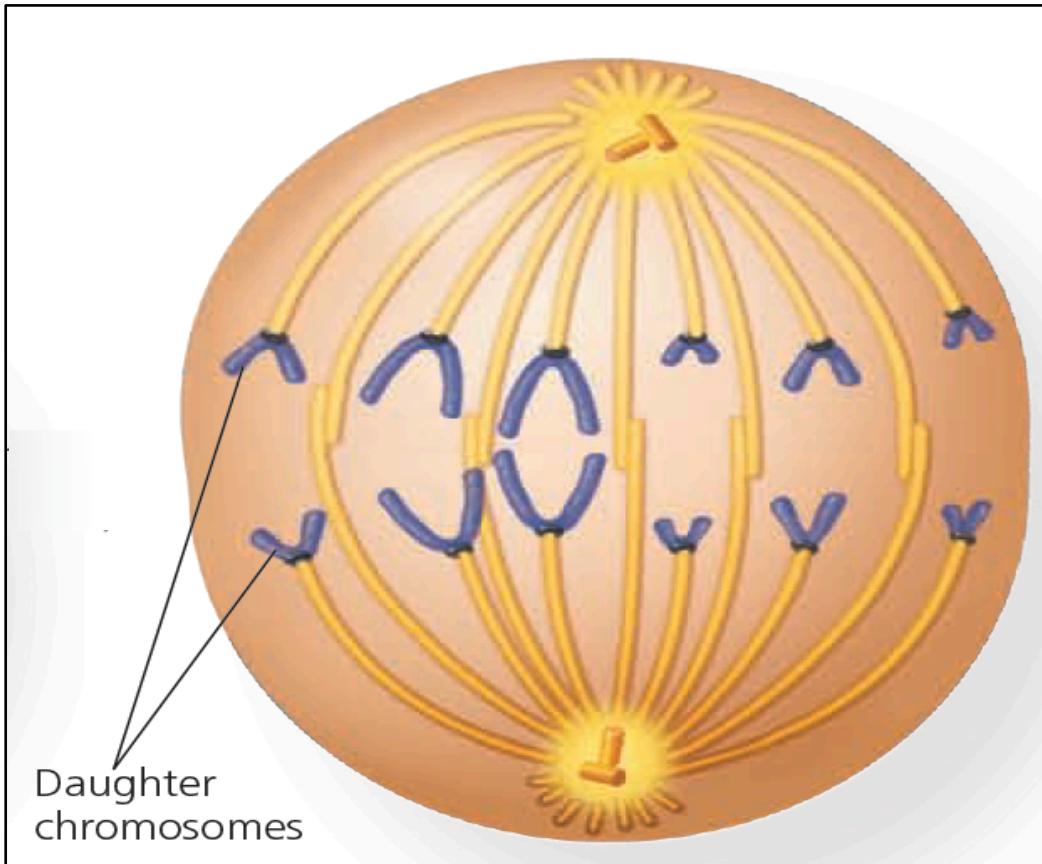
- Nuclear membrane fragments, microtubules grow
- Each of the two chromatids have kinetochore proteins at the centromere
- Microtubules attached to kinetochores “kinetochore microtubules”

Mitosis: Metaphase



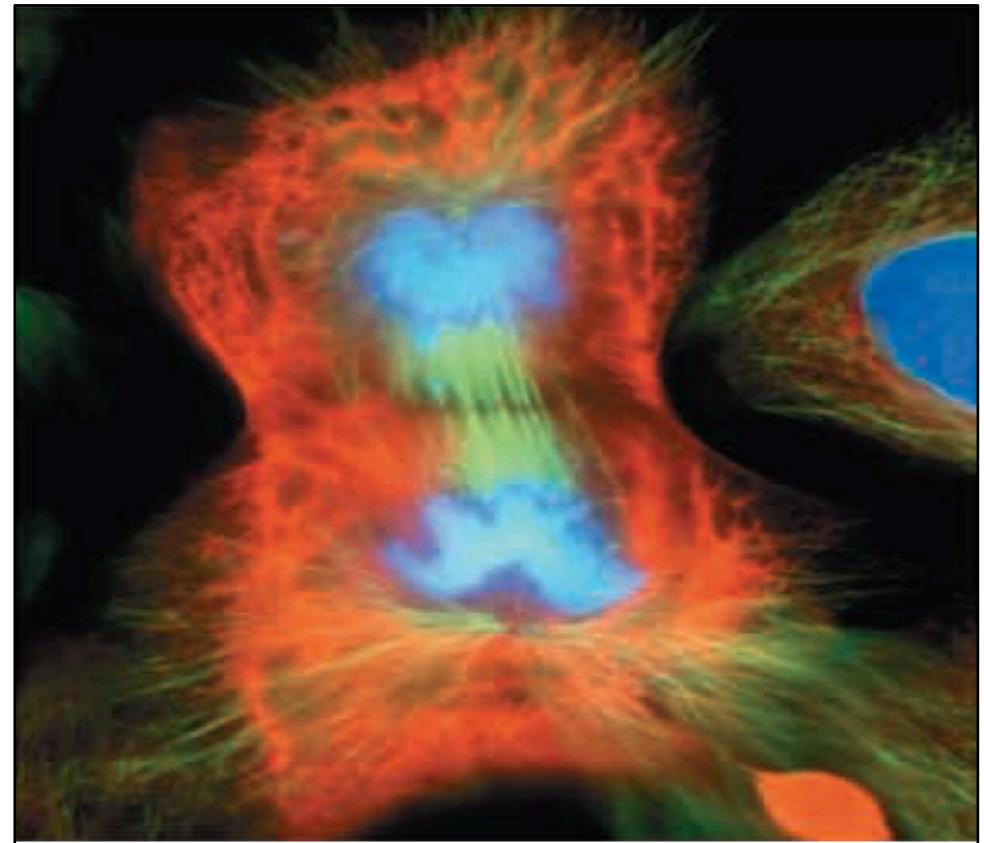
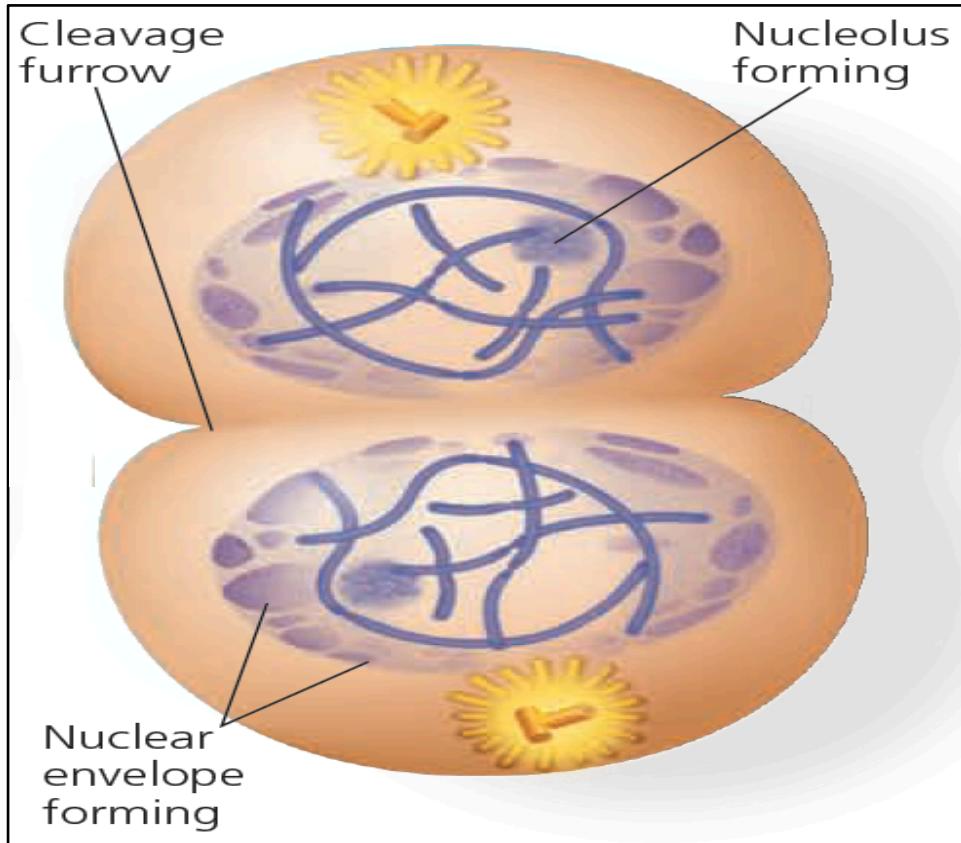
- Chromosomes assemble at *metaphase plate* “equidistant between spindle’s 2 poles”
- Each chromosome sister chromatids are attached to microtubules arising from opposite poles

Mitosis: Anaphase



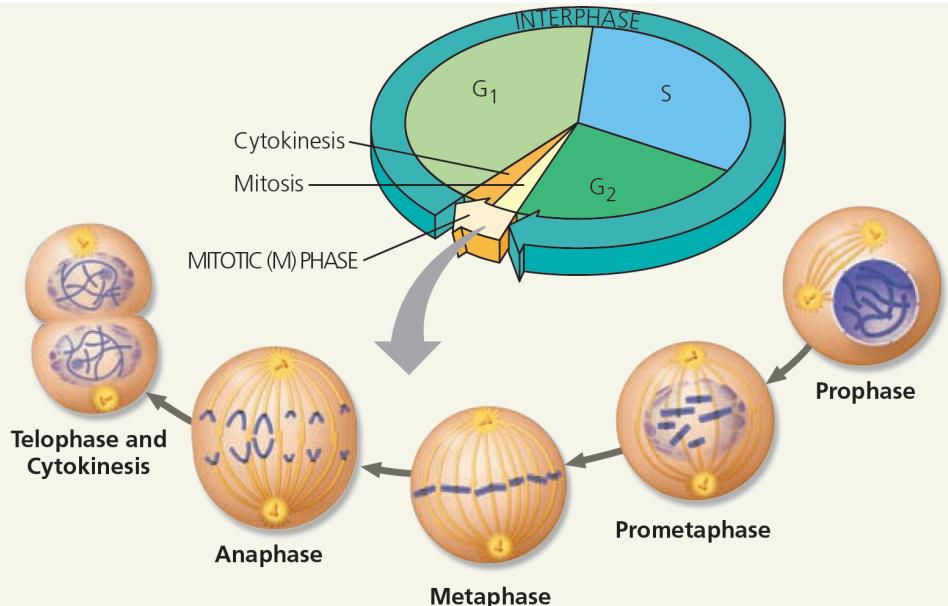
- Sister chromatids separate & each chromatid behaves as a chromosome
- A protein “cohesin” helps in cleavage process
- Daughter chromosomes move towards opposite poles

Mitosis: Telophase & Cytokinesis

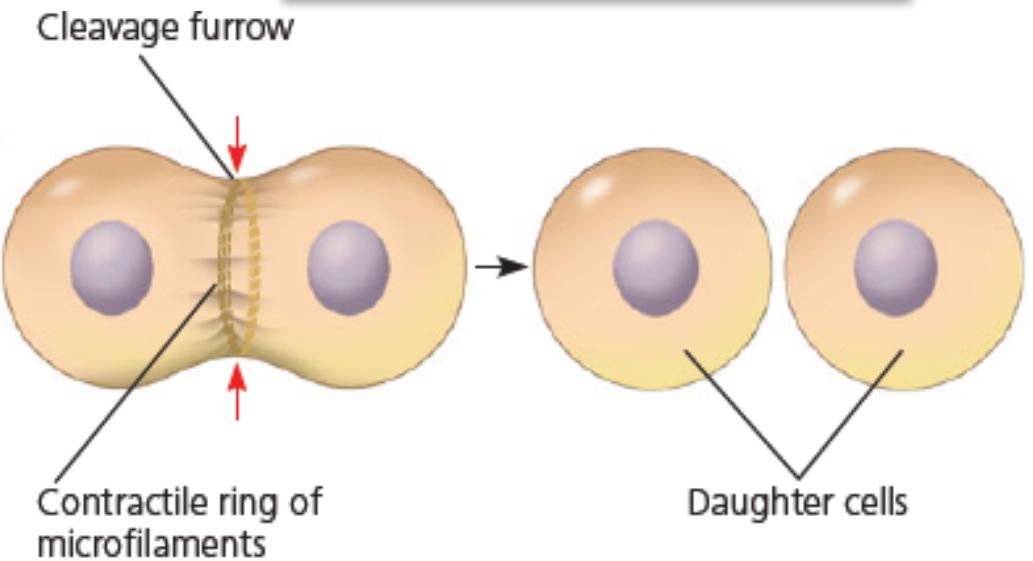


- Two daughter nuclei form in the cell, nuclear envelope reappears
- Spindle microtubules depolymerize, chromosomes become less condensed; karyokinesis (division of nucleus) completes

Mitosis: Cytokinesis



Cytokinesis



- Formation of cell furrow
- Division of cytoplasm to give rise to two daughter cells

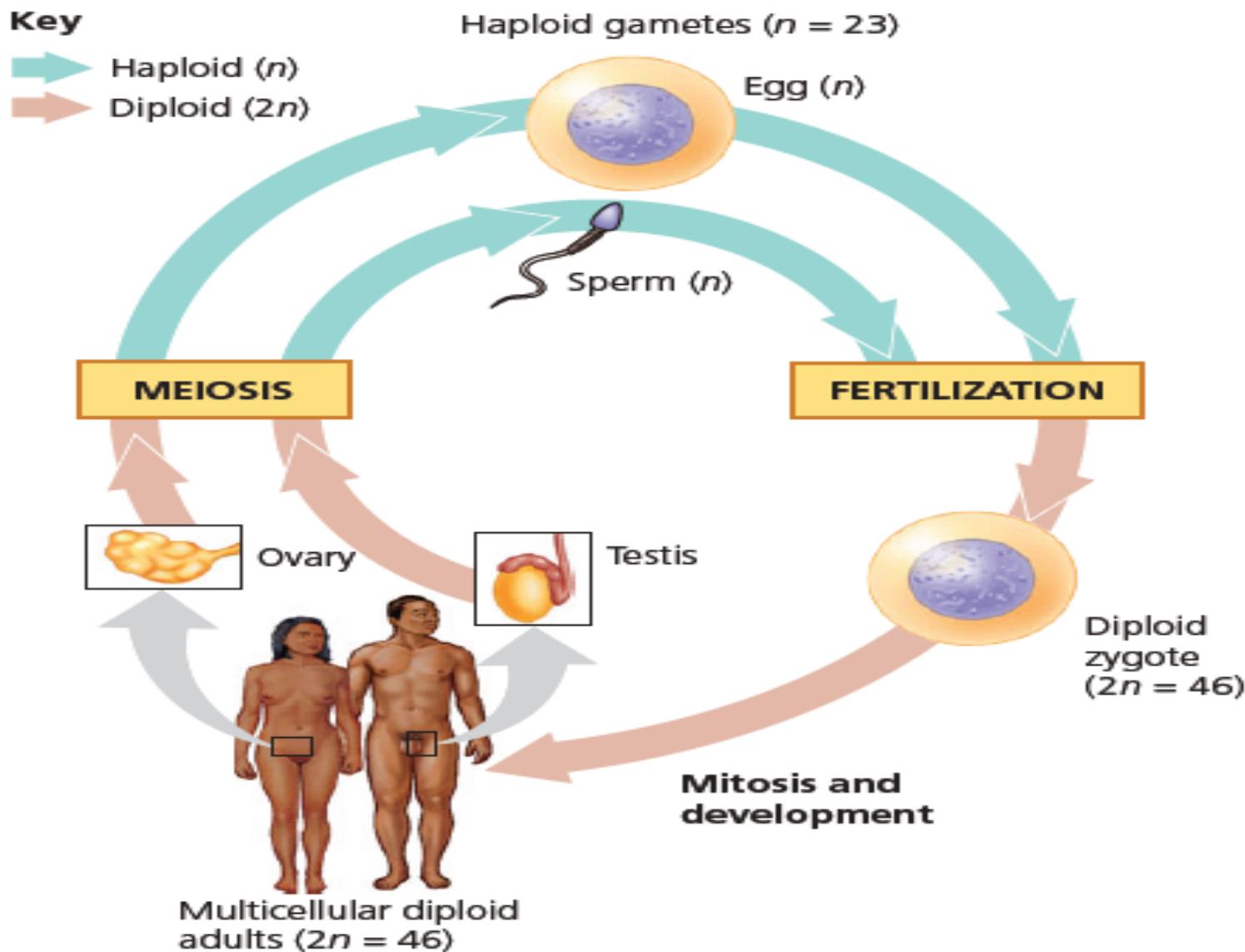


Meiosis

Why meiosis is important?

Able to generate genetic variation in offspring because the process of meiosis randomly shuffles genes across chromosomes

Meiosis Central to Reproduction

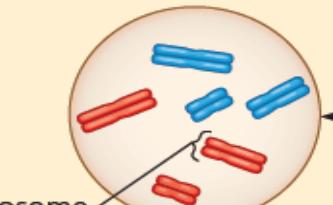


Cell Division: Mitosis vs. Meiosis

MITOSIS

Prophase

Duplicated chromosome
(two sister chromatids)



Parent cell
(before chromosome duplication)
 $2n = 6$

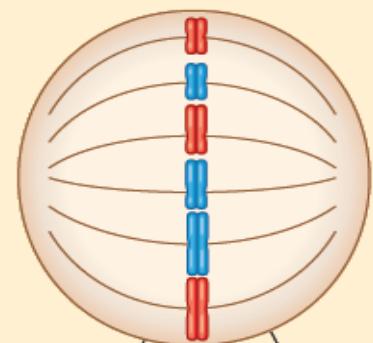
Chromosome duplication

Chiasma (site of crossing over)

MEIOSIS I

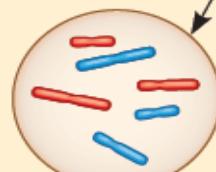
Metaphase

Individual chromosomes line up at the metaphase plate.



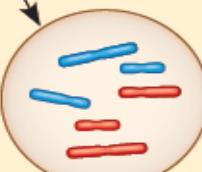
Anaphase Telophase

Sister chromatids separate during anaphase.



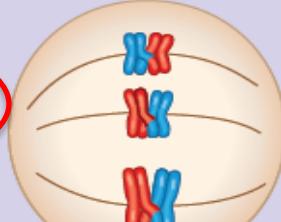
$2n$

Daughter cells of mitosis



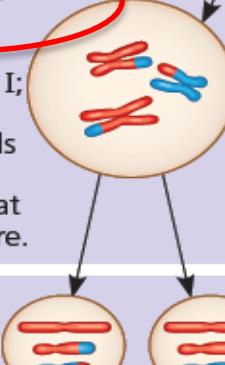
$2n$

Pairs of homologous chromosomes line up at the metaphase plate.



Metaphase I

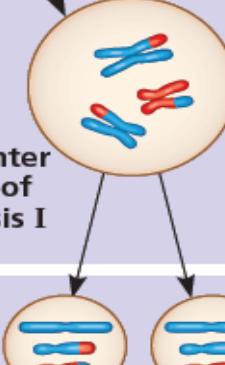
Homologs separate during anaphase I; sister chromatids remain attached at centromere.



Daughter cells of meiosis I

Anaphase I Telophase I

Haploid
 $n = 3$

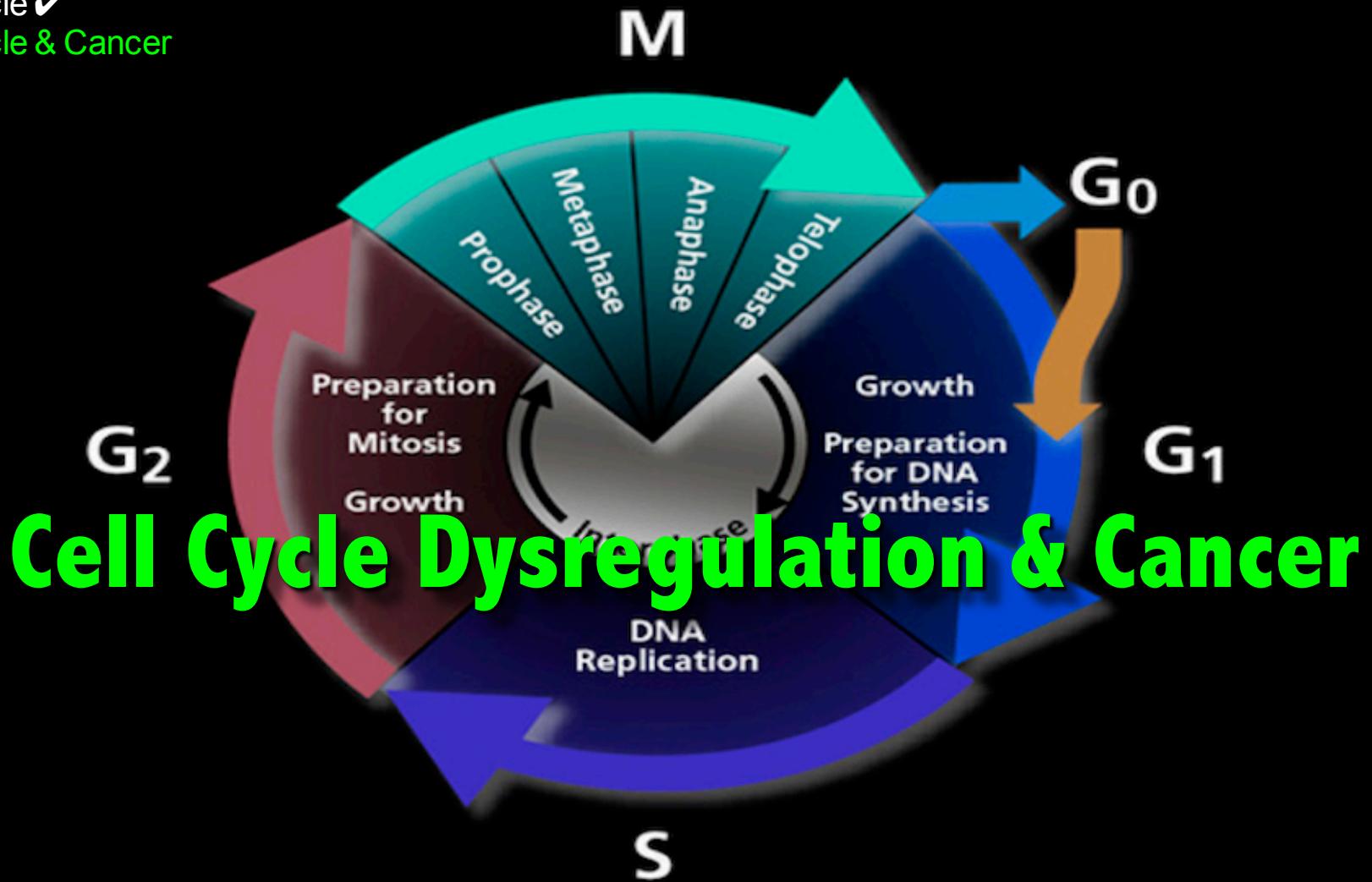


Sister chromatids separate during anaphase II.

Daughter cells of meiosis II

MEIOSIS II

- Cell and its Properties ✓
- Cell cycle ✓
- Cell cycle & Cancer



Cancer cells disrupt normal cell cycle regulation and divide out of control, forming tumors

Cell Cycle Checkpoints

Checkpoints are constituted by the proteins that regulate the cell cycle by giving “stop” and “go ahead” signals

- G1 checkpoint or restriction checkpoint
- G2 checkpoint
- Mitotic checkpoint

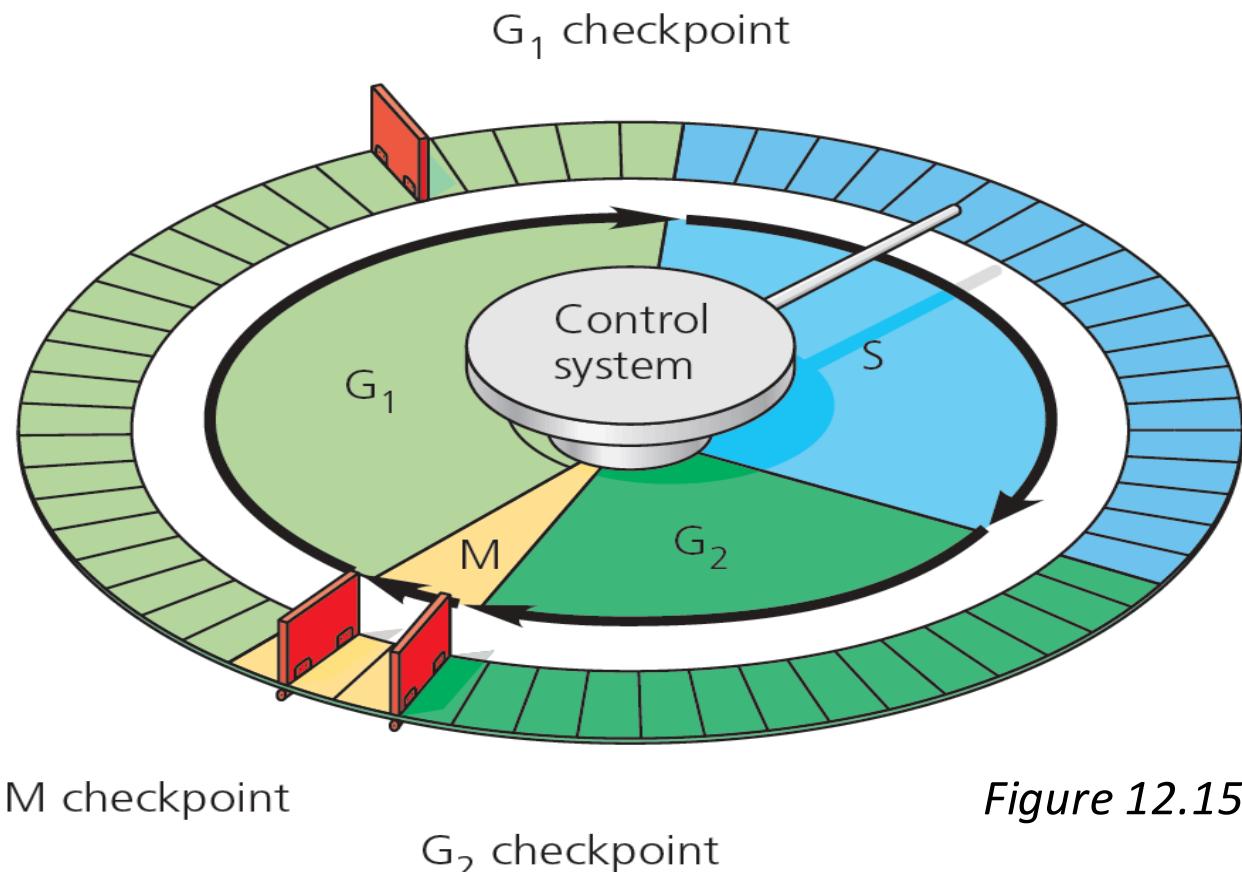
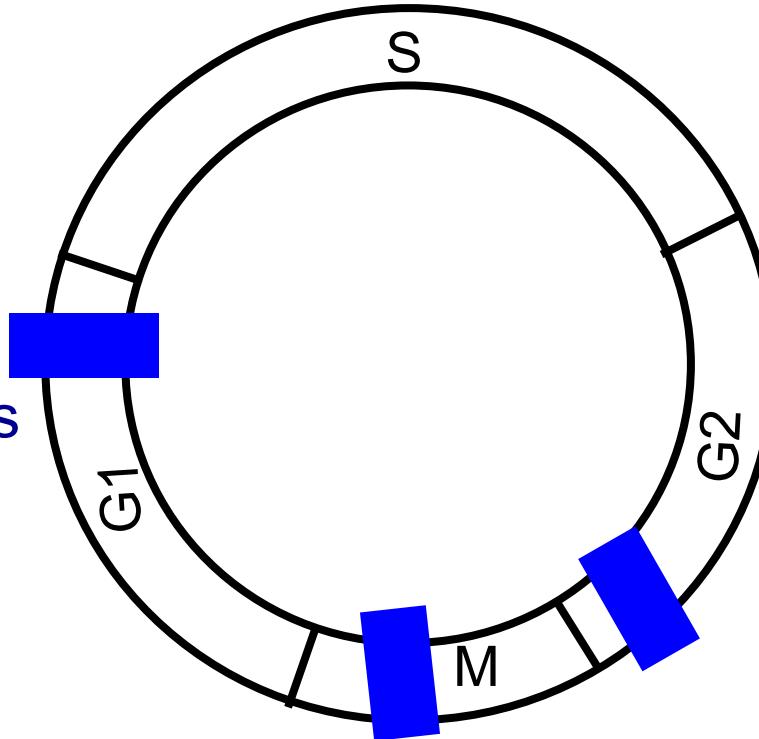


Figure 12.15

Cell Cycle Checkpoints

Parent DNA strands are intact before DNA replication begins

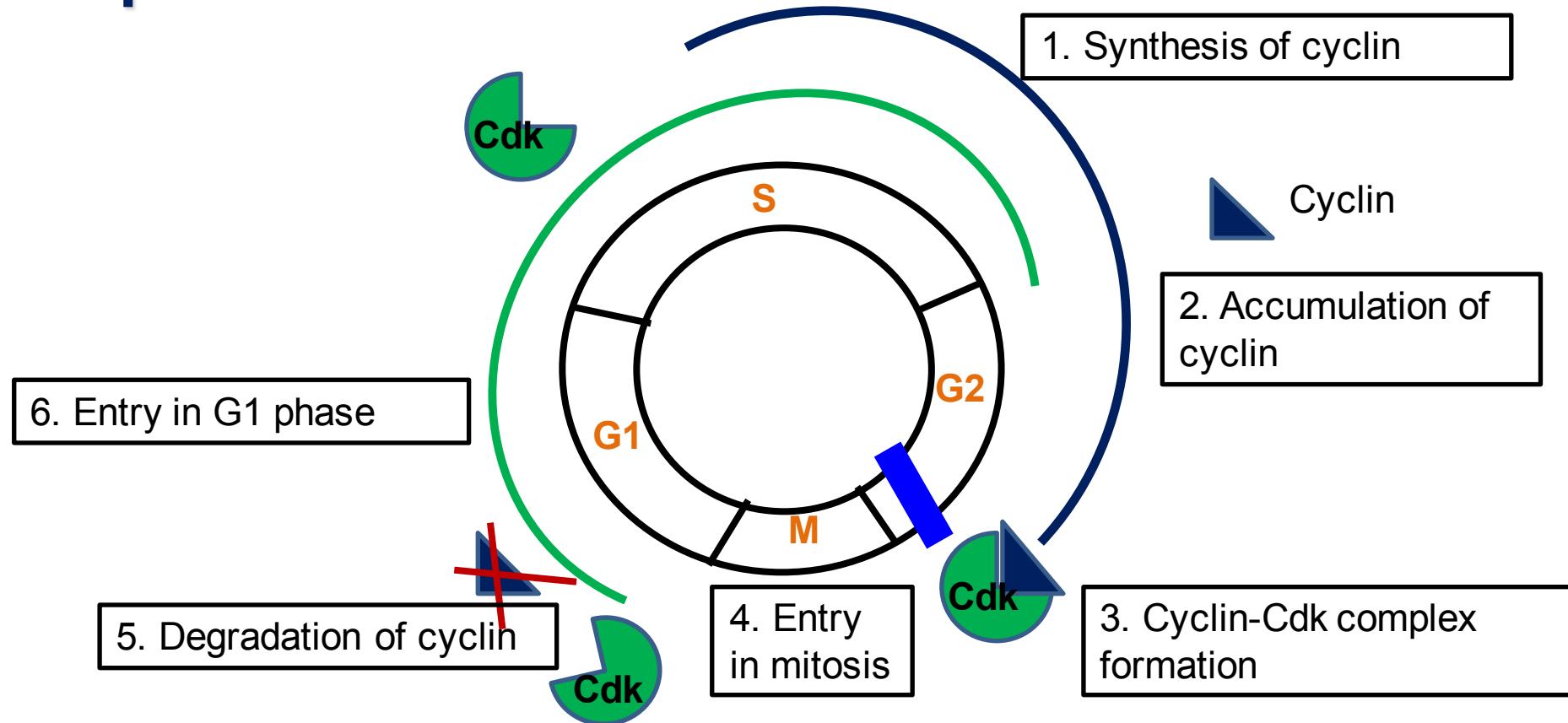


Newly synthesized DNA strands are complete and intact before Mitosis

Chromosomes are aligned properly at the metaphase plate before Anaphase

Checkpoints are essential for the correct distribution of complete chromosome sets between daughter cells

Regulation of Cell Cycle by Cyclins and Cyclin Dependent Kinases



- Family of Cyclins and CDKs are major proteins involved in cell cycle regulation
- Cdks are expressed throughout the cell cycle but activated only after binding with cyclins, which are synthesized during S phase & accumulate in G2 phase
- Cyclins get degraded after metaphase and cell enters the G1 phase

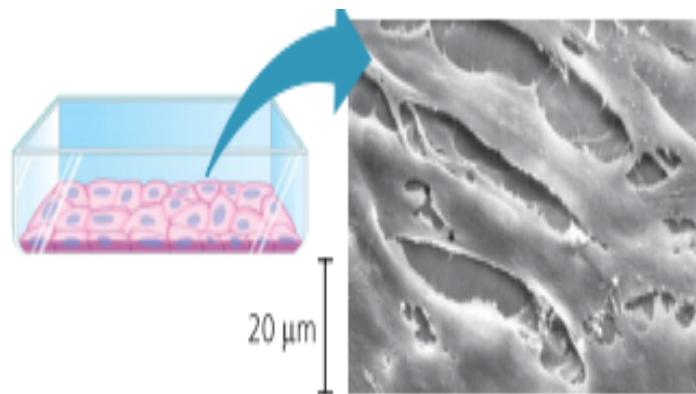
Regulation of Cell Cycle by External Signals

In addition to the internal signals following external signals are also required for the progression of cell cycle

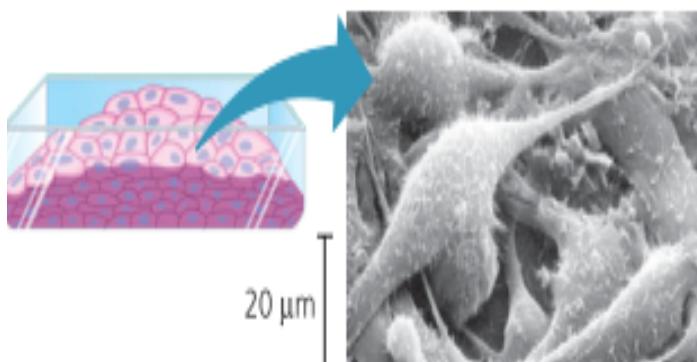
- Nutrients
- Growth factors
- Space (Crowded cells stop dividing) also known as **density dependent inhibition**
- Substratum for anchorage (**anchorage dependence**)

Cancer cells lose Dependence on Internal and External signals for Proliferation

- Cancer cells do not stop at cell cycle checkpoints
- Do not exhibit density dependent inhibition (form multiple layers of cells)
- Do not require anchorage with the substratum



Normal mammalian cells



Cancer cells

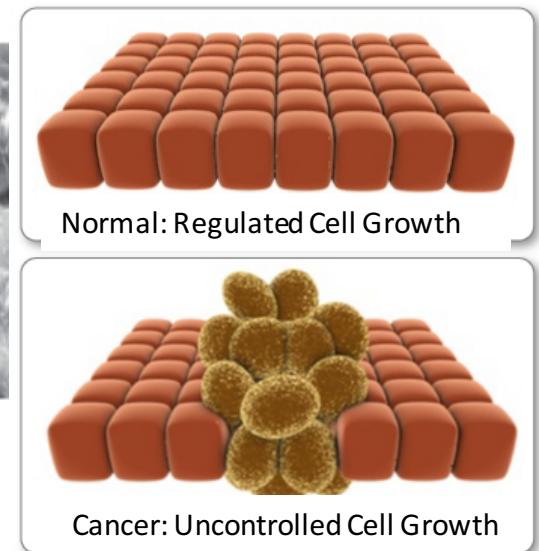
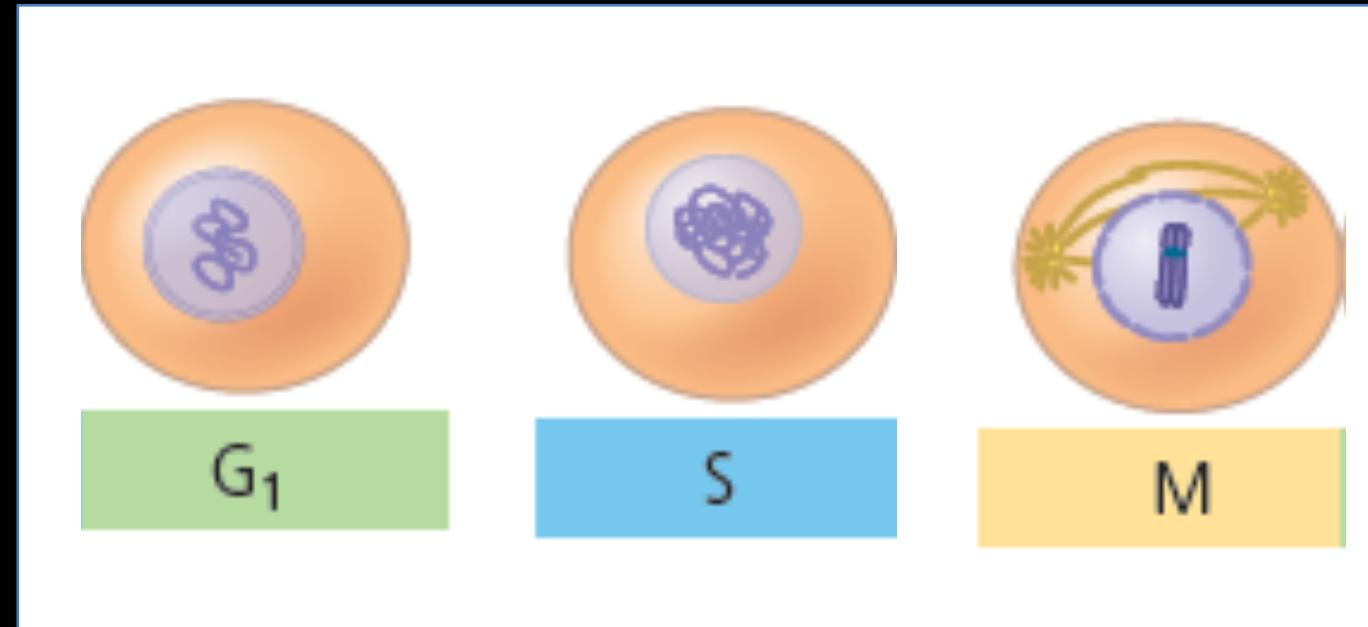


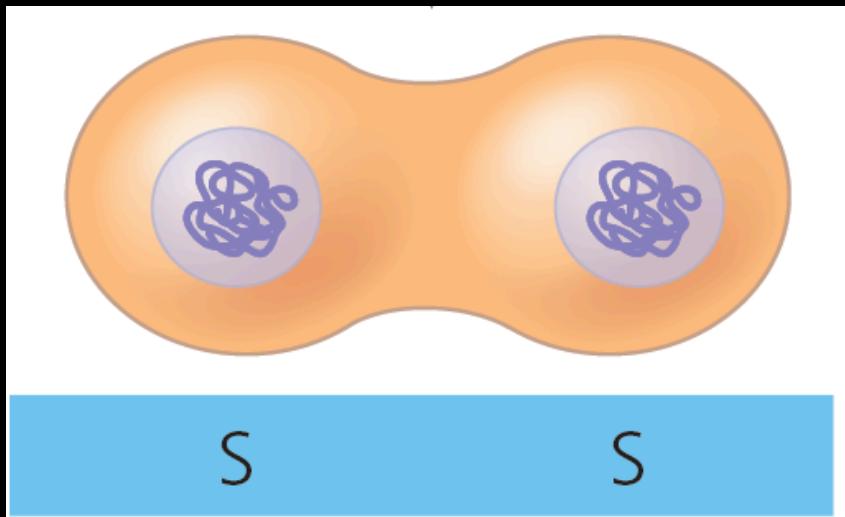
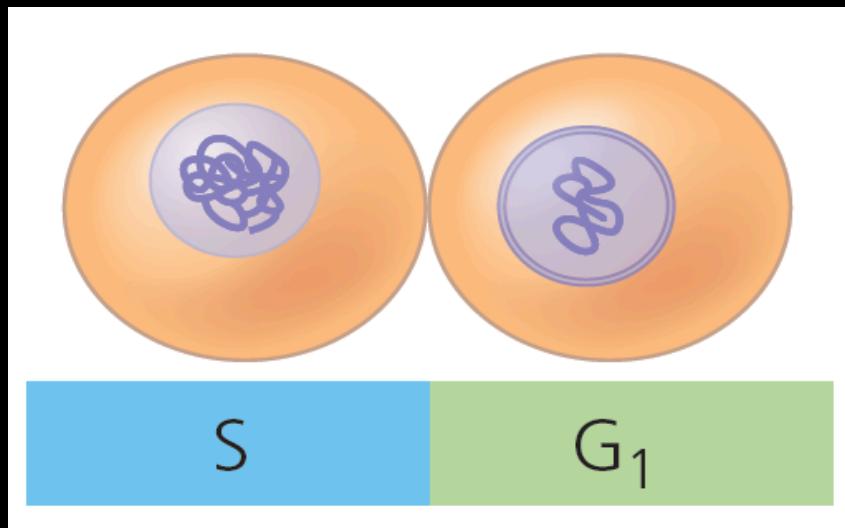
Figure 12.19 54

Do molecular signals in the cytoplasm regulate the cell cycle?

How to test this experimentally?



Experiment-1



Experiment-2

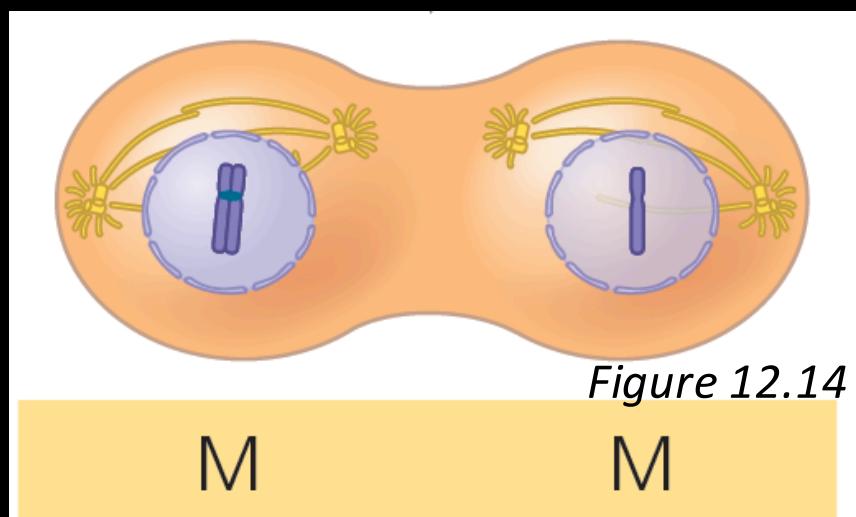
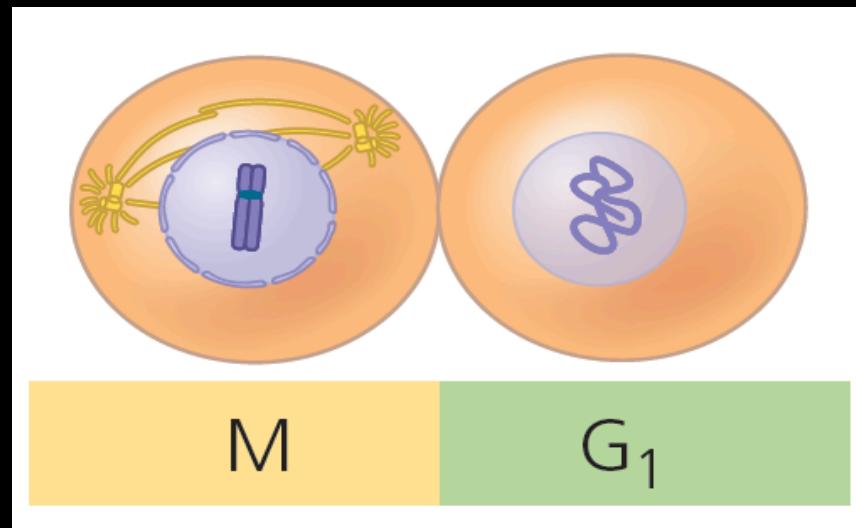


Figure 12.14

Fusion of G₁ cell with S or M phase cell suggest that molecules present in cytoplasm during S/M phase control progression to those phases

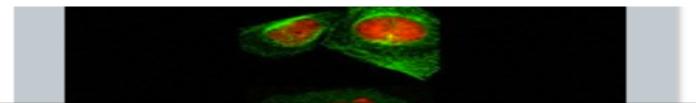
Food for thought: How do Healthy Cells become Cancerous?

Why is cell growth a problem in cancer?

A cell is continuously receiving messages, both from its own genes and from other cells. Some tell it to grow and multiply,

others tell it to rest, or even to stop growing. In a cancer cell, the messages to grow may be stronger than those to die. This means that the cell begins to grow uncontrollably often.

[Back to top](#)



How long do cancer cells live for?

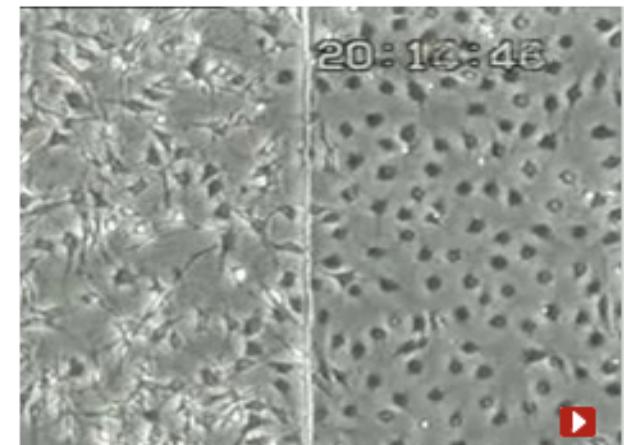
Every time a normal cell divides, the ends of its chromosomes become shorter. Once they have worn down, the cell dies and is replaced. Cancer cells cheat this system - they retain their long chromosomes by continually adding bits back on. This process allows cancer cells to live forever. Cells from Henrietta Lacks, an American woman who was diagnosed with cervical cancer in 1951, are still growing. They are used in research laboratories all over the world, many years following her death.

[Back to top](#)



Why are cancer cells so powerful?

All the cells in your body usually work together as a community. But if a cell acquires a gene mutation that makes it multiply when it should not, or helps it survive when other cells die, it has an advantage over the others. Eventually, the abnormal cells acquire mutations in more genes, causing uncontrolled growth. These abnormal cells have a competitive advantage over normal cells. This is like natural selection in evolution, where a species that produces more offspring has a better chance of survival.

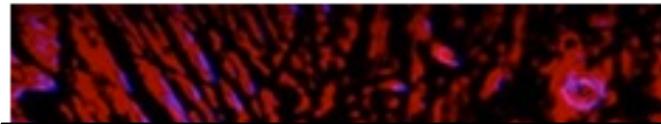


The growth of cancer cells (left) compared to normal cells (right).

Food for thought: How do Healthy Cells become Cancerous?

Why don't cancer cells die normally?

In normal cells, gene damage is usually quickly repaired. If the damage is too severe, the cell is forced to die. An important protein called p53 checks for gene damage in normal cells, and kills them if the damage is too great to repair. However, in cancer cells these checking mechanisms are defective. Cancer cells often have an altered p53 protein, which does not work properly, allowing cancer cells to survive, despite their dangerously garbled genetic material.



Missing checkpoints?

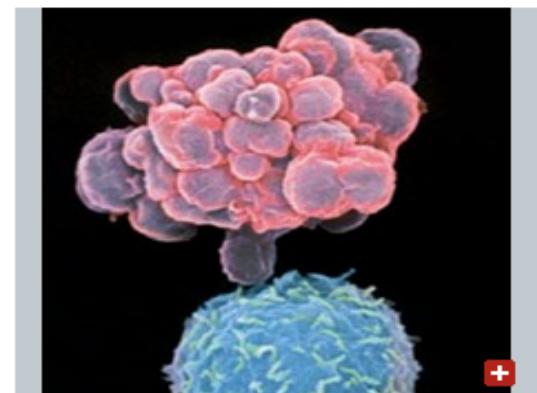
Every time a healthy human cell divides, it copies all its genes, which are bundled up into 46 chromosomes. This process has several checkpoints to ensure that each new cell gets a near-perfect copy. But in a cancer cell, these checkpoints are often missing. The result is chaos: parts of chromosomes may be lost, rearranged or copied many times and the genes are more likely to acquire further mutations. Some of these may allow the cell to escape other checking and repair mechanisms.



How do cancer cells escape destruction?

When you are healthy, every part of your body has just the right number of cells: the birth and death of each one is carefully controlled. Any cells that start to multiply too much or in the wrong place are either stopped from growing, or forced into suicide by the process of apoptosis. In cancer cells, these instructions are either missing, altered or ignored. So cancer cells escape destruction, and continue to multiply in an uncontrolled way.

[Back to top](#)

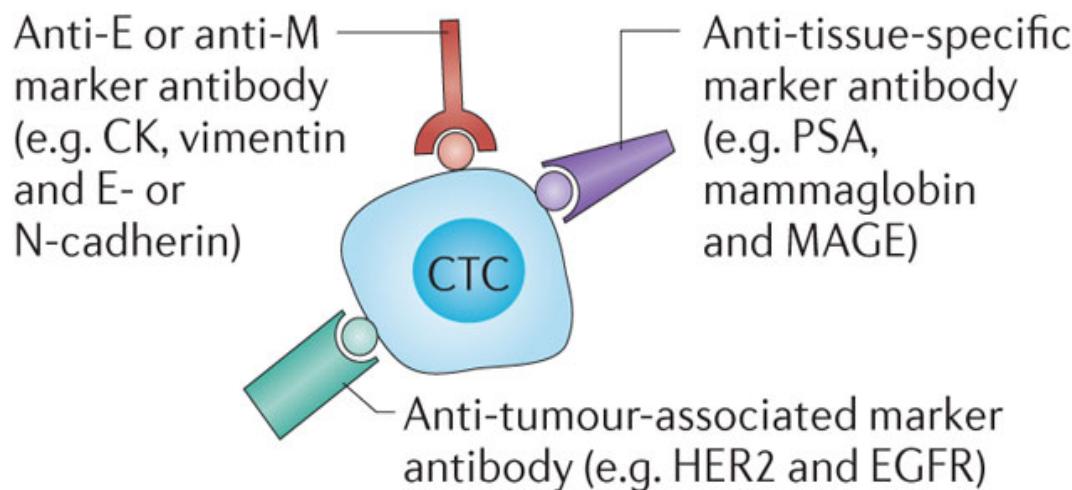


Cell death is controlled in the process of apoptosis.

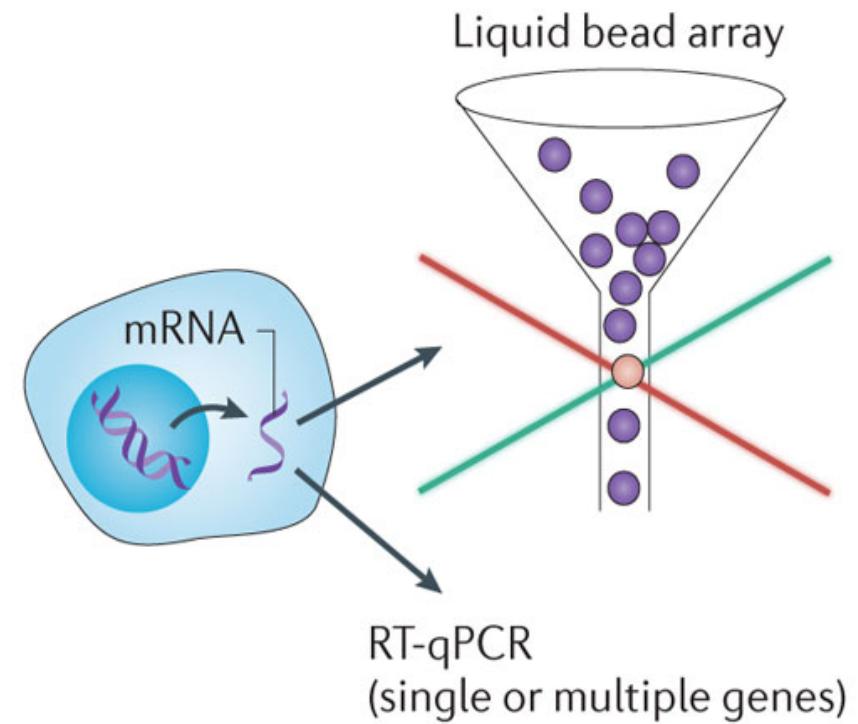
Food for thought: Circulating Tumour Cell (CTC) Detection Technologies

US Food and Drug Administration (FDA)-cleared technology that allows a sensitive positive capture of CTCs by antibodies against epithelial cell adhesion molecule (EPCAM) coated with ferrofluids

a Immunocytological technologies



b Molecular (RNA-based) technologies



Technologies

- Immunocytochemistry
- CellSearch® system
- Flow cytometry
- DEPArray®

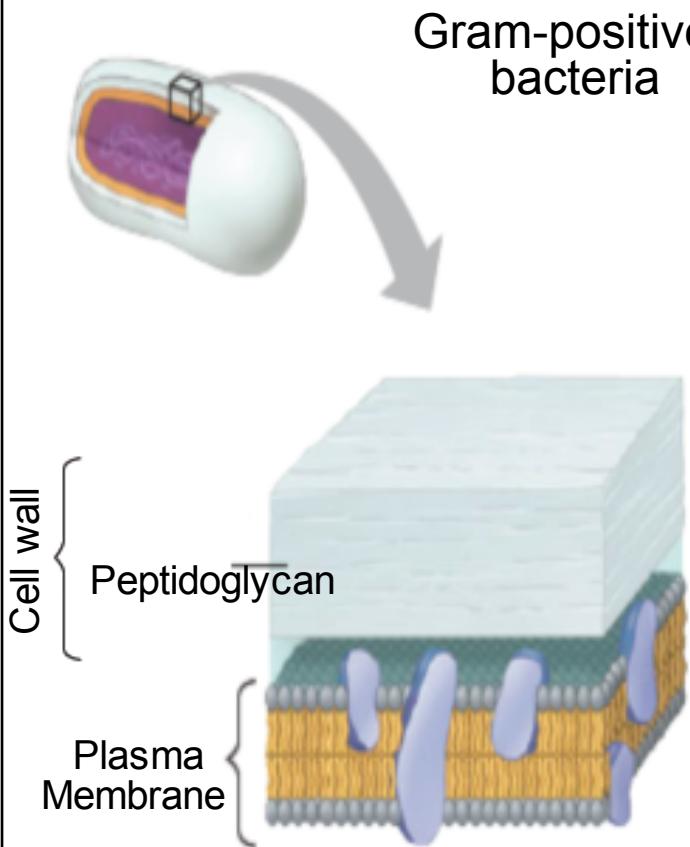
Experiment: Gram Staining

Experimental Demonstration

Cells Under Microscope

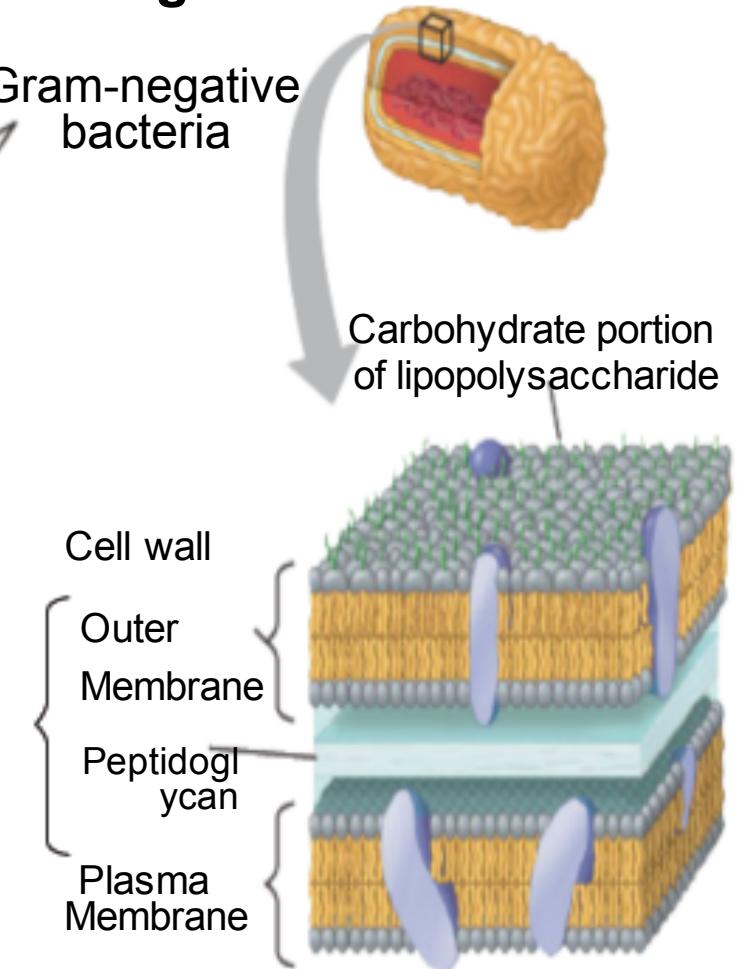
Structure of Bacterium Cell Wall & Staining

Gram-positive bacteria



Thick cell wall made of peptidoglycan;
it traps crystal violet; alcohol rinse does
not remove the crystal violet

Gram-negative bacteria



Thin layer of peptidoglycan;
Crystal violet easily rinsed from cytoplasm.
Cell appears pink or red

Figure 27.3

Experimental Demo

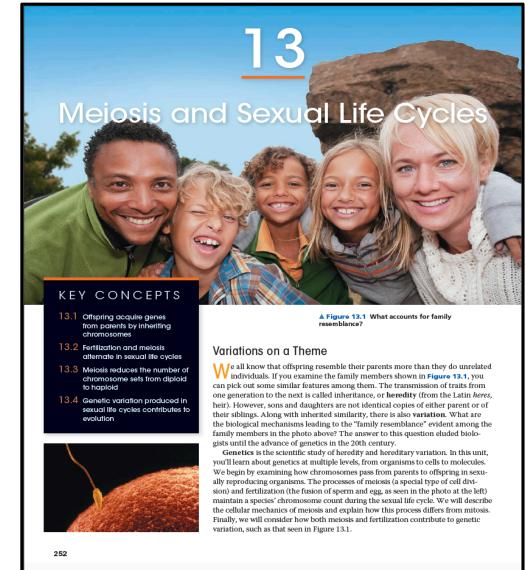
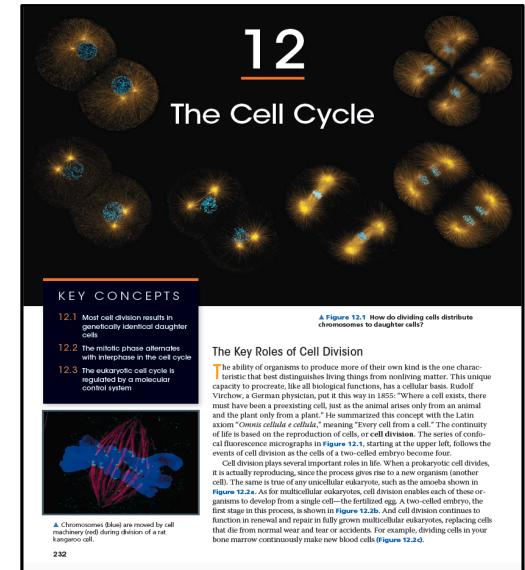


Summary

- Origin of cell and evolutionary context
- Cell complexity, a living unit which is greater than the sum of its parts
- Cell division results in genetically identical daughter cells
- In cell cycle mitotic phase alternates with interphase
- Meiosis reduces the number of chromosome sets from diploid to haploid
- Cancer cells disrupt normal cell cycle regulation and divide out of control, forming tumors

References

- Campbell Biology - Reece, Urry, Cain, Wasserman, Minorsky, Jackson 10th Edition, Pearson
- Video contents (modified)
 - Cell basics, Cell division overview, Gram staining



Next Lecture.. Development