Module 1

The Facts of Life

Learning biology by numbers: Size and Geometry of cells, viruses and molecules; measurements in biology;

Cellular building blocks: four classes of macromolecules, nucleic acids and proteins are polymer languages with different alphabets.

The smallest functional unit of life is cell, discovered by Robert Hooke in 1665.

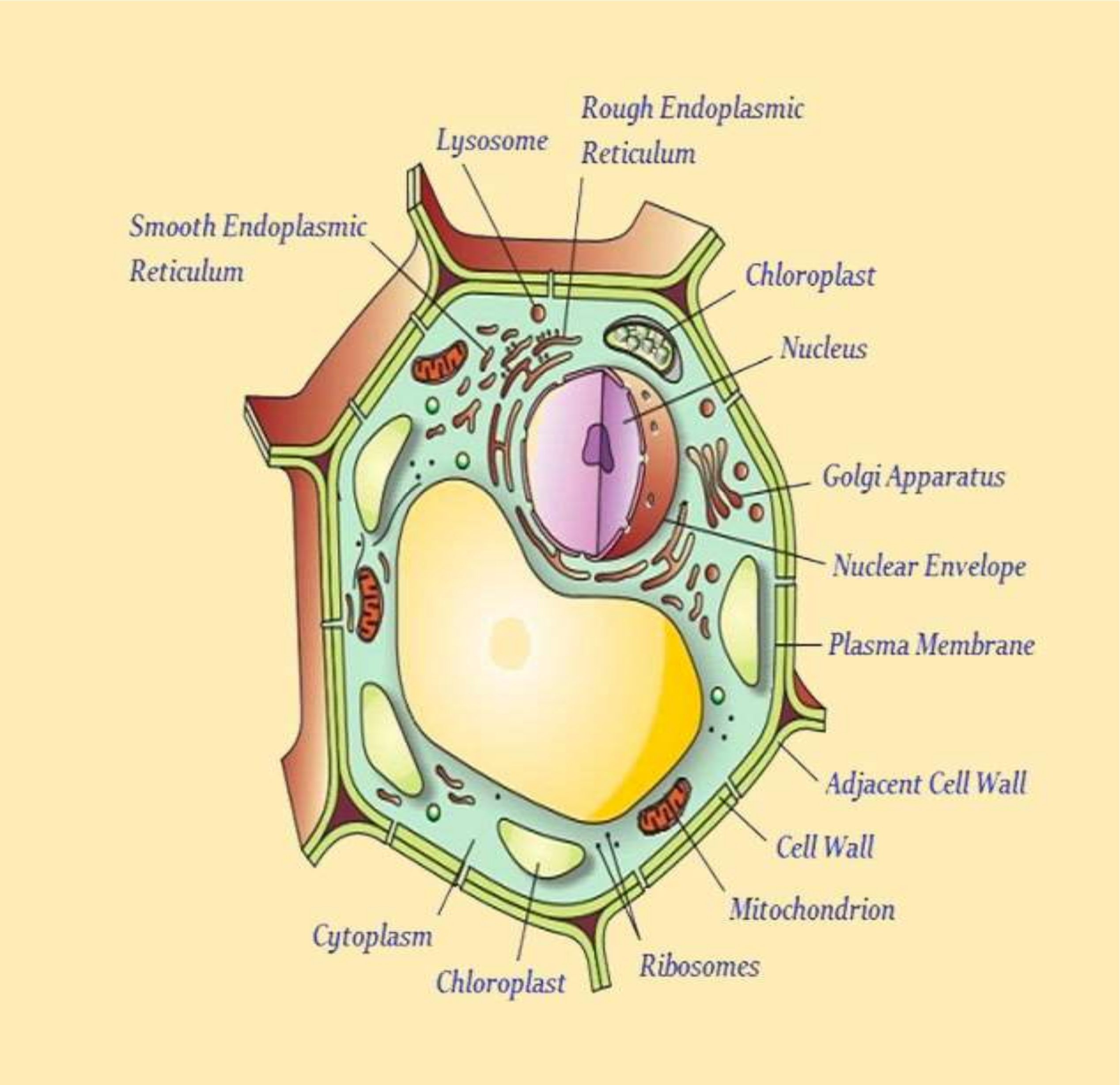
A cell can independently perform all necessary activities to sustain life. Hence cell is the basic unit of life.

There are two types of cells → plant cell and animal cell.

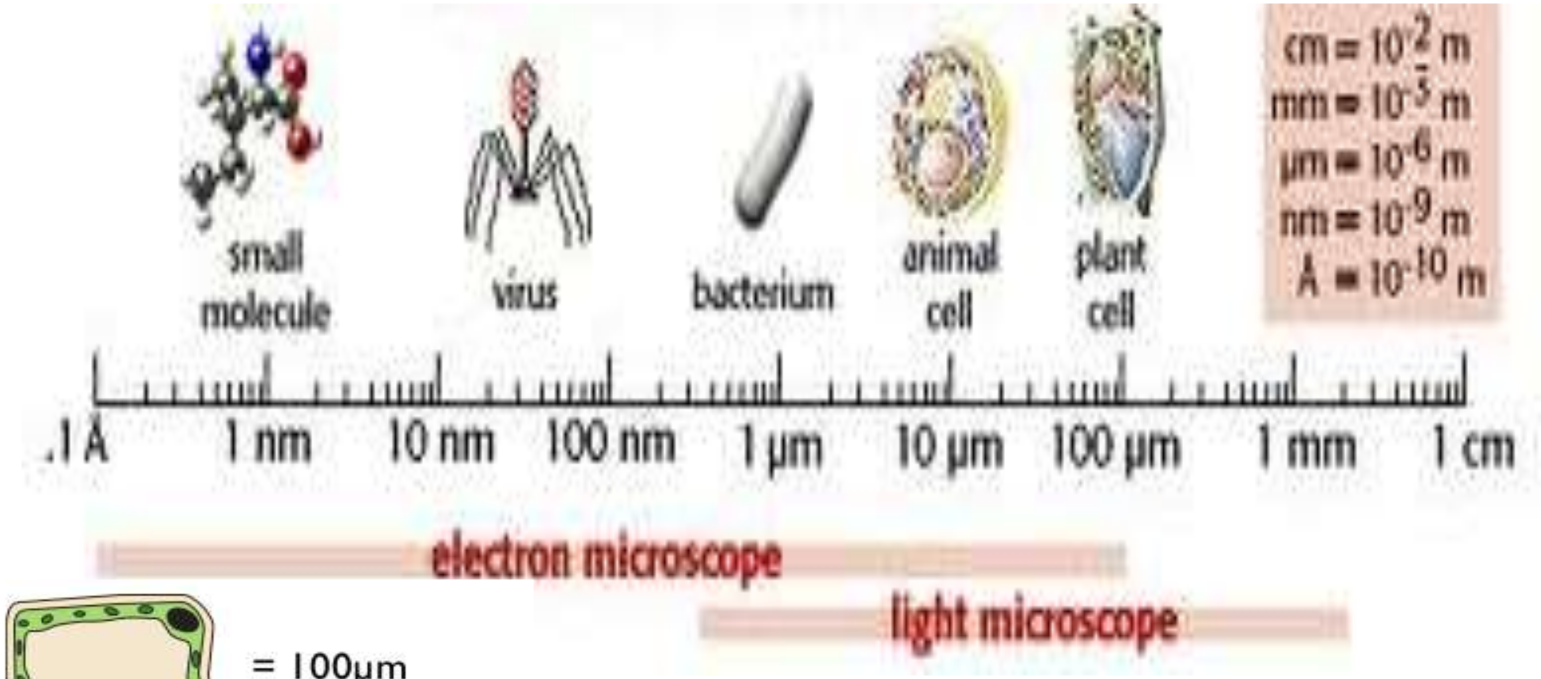
Cells have different organelles, each one with a distinct function.

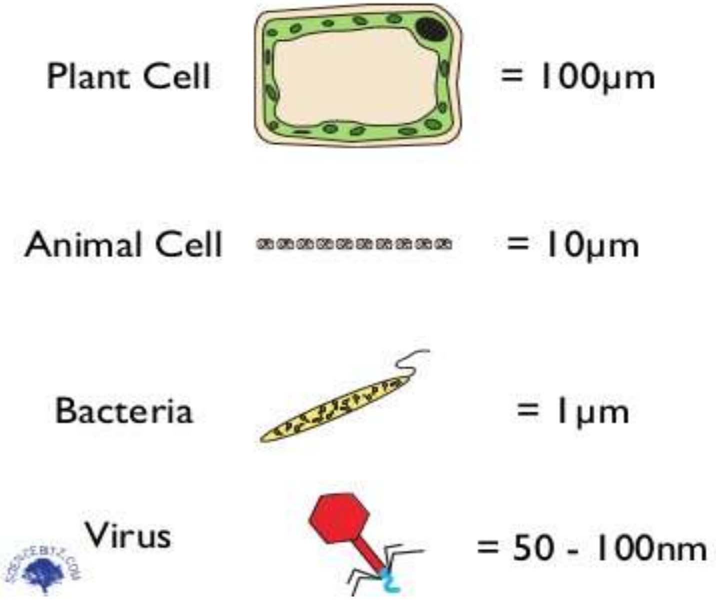
Size of cells vary greatly

Generally small and seen only with microscope

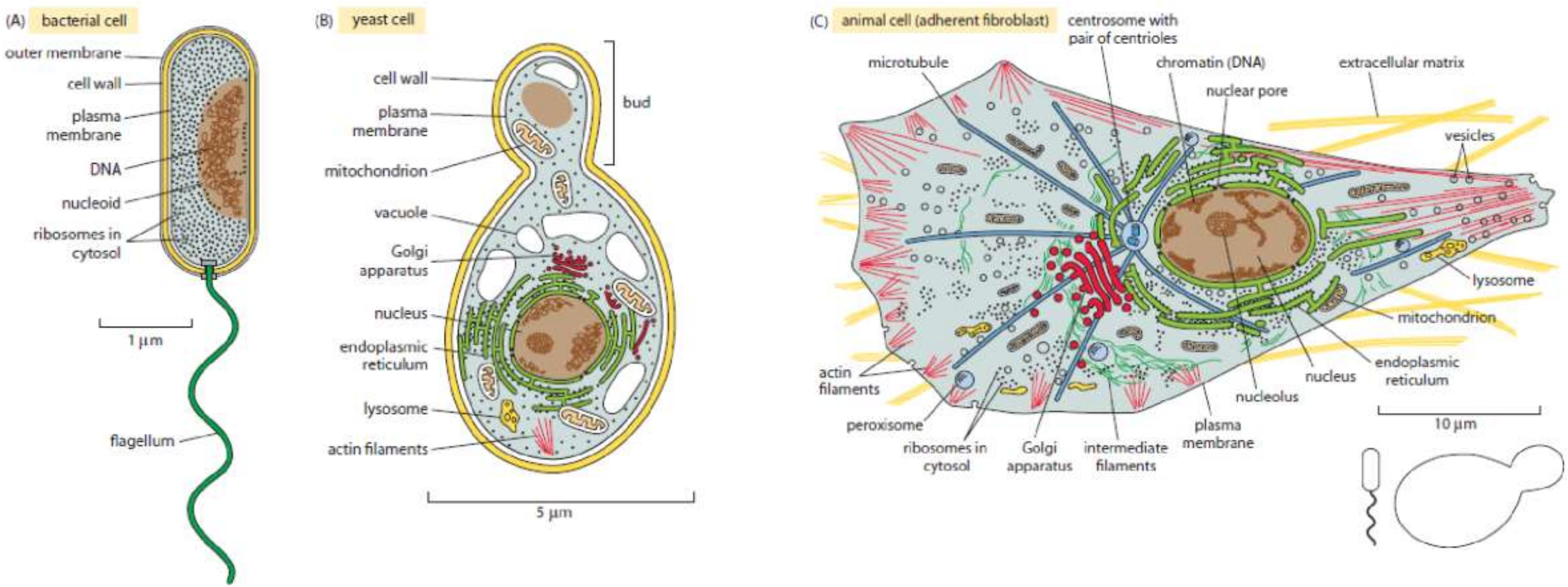


Relative sizes of the cells





Size and Geometry of cells

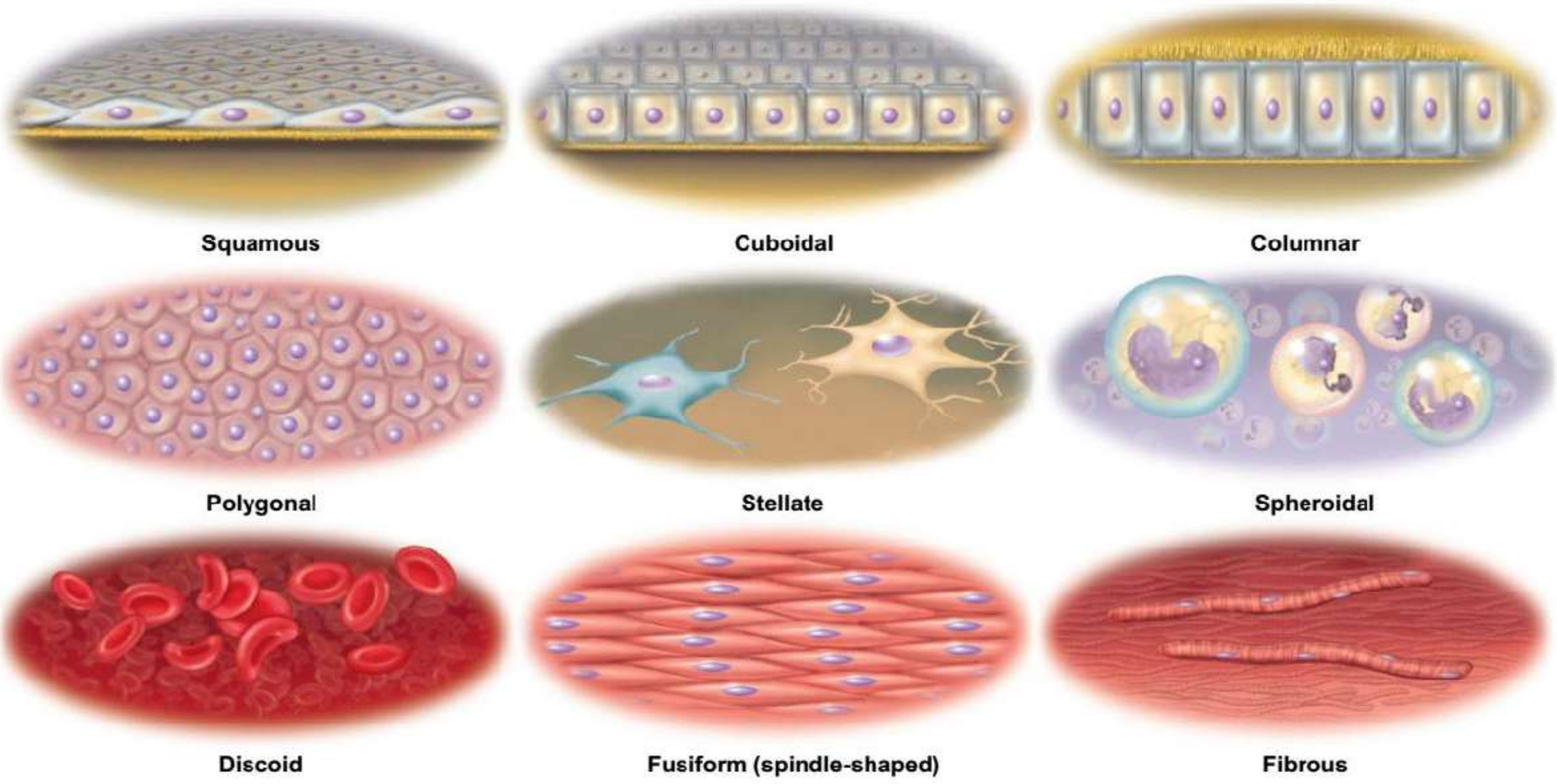


The standard cells. (A) A schematic bacterium revealing the characteristic size and components of *E. coli*. (B) A budding yeast cell showing its characteristic size, its organelles, and various classes of molecules present within it. (C) An adherent human cell. (adapted from Alberts B, Johnson A, Lewis J et al. [2015] Molecular Biology of the Cell, 6th ed. Garland Science.)

Both plant and animal cells show diverse shapes such as –

Cell	Shape	Function
Human Red Blood Carpuscles	circular and biconcave	to pass through narrow capillaries and transport oxygen.
White Blood Carpuscles	amoeboid with pseudopodia so that it can change shape.	to engulf the foreign microorganisms that enter in the body.
Nerve cells	long and elongated	to conduct impulse from distant parts of the body to the brain and vice-versa.
Muscle cells	long, spindle shape, contractile	to pull or squeeze the parts.
Guard cells (Stomata)	bean shaped	to open or close the pores.

Cell Shapes and Sizes



Cell Theory

Cells were discovered in 1665 by Robert Hooke.

Early studies of cells were conducted by

- Mathias Schleiden (1838)
- Theodor Schwann (1839)

Schleiden and Schwann proposed the Cell Theory.

Cell Theory

Cell Theory

1. All organisms are composed of cells.
2. Cells are the smallest living things.
3. Cells arise only from pre-existing cells.

All cells today represent a continuous line of descent from the first living cells.

Cell Theory

Microscopes are required to visualize cells.

Cell size is limited.

-As cell size increases, it takes longer for material to diffuse from the cell membrane to the interior of the cell.

Light microscopes can resolve structures that are 200nm apart.

Electron microscopes can resolve structures that are 0.2nm apart.

Cell Theory

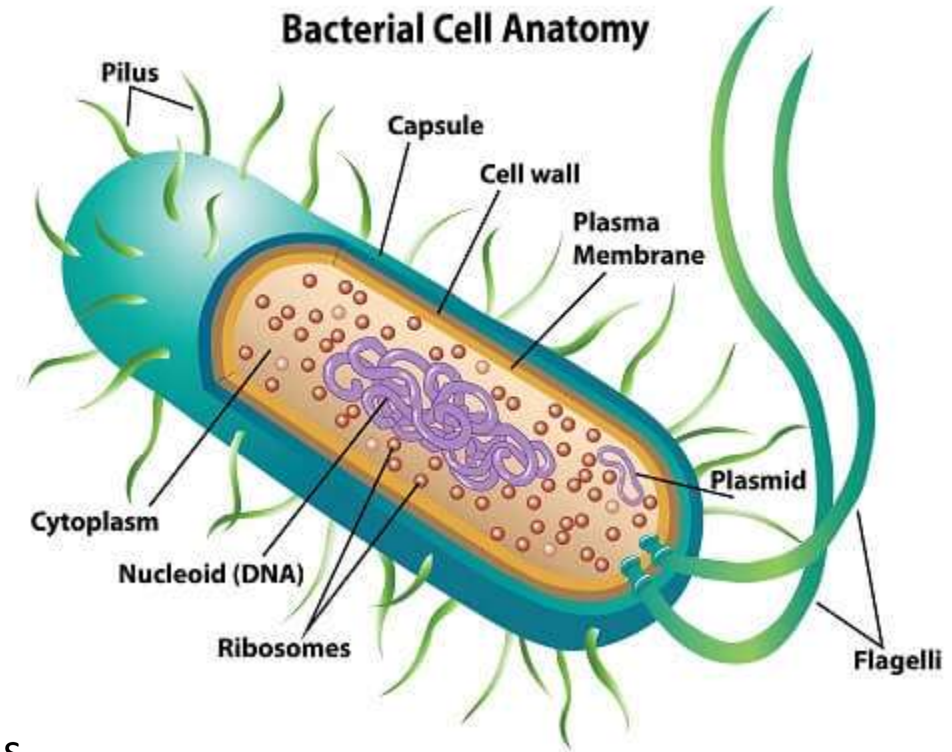
All cells have certain structures in common.

1. genetic material – in a nucleoid or nucleus
2. cytoplasm – a semifluid matrix
3. plasma membrane – a phospholipid bilayer

Why are cells so small?

- Cells need to produce chemical energy (via metabolism) to survive and this requires the exchange of materials with the environment
- The *rate of metabolism* of a cell is a function of its mass / volume (larger cells need more energy to sustain essential functions)
- The *rate of material exchange* is a function of its surface area (large membrane surface equates to more material movement)
- As a cell grows, volume (units^3) increases faster than surface area (units^2), leading to a decreased SA:Vol ratio
- If metabolic rate exceeds the rate of exchange of vital materials and wastes (low SA:Vol ratio), the cell will eventually die
- Hence growing cells tend to divide and remain small in order to maintain a high SA:Vol ratio suitable for survival
-

Prokaryotic Cells



Prokaryotic cells lack a membrane-bound nucleus.

-genetic material is present in the **nucleoid**

Two types of prokaryotes:

-archaea

-bacteria

Prokaryotic Cells

Prokaryotic cells possess

-genetic material in the nucleoid

-cytoplasm

-plasma membrane

-cell wall

-ribosomes

-no membrane-bound organelles

Flagella

-present in some prokaryotic cells

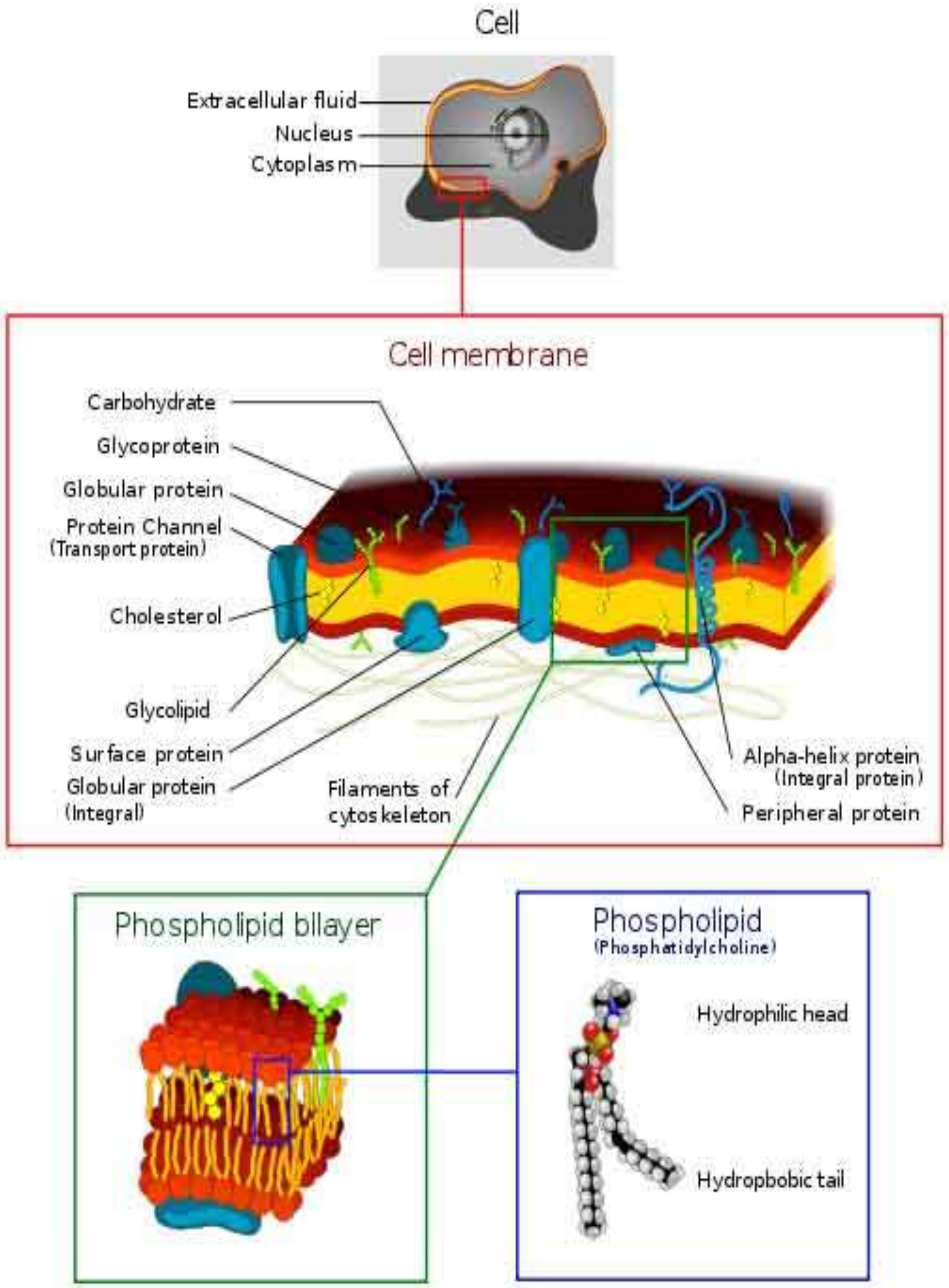
-used for locomotion

-rotary motion propels the cell

Prokaryotes

Plasma Membrane

- Separates the cell from its environment.
- Phospholipid molecules oriented so that hydrophilic **water-loving** heads directed outward and hydrophobic **water-hating** tails directed inward.
- Proteins embedded in two layers of lipids (lipid bilayer).
- Membrane is **semi-permeable.** **Q: What does that mean?**



Prokaryote Genetics

Nucleoid

- Region of cytoplasm where prokaryote's **genome** (DNA) is located.
- Usually a singular, circular chromosome.

Plasmid

- Small extra piece of chromosome/genetic material.
- 5 - 100 genes
- Not critical to everyday functions.
- Can provide genetic information to promote:

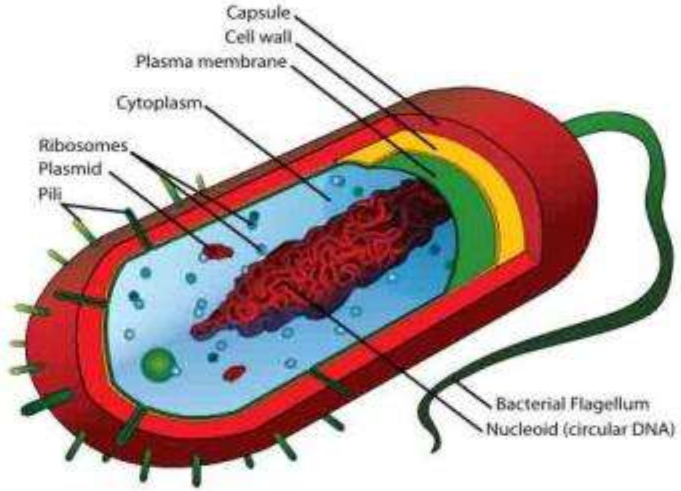
  - Antibiotic resistance

  - Virulence factors

  (molecules produced by pathogen that specifically influence host's function to allow the pathogen to thrive)

  - Promote **conjugation**

  (transfer of genetic material between bacteria through cell-to-cell contact)



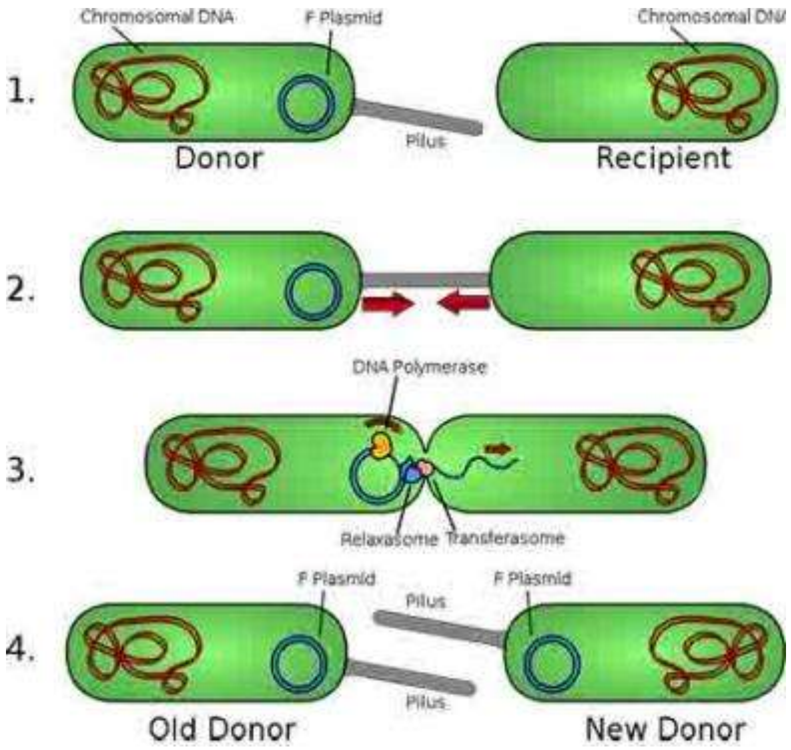
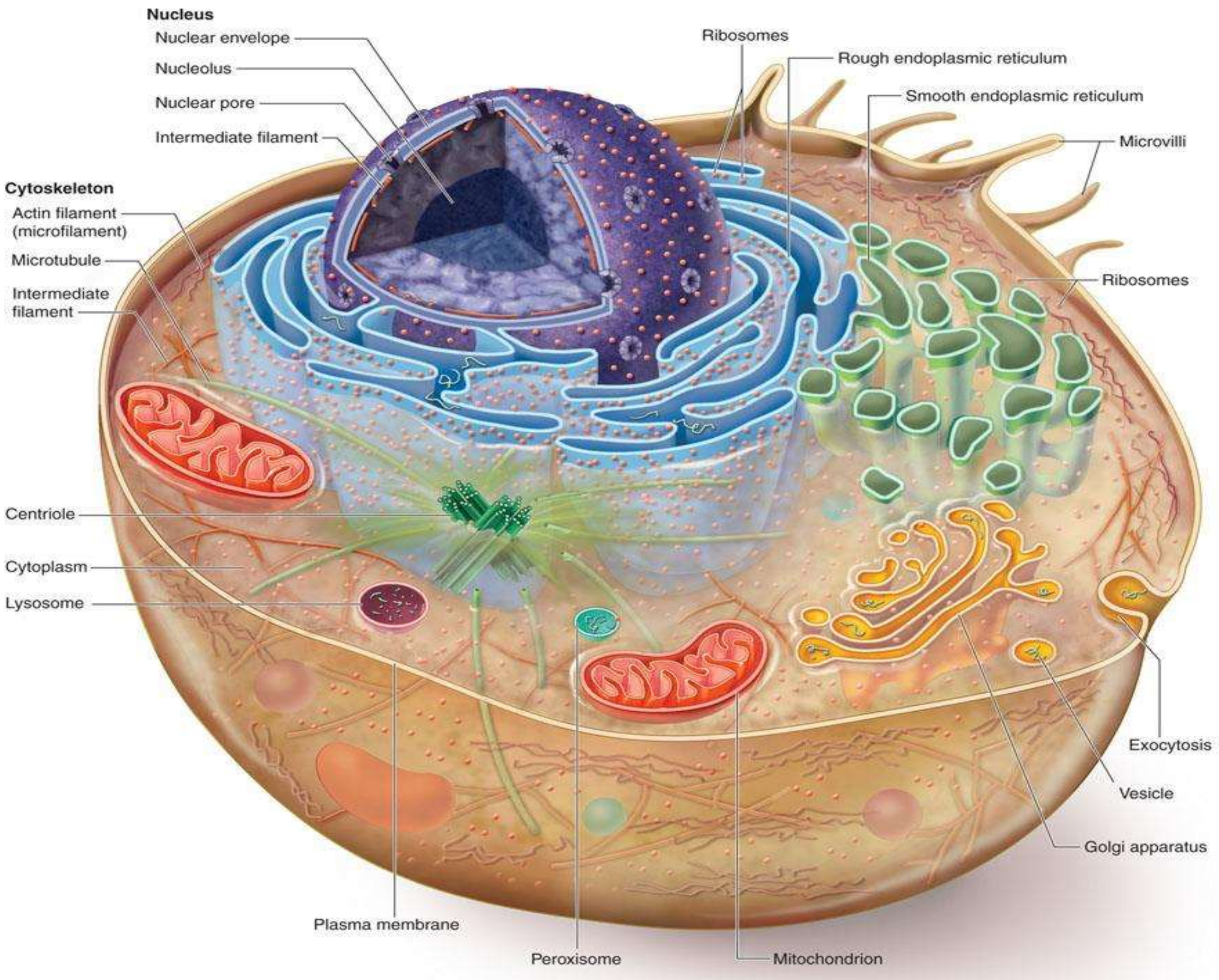


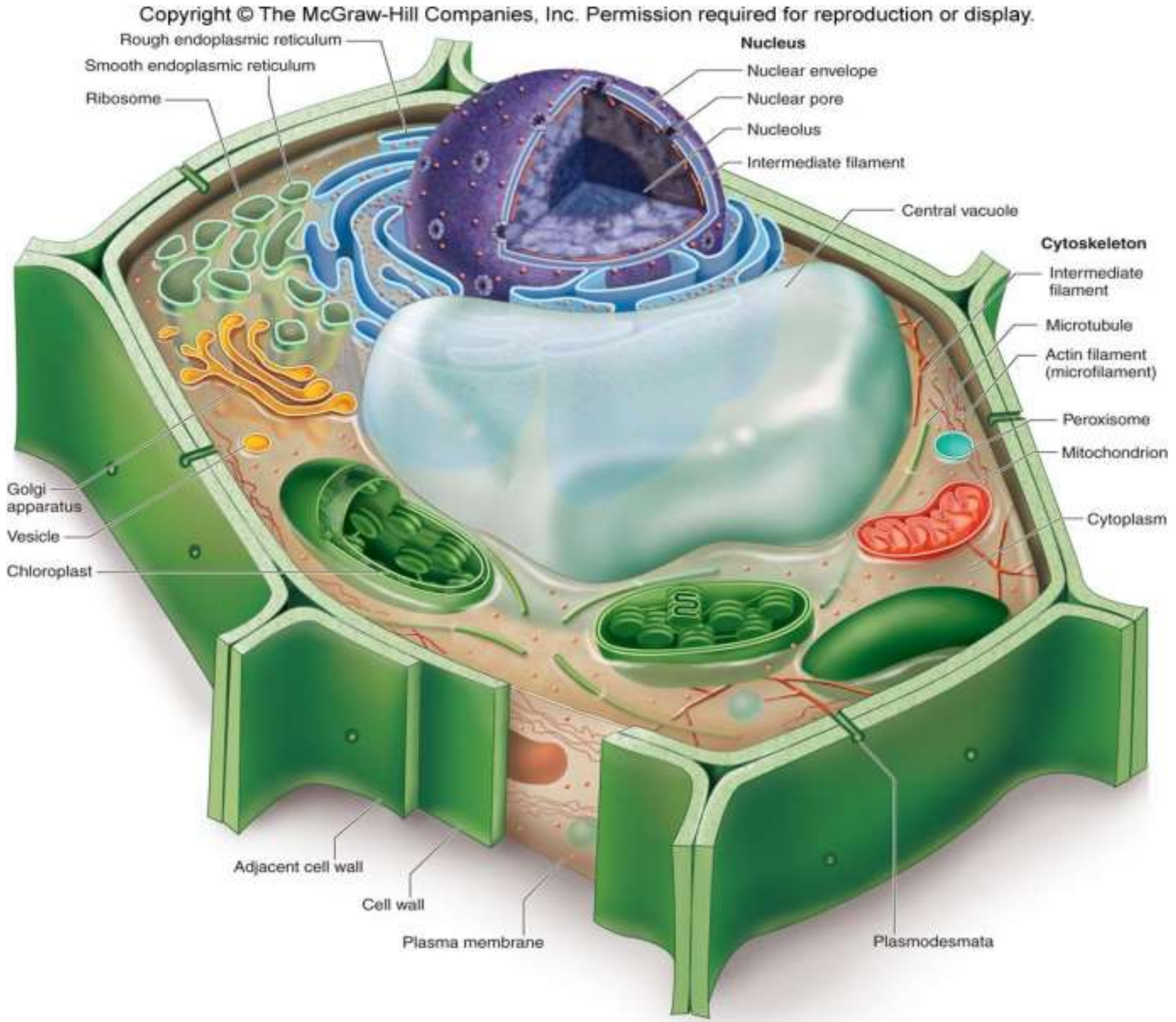
Image: Prokaryotic Cell Diagram: M. Ruiz, Bacterial conjugation, Adenosine

From the Virtual Microbiology Classroom on ScienceProfOnline.com

Eukaryotic Cells



Eukaryotic Cells



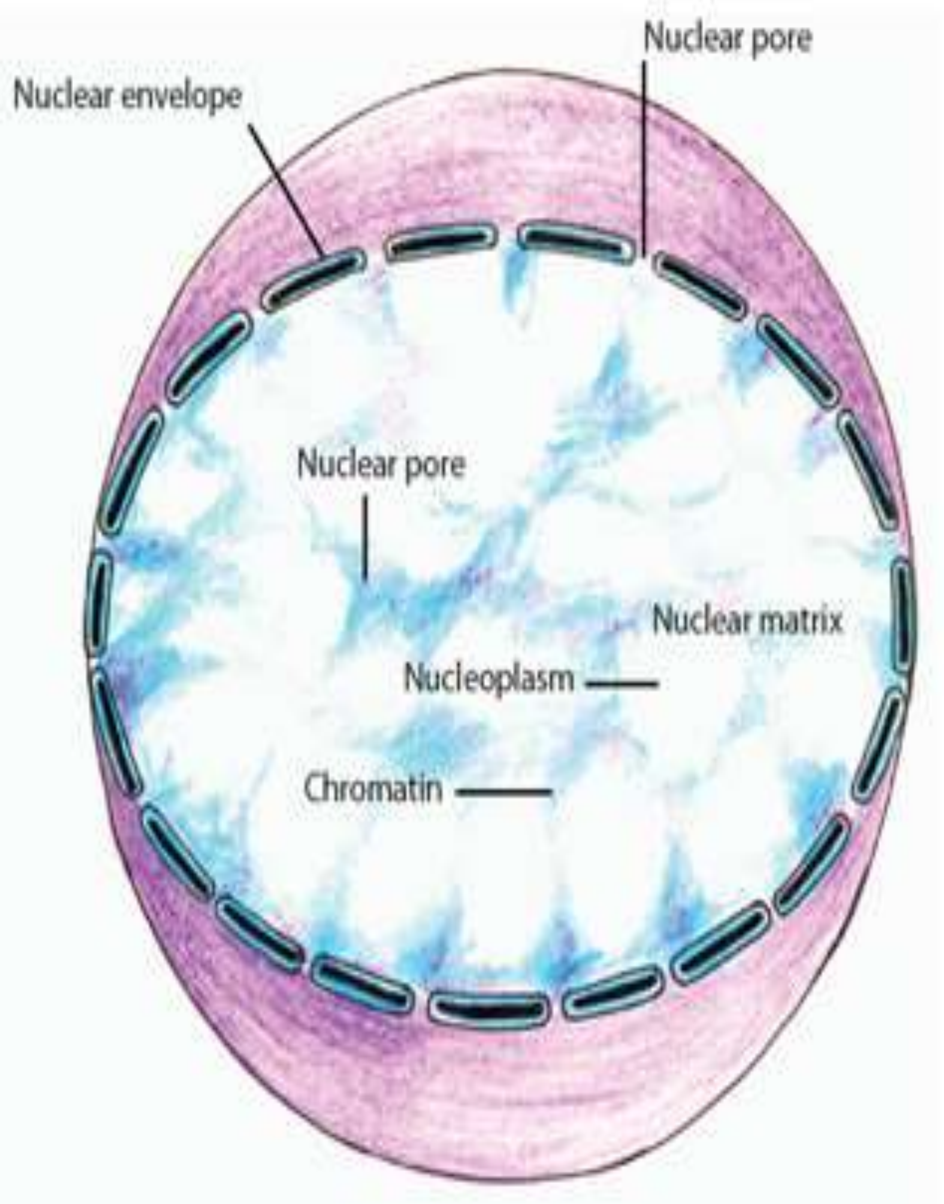
Eukaryotic Cells

Nucleus

-stores the genetic material of the cell in the form of multiple, linear chromosomes

-surrounded by a **nuclear envelope** composed of 2 phospholipid bilayers

-in chromosomes – DNA is organized with proteins to form **chromatin**



Function of nucleus

- Storage of hereditary material, the genes in the form of long and thin DNA (deoxyribonucleic acid) strands, referred to as chromatins.
- Storage of proteins and RNA (ribonucleic acid) in the nucleolus.
- Nucleus is a site for transcription in which messenger RNA (mRNA) are produced for the protein synthesis.
- Exchange of hereditary molecules (DNA and RNA) between the nucleus and rest of the cell.
- During the cell division, chromatins are arranged into chromosomes in the nucleus.
- Production of ribosomes (protein factories) in the nucleolus.
- Selective transportation of regulatory factors and energy molecules through nuclear pores.
- As the nucleus regulates the integrity of genes and gene expression, it is also referred to as the control center of a cell. Overall, the cell nucleus stores all the chromosomal DNA of an organism.

Endomembrane System

Endomembrane system

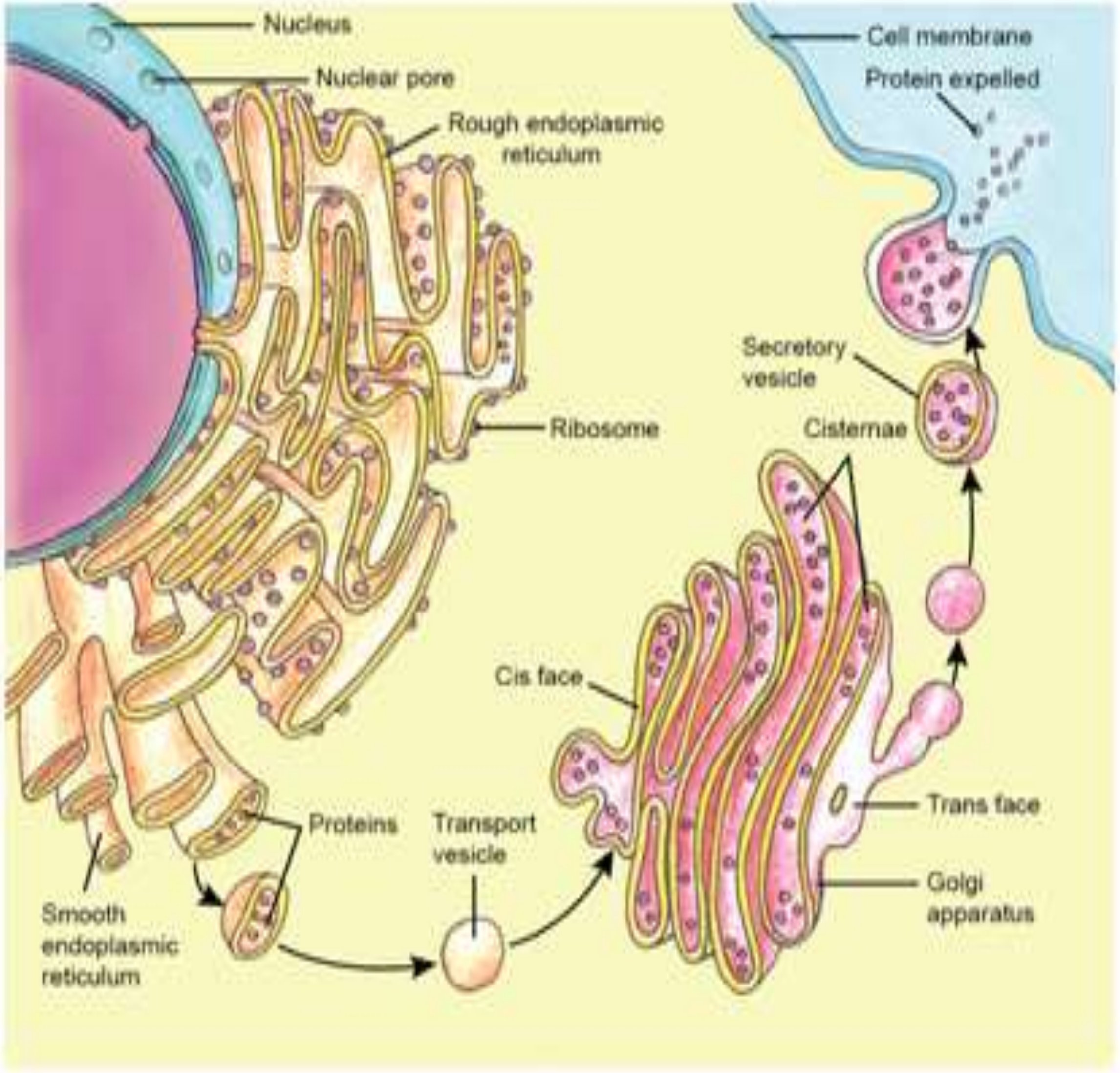
-a series of membranes throughout the cytoplasm

-divides cell into compartments where different cellular functions occur

1. endoplasmic reticulum
2. Golgi apparatus
3. lysosomes

Endoplasmic reticulum

Endoplasmic reticulum is a network of interconnected internal membranes generally, the largest membrane in a eukaryotic cell—an extensive network of closed, flattened membrane-bounded sacs called cisternae (Figure 3). The name "endoplasmic reticulum" was coined in 1953 by Porter, who had observed it in electron micrographs of liver cells. The endoplasmic reticulum has a number of functions in the cell but is particularly important in the synthesis of lipids, membrane proteins, and secreted proteins.



Endomembrane System

Rough endoplasmic reticulum (RER)

-membranes that create a network of channels throughout the cytoplasm

-attachment of ribosomes to the membrane gives a rough appearance

-synthesis of proteins to be secreted, sent to lysosomes or plasma membrane

Endomembrane System

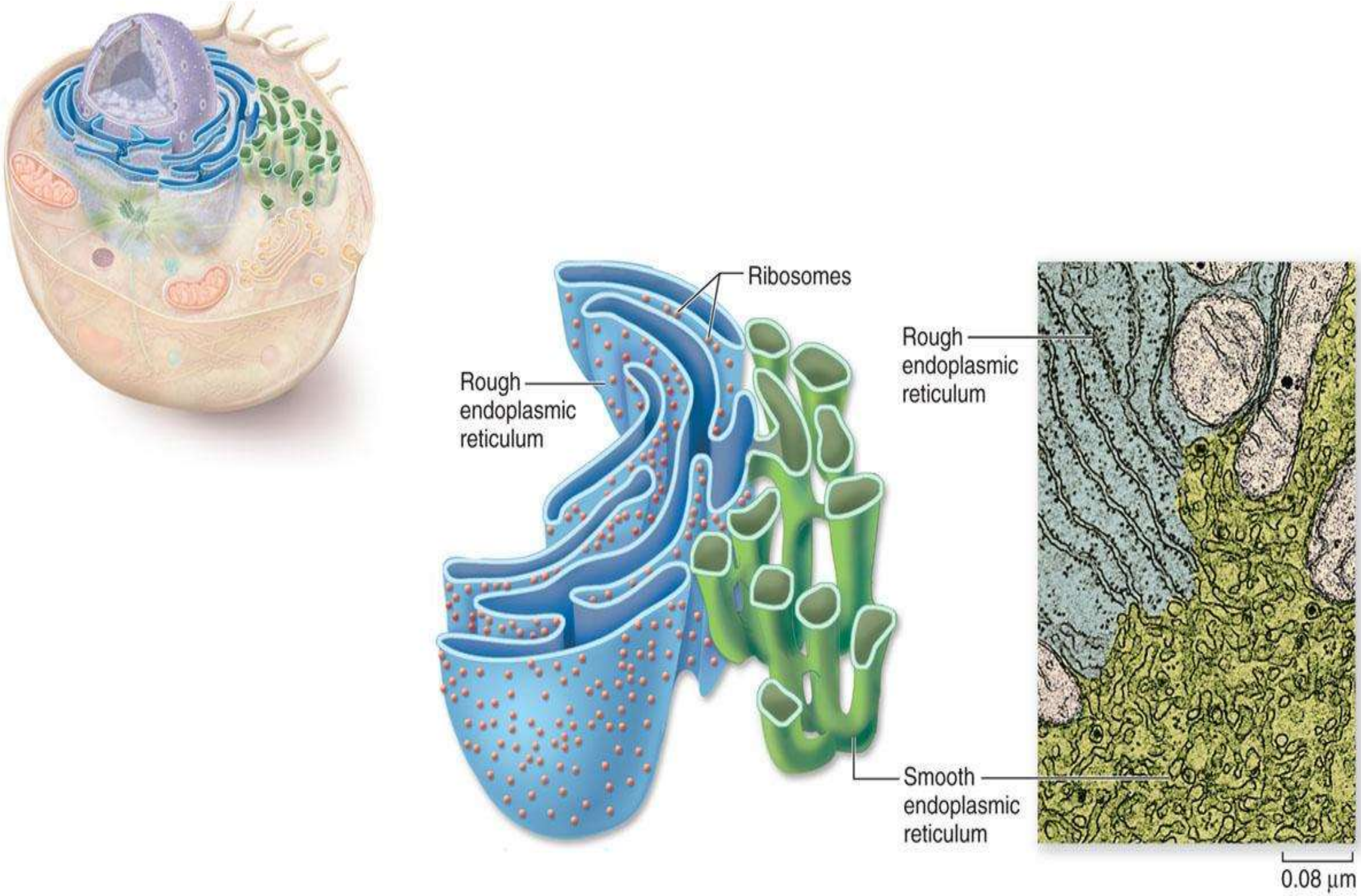
Smooth endoplasmic reticulum (SER)

-relatively few ribosomes attached

-functions:

- -synthesis of membrane lipids
- -calcium storage
- -detoxification of foreign substances

Endomembrane System



(bottom right): © R. Bolender & D. Fawcett/Visuals Unlimited

Common functions of SER and RER:

1. The endoplasmic reticulum provides an ultrastructural skeletal framework to the cell and gives mechanical support to the colloidal cytoplasmic martix.

2. The exchange of molecules by the process of osmosis, diffusion and active transport occurs through the membranes of endoplasmic reticulum. The ER membrane has permeases and carriers.

3. The endoplasmic membranes contain many enzymes which perform various synthetic and metabolic activities and provides increased surface for various enzymatic reactions.

4. The endoplasmic reticulum acts as an intracellular circulatory or transporting system. Various secretory products of granular endoplasmic reticulum are transported to various organelles as follows: Granular ER- agranular ER - Golgi membrane-lysosomes, transport vesicles or secretory granules. Membrane flow may also be an important mechanism for carrying particles, molecules and ions into and out of the cells. Export of RNA and nucleoproteins from nucleus to cytoplasm may also occur by this type of flow.

5. The ER membranes are found to conduct intra-cellular impulses. For example, the sarcoplasmic reticulum transmits impulses from the surface membrane into the deep region of the muscle fibers.

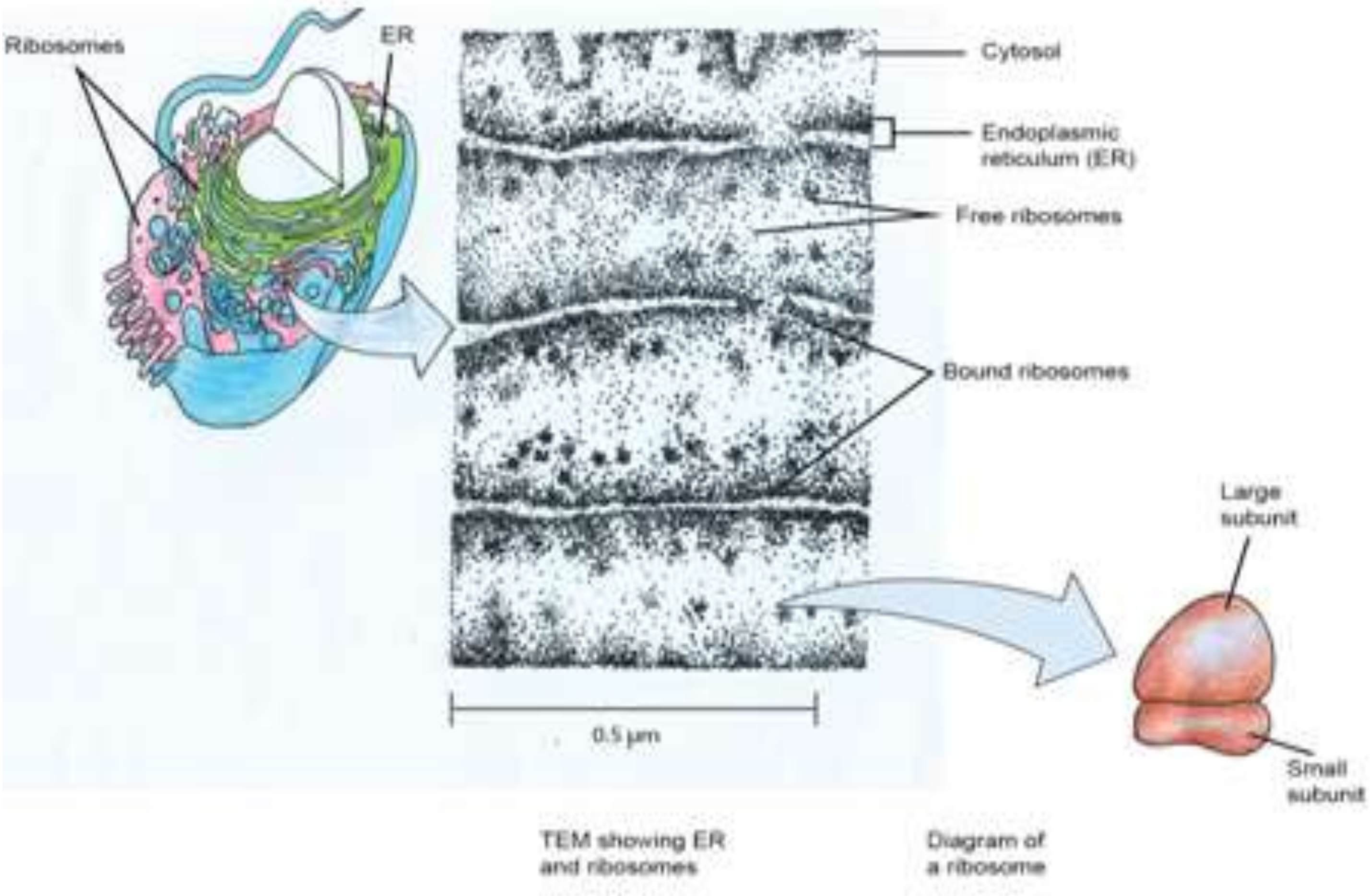
6. The sarcoplasmic reticulum plays a role in releasing calcium when the muscle is stimulated and actively transporting calcium back into the sarcoplasmic reticulum when the stimulation stops and the muscle must be relaxed.

Ribosomes

-the site of protein synthesis in the cell

-composed of **ribosomal RNA** and proteins

-found within the cytosol of the cytoplasm and attached to internal membranes



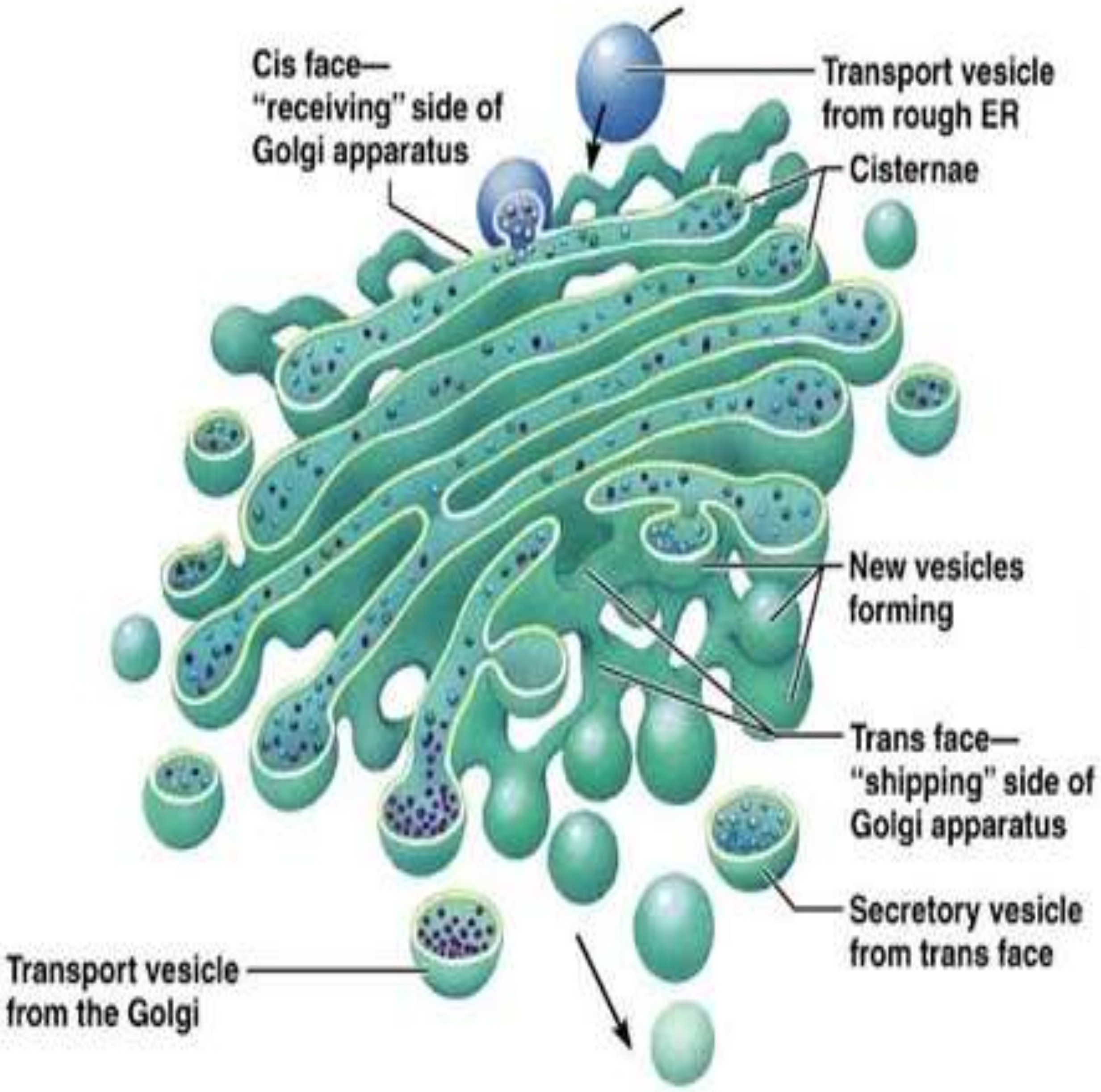
- **Types of ribosomes:**
  Ribosomes are classified into two types based on their sedimentation coefficient, 70S and 80S. S stands for Svedberg unit and related to sedimentation rate (sedimentation depends on mass and size). Thus, the value before S indicates size of ribosome.
- **70S Ribosomes:** Prokaryotes have 70S ribosomes. The 70S ribosomes are comparatively smaller in size and have sedimentation coefficient 70S with molecular weight 2.7×10^6 daltons. They occur in the prokaryotic cells of the blue green algae and bacteria and also in mitochondria and chloroplasts of eukaryotic cells.
- **80S Ribosomes:** Eukaryotes have 80S ribosomes. The 80S ribosomes have sedimentation coefficient of 80S and molecular weight 40×10^6 daltons. The 80S ribosomes occur in eukaryotic cells of the plants and animals. The ribosomes of mitochondria and chloroplasts are always smaller than 80S cytoplasmic ribosomes and are comparable to prokaryotic ribosomes in both size and sensitivity to antibiotics.

Golgi apparatus

-flattened stacks of interconnected membranes

-packaging and distribution of materials to different parts of the cell

-synthesis of cell wall components

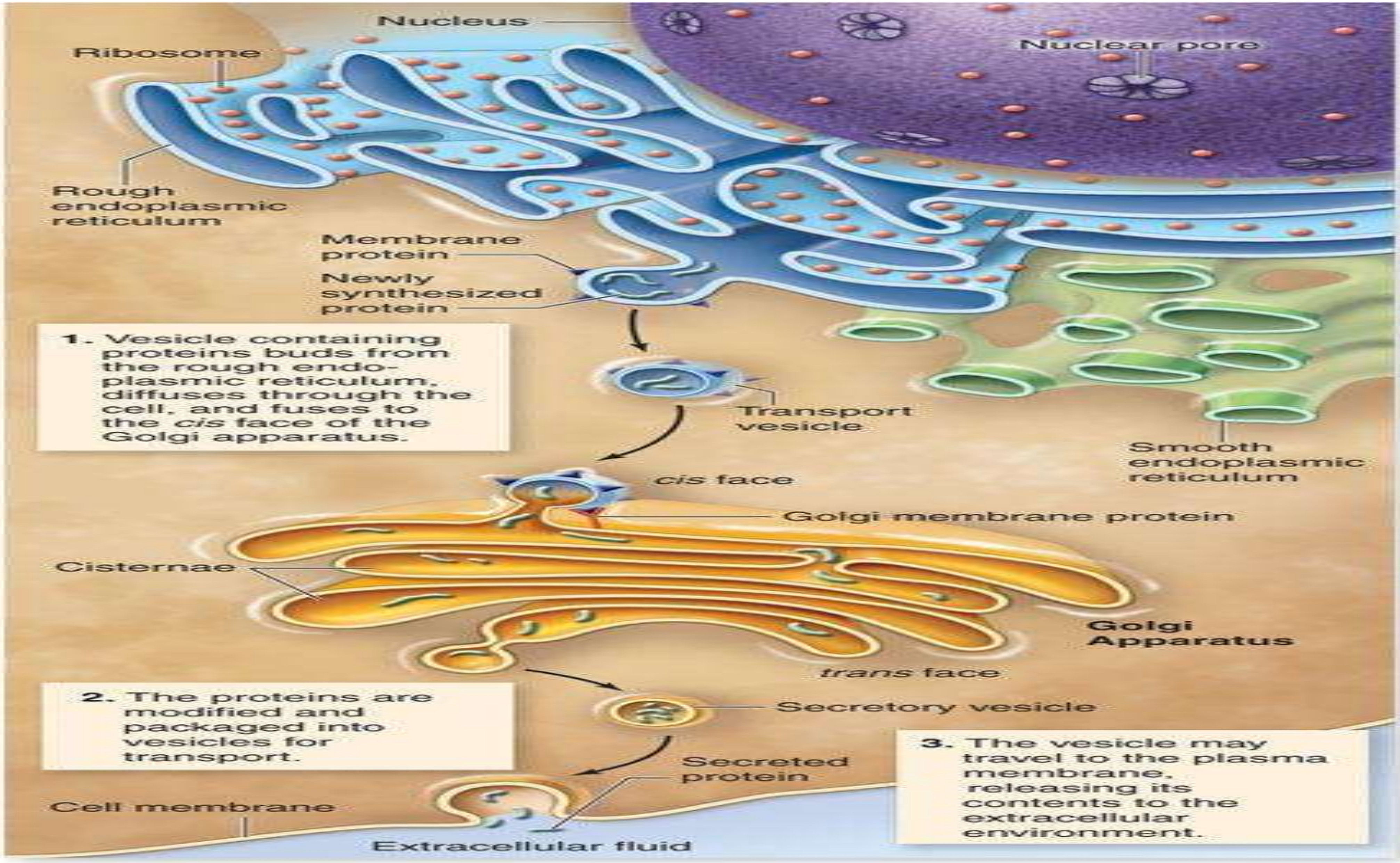


Modifying, sorting, and packaging of macromolecules for cell secretion:

- The golgi complex is involved in the transport of lipids around the cell, and the creation of lysosomes. Proteins are modified by enzymes in cisternae by glycosylation and phosphorylation by identifying the signal sequence of the protein in question. For example, the Golgi apparatus adds a mannose-6-phosphate label to proteins destined for lysosomes. One molecule that is phosphorylated in the Golgi is Apolipoprotein, which forms a molecule known as VLDL that is a constituent of blood serum. The phosphorylation of these molecules is important to help aid in their sorting for secretion into the blood serum.

- **Golgi Functions in Animals:**
  In animals, Golgi apparatus is involved in the packaging and exocytosis of the following: Zymogen of exocrine pancreatic cells; Mucus (a glycoprotein) secretion by goblet cells of intestine; Lactoprotein (casein) secretion by mammary gland cells (Merocrine secretion); Secretion of compounds (thyroglobulins) of thyroxine hormone by thyroid cells; Secretion of tropocollagen and collagen; Formation of melanin granules and other pigments; and Formation of yolk and vitelline membrane of growing primary oocytes. It is also involved in the formation of certain cellular organelles such as plasma membrane, lysosomes, acrosome of spermatozoa and cortical granules of a variety of oocytes.

- **Golgi Functions in Plants:**
  In plants, Golgi apparatus is mainly involved in the secretion of materials of primary and secondary cell walls (formation and export of glycoproteins, lipids, pectins and monomers for hemicellulose, cellulose, lignin). During cytokinesis of mitosis or meiosis, the vesicles originating from the periphery of Golgi apparatus, coalesce in the phragmoplast area to form a semisolid layer, called cell plate. The unit membrane of Golgi vesicles fuses during cell plate formation and becomes part of plasma membrane of daughter


Nucleus
Ribosome
Nuclear pore
Rough endoplasmic reticulum
Membrane protein
Newly synthesized protein
1. Vesicle containing proteins buds from the rough endo-plasmic reticulum, diffuses through the cell, and fuses to the *cis* face of the Golgi apparatus.
Transport vesicle
Smooth endoplasmic reticulum
cis face
Golgi membrane protein
Cisternae
Golgi Apparatus
trans face
2. The proteins are modified and packaged into vesicles for transport.
Secretory vesicle
Secreted protein
3. The vesicle may travel to the plasma membrane, releasing its contents to the extracellular environment.
Cell membrane
Extracellular fluid

Endomembrane System

Lysosomes

The lysosomes are round vacuolar structures bounded by single unit membrane. Their shape and density vary greatly. Lysosomes are 0.2 to 0.5µm in size. Since, size and shape of lysosomes vary from cell to cell and time to time (they are polymorphic), their identification becomes difficult.

The lysosomes occur in most animal and few plant cells. They are absent in bacteria and mature mammalian erythrocytes. Few lysosomes occur in muscle cells or in acinar cells of the pancreas. Leucocytes, especially granulocytes are a particularly rich source of lysosomes.

-membrane bound vesicles containing digestive enzymes to break down macromolecules

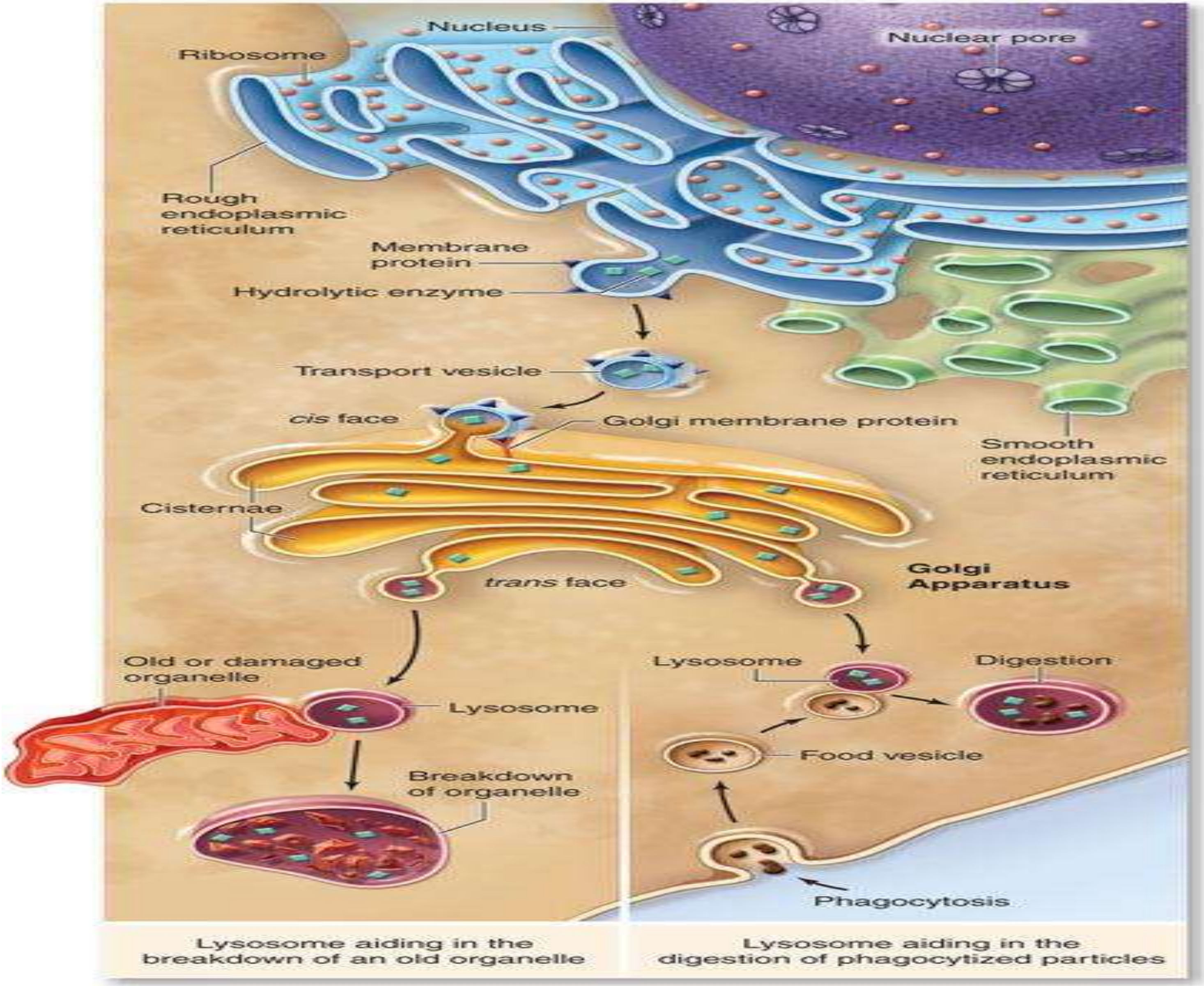
-destroy cells or foreign matter that the cell has engulfed by phagocytosis

1. Lysosomes serve as digestion compartments for cellular materials that have exceeded their lifetime or are otherwise no longer useful by autophagy. When a cell dies, the lysosome membrane ruptures and enzymes are liberated. These enzymes digest the dead cells. In the process of metamorphosis of amphibians and tunicates many embryonic tissues,

   e.g., gills, fins, tail, etc., are digested by the lysosomes and utilized by the other cells.

2. Lysosomes break down cellular waste products, fats, carbohydrates, proteins, and other macromolecules into simple compounds, which are then transferred back into the cytoplasm as new cell-building materials. To accomplish the tasks associated with digestion, the lysosomes utilize about 40 different types of hydrolytic enzymes, all of which are manufactured in the endoplasmic reticulum and modified in the Golgi apparatus.

3. Digestion of large extracellular particles: The lysosomes digest the food contents of the phagosomes or pinosomes. The lysosomes of leucocytes enable the latter to devour the foreign proteins, bacteria and viruses.


Nucleus
Nuclear pore
Ribosome
Rough endoplasmic reticulum
Membrane protein
Hydrolytic enzyme
Transport vesicle
cis face
Golgi membrane protein
Smooth endoplasmic reticulum
Cisternae
trans face
Golgi Apparatus
Old or damaged organelle
Lysosome
Breakdown of organelle
Lysosome
Digestion
Food vesicle
Phagocytosis
Lysosome aiding in the breakdown of an old organelle
Lysosome aiding in the digestion of phagocytized particles

Endomembrane System

Microbodies

-membrane bound vesicles

-contain enzymes

-not part of the endomembrane system

-**glyoxysomes** in plants contain enzymes for converting fats to carbohydrates

-**peroxisomes** contain oxidative enzymes and catalase

Endomembrane System

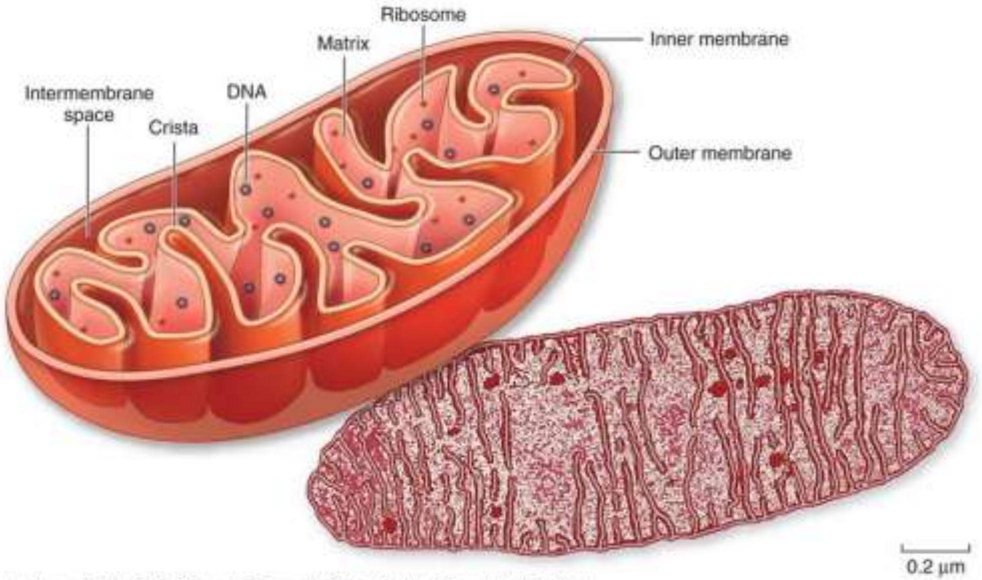
Vacuoles

-membrane-bound structures with various functions depending on the cell type

There are different types of vacuoles:

- **central vacuole** in plant cells
- contractile vacuole of some protists
- vacuoles for storage

Mitochondria



(bottom right): © Dr. Donald Fawcett & Dr. Porter/Visuals Unlimited

Mitochondria

-organelles present in all types of eukaryotic cells

-contain oxidative metabolism enzymes for transferring the energy within macromolecules to ATP

-found in all types of eukaryotic cells

-surrounded by 2 membranes

-smooth outer membrane

-folded inner membrane with layers called **cristae**

-**matrix** is within the inner membrane

-**intermembrane space** is located between the two membranes

-contain their own DNA

Mitochondria are found to contain 65 to 70 per cent proteins, 25 to 30 per cent lipids, 0.5 per cent RNA and small amount of the DNA. The lipid contents of the mitochondria is around 90 per cent phospholipids (lecithin and cephalin), 5 per cent or less cholesterol and 5 per cent free fatty acids and triglycerides. The inner membrane is rich in one type of phospholipid, called cardiolipin which makes this membrane impermeable to a variety of ions and small molecules (Na^+, K^+, Cl^-, NAD^+,AMP, GTP, CoA and so on)

- **Function of mitochondria**
- The most important function of the mitochondria is to produce energy. The food that we eat is broken into simpler molecules like carbohydrates, fats, etc., in our bodies. These are sent to the mitochondrion where they are further processed to produce charged molecules that combine with oxygen and produce ATP molecules. This entire process is known as oxidative phosphorylation.
- It is important to maintain proper concentration of calcium ions within the various compartments of the cell. Mitochondria help the cells to achieve this goal by serving as storage tanks of calcium ions.
- Mitochondria help in the building of certain parts of the blood, and hormones like testosterone and estrogen.
- Mitochondria in the liver cells have enzymes that detoxify ammonia.

Although most of the genetic material of a cell is contained within the nucleus, the mitochondria have their own DNA. They have their own machinery for protein synthesis and reproduce by the process of fission like bacteria do. Due to their independence from the nuclear DNA and similarities with bacteria, it is believed that mitochondria have originated from bacteria by endosymbiosis.

Chloroplasts

Chloroplasts

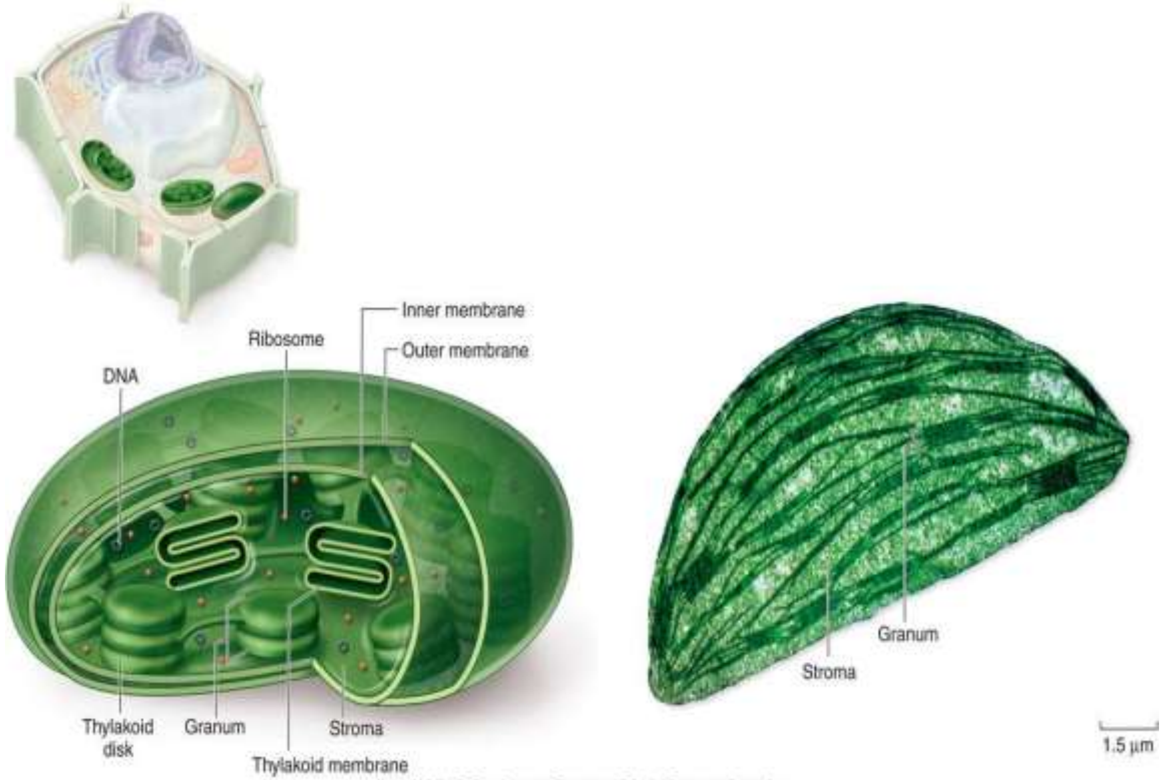
-organelles present in cells of plants and some other eukaryotes

-contain chlorophyll for photosynthesis

-surrounded by 2 membranes

-**thylakoids** are membranous sacs within the inner membrane

-**grana** are stacks of thylakoids



(top right): © Dr. Jeremy Burgess/Photo Researchers Inc.

Chloroplasts

The chloroplast (*chlor*=green; *plast*=living) is most widely occurring chromoplast of the plants. It occurs mostly in the green algae and higher plants. The chloroplast contains the pigment chlorophyll a and chlorophyll b and DNA and RNA.

Chloroplasts:

Chloroplasts were described as early as seventeenth century by Nehemiah Grew and Antonie van Leeuwenhoek.

Distribution:

The chloroplasts remain distributed homogeneously in the cytoplasm of plant cells. But in certain cells, the chloroplasts become concentrated around the nucleus or just beneath the plasma membrane. The chloroplasts have a definite orientation in the cell cytoplasm. Chloroplasts are motile organelles, and show passive and active movements.

- Electron-transfer reactions or the light reactions: In the choloroplast, energy derived from sunlight energizes an electron of chlorophyll, enabling the electron to move along an electron-transport chain in the thylakoid membrane in much the same way that an electron moves along the respiratory chain in mitochondria. The chlorophyll obtains its electrons from water (H_2O), producing O_2 as a by-product. During the electron-transport process, H^+ is pumped across the thylakoid membrane, and the resulting electrochemical proton gradient drives the synthesis of ATP in the stroma. As the final step in this series of reactions, high-energy electrons are loaded onto $NADP^+$, converting it to NADPH. All of these reactions are confined to the chloroplast.

Carbon-fixation reactions or the dark reactions wherein the ATP and the NADPH produced by the photosynthetic electron-transfer reactions serve as the source of energy and reducing power, respectively, to drive the conversion of CO_2 to carbohydrate. The carbon-fixation reactions, which begin in the chloroplast stroma and continue in the cytosol, produce sucrose and many other organic molecules in the leaves of the plant. The sucrose is exported to other tissues as a source of both organic molecules and energy for growth.

Mitochondria & Chloroplasts

Endosymbiosis

-proposal that eukaryotic organelles evolved through a symbiotic relationship

-one cell engulfed a second cell and a symbiotic relationship developed

-mitochondria and chloroplasts are thought to have evolved this way

Mitochondria & Chloroplasts

Much evidence supports this endosymbiosis theory.

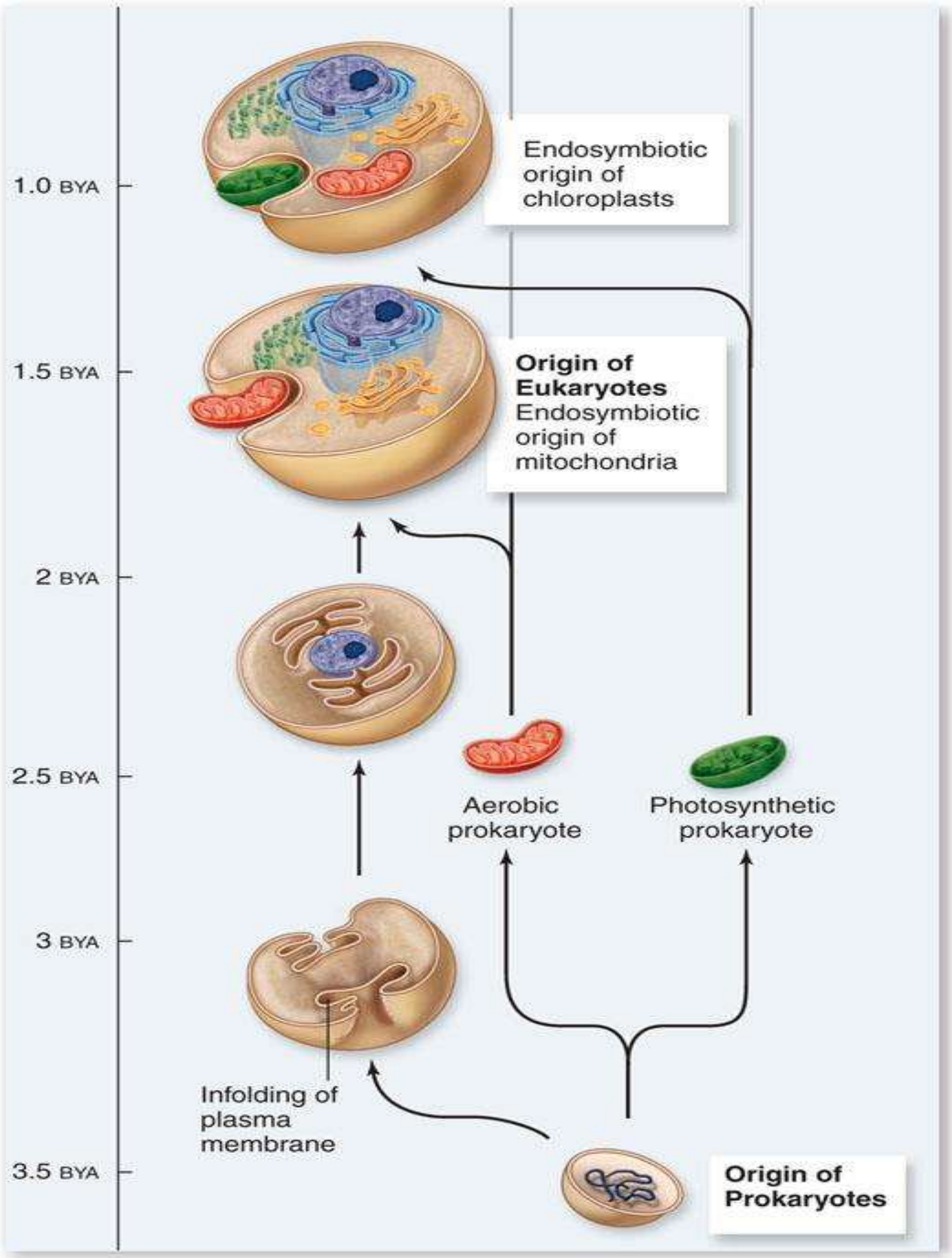
Mitochondria and chloroplasts:

-have 2 membranes

-possess DNA and ribosomes

-are about the size of a prokaryotic cell

-divide by a process similar to bacteria



Cytoskeleton

Cytoskeleton

-network of protein fibers found in all eukaryotic cells

-supports the shape of the cell

-keeps organelles in fixed locations

-helps move materials within the cell

The primary types of fibers comprising the cytoskeleton are:

Microfilaments
Intermediate filaments
Microtubules

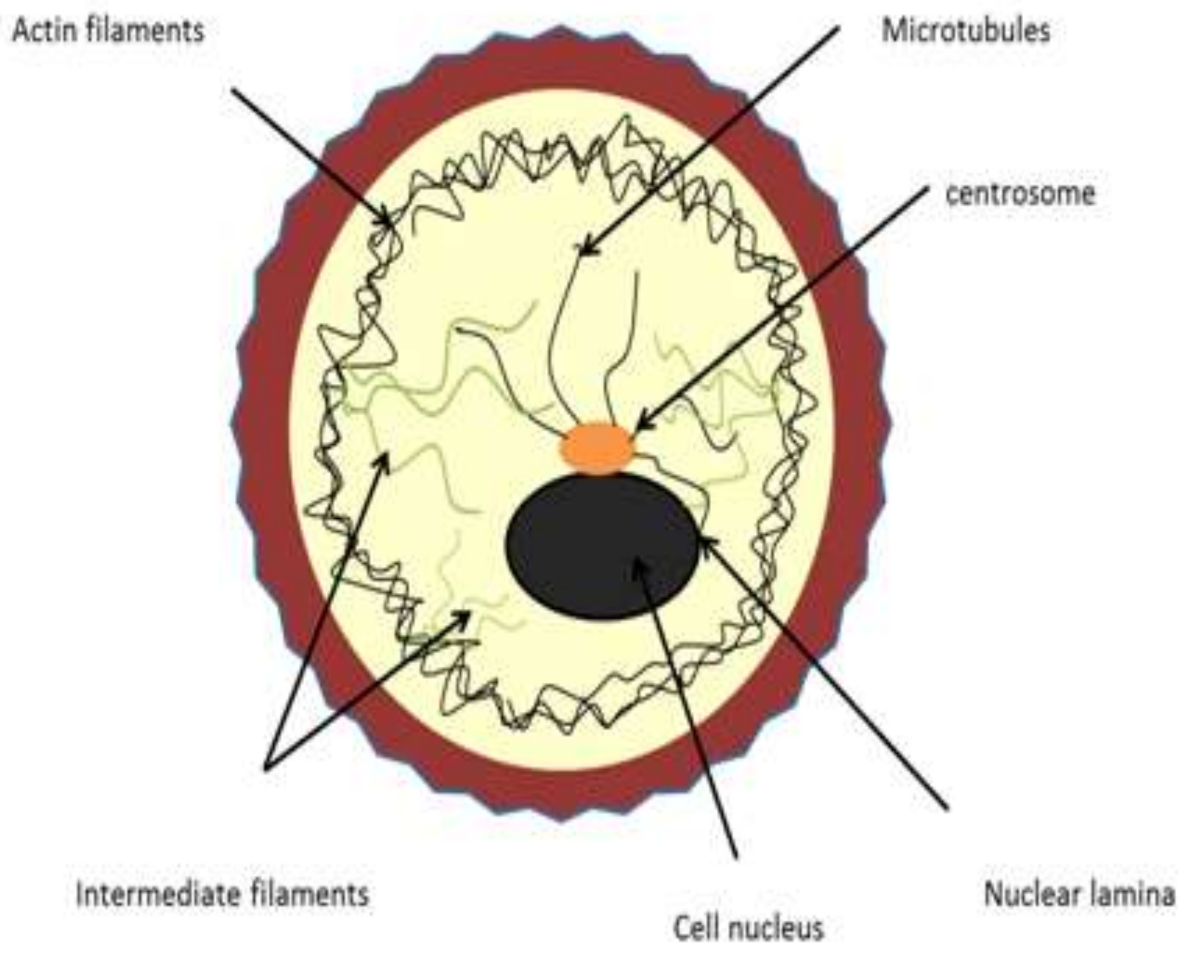
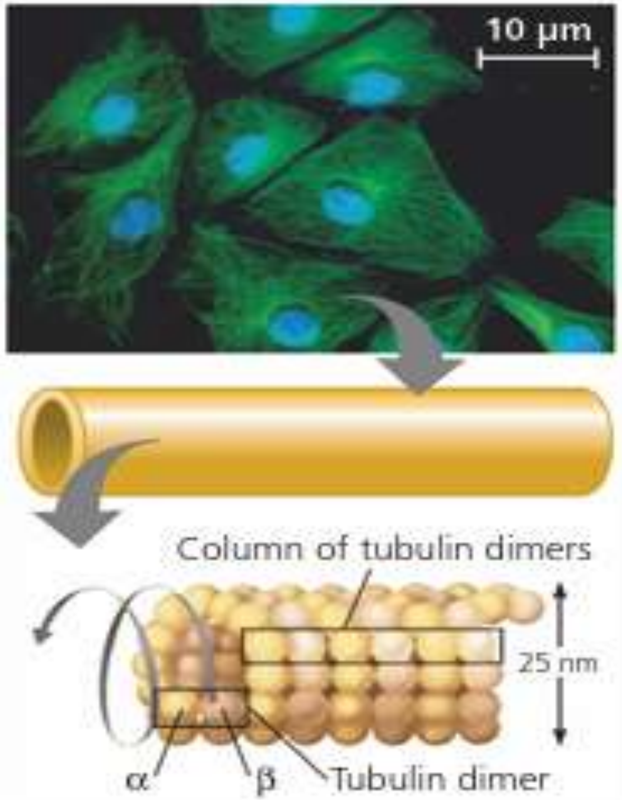
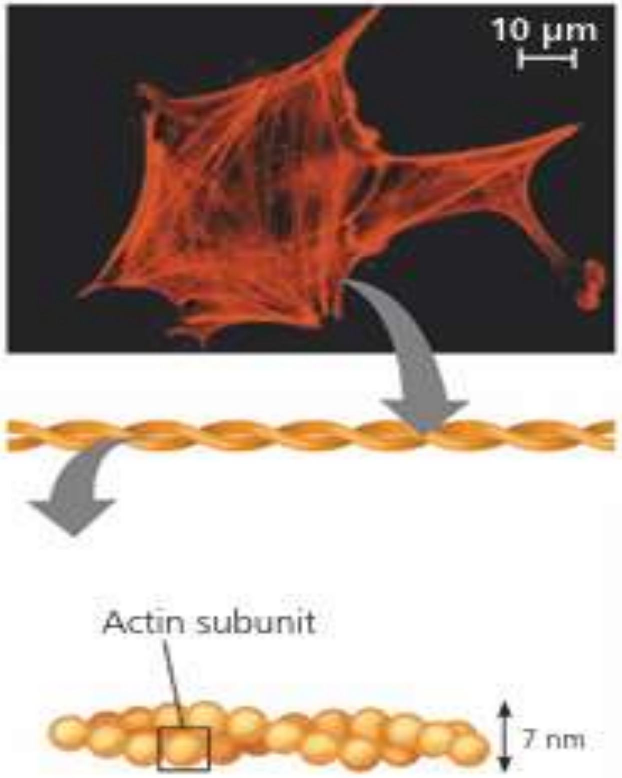
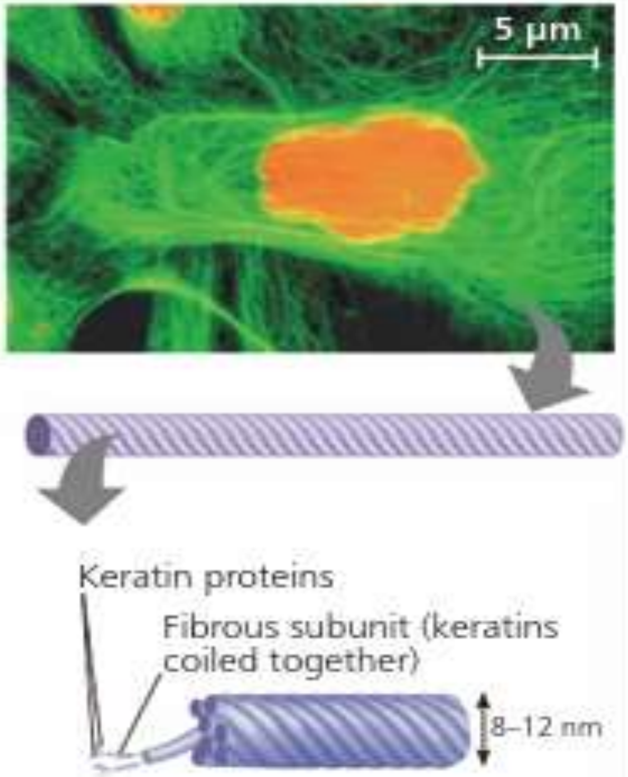


Table 6.1 The Structure and Function of the Cytoskeleton

<table>
<tr><th>Property</th><th>Microtubules (Tubulin Polymers)</th><th>Microfilaments (Actin Filaments)</th><th>Intermediate Filaments</th></tr>
<tr><td>Structure</td><td>Hollow tubes</td><td>Two intertwined strands of actin</td><td>Fibrous proteins coiled into cables</td></tr>
<tr><td>Diameter</td><td>25 nm with 15-nm lumen</td><td>7 nm</td><td>8–12 nm</td></tr>
<tr><td>Protein subunits</td><td>Tubulin, a dimer consisting of α-tubulin and β-tubulin</td><td>Actin</td><td>One of several different proteins (such as keratins)</td></tr>
<tr><td>Main functions</td><td>Maintenance of cell shape (compression-resisting "girders"); cell motility (as in cilia or flagella); chromosome movements in cell division; organelle movements</td><td>Maintenance of cell shape (tension-bearing elements); changes in cell shape; muscle contraction; cytoplasmic streaming in plant cells; cell motility (as in amoeboid movement); division of animal cells</td><td>Maintenance of cell shape (tension-bearing elements); anchorage of nucleus and certain other organelles; formation of nuclear lamina</td></tr>
<tr><td>Fluorescence micrographs of fibroblasts. Fibroblasts are a favorite cell type for cell biology studies. In each, the structure of interest has been tagged with fluorescent molecules. The DNA in the nucleus has also been tagged in the first micrograph (blue) and third micrograph (orange).</td><td></td><td></td><td></td></tr>
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Function

- The most obvious function of the cytoskeleton is to give mechanical support to the cell and maintain its shape. This is especially important for animal cells, which lack walls.

Cell Movement

Cell movement takes different forms.

-Crawling is accomplished via actin filaments and the protein **myosin**.

-**Flagella** undulate to move a cell.

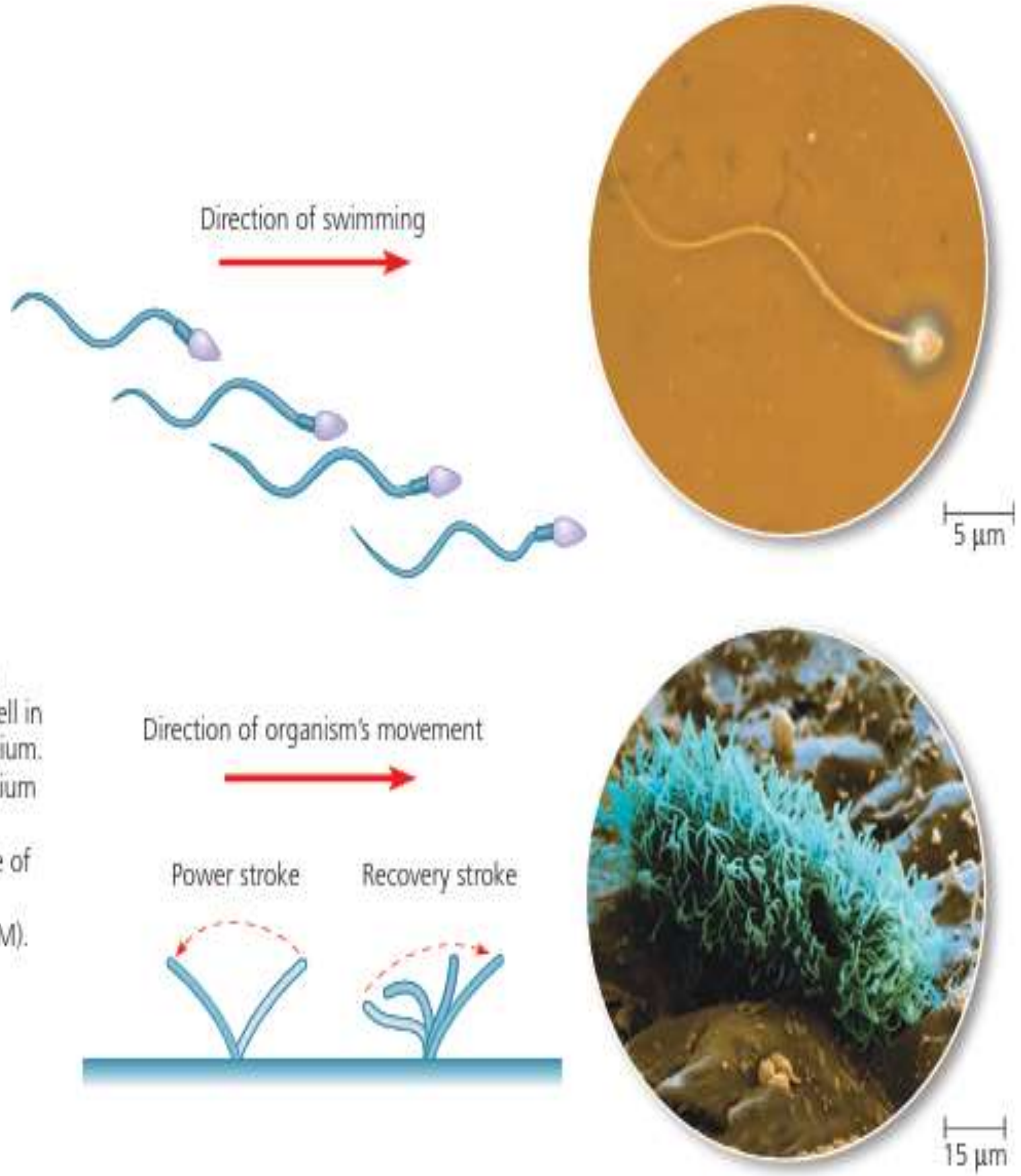
-**Cilia** can be arranged in rows on the surface of a eukaryotic cell to propel a cell forward.

Cell Movement

The cilia and flagella of eukaryotic cells have a similar structure:

9+2 structure: 9 pairs of microtubules surrounded by a 2 central microtubules

Cilia are usually more numerous than flagella on a cell.

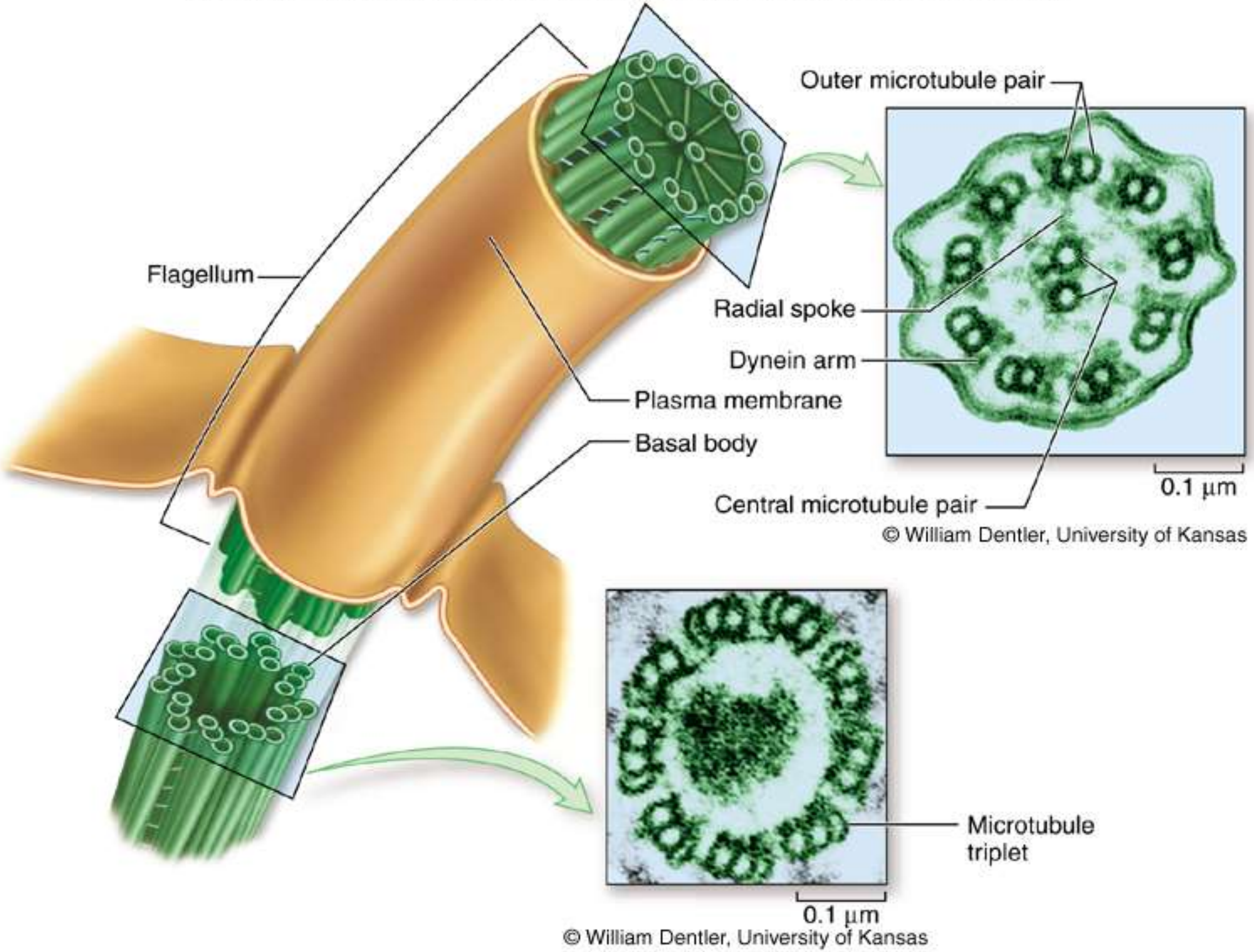


(a) Motion of flagella. A flagellum usually undulates, its snakelike motion driving a cell in the same direction as the axis of the flagellum. Propulsion of a human sperm cell is an example of flagellate locomotion (LM).

(b) Motion of cilia. Cilia have a back-and-forth motion. The rapid power stroke moves the cell in a direction perpendicular to the axis of the cilium. Then, during the slower recovery stroke,the cilium bends and sweeps sideways, closer to the cell surface. A dense nap of cilia, beating at a rate of about 40 to 60 strokes a second, covers this *Colpidium*, a freshwater protist (colorized SEM).

▲ **Figure 6.23 A comparison of the beating of flagella and motile cilia.**

Cell Movement



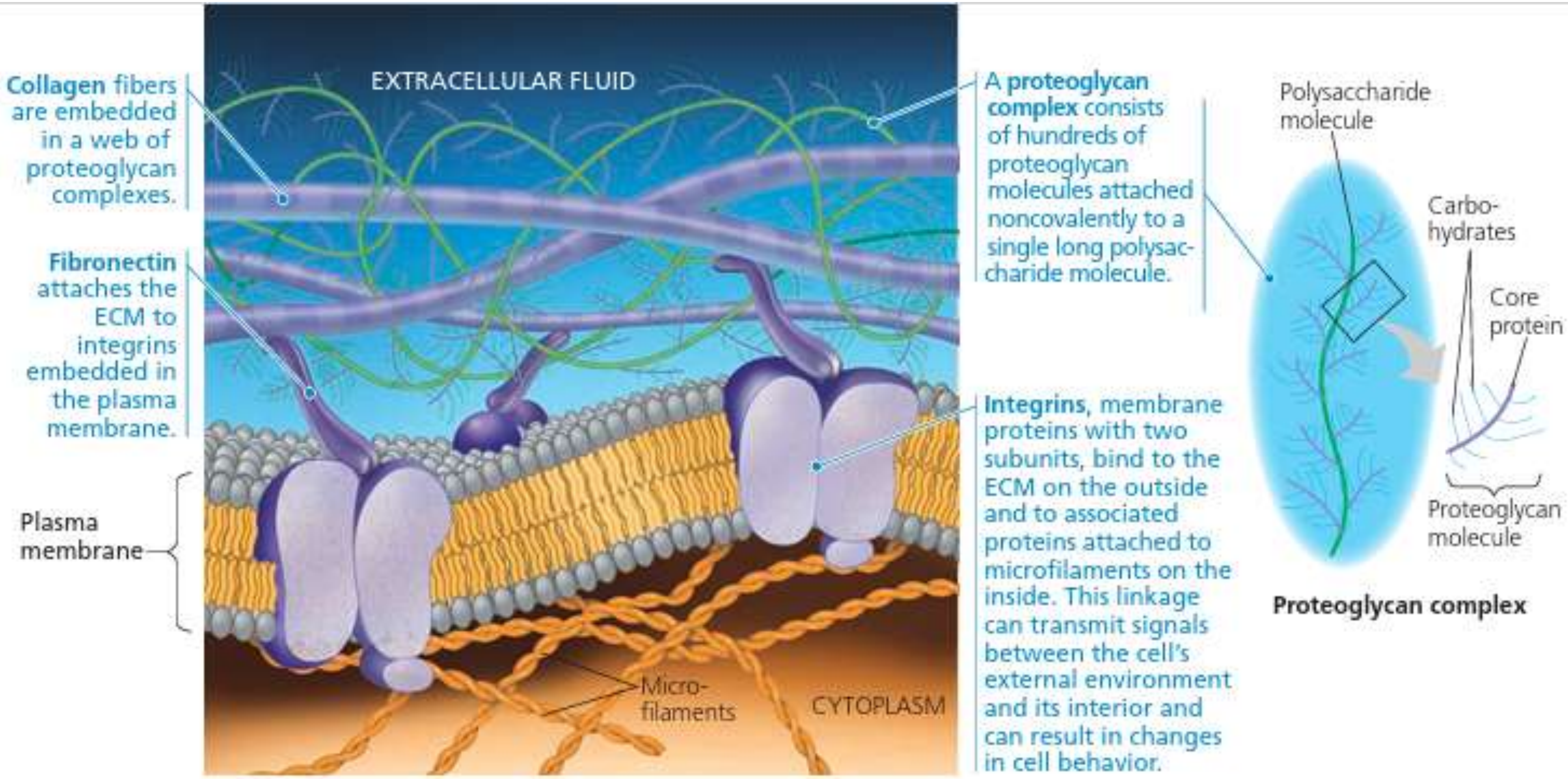
Extracellular Structures

Extracellular matrix (ECM)

-surrounds animal cells

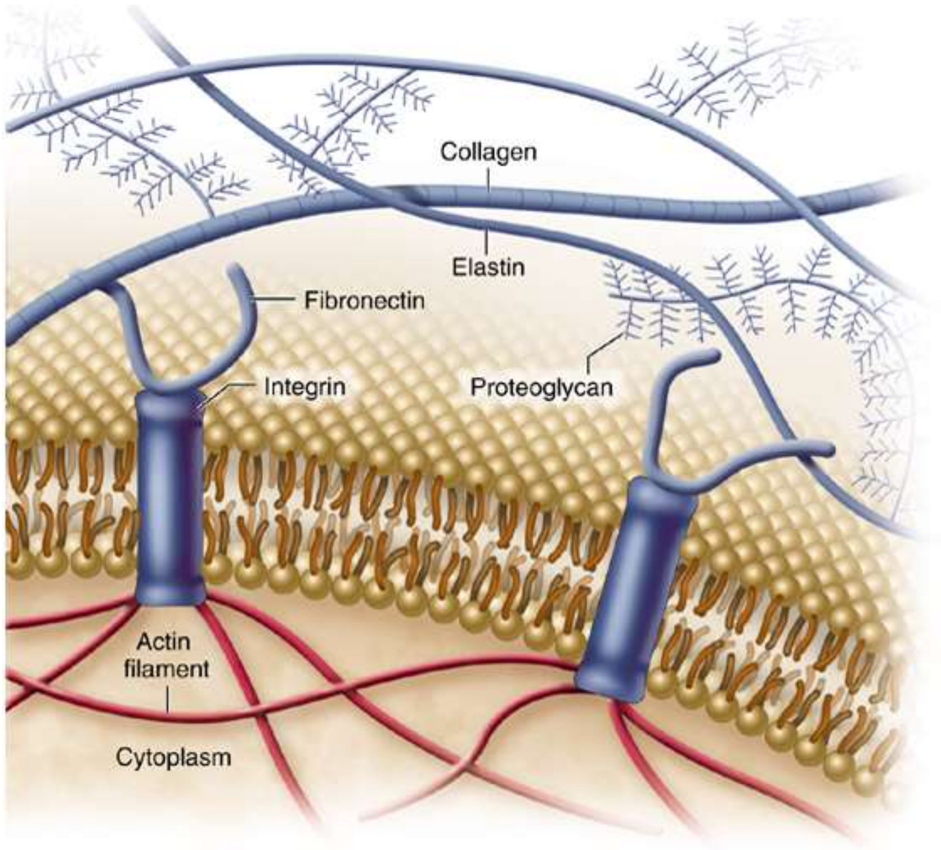
-composed of glycoproteins and fibrous proteins such as collagen

-may be connected to the cytoplasm via **integrin** proteins present in the plasma membrane



▲ **Figure 6.28 Extracellular matrix (ECM) of an animal cell.** The molecular composition and structure of the ECM vary from one cell type to another. In this example, three different types of ECM molecules are present: proteoglycans, collagen, and fibronectin.

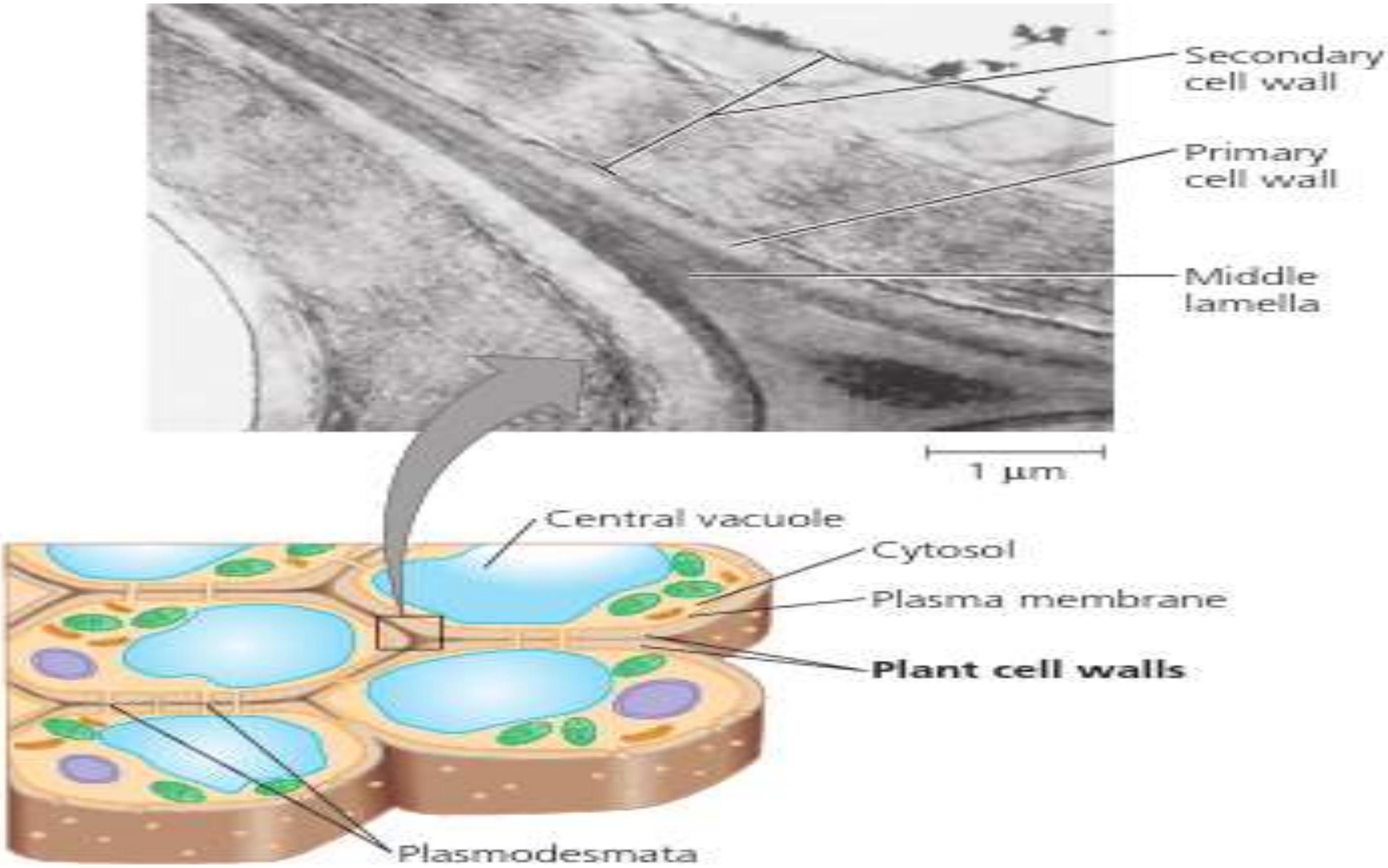
Extracellular Structures



Cell Walls of Plants

The cell wall is an extracellular structure of plant cells that distinguishes them from animal cells. The wall protects the plant cell, maintains its shape, and prevents excessive uptake of water. On the level of the whole plant, the strong walls of specialized cells hold the plant up against the force of gravity. Prokaryotes, fungi, and some unicellular eukaryotes also have cell walls.

Plant cell walls are much thicker than the plasma mem brane, ranging from 0.1 μm to several micrometers. The exact chemical composition of the wall varies from species to species and even from one cell type to another in the same plant, but the basic design of the wall is consistent. Micro fibrils made of the polysaccharide cellulose. are synthesized by an enzyme called cellulose synthase and secreted to the extracellular space, where they become em bedded in a matrix of other polysaccharides and proteins



▲ **Figure 6.27 Plant cell walls.** The drawing shows several cells, each with a large vacuole, a nucleus, and several chloroplasts and mitochondria. The transmission electron micrograph shows the cell walls where two cells come together. The multilayered partition between plant cells consists of adjoining walls individually secreted by the cells.

- **Cell Junctions**

Cells in an animal or plant are organized into tissues, organs, and organ systems. Neighboring cells often adhere, interact, and communicate via sites of direct physical contact.

Plasmodesmata in Plant Cells

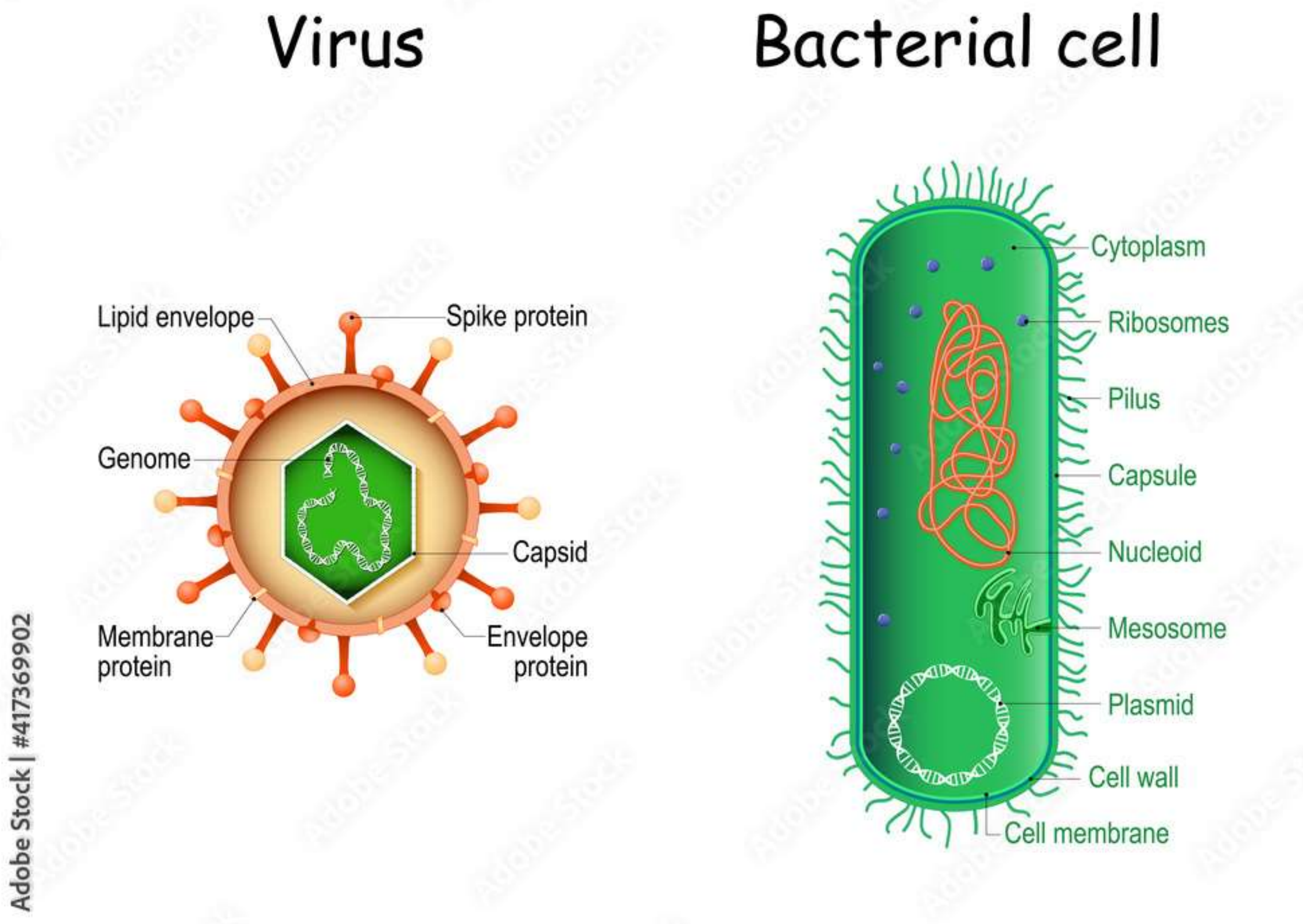
In animals, there are three main types of cell junctions: tight junctions, desmosomes, and gap junctions.

TABLE 4.3 A Comparison of Prokaryotic, Animal, and Plant Cells

	Prokaryote	Animal	Plant
EXTERIOR STRUCTURES			
Cell wall	Present (protein-polysaccharide)	Absent	Present (cellulose)
Cell membrane	Present	Present	Present
Flagella/cilia	Flagella may be present	May be present (9 + 2 structure)	Absent except in sperm of a few species (9 + 2 structure)
INTERIOR STRUCTURES			
ER	Absent	Usually present	Usually present
Ribosomes	Present	Present	Present
Microtubules	Absent	Present	Present
Centrioles	Absent	Present	Absent
Golgi apparatus	Absent	Present	Present
Nucleus	Absent	Present	Present
Mitochondria	Absent	Present	Present
Chloroplasts	Absent	Absent	Present
Chromosomes	A single circle of DNA	Multiple; DNA–protein complex	Multiple; DNA–protein complex
Lysosomes	Absent	Usually present	Present
Vacuoles	Absent	Absent or small	Usually a large single vacuole

	Prokaryotes	Eukaryotes	Mitochondria of Eukaryotic cells	Chloroplasts of Photosynthetic eukaryotes
DNA	1 single, circular chromosome	Multiple linear chromosomes compartmentalized in a nucleus	1 single, circular chromosome	1 single, circular chromosome
Replication	Binary Fission	Mitosis	Binary Fission	Binary Fission
Ribosomes	"70 S"	"80 S"	"70 S"	"70 S"
Electron Transport Chain	Found in the plasma membrane around cell	Not found in the plasma membrane around cell	Found in the plasma membrane around mitochondrion	Found in the plasma membrane around chloroplast
Size (approximate)	~1-10 microns	~50 - 500 microns	~1-10 microns	~1-10 microns
Appearance on Earth	Anaerobic bacteria: ~3.8 Billion years Photosynt.bacteria: ~3.2 Billion years Aerobic bacteria: ~2.5 Billion years	~1.5 billion years ago	~1.5 billion years ago	~1.5 billion years ago

VIRUSES



- A virus is an infectious microbe consisting of a segment of nucleic acid (either DNA or RNA) surrounded by a protein coat.
- A virus cannot replicate alone; instead, it must infect cells and use components of the host cell to make copies of itself.
- Often, a virus ends up killing the host cell in the process, causing damage to the host organism.
- Well-known examples of viruses causing human disease include AIDS, COVID-19, measles and smallpox.

General Characteristics of Viruses

1. **Viral structure:**Typical viral components are shown in Fig. 2. These components are a **nucleic acid core** and a surrounding protein coat called a **capsid**. In addition some viruses have a surrounding lipid bilayer membrane called an **envelope**.

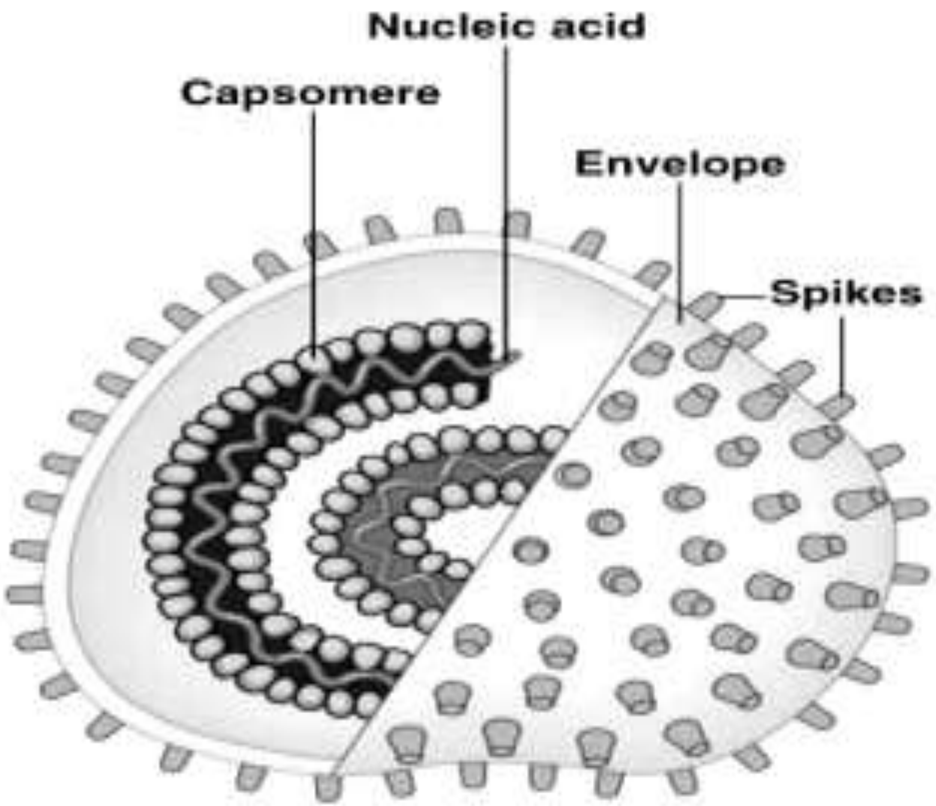


Fig. 2.The components of helical virus

A. Nucleic acid

- ✓ Viral genomes are either DNA or RNA (not both)
- ✓ Nucleic acid may be single- or double-stranded

Fig. 3.Types of virus genomes

B. Capsid

- ✓ protein coat
- ✓ Protection of Nucleic Acid
- ✓ Provides Specificity for Attachment
- ✓ Capsomeres are subunits of the capsid

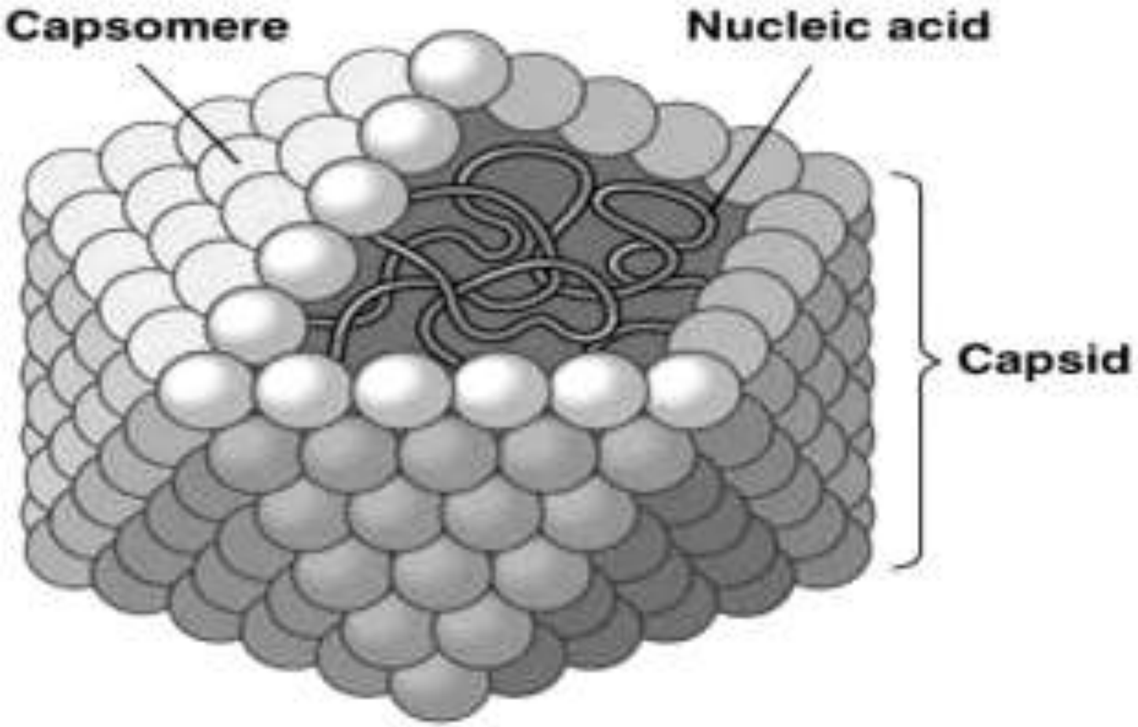
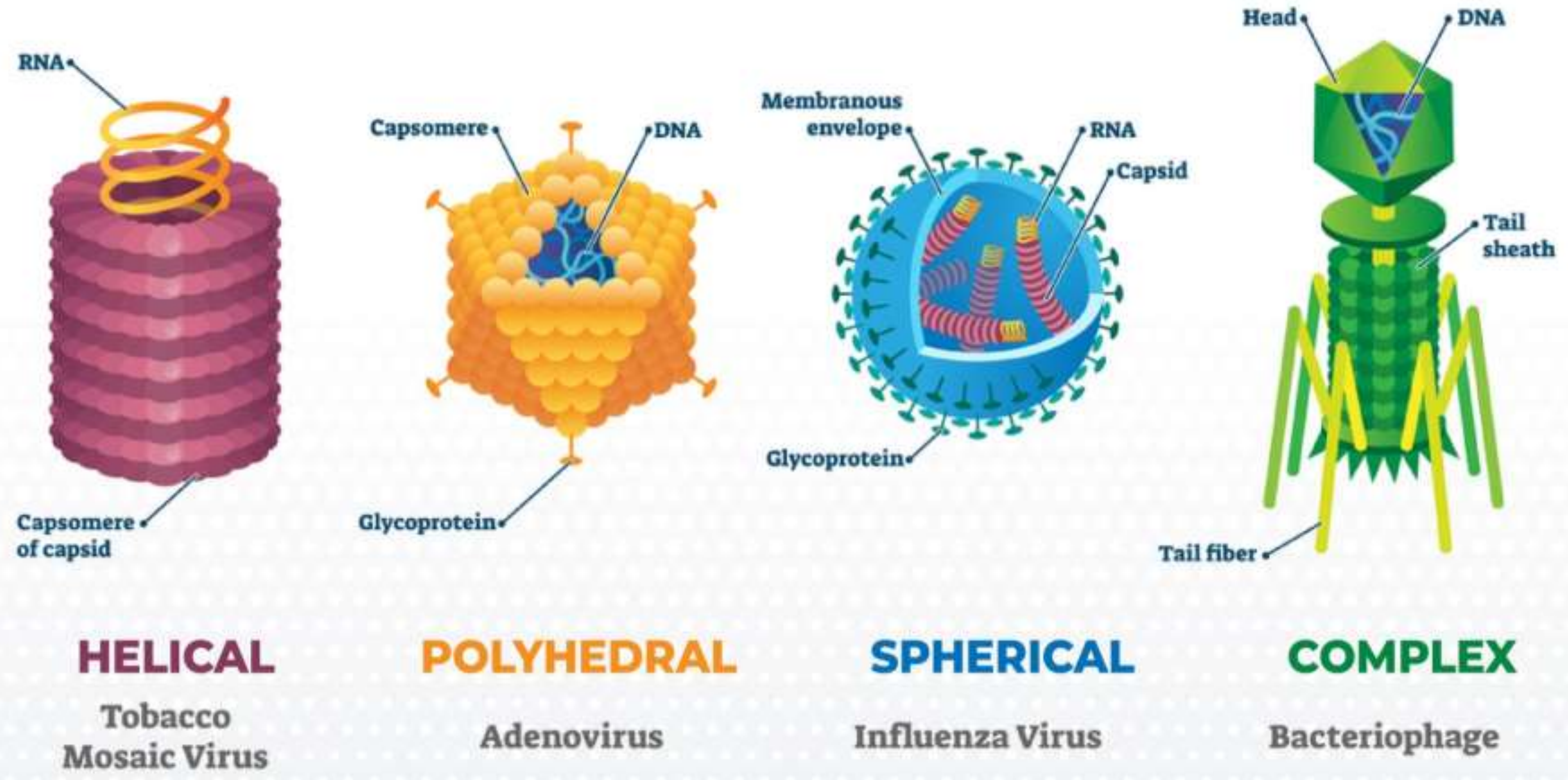


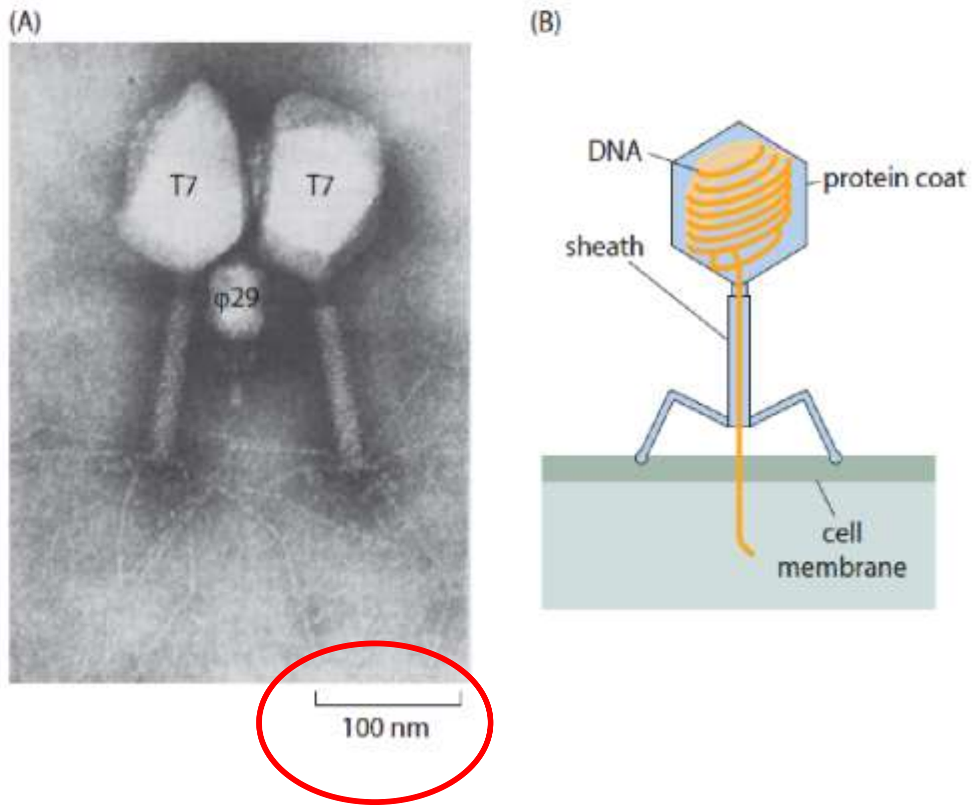
Fig. 4.Capsid structure

TYPES OF VIRUSES



- Viruses are much smaller than the cells they infect.
- They could pass through filters small enough to remove pathogenic bacterial cells.
- These genomes can be DNA or RNA, single-stranded or double-stranded (that is, ssDNA, dsDNA, ssRNA, or dsRNA) with characteristic sizes ranging from 103–106 bases

virus	size (nm)	genome size (nucleotides)	genome type, capsid structure
porcine circovirus (PCV)	17	1760	circular ssDNA, icosahedral
cowpea mosaic virus (CPMV)	28	9400	2 ssRNA molecules, icosahedral
cowpea chlorotic mottle virus (CCMV)	28	7900	3 ssRNA molecules, icosahedral
φX174 (*E. coli* bacteriophage)	32	5400	ssDNA, icosahedral
tobacco mosaic virus (TMV)	40 × 300	6400	ssRNA, rod shaped
polio virus	30	7500	ssRNA, icosahedral
φ29 (*Bacillus* phage)	45 × 54	19,000	dsDNA, icosahedral (T3)



(A) Electron microscopy image of phi29 and T7 bacteriophages as revealed by electron microscopy. (B) Schematic of the structure of a bacteriophage. (A, adapted from Grimes S, Jardine PJ & Anderson D [2002] *Adv Virus Res* 58:255–280.)

Diversity of Biological Molecules

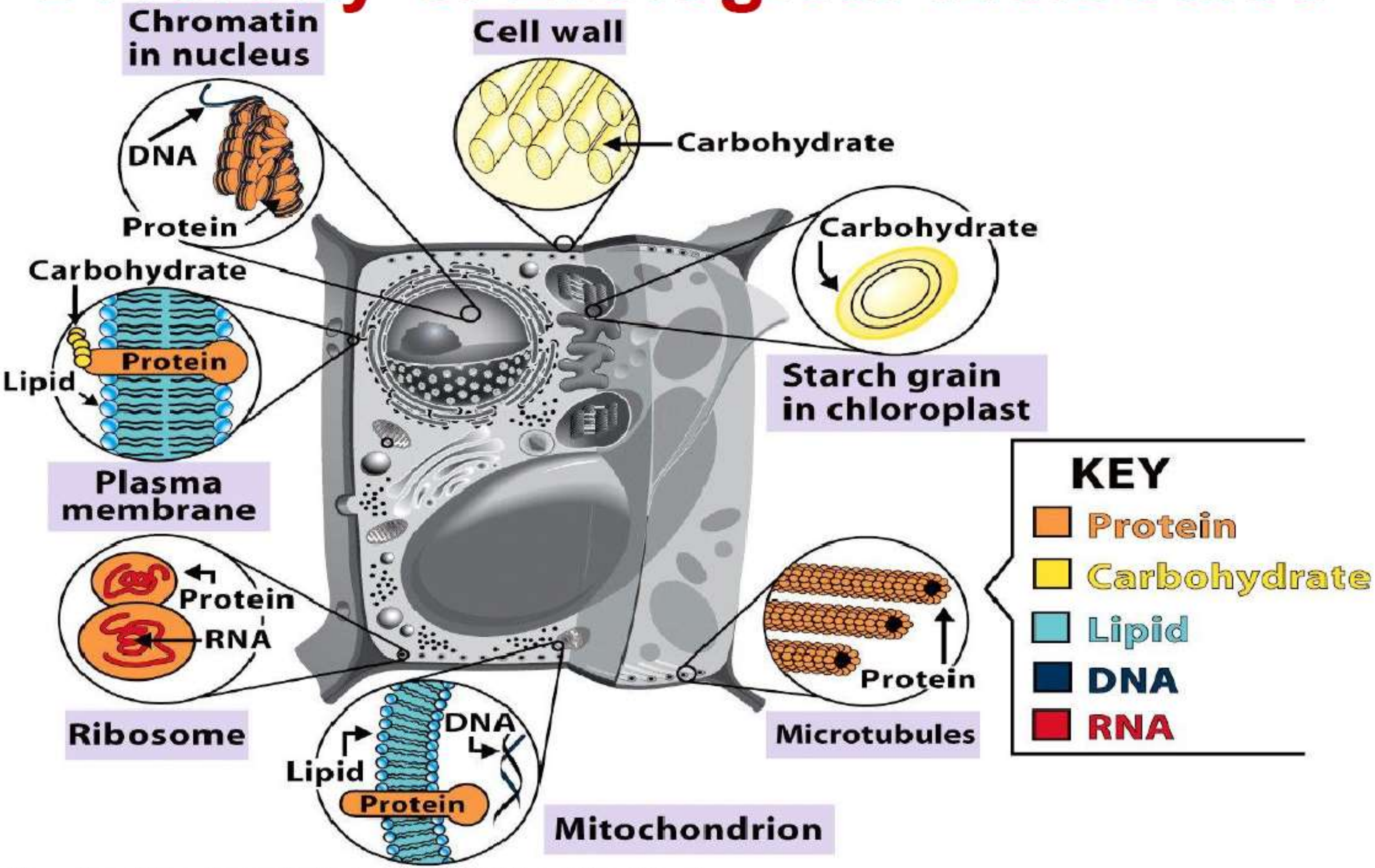
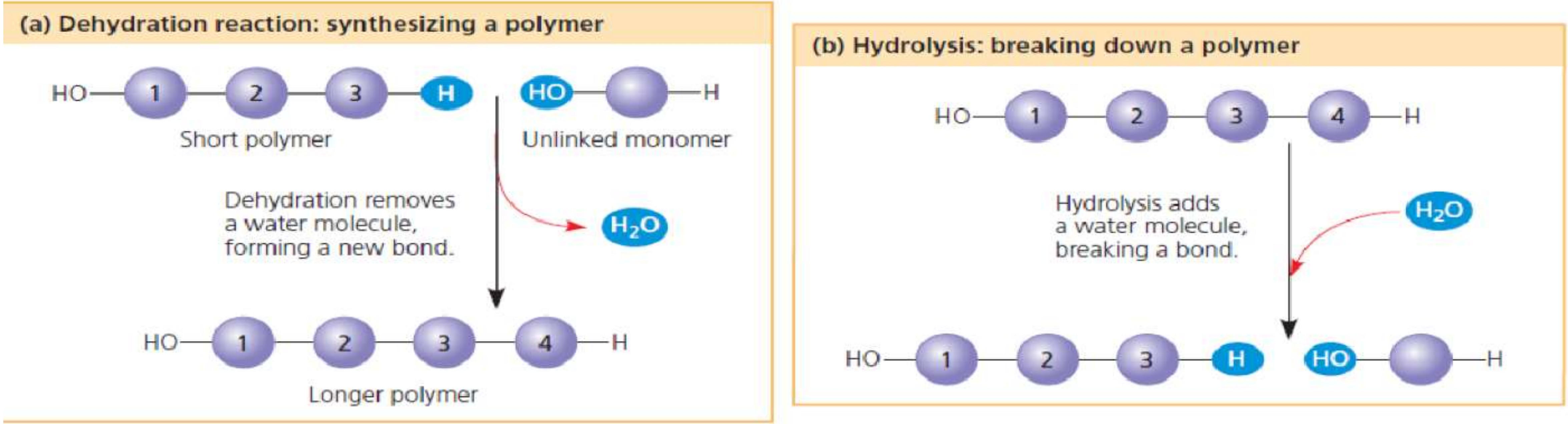


Figure 2-11 Cell and Molecular Biology, 4/e (© 2005 John Wiley & Sons)

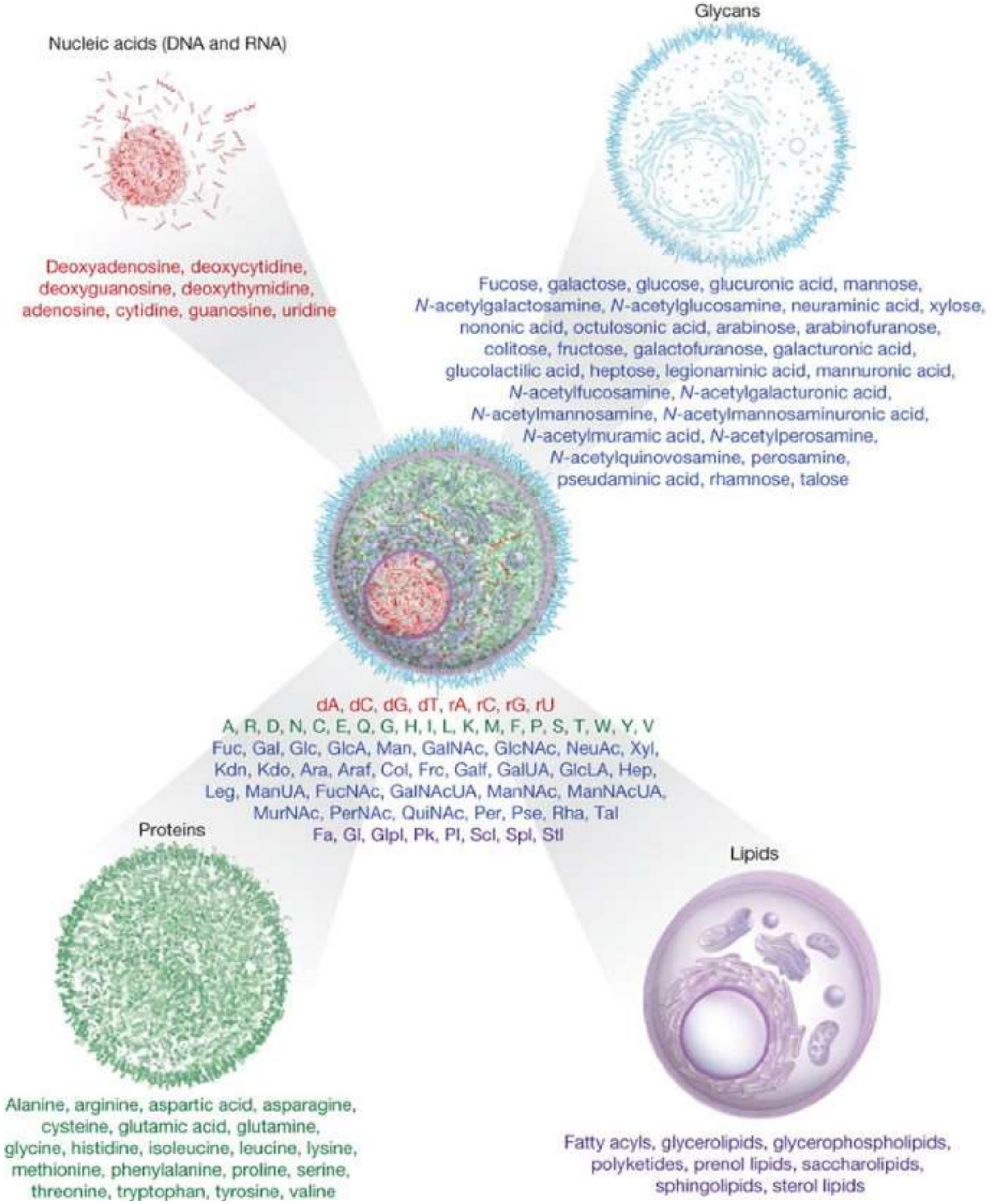
Large Biological Molecules

Macromolecules are polymers, built from monomers



Basic Functions

	Carbs	Lipids	Nucleic Acids	Proteins
Functions	• Energy • Storage • Structure	• Long term storage • Insulation • Protection	• Inheritance • Blueprint for metabolism	• Catalysts • Hormones • Structure
Forms	• Starch • Glycogen • Glucose • Sucrose • Cellulose	• Lipid • Fats • Oils • Waxes	• DNA • RNA • ATP	• Proteins • Enzymes



- Cells of all organisms consist of four fundamental macromolecular components: nucleic acids (including DNA and RNA), proteins, lipids and glycans.
- From the construction, modification and interaction of these components, the cell develops and functions.
- DNA and RNA are produced from the 8 nucleosides. Although deoxyribose (d) and ribose (r) are saccharides, they are an integral part of the energetically charged nucleoside building blocks that are used to synthesize DNA and RNA.
- There are 20 natural amino acids used in the synthesis of proteins.
- Glycans derive initially from 32, and possibly more, saccharides used in the enzymatic process of glycosylation and are often attached to proteins and lipids.
- Lipids are represented by 8 recently classified categories and contain a large repertoire of hydrophobic and amphipathic molecules.

What are nucleic acids? :

- Nucleic acids are the most important biomolecules of the cells forming very basis of central dogma of life.

  • Most importantly, the nucleic acids : deoxyribonucleic acid (DNA) and ribonucleic acid (RNA), are the molecular repositories of genetic informations. DNA is the master molecule responsible for heredity. The ability to store and transmit genetic information from one generation to the next is a fundamental condition for life.

  • The structure of every protein, and ultimately of every biomolecule and cellular component, is a product of information programmed into the nucleotide sequence of a cell's DNA. This way nucleic acid governs the functions and physiology of the cells.

  • Nucleotides are monomeric unit or building blocks of nucleic acids.

Functions of Nucleic acid :

- The concept of Central Dogma explains the functions of nucleic acid in nutshell as below :

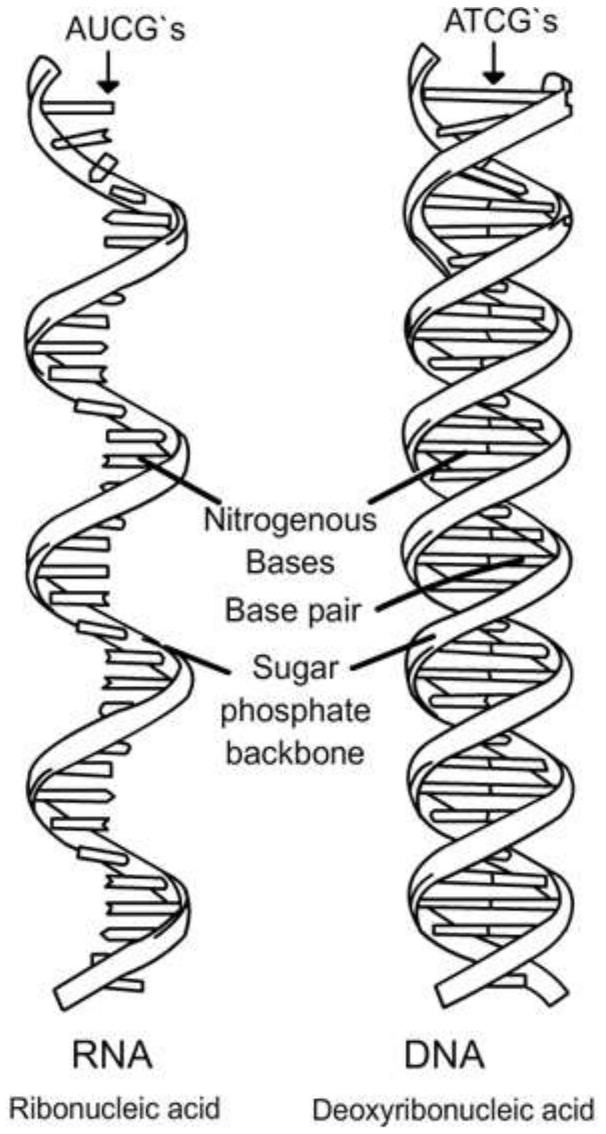
DNA

Reverse transcription ↑↓ *Transcription*

m-RNA

↓ *Translation*

Proteins



- DNA is very basis of life. It is the master molecule responsible for hereditary and genetic material of the cell carrying all the in formations.

- It is able to replicates it self during cell division and the process called replication.

- It synthesises a complementary messenger RNA which is responsible for carrying the information for protein synthesis.

- It also regulates protein synthesis.

DNA Content of Organisms :

- The overall DNA contained in one cell is called a genome.

- Prokaryotic cells contain one molecule of DNA, while human somatic cells contain 46 molecules of DNA per nucleus.

- The somatic cells of eukaryotes commonly have two sets of genes derived from both parents, and these cells are called diploids.

- Cells that have only one set of genes are called haploids. For example, most prokaryotes are haploids.

- DNA content greatly varies among organisms. Generally, DNA content per cell is larger in eukaryotes than in prokaryotes.

- Human somatic cells contain approximately 1,000 times as much DNA as those of E. coli (per haploid). For diploid cells, the amount per cell is 6 pg.

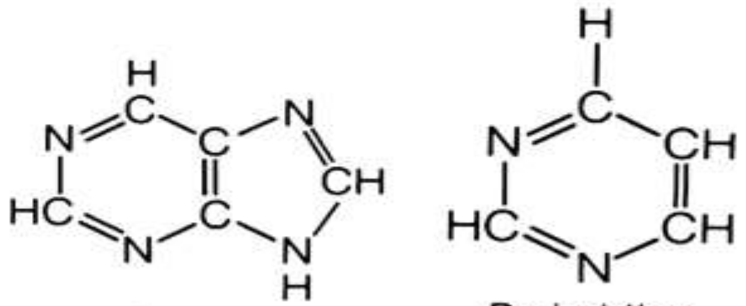
- Although it may generally be seen that among eukaryotes, the higher an organism, the more DNA content, there can be variations among organisms of the same group.

- For example, among vertebrates, such variations may be seen in fish and amphibians, with some species having more DNA content than humans.

- Some higher plant species also have more DNA than humans.

The nitrogenous bases :

- Purines and Pyrimidines are two types of bases which occur in nucleic acids.

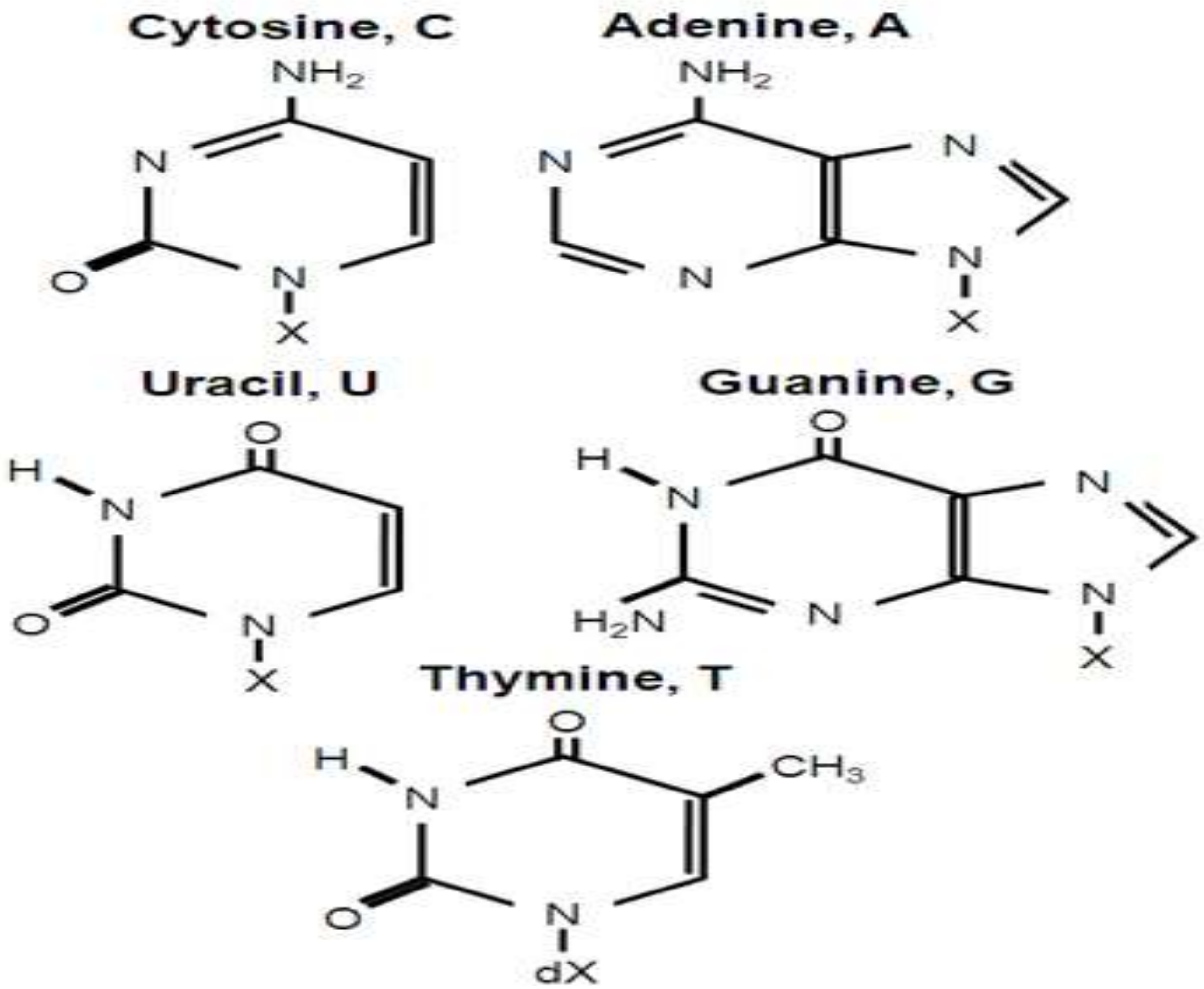


Purine Pyrimidine

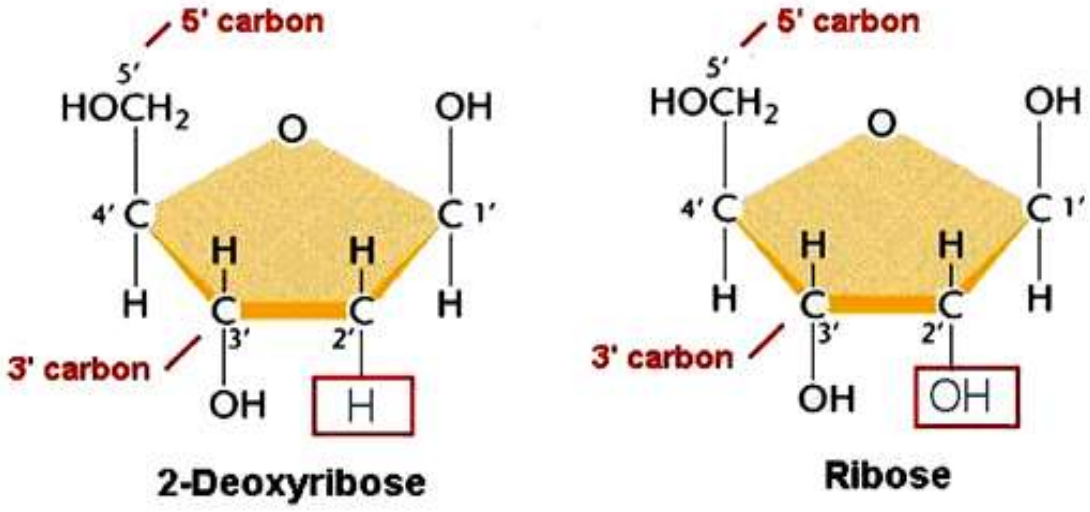
- There are five major bases found in cells. The derivatives of purine are called **adenine** and **guanine**, while those of pyrimidine are called **thymine**, **cytosine** and **uracil**.

- The common abbreviations used for these five bases are, A, G, T, C and U. DNA contains A, G, C and T, whereas RNA contains A, G, C and U bases.

Structure of nitrogenous bases :



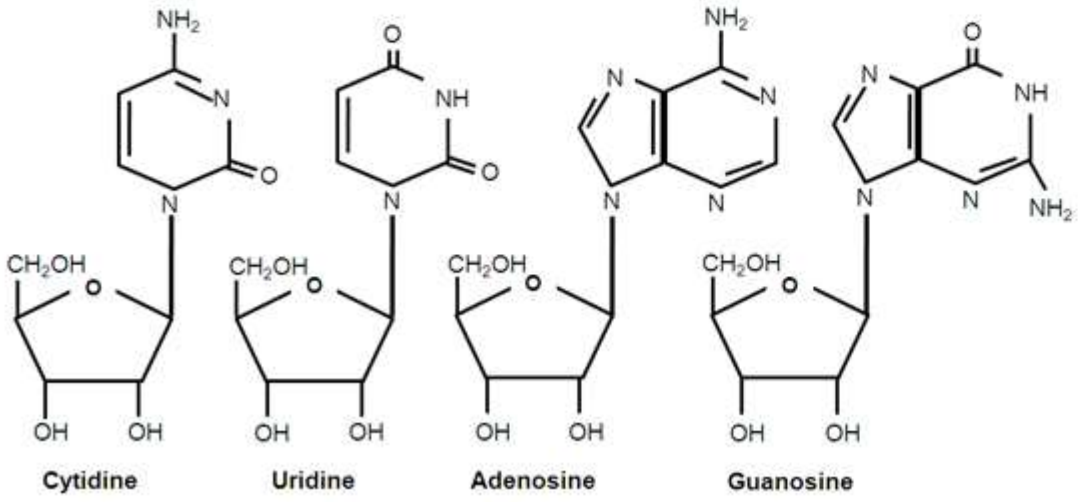
- • **Sugar :** Ribose and 2-deoxy ribose are the two sugars found in RNA and DNA respectively. The recurring deoxyribonucleotide units of DNA contain 2- deoxy-D-ribose, and the ribonucleotide units of RNA contain D-ribose. In nucleotides, these are found in their furanose (closed five-membered ring) form.



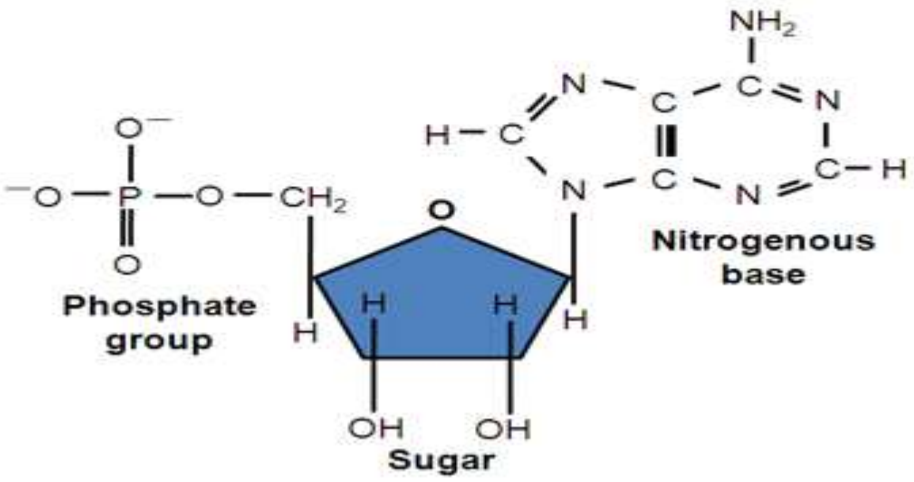
- **Phosphoric acid**

gets attached to C-5 OH group of the sugar.

- The base and sugar are called **"nucleoside"**. The bond between them is called the beta-glycosidic linkage. The position of attachment is shown below. Examples of nucleosides include cytidine, uridine, adenosine, guanosine, thymidine.



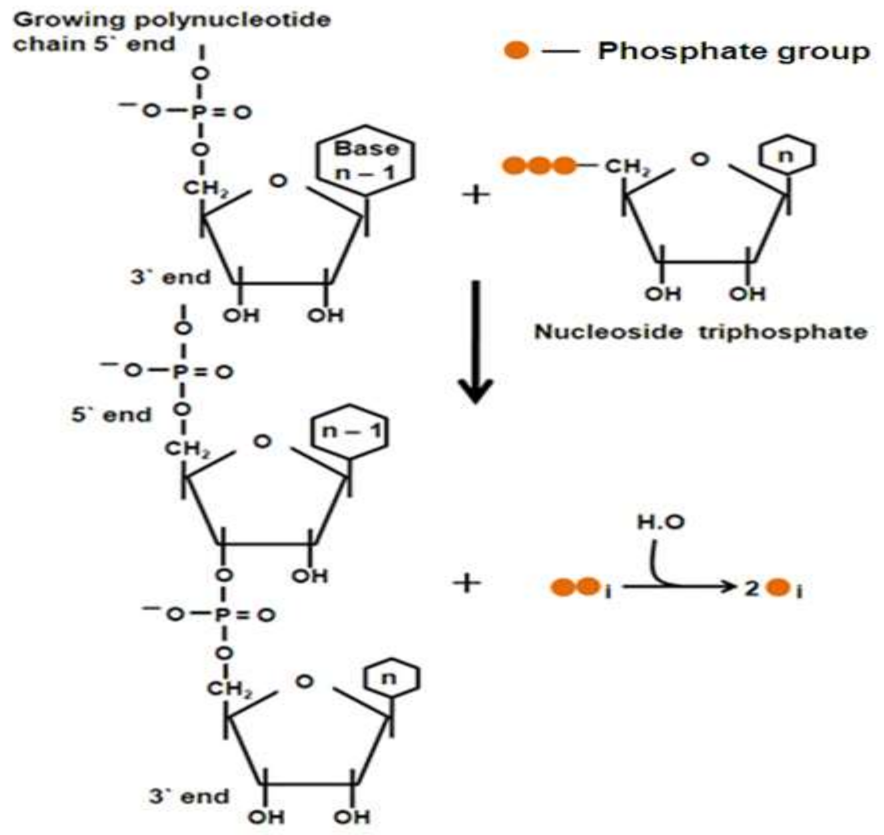
- **Nucleotides**
- are composed of three components namely nitrogenous bases, pentose sugar and phosphate group. The phosphate is attached to 5’ CH_2OH group of sugar part of nucleoside. A typical nucleotide is shown below :
  The base of a nucleotide is joined covalently (at N-1 of pyrimidines and N-9 of purines) in an N—glycosyl bond to the 1 carbon of the pentose, and the phosphate is esterified to the 5 carbon. The N-glycosyl bond is formed by removal of a water molecule.



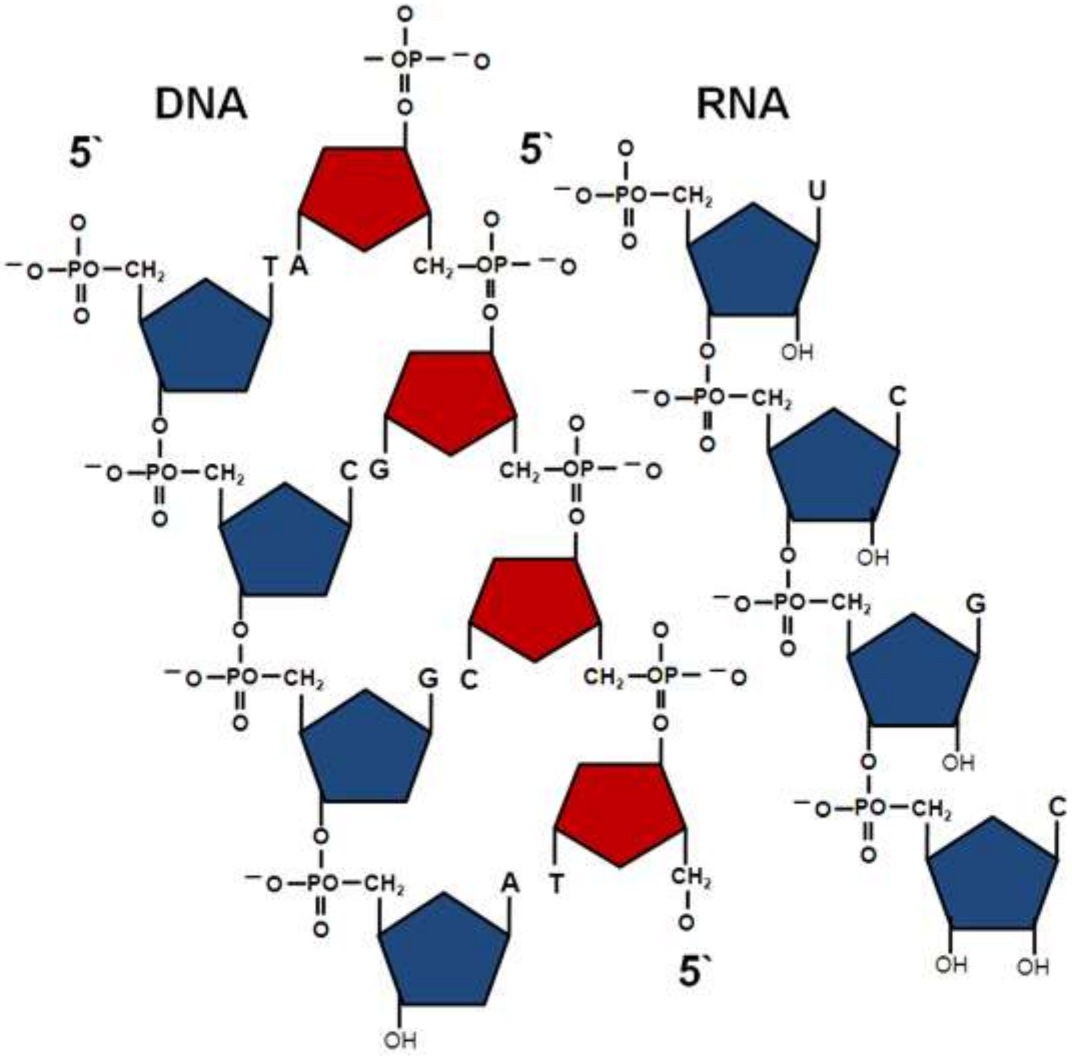
Polynucleotides :

- **Polynucleotides** are formed by joining of nucleotides by phosphodiester linkages.

  - The bond formation takes place between the alcohol of a 5'-phosphate of one nucleotide and the 3'-hydroxyl of the next, resulting into a phosphodiester bond.



• DNA and RNA are polynucleotides



• In DNA and RNA the nucleotides are arranged in linear way and proceeds in the 5' ----> 3' direction. A common representation of ploynucleotide for example can be seen as below : 5'pApTpGpC OH3'

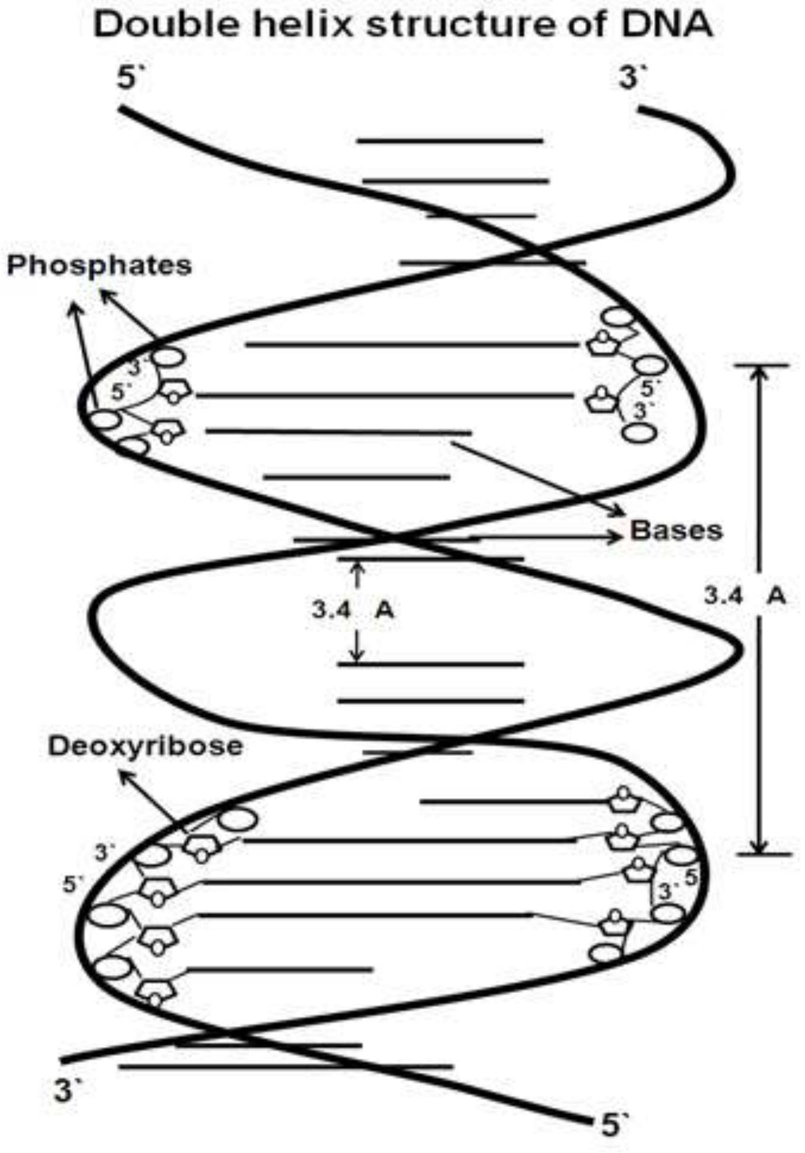
Structure of DNA

- The discovery of DNA structure is one of the hall mark of the modern molecular biology.

- Based on the assumptions of Chargoff and utilizing X-ray diffraction data, obtained from crystals of DNA by Rosalind Franklin and Maurice Wilkins, James Watson and Francis Crick proposed a model for the structure of DNA in 1953.

- They established that DNA has a double helical structure comprising of two complementary antiparallel polynucleotide strands, wound around each other in a rightward direction.

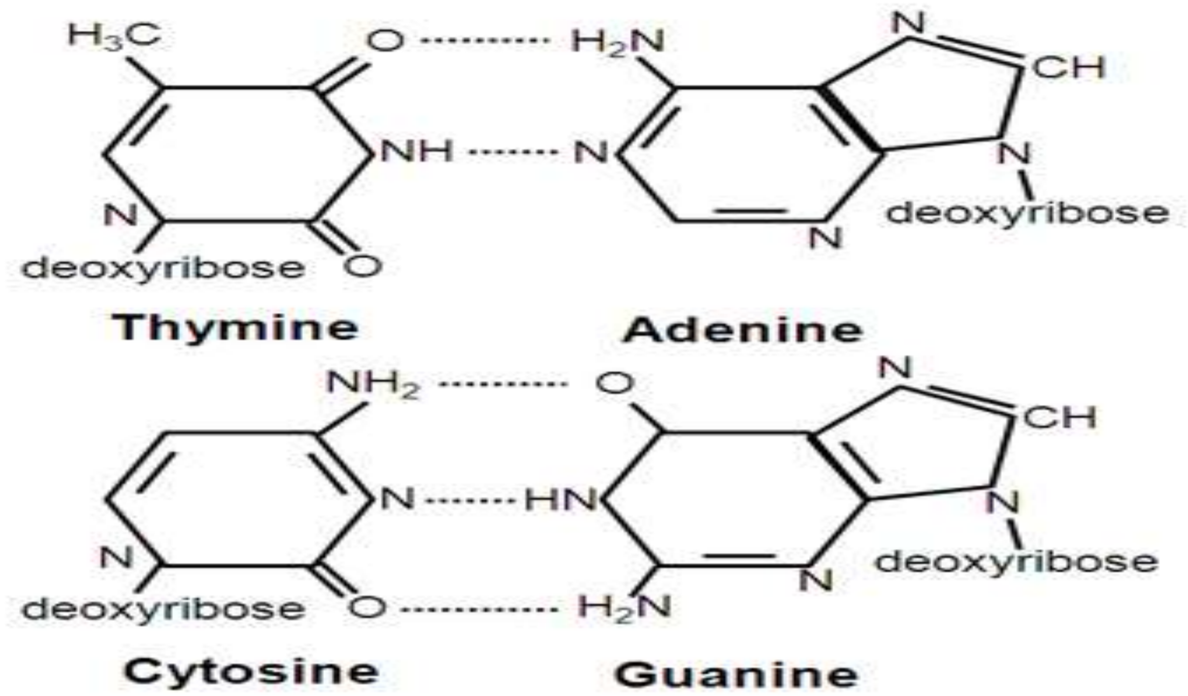
- The backbone of the helix is sugar-phosphate and the bases are in the interior of the helix and extended at 90^0 perpendicular to the axis of the helix. Bases from opposite helix pair with each other. Purines form base pairs with pyrimidene as a thumb rule- A will pair with T, and C with G. According to this pattern, known as Watson-Crick base-pairing.



Specific features of DNA structure :

- It is double helical structure. One polynucleotide chain forms one strand. Two such strands form double helix.
- Chain has sugar phosphate backbone and the bases are arranged perpendicular to the chain.
- Two strands are antiparallel to each other: one in 5' ---> 3' direction and the other in the 3' ---> 5' direction.
- A and T ; and G and C occur as complementary and form base pair with corresponding complementary base in opposite strand.
- One turn of the helix is 36 A and 10 base pairs are found per turn with rise of 3.6A.
- On the surface of double helix two deep grooves are found which are called major and **minor grooves**.
- Helix is right handed along the axis.

The bases pairs are hydrogen bonds with each other and impart stability to the structure. The base-pairs composed of G and C contain three H-bonds, whereas those of A and T contain two H-bonds. For this reason G-C base-pairs are stronger than A-T base-pairs. The outcome will be that DNA having more GC base pairs will be more stable than the one having more AT pairs.

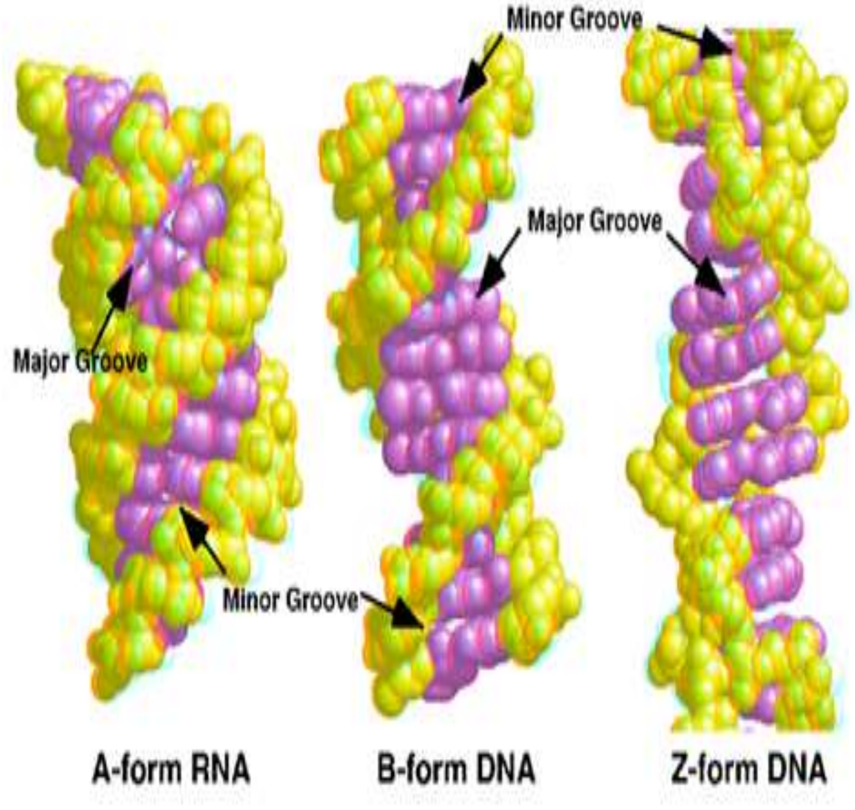


Various conformations of DNA :

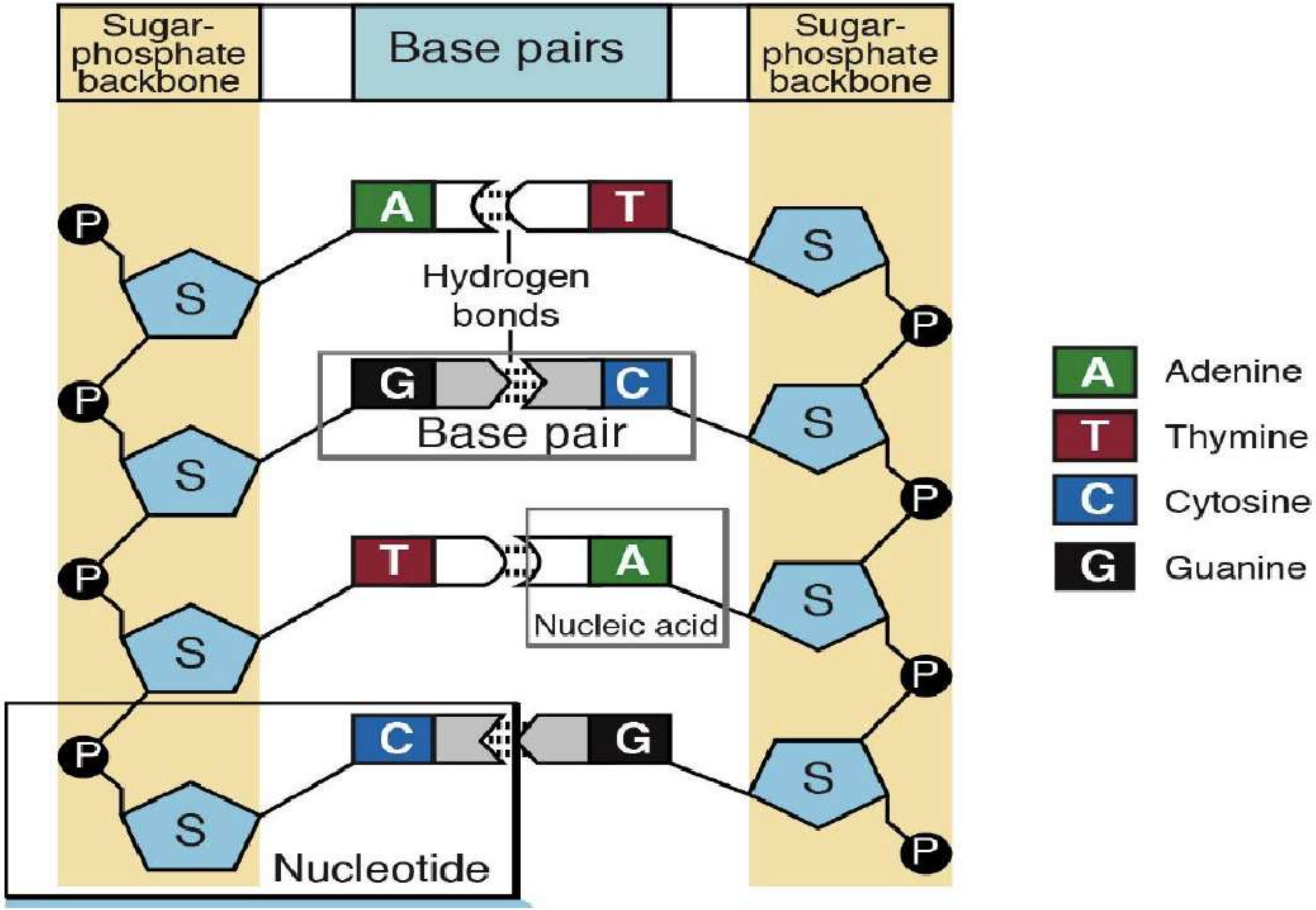
- One of the properties of the DNA is that it shows conformational flexibility, and could exist in alternative structural forms. The Watson-Crick structure is the B-form DNA or B-DNA.

- The B from is the most stable structure for a random sequence DNA molecule under physiological conditions and is therefore “the standard point of reference in any study of the properties of DNA”.The B-DNA predominates in the cell.

- There are two other structural variants of DNA that have been well characterized in crystal structures. They are the A-DNA and Z-DNA. These DNA variants differ in their helical sense, diameter, base pairs per helical turn, helix rise per base pair, base tilt normal to the helix axis, sugar pucker conformation, and glycosyl bond conformation.



DNA (Deoxyribonucleic Acid)



DNA (Deoxyribonucleic acid)

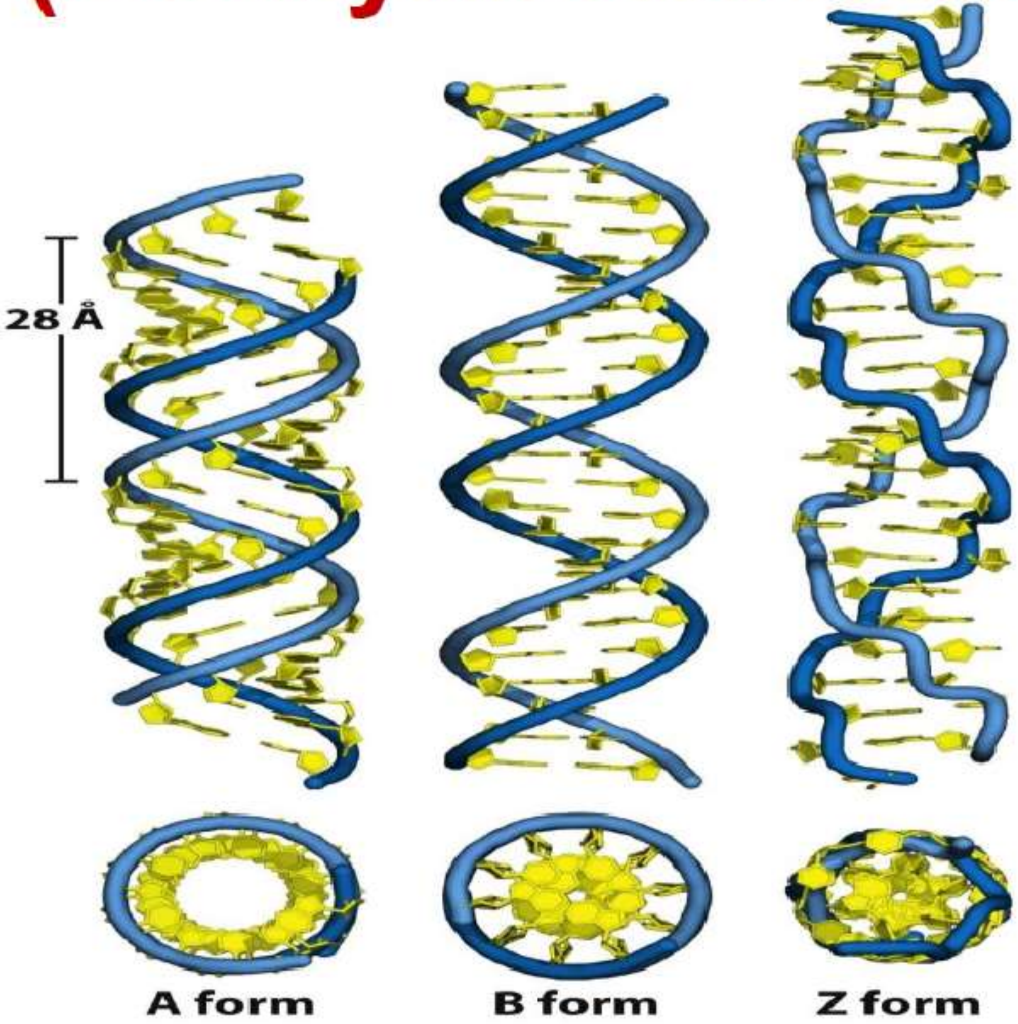
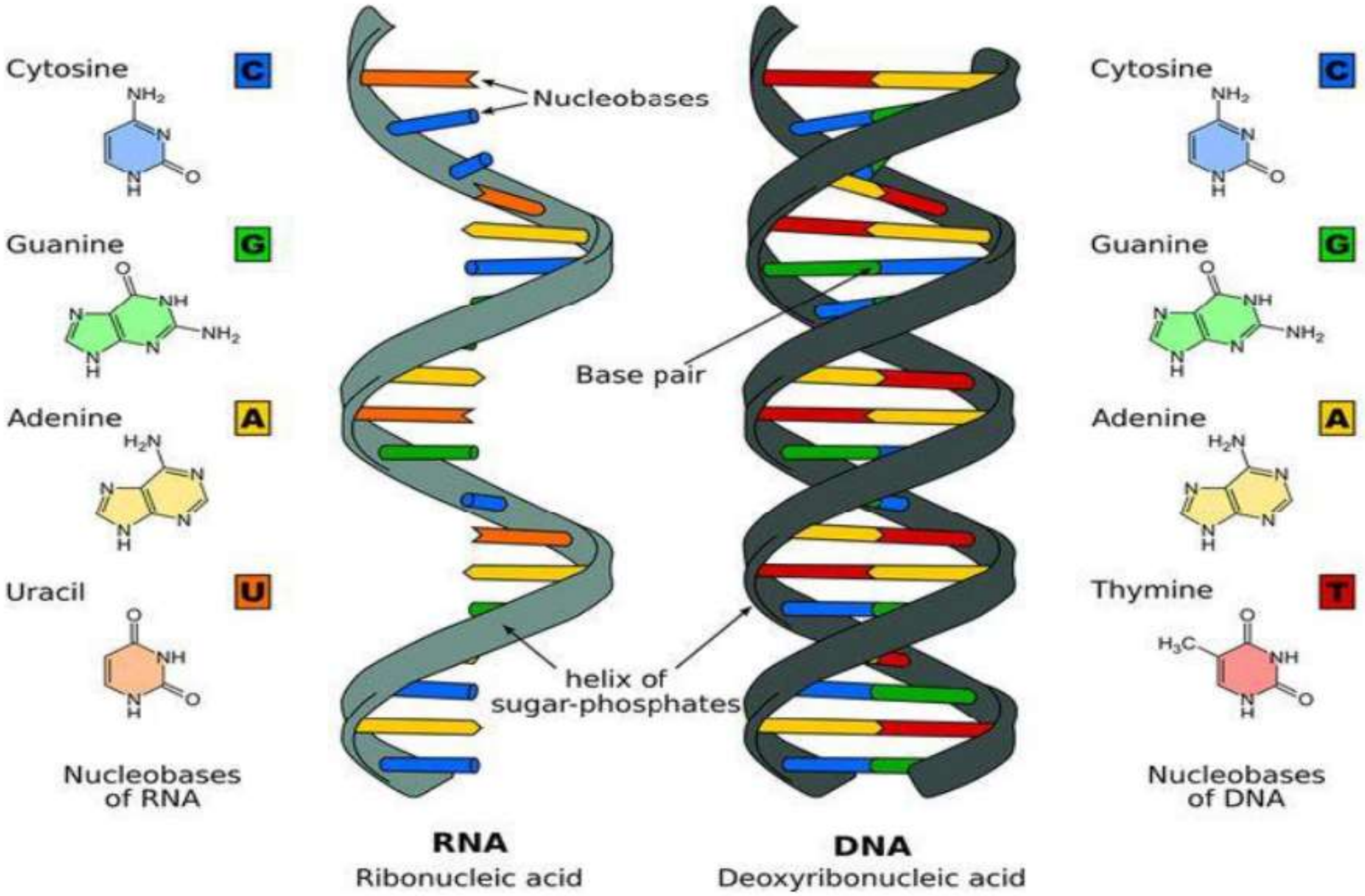


Figure 8-17 part 1
Lehninger Principles of Biochemistry, Sixth Edition

All prokaryotes and eukaryotes have B form of DNA

RNA (Ribonucleic Acid)

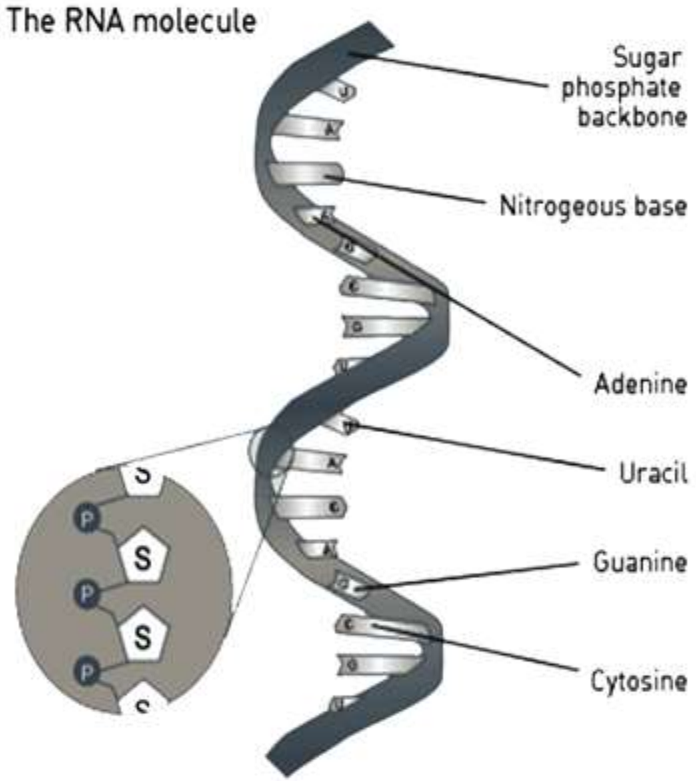


RNA molecules perform a variety of roles in the cell but are mainly involved in the process of **protein synthesis (translation)** and its regulation

Structure of RNA :

Unlike DNA, RNA are single stranded polynucleotide. It contains uracil base instead of thymine, thus four bases of RNA are A, U, G and C. There are three types of RNA present in the cell :

A.



Messenger RNA :

- Messenger RNA are designated as m-RNA.

- m-RNA does not contain very organized secondary structure.

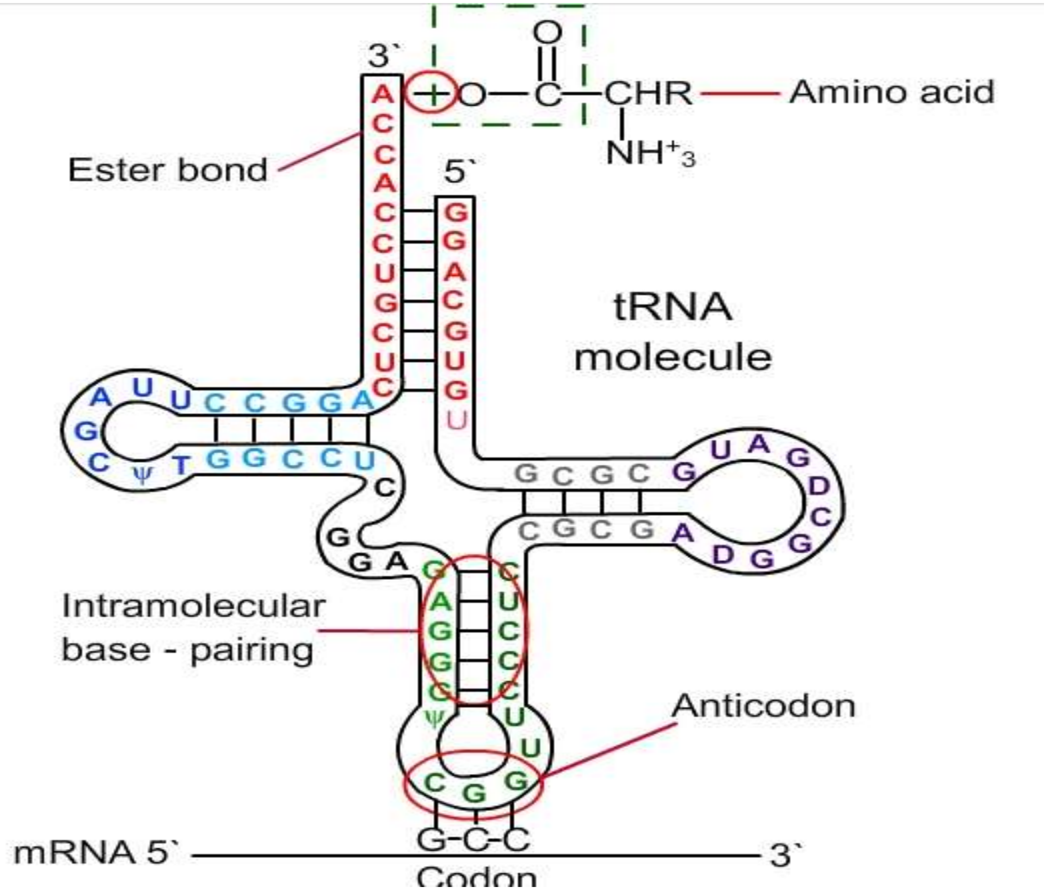
- The polypeptide is linear in general, except acquiring hairpin structure at some places due to the base pairing between complementary base pairs of the chain. Messenger RNA is generated in the nucleus as the complementary copy of DNA strand, by a process called transcription.

- It carries the genetic information of the DNA to be used for protein synthesis.

Transfer RNA :

- Designated as t-RNA. They have well defined clover leaf structure as shown in figure. It has four arms, which are designated as Dihydrouridine (DHU), anticodon, pseudouridine (T Ψ C) arms and one small optional arm. 3′ of the t-RNA has conserved sequence CCA at which specific amino acid is attached.

- It acts as adapter molecule. Anticodons located at anticodon arm form complementary base pairs with codon during protein synthesis process. Thus the role of t-RNA is to transfer amino acid for protein synthesis.

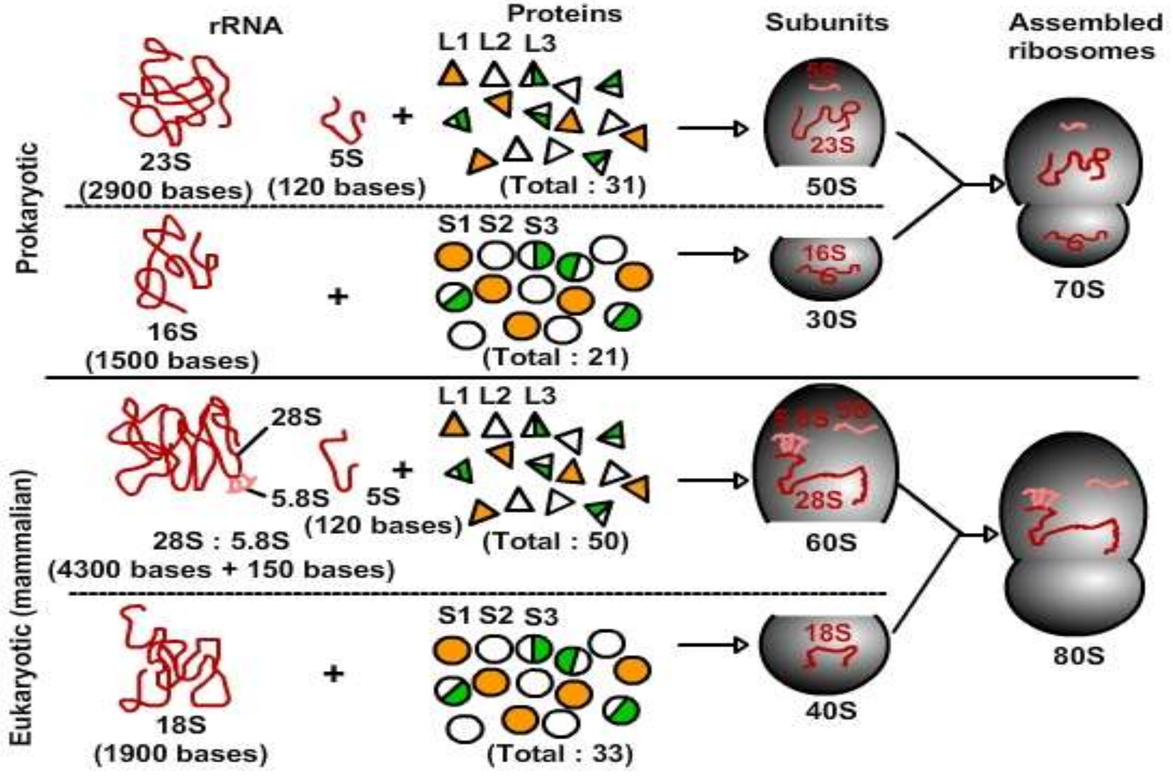


Ribosomal RNA :

● Designated as r-RNA.

● In the cytoplasm, ribosomal RNA and protein combine to form a nucleoprotein called a ribosome. The ribosome binds mRNA and carries out protein synthesis.

Several ribosomes may be attached to a single mRNA at any time.



Micro RNAs :

- Micro RNAs (miRNA) are single - stranded RNA molecules of 21 - 23 nucleotides length. miRNAs are post - transcriptional regulators that bind to complementary sequences on mRNA transcripts leading to repression of translation or gene silencing.

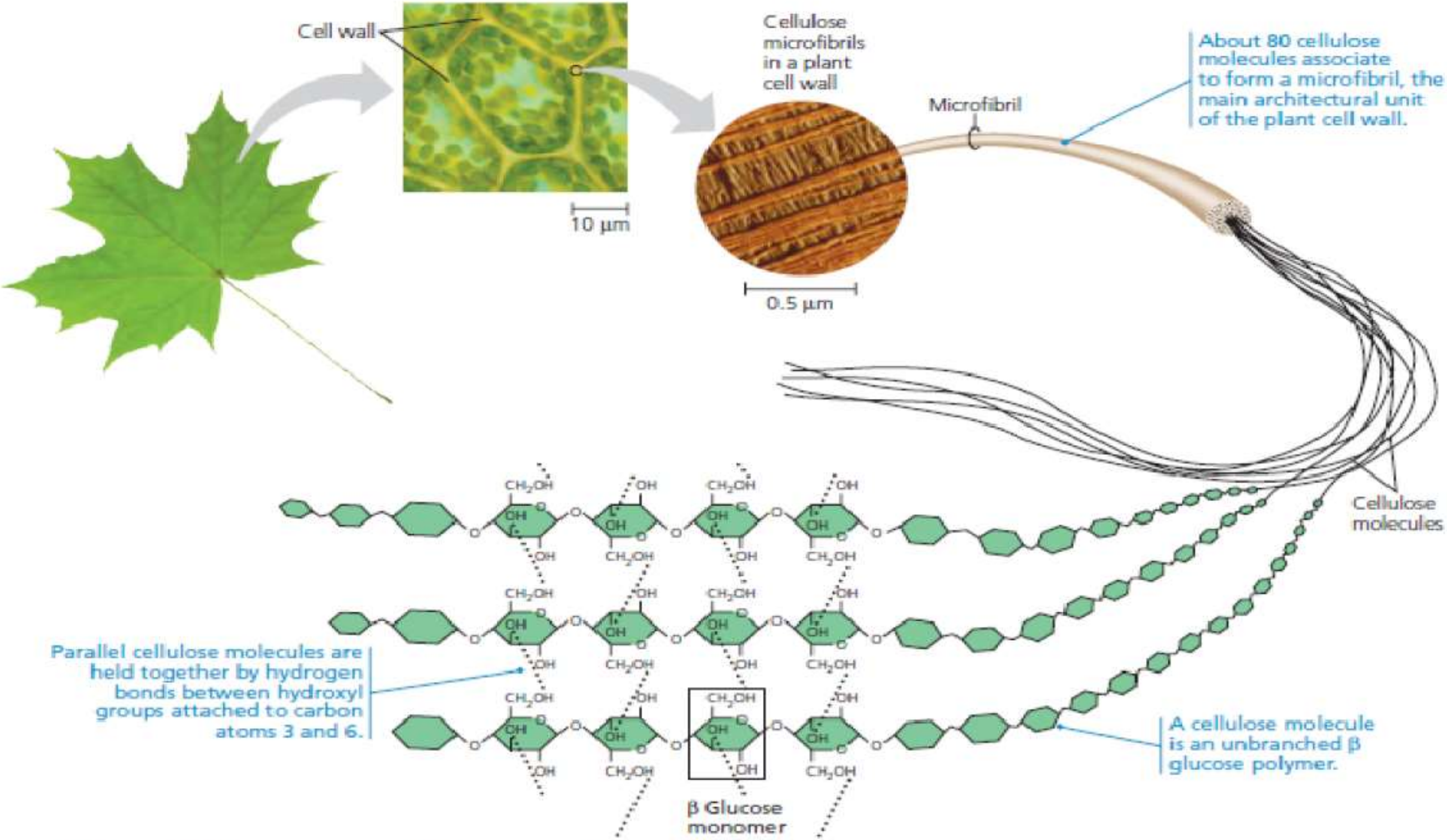
- miRNAs are encoded by genes transcribed from DNA but not translated into protein (non - coding RNA);

- They are processed from primary transcripts known as pri - miRNA to short stem - loop structures called pre - miRNA and finally to functional miRNA.

- The main function of mature miRNA molecules appears to be in regulation of gene expression. This effect was first described in 1993 for the worm *C.elegans* by Victor Ambros and his group. Since 2002, miRNAs have been confirmed in various plants and animals for eg. *C.elegans* and the plant *Arabidopsis thaliana*.

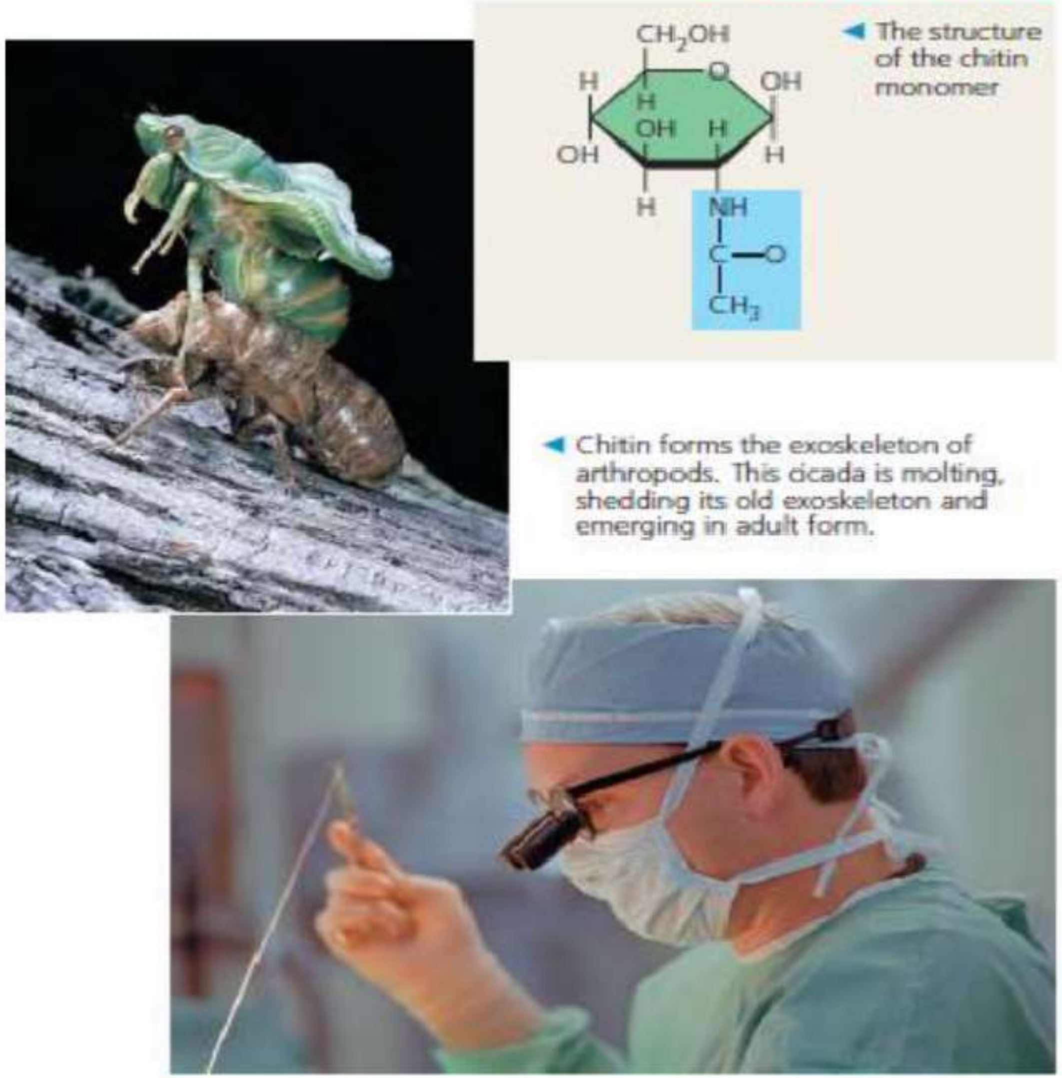
- The human genome encodes over 1000 miRNAs and abundantly found in many human cell types.

Carbohydrates



▲ **Figure 5.8 The arrangement of cellulose in plant cell walls.**

Carbohydrates



The structure of the chitin monomer

Chitin forms the exoskeleton of arthropods. This cicada is molting, shedding its old exoskeleton and emerging in adult form.

Chitin is used to make a strong and flexible surgical thread that decomposes after the wound or incision heals.

Figure 5.9 Chitin, a structural polysaccharide.

Several functions

- Cellulose
- Chitin
- Starch

What are Carbohydrates ? :

Carbohydrates are defined as polyhydroxy aldehyde or ketone with empirical formula $(CH_2O)_n$., the simplest being glyceraldehyde or dihydroxy acetone. Carbohydrates include sugars, starches, cellulose and many other compounds found in living organisms.

<u>What are saccharides? :</u>

- Saccharide is a term derived from the Latin for sugar (origin = "sweet sand").The term carbohydrate is most common in biochemistry where it is a synonym of **saccharide**.

- Carbohydrates are often classified according to the number of saccharide units they contain. They are divided into four chemical groupings: monosaccharides, disaccharides, oligosaccharides and ploysaccharides.

- In their basic form, carbohydrates are simple sugars or monosaccharides. These simple sugars can combine with each other to form more complex carbohydrates. The combination of two simple sugars is a disaccharide. Carbohydrates comprising of 2-10 monosaccharide units are called oligosaccharides, and those with a larger number are called polysaccharides.

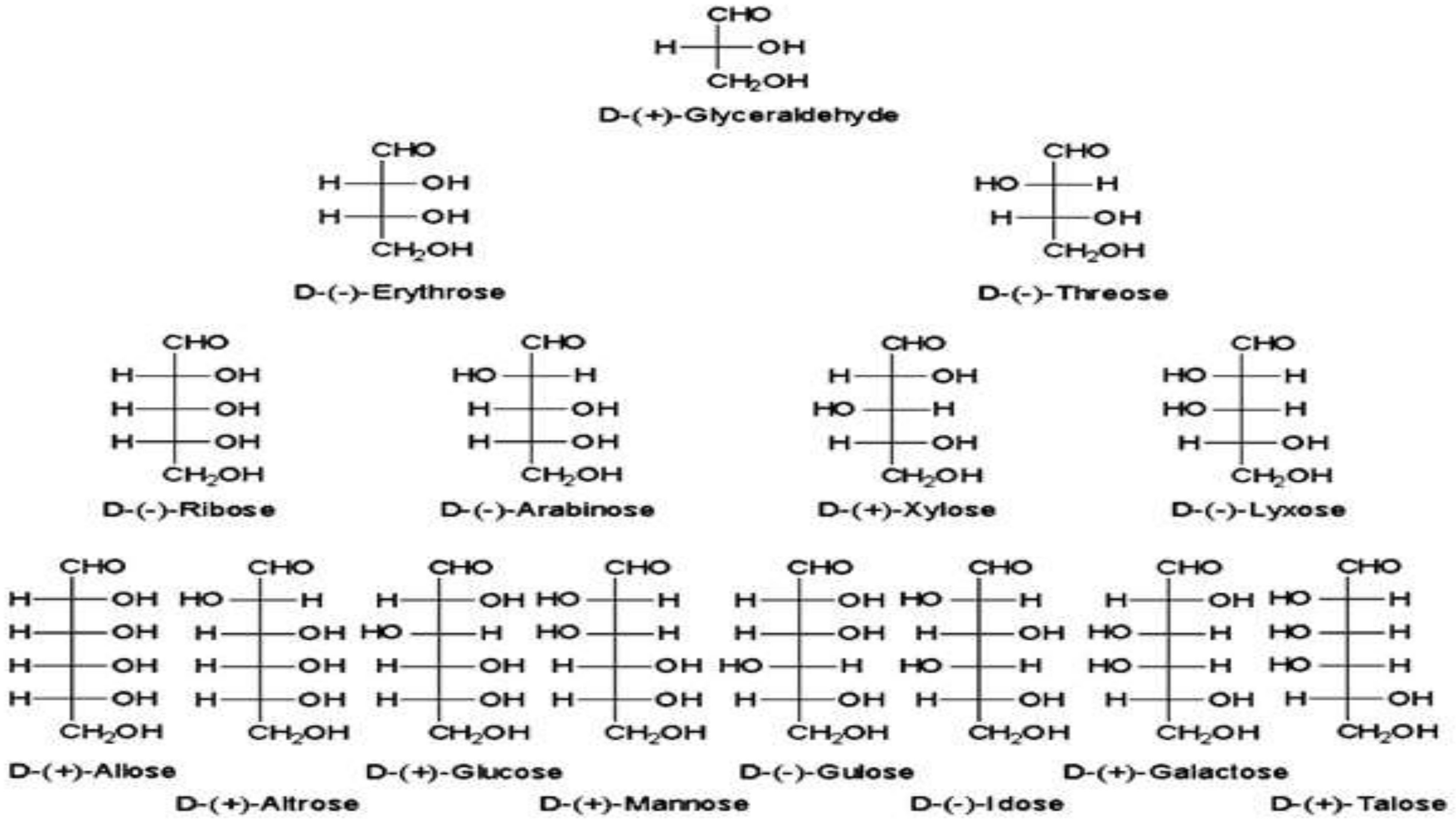
Basic Structure :

- The saccharides encountered in liviBg sytems are generally built of monosaccharides with general formula $(CH_2O)_n$ where n is three or more.

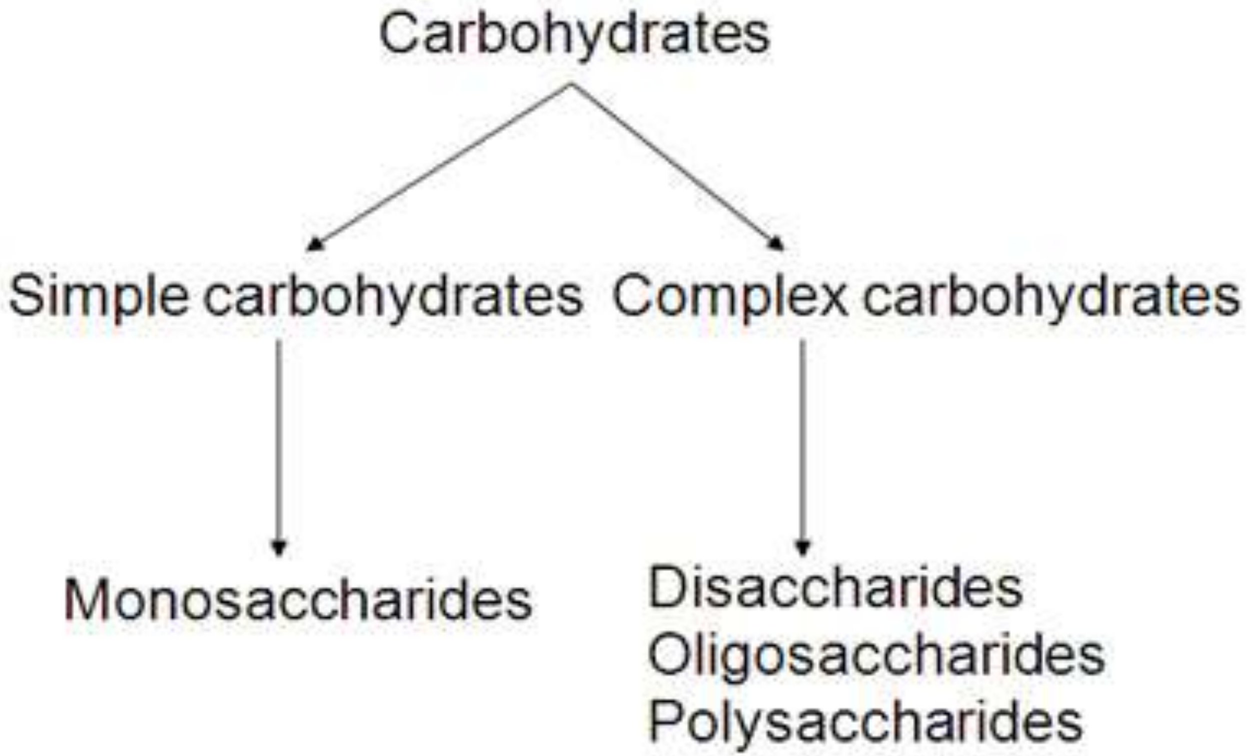
- A typical monosaccharide has the structure H -$(CHOH)_x$ (C = O) - $(CHOH)_y$ - H, containing a ketonic functional group or H - (C = O) - $(CHOH)_x$ - H, containing an aldehydic functional group. It has hydroxyl groups on each carbon atom, excluding the functional group carbon atom.

- Glucose, fructose , ribose, deoxyribose and glyceraldehyde are most commonly occurring monosacchrides in the living systems.

- It is important to note that there are many chemicals that may have the same formula but are not considered to be monosaccharides (e.g., formaldehyde CH_2O and inositol $(CH_2O)_6$.


D-(+)-Glyceraldehyde
D-(-)-Erythrose
D-(-)-Threose
D-(-)-Ribose
D-(-)-Arabinose
D-(+)-Xylose
D-(-)-Lyxose
D-(+)-Allose
D-(+)-Altrose
D-(+)-Glucose
D-(+)-Mannose
D-(-)-Gulose
D-(-)-Idose
D-(+)-Galactose
D-(+)-Talose

Classification of carbohydrates :



Simple Carbohydrates :

- These are made up of a single basic sugar. Simple carbohydrates are responsible for the sweet taste in our food. Fruit sugar, table sugar or corn sugar are all simple sugars. On consumption, these sugars are directly absorbed in the blood and generally used for energy requirements of the body.

- Glucose provides instant energy and reaches different parts of the body via blood, by being quickly metabolized.

- Simple sugars are occur in plenty in natural foods like fruits, vegetables, milk and milk products. Additionally, honey, molasses, corn and maple syrup are also rich sources of simple sugars.

Monosaccharides :

- 'Mono' refers to single.

- These are the basic compounds consisting of carbon, hydrogen and oxygen in the ratio 1:2:1 having the emperical formula of $(CH_2O)_n$.

- Monosaccharides are sweet to taste, colourless crystalline solids, freely soluble in water but insoluble in nonpolar solvents.

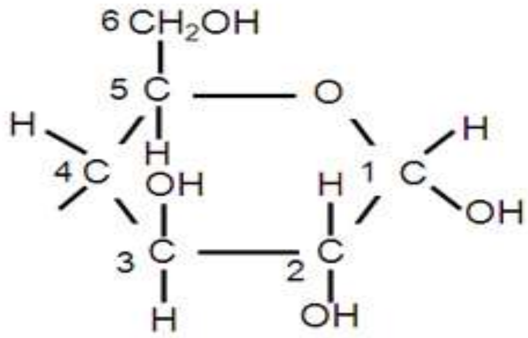
- Glucose, fructose and galactose are types of monosaccharides.

Properties of monosaccharides :

- Simple monosaccharides are reducing agents because of their ability to reduce potential oxidising agents like Cu^{2+} and hydrogen peroxide.They are thus called "reducing sugars".

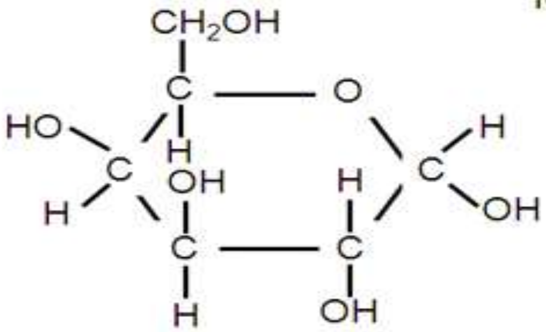
- This reaction forms the basis of Bendict's test for qualitative analysis of simple sugars.

- Glucose, the "blood sugar" and an immediate source of energy for cellular respiration.



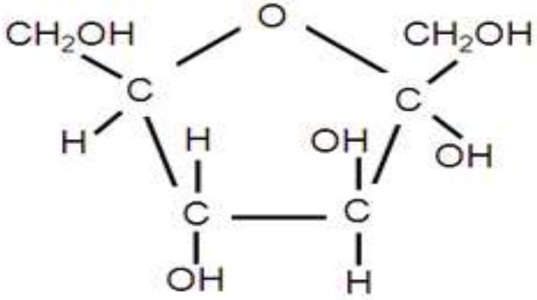
Glucose

Galactose :



Galactose

Fructose, a ketohexose sugar found in honey fruits.



Fructose

Disaccharides :

- When two monosaccharides bond together by a condensation reaction, thereby releasing a molecule of water, a disaccharide is formed. The two monosaccharide units are linked by **glycosidic bond** in α or β anomeric carbon.

- Commonly available disaccahrides are sucrose, maltose and lactose.

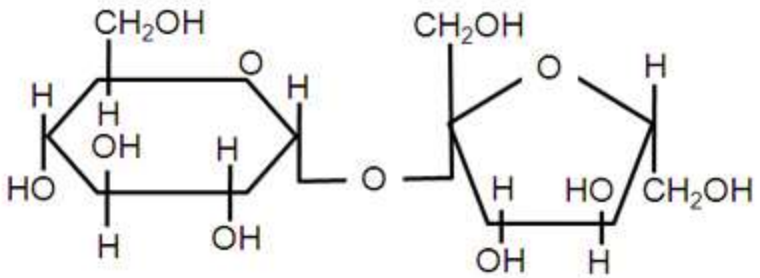
- Disaccharides cannot be absorbed through the wall of the small intestine into the bloodstream. They are therefore hydrolyzed to respective monosaccharides by carbohydares present in small intestine, specifically sucrase or invertase, maltase and lactase (β - galactosidase).

Major Disaccharides :

Sucrose :

- Major carbohydrate present in canesugar, commonly called table sugar.

- Glucose +fructose are linked by α(1 --> 1) glycosidic bonds.



Haworth projection of sucrose

Lactose :

- A major sugar in milk and milk products.
- Glucose + galactose units linked by α(1 --> 4) glycosidic bonds.

Maltose :

- Simplest sugar; present in barley malt and also a product of starch digestion.
- Glucose + glucose linked by α (1 --> 4) glycosidic bonds.

Cellobiose :

The molecule is derived from the condensation of two glucose molecules linked in a β(1 --> 4) fashion. It can be obtained by enzymatic or acidic hydrolysis of cellulose and cellulose rich materials such as cotton, jute or paper.

Oligosaccharides :

- Carbohydrates having more than two or up to ten monosaccharide units are termed as oligosaccharides. Raffinose and stachyose are two major examples of oligosaccharides which consist of repetitive chains of fructose, galactose and glucose.

Polysaccharides :

- Polysaccharides are polymeric carbohydrate structures, formed of repeating units (either mono- or di-saccharides) joined together by glycosidic bonds.

- Polysaccharides have a general formula of $C_x(H_2O)_y$ where x is usually a large number between 200 and 2500.

- These structures are often linear, but may contain various degrees of branching.

- They may be amorphous or even insoluble in water.

Based on the monosccharide units, polysaccharides are broadly put into two categories :

- **Homopolysaccharides :**

If the polysaccharides consists of only one type of monosaccharide units, these are called homopolysaccharides.Common example of homopolysaccharide is starch which comprises of only D - glucose units.

- **Heteropolysaccharides :** When more than one type of monosaccharides are present in a polysaccharide, they are called heteropolysaccharides e.g. pectin (polymer of galactouranic acid and its methylated ester).

Major storage polysaccharides :

Starch :

- Starch constitutes the most predominant storage polysaccharide in nature and is a characteristic storage sugar of all plant cells.

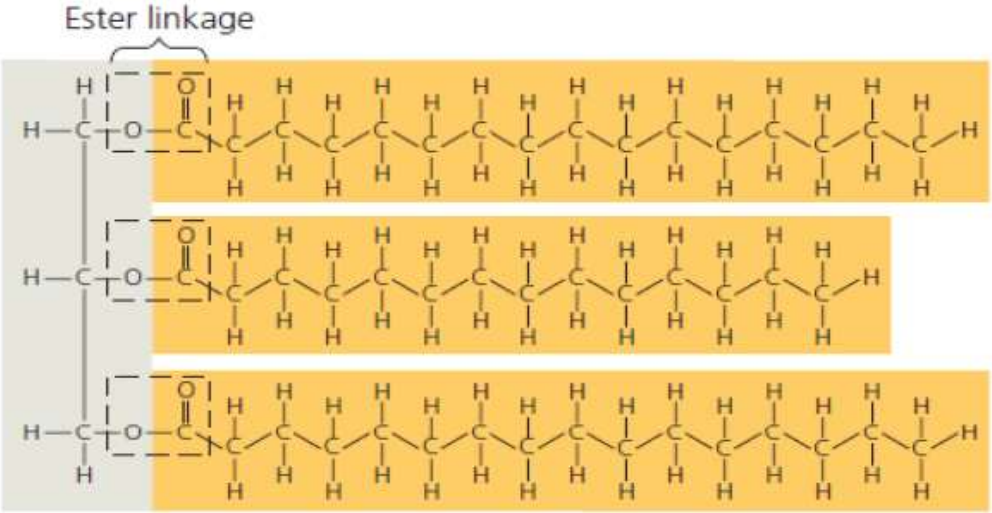
- This is abundant in tubers, like potatoes and corn seeds.

- Starch is a polymer of glucose and contains two types of glucose polymers namely :

(a) **Amylose :** Amylose consists of linear, unbranched chains of several hundred D-glucose residues. The glucose residues are linked by a α(1 --> 4) glycosidic bond between their C1 and C4 carbon atoms. Molecular weight of such chains may extend upto 50000.

Lipids

Fats in Practice



Fat in Theory

Fatty acids, oils, phospholipids, and steroids

What are lipids? :

- Lipids are one among the four major biomolecules of living systems.

- By definition, these are the class of biomolecules which are insoluble or sparingly soluble in aqueous solutions and soluble in organic solvents.

- Fatty acids are major constituents of lipids. Fatty acids are mono carboxylic acid containing short/ long-chain hydrocarbon molecules. Some important fatty acids are enlisted below.

- The numbering of carbons in fatty acids begins with the carbon of the carboxylate group. Fatty acid represented by the total number of carbons e.g, palmitic acid a 16-carbon fatty acid $CH3(CH_2)_{14}COOH$ is designated as C16.

- It is customary to write it as C 16:0 where zero represent that there is no double bond in the fatty acid). If there is one double bond, then it will be written as C:16:1

Representation	Common Name	Structure
4:0	Butyric acid	$CH3(CH_2)_2COOH$
6:0	Caproic acid	$CH3(CH_2)_4COOH$
10:0	Decanoic acid	$CH3(CH_2)_8COOH$
12:0	Lauric acid	$CH3(CH_2)_{10}COOH$
14:0	Myristic acid	$CH3(CH_2)_{12}COOH$
16:0	Palmitic acid	$CH3(CH_2)_{14}COOH$
18:0	Stearic acid	$CH3(CH_2)_{16}COOH$
20:0	Arachidic acid	$CH3(CH_2)_{18}COOH$

Types of fatty acids :

• Saturated fatty acids :

All sets of examples in the previous table were fatty acids that contained no carbon-carbon double bonds. These are called saturated fatty acids. Saturated fatty acids having short carbon chain are liquid at room temperature, whereas long carbon chain fatty acids are solid.

• Unsaturated fatty acids :

These have carbon-carbon double bonds in between, thus leading to unsaturation. The representations for these fatty acids consists of the number of carbon atoms, followed by the number double bond and the place of unsaturation. The place of unsaturation in a fatty acid is indicated by the symbol (Δ) and the number of the first carbon of the double bond in superscript form. Thus oleic acid a 16-carbon fatty acid with one site of unsaturation between carbons 9 and 10, and will be represented by $C16{:}1\Delta^{9}$.

Some commonly occurring unsaturated fatty acids are:

$18{:}1\Delta^{9}$	Oleic acid	$CH_3(CH_2)_7C{=}C(CH_2)_7COOH$
$18{:}2\,\Delta^{9,12}$	Linoleic acid	$CH_3(CH_2)_4C{=}CCH_2C{=}C(CH_2)_7COOH$
$18{:}3\,\Delta^{9,12,15}$	Linolenic acid	$CH_3CH_2C{=}CCH_2C{=}CCH_2C{=}C(CH_2)_7COOH$
$20{:}4\,\Delta^{5,8,11,14}$	Arachidonic acid	$CH_3(CH_2)_3(CH_2C{=}C)_4(CH_2)_3COOH$

The presence of double bonds in unsaturated fatty acids significantly lowers the melting point making them liquid. More the no. of bonds lower the MP.

Biological functions of lipids :

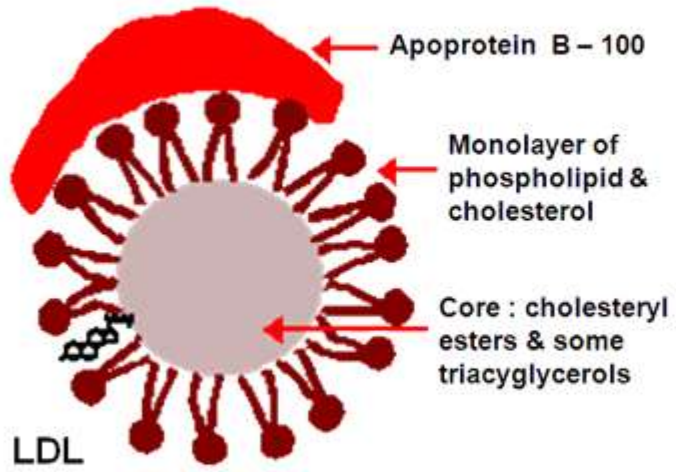
Lipids perform and are involved in variety of important cellular functions. However, following are some of the major physiological functions attributed to lipids :

- Energy source in animals, insects, birds and high lipid seeds e.g. triacyl glycerols.
- Activators of enzymes namely glucose-6-phosphatase, stearoyl CoA desaturase, monooxygenases which are important mitochondrial enzymes.
- Some of the lipids derivatives serve as vitamins and hormones e.g. Prostaglandins.
- Essential components of biological membranes e.g. shingolipids and glycoloipids.
- As lipoproteins in protein modification and recognitions.
- Components of the electron transport system in the inner membrane of mitochondria.

Lipoproteins :

- A lipoprotein is a complex assembly containing both proteins and lipids bonded covalently or non-covalently to the proteins. Enzymes, transporters, structural proteins, antigens, adhesins and toxins are lipoproteins. For eg: HDL (high density lipoprotein), LDL (low density lipoprotein). The lipoprotein particle is composed of an outer shell of phospholipid, which makes it water soluble; a core of fats and a surface apoprotein molecule that allows recognition by the tissues and uptake of the particle.

- The general structure of a lipoprotein is given below :

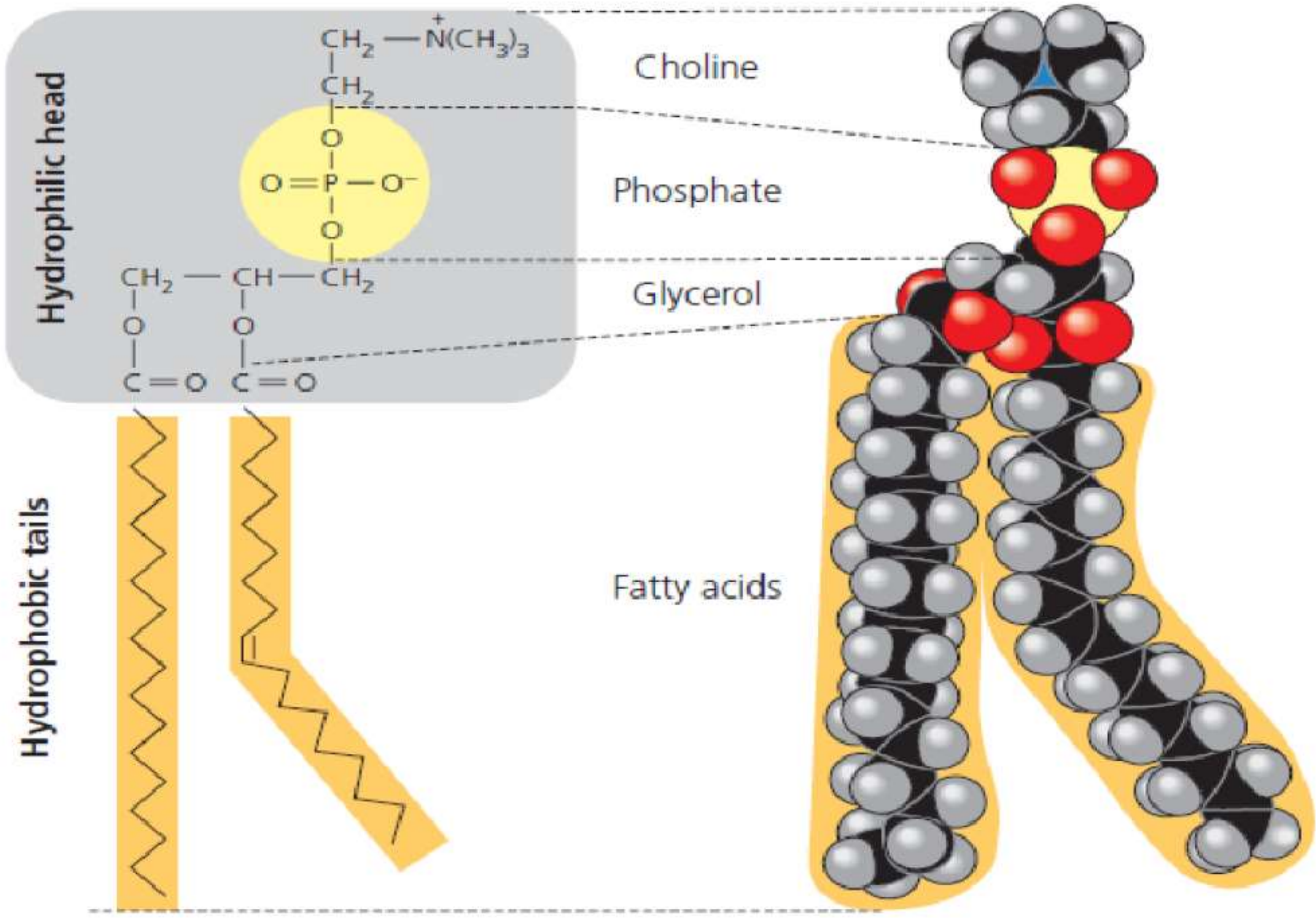


Classification and functions of lipoproteins :

The major function of lipoprotein particles is to transport lipids (fats) (such as triacylglycerol) around the body in the blood. Lipoproteins may be classified on the basis of their density. They may be categorised as :

- **Chylomicron(lowest in density)** which carry triglycerides from the intestine to the adipose tissue.
- **VLDL** (very low density lipoprotein); carry (newly ynthesised) triacylglycerol from the liver to adipose tissue.
- **IDL(intermediate density lipoprotein)**; internediate between LDL and VLDL.
- **LDL(low density lipoprotein)**; carry cholesterol from the liver to cell/tissues of the body.
- **HDL(high density lipoprotein)**; carry cholesterol from the body tissues back to the liver.

Phospholipids



(a) Structural formula

(b) Space-filling model

Phospholipids – Lipid Bilayer

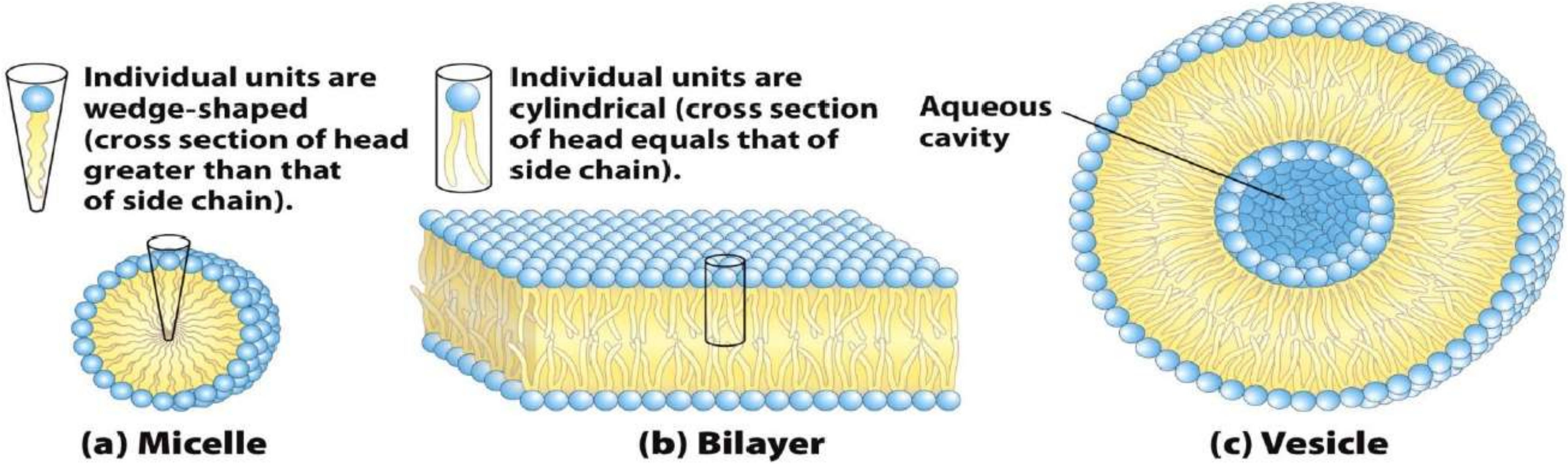


Figure 11-4
Lehninger Principles of Biochemistry, Sixth Edition

Cell Membrane

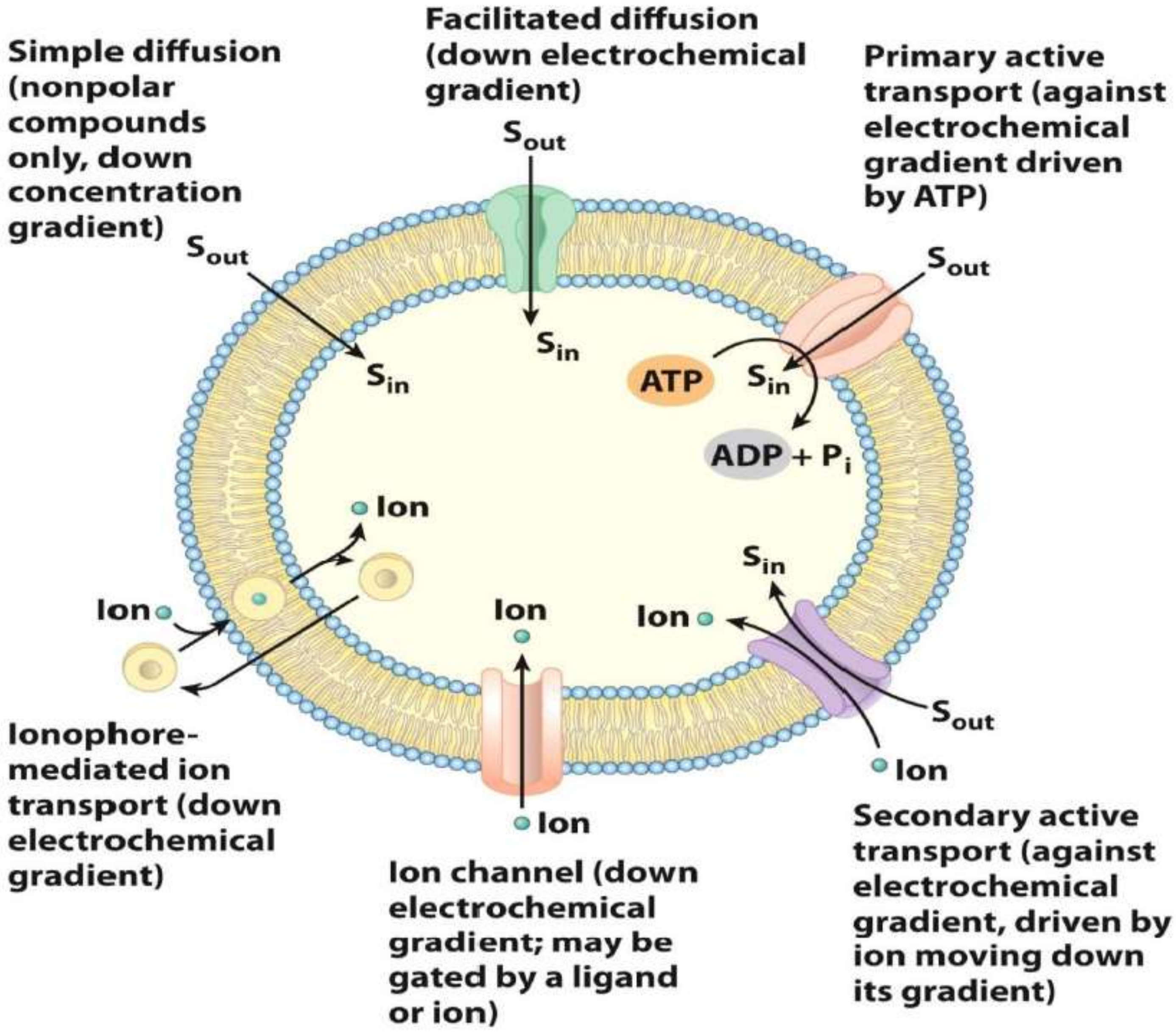


Figure 11-26
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Proteins

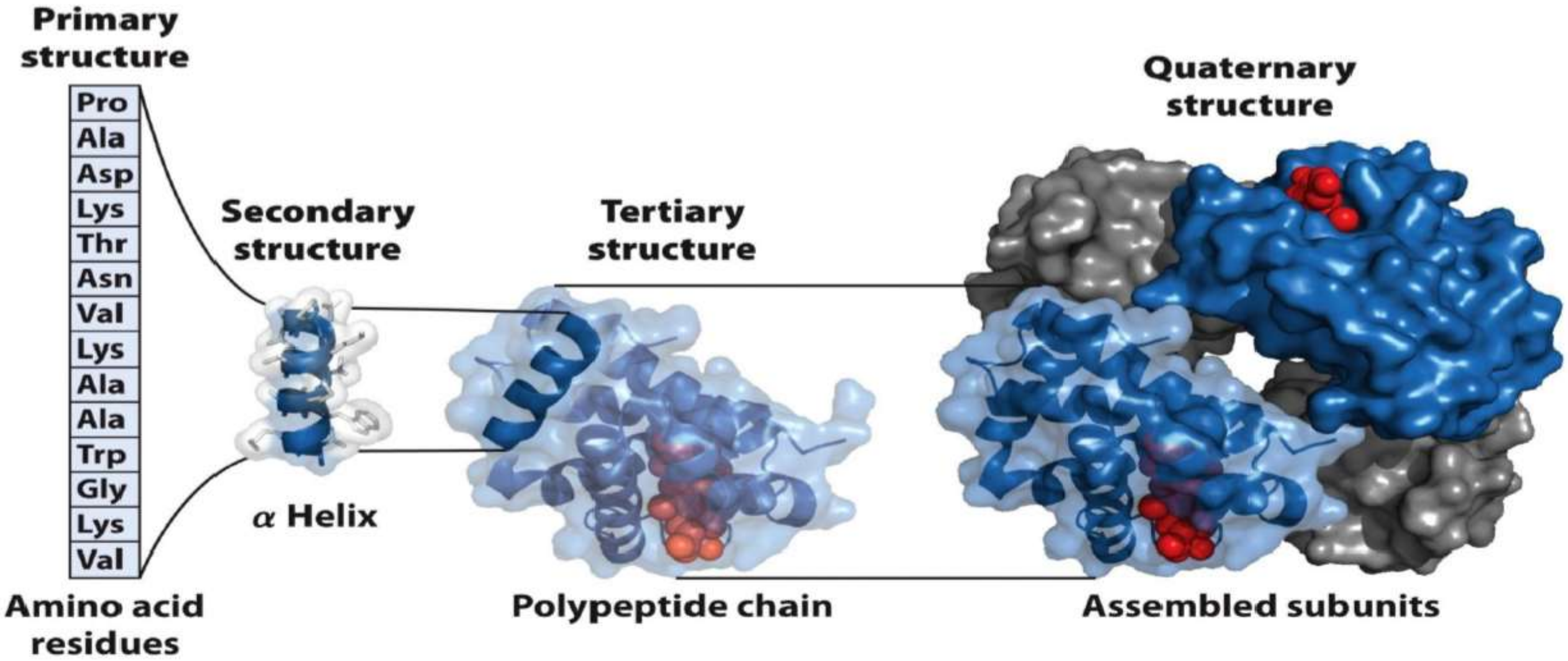


Figure 3-23
Lehninger Principles of Biochemistry, Sixth Edition

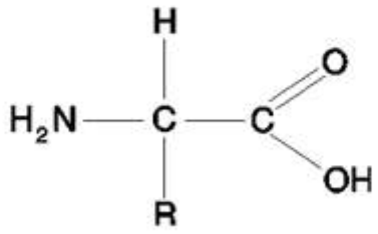
Proteins are made up of Amino Acids (building blocks for proteins)

Proteins

Amino acids-building blocks of proteins

- Proteins are one of the most important class of biomolecules which play pivotal roles in a wide array of cellular activities.

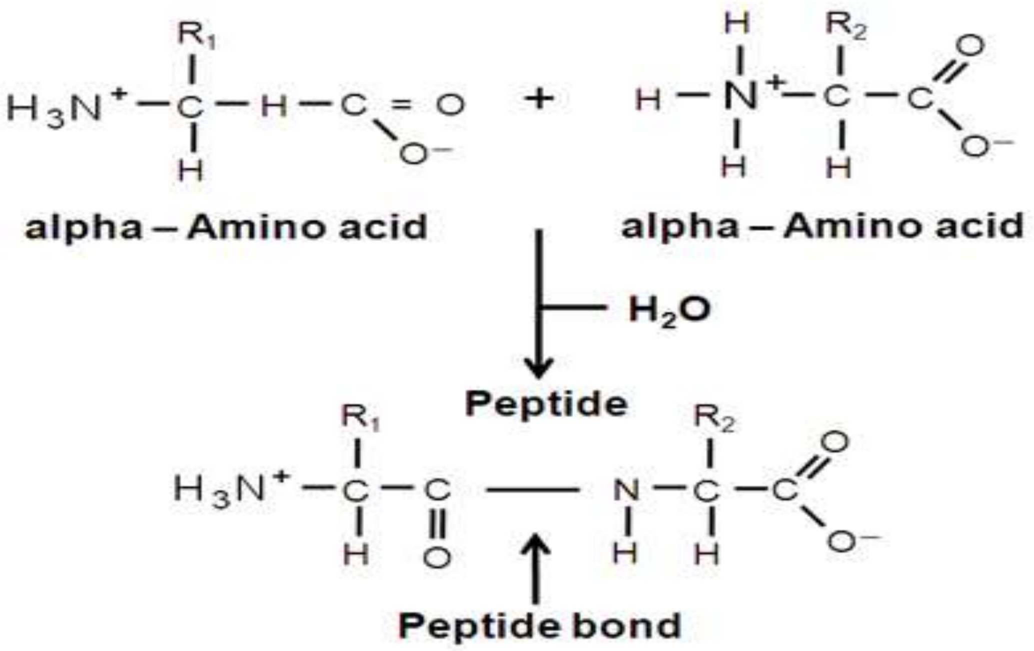
- Proteins are constituted by amino acids, as monomeric unit or building blocks. A typical amino acid has the amino, carboxyl moieties and "R" group (also called as side chain).



Amino acids :

- When dissolved in water, amino acids exists in solution as dipolar ion called "zwitter ion". It can act as an acid (proton donor) or a base (proton acceptor). Because of this dual nature, they are often called as ampholytes.

- Amino acids in the protein are linked by peptide bonds. Thus, two amino acids joined by peptide bond are called di-peptide, three- tripeptide, four- tetrapeptide. The longer chain is called polypeptide. Proteins are made of single or more polypeptide chains.

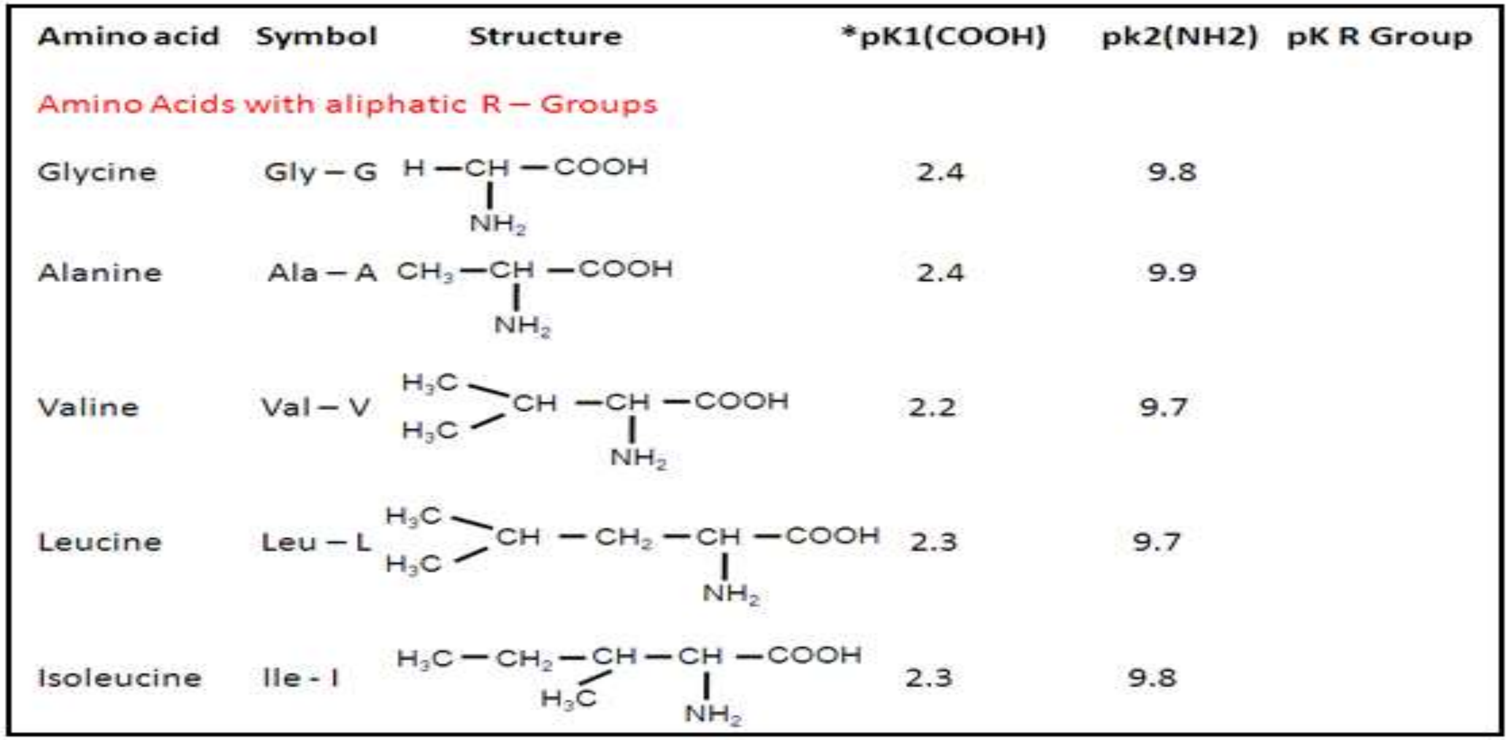


• There are twenty different kind of amino acids found in biological systems beside some unusual amino acids. The nature of R-group varies from amino acid to amino acid.

• Each functional group of amino acid has a fixed pKa value. pKa values of amino acid side chains play an important role in defining the pH-dependent characteristics of a protein. Thus, the ionization state of amino acids will be pH dependent.

• Each amino acid has a standard three letter and one letter abbreviations which are used instead of full name.

Functional groups and pKa values of different amino acids



Amino acid	Symbol	Structure	*pK1(COOH)	pk2(NH2)	pK R Group
Amino Acids with aliphatic R – Groups					
Glycine	Gly – G	$H-CH(NH_2)-COOH$	2.4	9.8	
Alanine	Ala – A	$CH_3-CH(NH_2)-COOH$	2.4	9.9	
Valine	Val – V	$(H_3C)_2CH-CH(NH_2)-COOH$	2.2	9.7	
Leucine	Leu – L	$(H_3C)_2CH-CH_2-CH(NH_2)-COOH$	2.3	9.7	
Isoleucine	Ile - I	$H_3C-CH_2-CH(CH_3)-CH(NH_2)-COOH$	2.3	9.8	

Non-Aromatic Amino Acids with Hydroxyl R-Groups :

Amino acid	Symbol	Structure	*pK1(COOH)	pk2(NH2)	pK R Group
Serine	Ser – S	$HO-CH_2-\underset{NH_2}{\underset{\vert}{CH}}-COOH$	2.2	9.2	~13
Threonine	Thr – T	$\genfrac{}{}{0pt}{}{H_3C}{HO}{>}CH-\underset{NH_2}{\underset{\vert}{CH}}-COOH$	2.1	9.1	~13

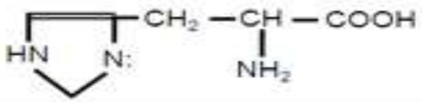
Amino Acids with Sulfur-Containing R-Groups :

Amino acid	Symbol	Structure	*pK1(COOH)	pk2(NH2)	pK R Group
Cysteine	Ser – S	$HS-CH_2-\underset{NH_2}{\underset{\vert}{CH}}-COOH$	1.9	10.8	8.3
Methionine	Met – M	$H_3C-S-(CH_2)_2-\underset{NH_2}{\underset{\vert}{CH}}-COOH$	2.1	9.3	

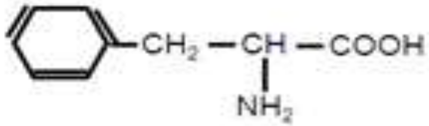
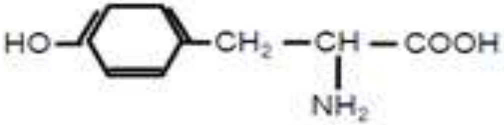
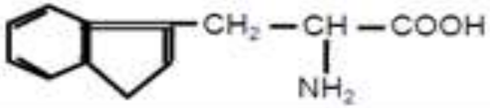
Acidic Amino Acids and their Amides :

Amino acid	Symbol	Structure	*pK1(COOH)	pk2(NH2)	pK R Group
Aspartic Acid	Asp – D	$HOOC-CH_2-CH(NH_2)-COOH$	2.0	9.9	3.9
Asparagine	Asn – N	$H_2N-C(=O)-CH_2-CH(NH_2)-COOH$	2.1	8.8	
Glutamic Acid	Glu – E	$HOOC-CH_2-CH_2-CH(NH_2)-COOH$	2.1	9.5	4.1
Glutamine	Gin – Q	$H_2N-C(O)-CH_2-CH_2-CH(NH_2)-COOH$	2.2	9.1	

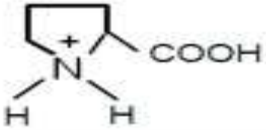
Basic Amino Acids :

Amino acid	Symbol	Structure	*pK1(COOH)	pk2(NH2)	pK R Group
Arginine	Arg – R	$H_2N-C(=NH)-HN-CH_2-CH_2-CH_2-CH(NH_2)-COOH$	1.8	9.0	12.5
Lysine	Lys – K	$H_2N-(CH_2)_4-CH(NH_2)-COOH$	2.2	9.2	10.8
Histidine	His – H		1.8	9.2	6.0

Amino Acids with Aromatic Rings :

Amino acid	Symbol	Structure	*pK1(COOH)	pk2(NH2)	pK R Group
Phenylalanine	Phe – F		2.2	9.2	
Tyrosine	Tyr – Y		2.2	9.1	10.1
Tryptophan T	Trp – W		2.4	9.4	

Imino Acids :

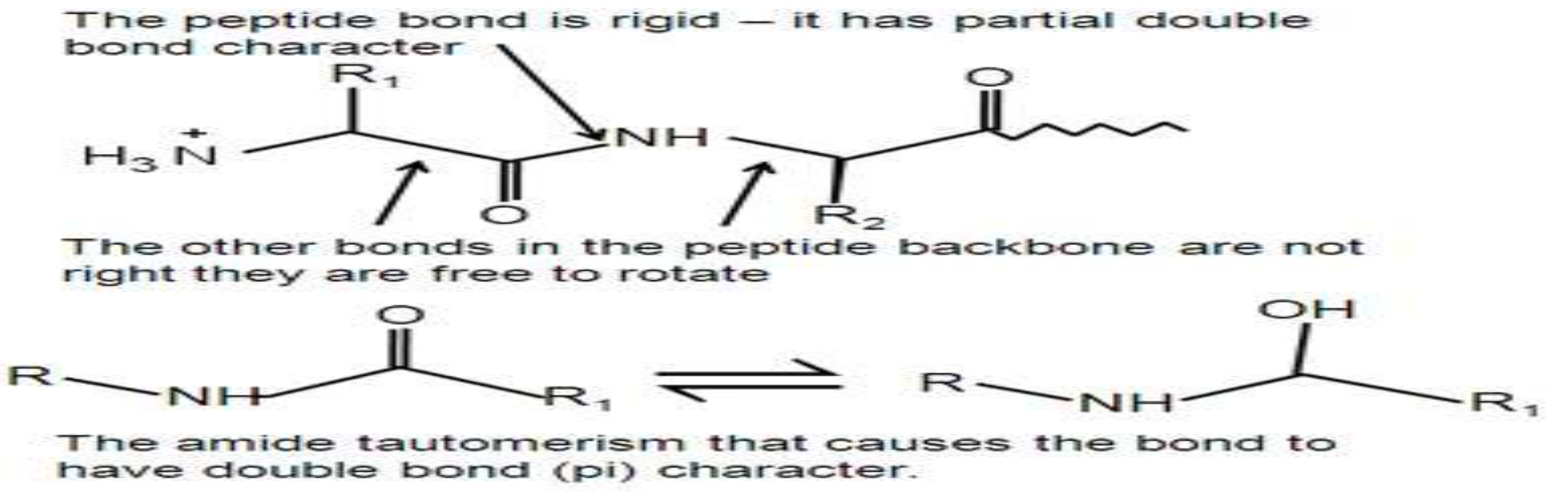
Amino acid	Symbol	Structure	*pK1(COOH)	pk2(NH2)	pK R Group
Proline	Pro – P		2.0		10.6

Peptide bonds :

- Protein chains are held together by peptide bonds, which are simply amide linkages between alpha amino and carboxylic group of neighbouring amino acids. Amino acids linked, through peptide bonds, forms polypeptide. Their molecular weights are expressed in Daltons, (1 Dalton is equal to 1 atomic mass unit).

- Each peptide chain has two free ends, the amino terminus or N-terminal, which is on the left, and the carboxyl terminus or C-terminal, which is on the right. The peptide chains is represented from N-terminal to C-terminal and the sequence of amino acid is written in three letter abbreviations e.g. N-Met-Ser-Tyr-Cys-Val-Lys-Ala-C.

- The peptide bond itself is rigid, and thus is not free to rotate. This rigidity leads to only a definite possible conformation to protein structure.



Protein conformation :

- The spatial arrangement of atoms in a protein is called its conformation.

- The possible conformations of a protein include any structural state that can be achieved without breaking covalent bonds. A change in conformation could occur, for example, by rotation about single bonds. Of the numerous conformations that are theoretically possible in a protein containing hundreds of peptide bonds, one or (more commonly) a few generally predominate under biological conditions.

- The need for multiple stable conformations reflects the changes that must occur in most proteins as they bind to other molecules or catalyze reactions.

- The conformations existing under a given set of conditions are usually the ones that are thermodynamically the most stable, having the lowest Gibbs free energy (G). Proteins in any of their functional, folded conformations are called native proteins.

Structure :

- Proteins have a total of four levels of structures.

- Primary structure.

- Secondary structure.

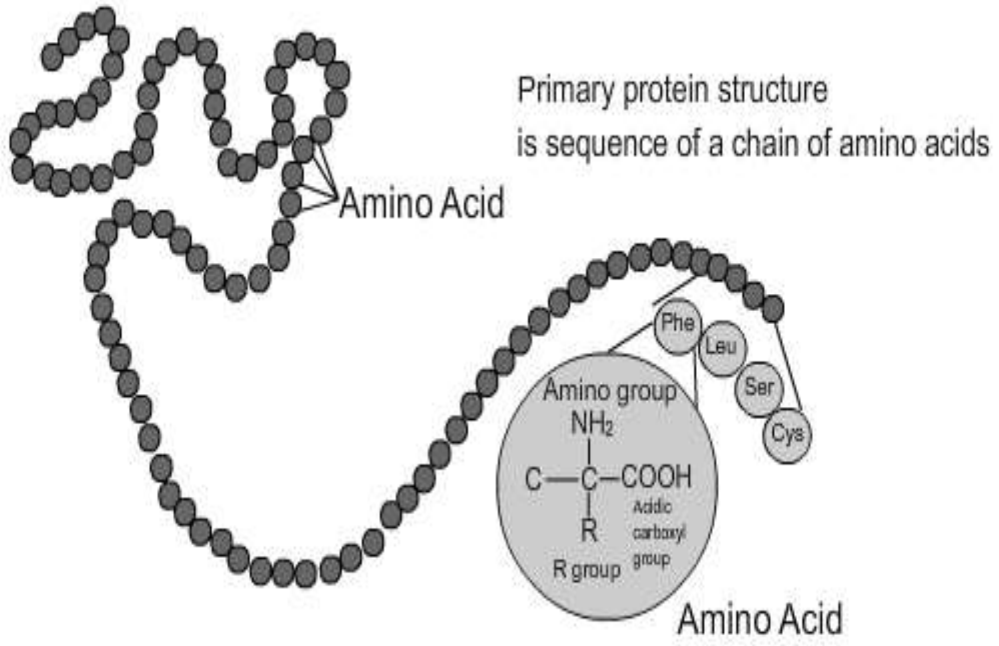
- Tertiary structure.

- Quaternary structure.

- **Primary structure :-**

• The simple amino acid sequence of a protein is called as its primary structure.

• Since the possible way of arrangement of the chain will depend on the sequence of amino acid residues leading to proper protein folding, the primary structure dictate three dimensional structure of the proteins.



- **Secondary structure :-**

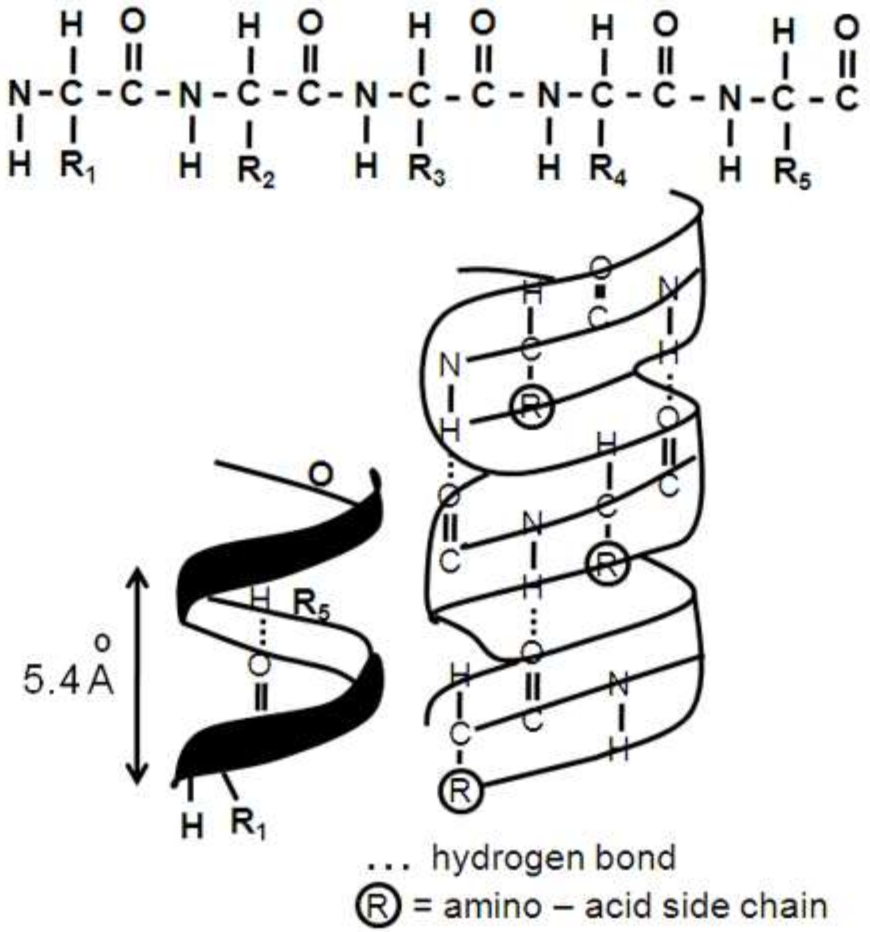
  • This defines the interaction of closely located amino acids in a chain. Two main types of secondary structures observed in the proteins are helices (α helices) and pleated sheets (β pleated sheets).

  • Alpha helix is a helical structure around an axis.

  • This is coiled in clockwise (right handed) manner. It has an average of 3.6 amino acids per turn. Please write other dimensions too.

  • There are 3.6 residue per turn with in a fix pitch of 5.4^0A

  • Thus the rise per residue come out to be 1.5^0A. In a typical α - helix ϕ value ranges from 113 to 132^0 and ψ from 123 to 136^0.

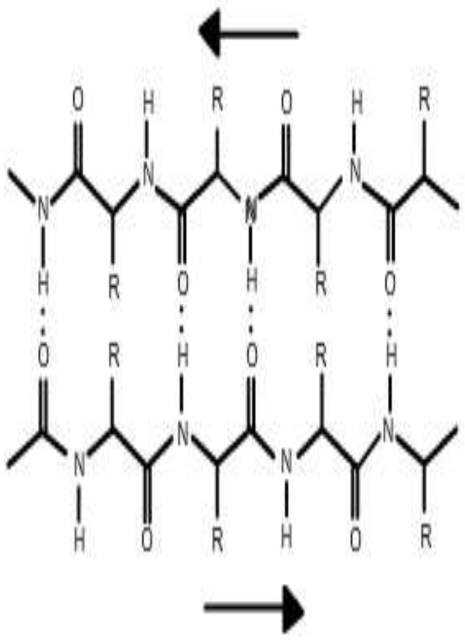


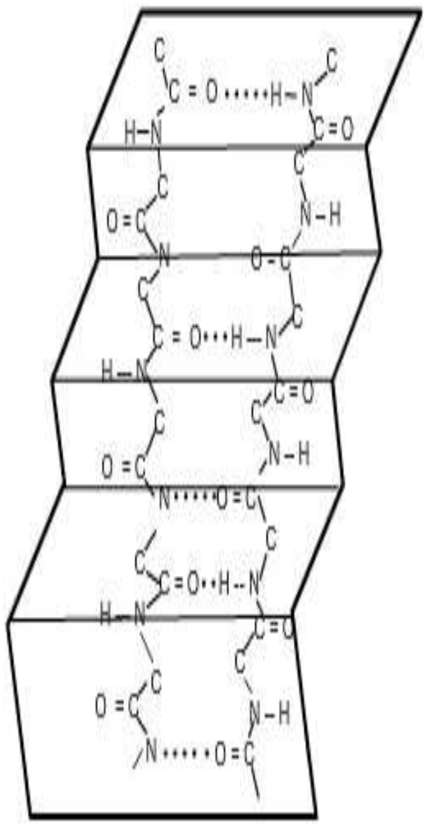
The reason as to why alpha helices form more readily in proteins than any other possible conformations is that these arrangements make optimal use of internal hydrogen bonds to attain stability. The helix is stabilized by hydrogen bonding between the carbonyl of each first amino acid of the chain to the NH of the amino acid four residues away. All main chain amino and carboxyl groups are thus hydrogen bonded, and the R groups stick out from the structure in a spiral arrangement.

- **Beta pleated sheet** is composed of two or more straight chains that are hydrogen bonded side by side. If the amino termini are on the same end of each chain, the sheet is termed parallel, and if the chains run in the opposite direction (amino terminal on opposite ends), the sheet is termed antiparallel.

  Pleated sheets may be formed from a single chain if it contains a beta turn, which forms a hairpin loop structure. Often a proline can be found in a beta turn, since it places a "kink" in the chain.

  Glycine and Ala are predominant amino acids in beta sheet.



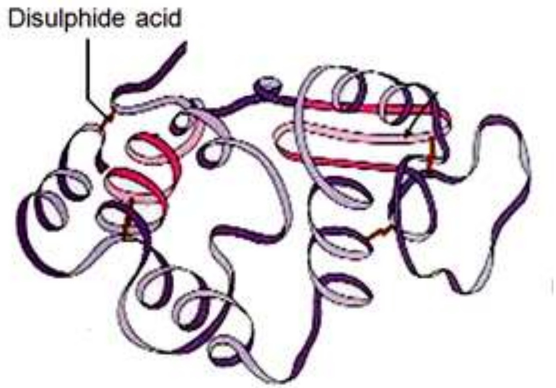


- • **Tertiary structure :-** refers to the arrangement of amino acids in the space i.e. in three dimensional form.

  • Distinct amino acid are brought closer in chain are further linked by :

  - polar-polar interaction,
  - hydrophobic interaction,
  - ionic interaction,
  - disulfide bonds,
  - Van der Waals forces.
  - hydrogen bonds.

  • **Hydrophobic amino acids :-** are buried inside the core of protein and charged and polar group are located on the surface which tend to cluster and exclude water. This allows a protein to have greater water solubility.



Tertiary Structure

• **Quaternary structure :-** If protein consists of more than one polypeptide chains, their association with each other – implies the Quaternary structure.

Accordingly protein are termed as dimeric (wherein one chain is referred as monomeric unit), trimeric or oligomeric. If the chains are similar i.e. have same amino acid sequence these are called homomeric or heteromeric if chains are different.

• Proteins have also been put into two major groups :

(a) **Fibrous proteins**, having polypeptide chains arranged in long strands or sheets.

(b) **Globular proteins**, having polypeptide chains folded into a spherical or globular shape.

• The two groups are **structurally distinct :** fibrous proteins usually consist largely of a single type of secondary structure; globular proteins often contain several types of secondary structure e.g a- keratins are predominantly alpha helix whereas silk proteins are beta –sheets.

• The two groups differ **functionally** in that the structures that provide structure, support, shape, and external protection to vertebrates are made of fibrous proteins, whereas most enzymes and regulatory proteins are globular proteins.

Quaternary Structure

Structural Organization of Proteins

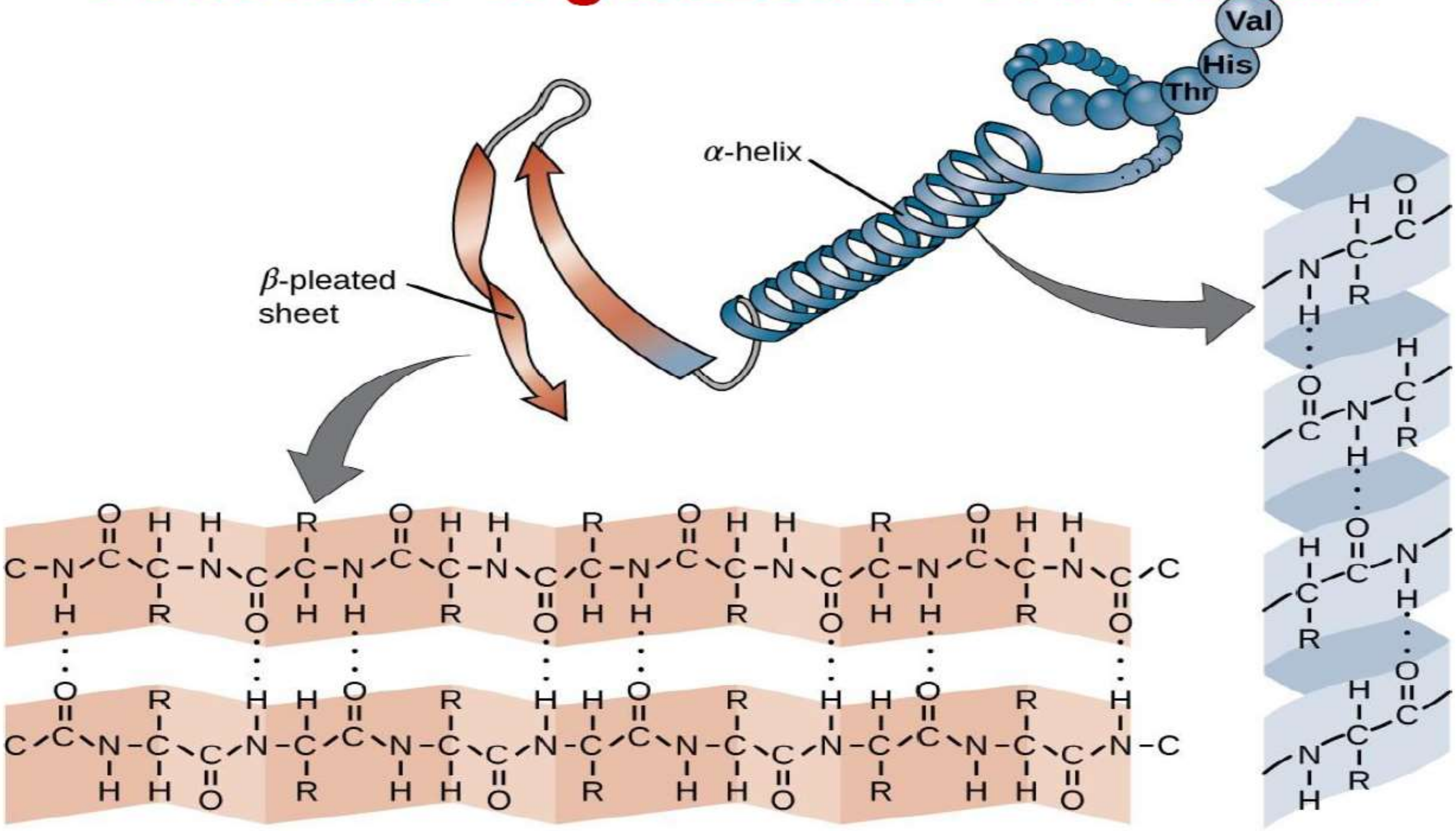
- **Primary Structure:** two dimensional, simple chain of AA with peptide (covalent) bond e.g. Insulin

- **Secondary Structure:** Various functional groups exposed on outer surface interact with hydrogen bonds
  α-helix – e.g. keratin, hair, fur, clans, hooves
  β-pleated – B. keratin of feathers, silk fibroin
  Collagen Helix: 3 α-helices coiled around one another

- **Tertiary Structure:** Additional bonds between functional groups, twisting of secondary structure, weak covalent and high energy disulphide bonds are formed e.g. Myoglobin

- **Quaternary** Structure: Formed as a result of 2-more polypeptide chain and have specific orientation

Structural Organization of Proteins



Different Types of Proteins

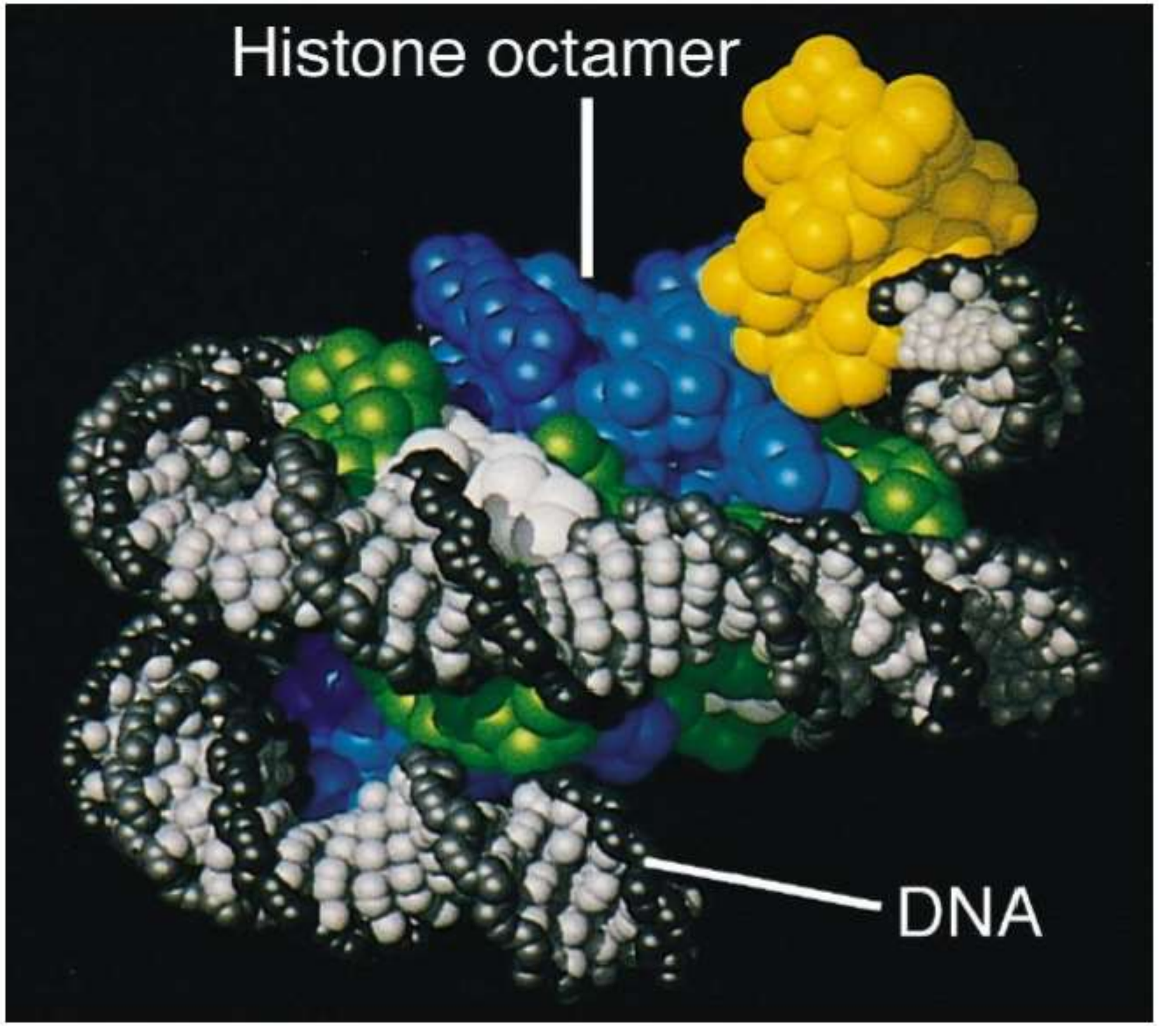
Types of proteins according to structure

1. **Fibrous** – collagen fibres, keratin, elastin, fibrin, fibroin, actin, myosin
2. **Globular** – glutelin, protemine, globulin, albumin, glutenin, orygemin.
3. **Intermediate** – myosin, fibrinogen

Types of proteins according to chemical nature

1. **Simple** – only AA. Albumin, globulin, protanine, fish, prolamine (corn, pl, wheat), histone (corn, wheat), glutelin (glutenin), keratin.
2. **Conjugated** – protein + non protein (prosthetic group) e.g. **Nucleoprotein** (nucleic acid), **chromoprotein** (Hb, cytochrome), **metallo** (with metals Zn, Fe), **lipoprotein**, **glycoprotein** etc.

Structural Proteins



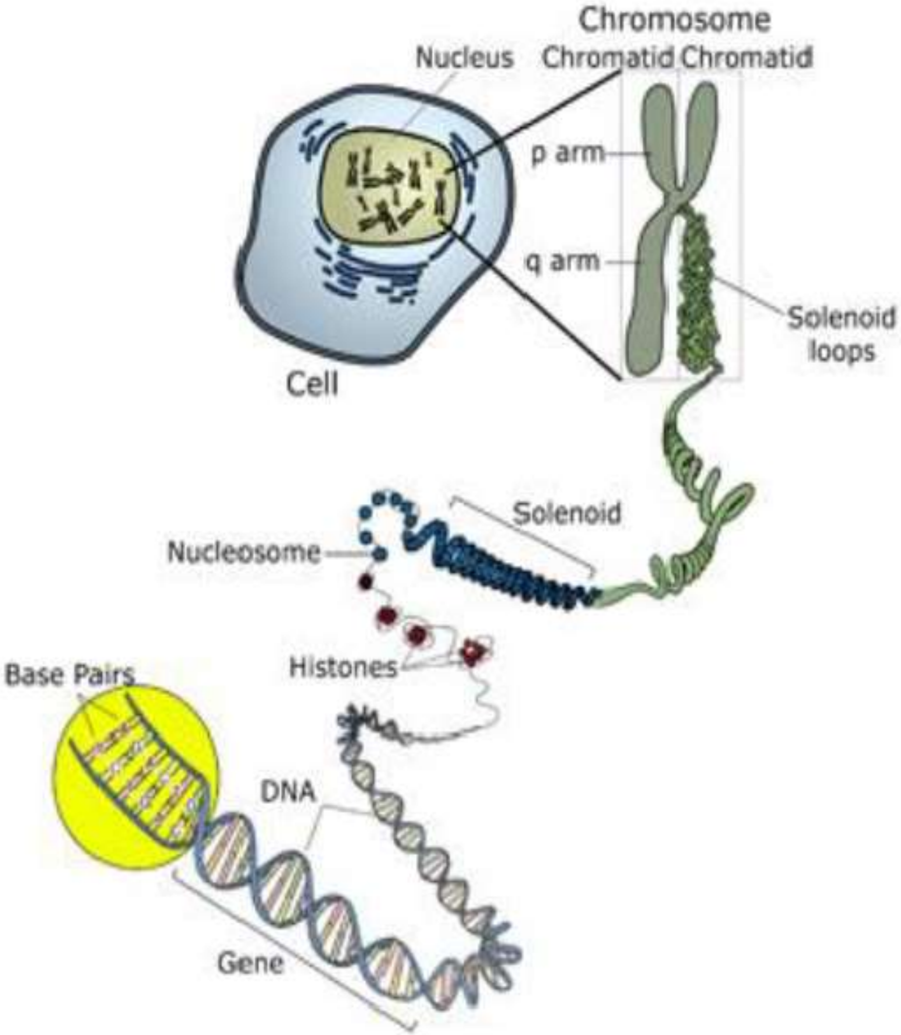
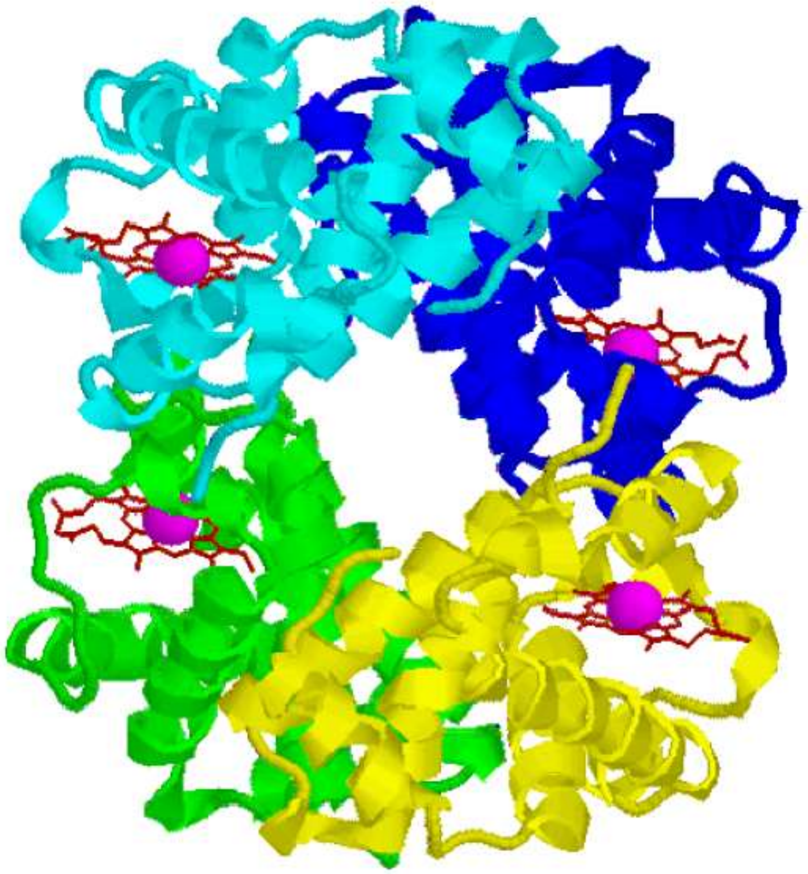
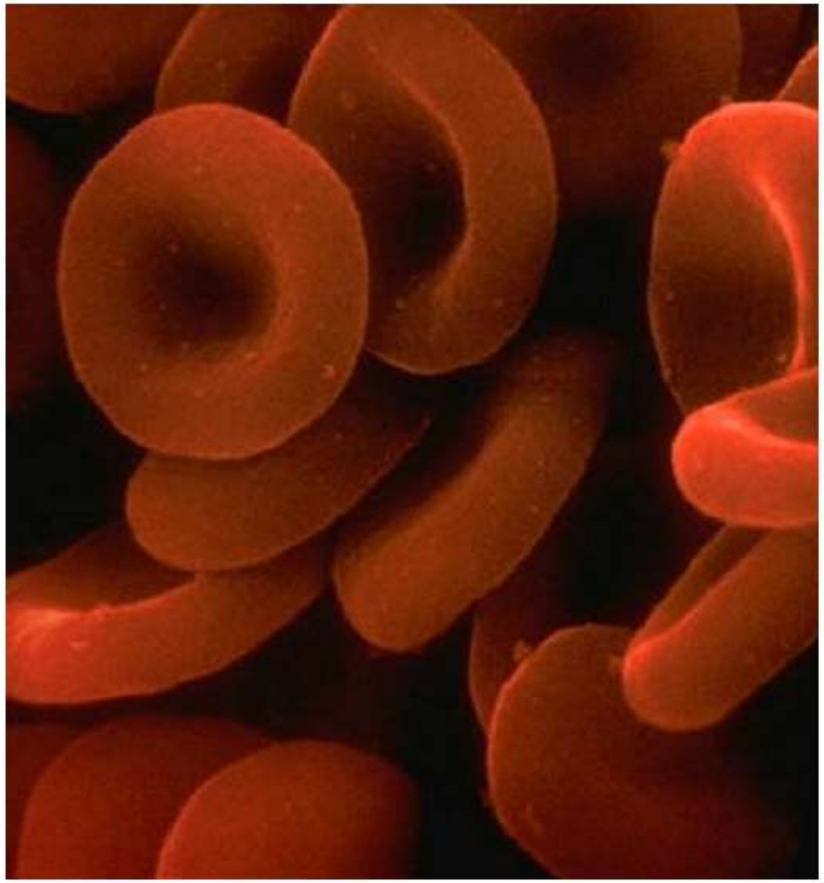


Image adapted from: National Human Genome Research Institute.

Transport Proteins

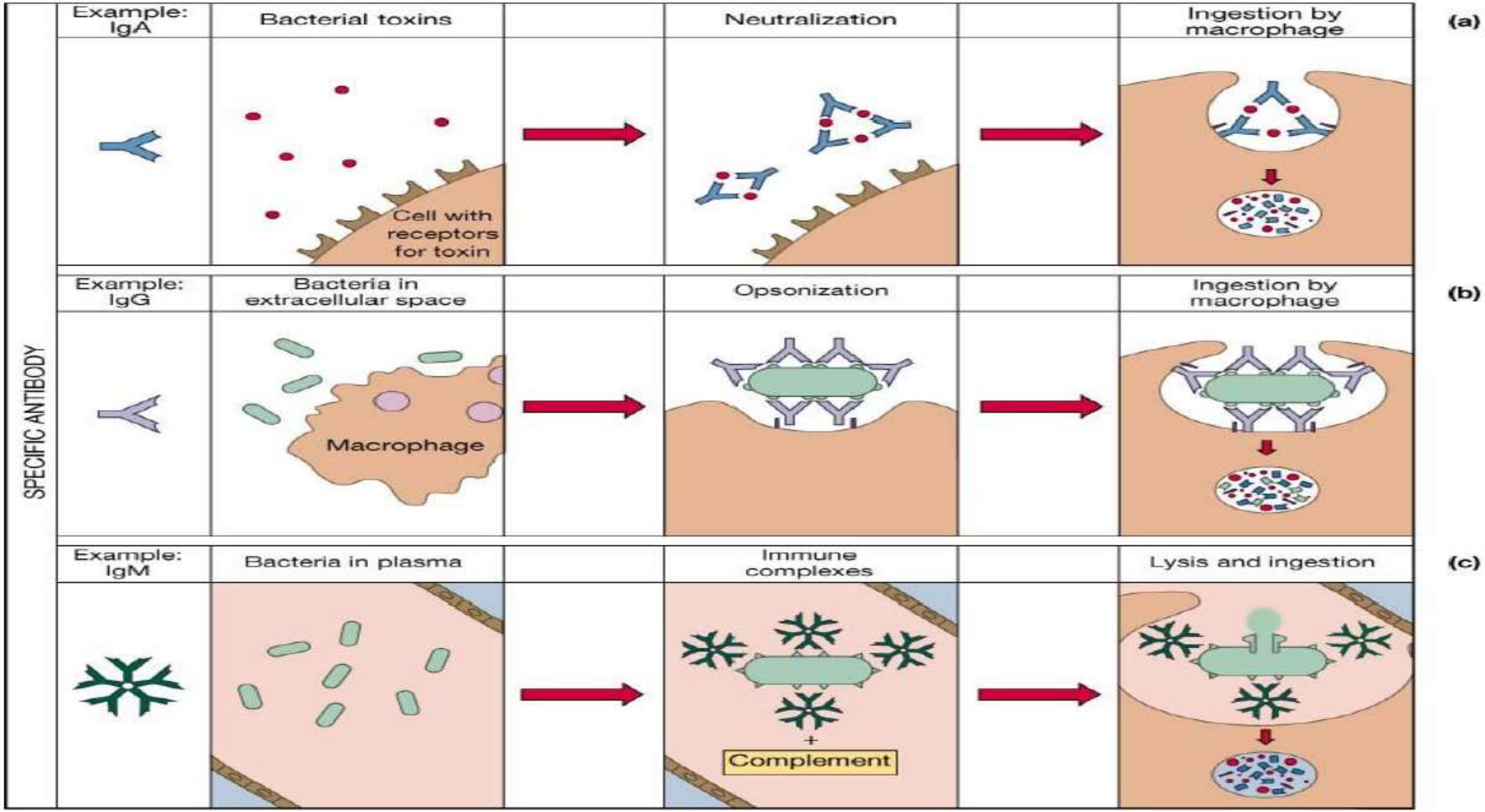


Hemoglobin

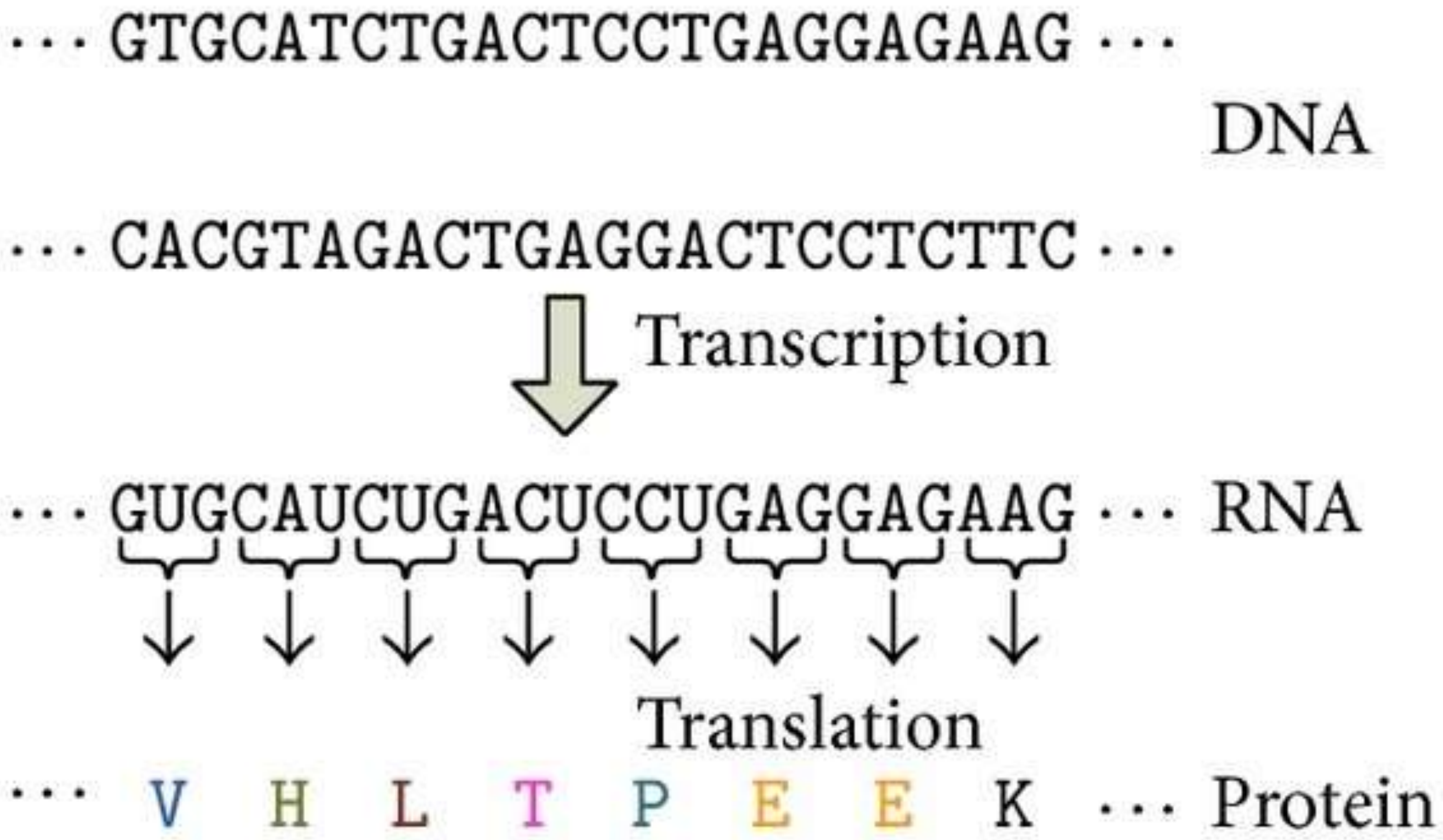


Red Blood Cell

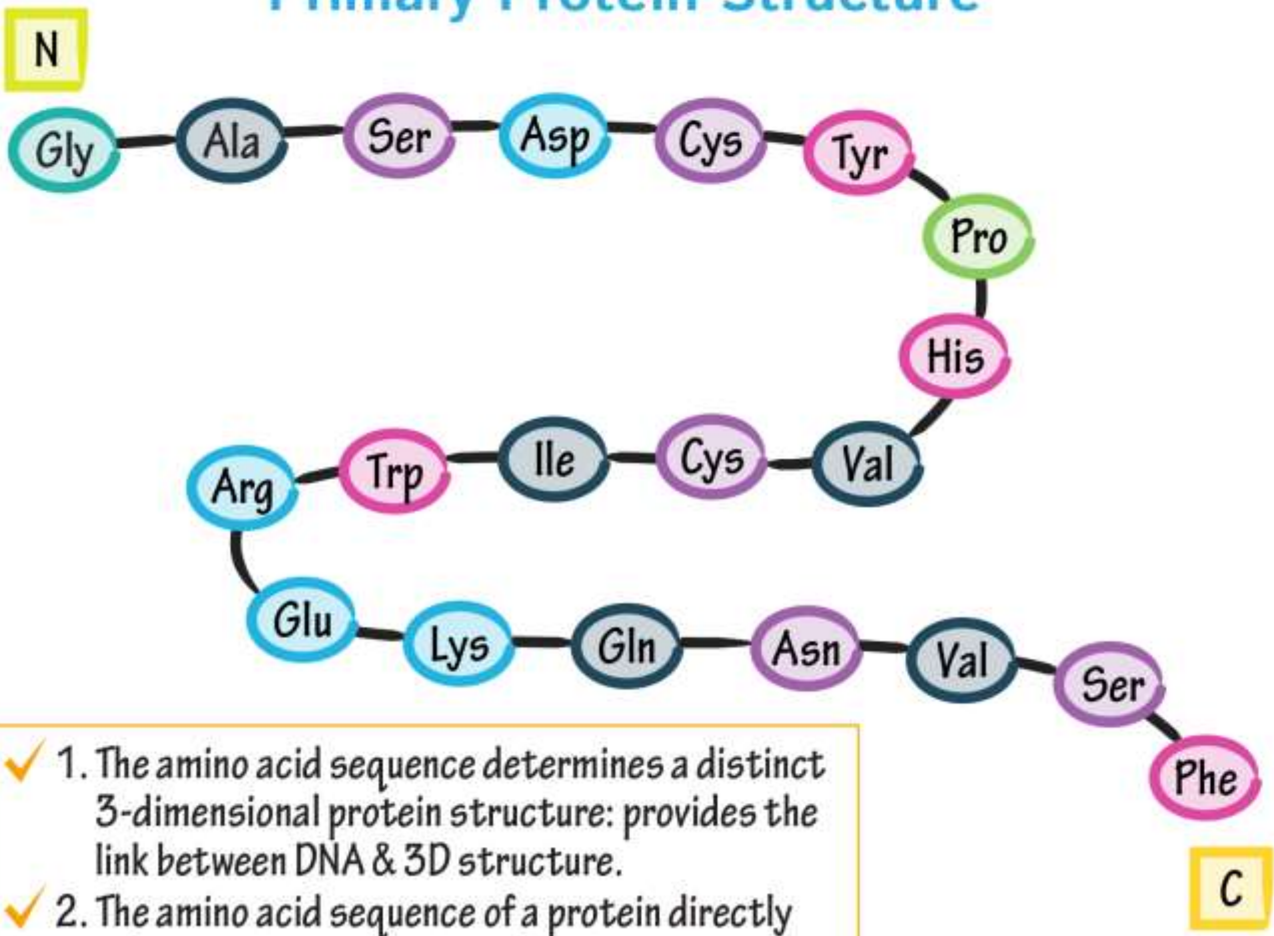
Immunity: Antibodies



The central dogma of Life

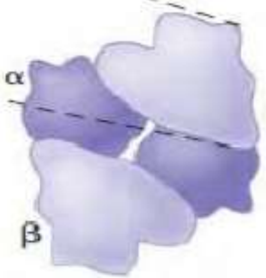
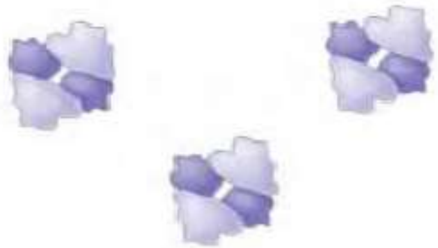
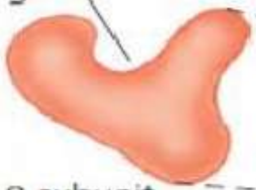
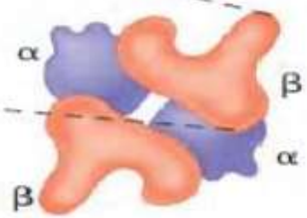
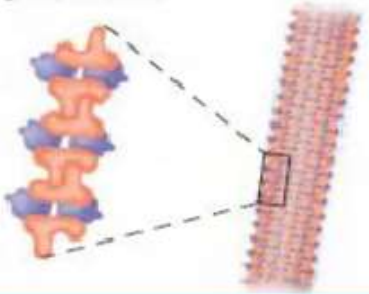


Primary Protein Structure



- ✓ 1. The amino acid sequence determines a distinct 3-dimensional protein structure: provides the link between DNA & 3D structure.
- ✓ 2. The amino acid sequence of a protein directly relates to its mechanism of action.
- ✓ 3. Changes in amino acid sequence (even of a single amino acid) can disrupt normal protein function and result in disease.
- ✓ 4. Protein sequence gives insight into its evolutionary history as proteins with a common ancestor have similar sequences.

Sickle-cell Anemia

	Primary Structure	Secondary and Tertiary Structures	Quaternary Structure	Function	Red Blood Cell Shape
Normal hemoglobin	1 Val 2 His 3 Leu 4 Thr 5 Pro 6 Glu 7 Glu	 β subunit	Normal hemoglobin  	Molecules do not associate with one another; each carries oxygen. 	Normal red blood cells are full of individual hemoglobin molecules, each carrying oxygen.  10 μm
Sickle-cell hemoglobin	1 Val 2 His 3 Leu 4 Thr 5 Pro 6 Val 7 Glu	Exposed hydrophobic region  β subunit	Sickle-cell hemoglobin  	Molecules interact with one another and crystallize into a fiber; capacity to carry oxygen is greatly reduced. 	Fibers of abnormal hemoglobin deform red blood cell into sickle shape.  10 μm

Functions of proteins :

Proteins carry out most diverse and possibly the largest volumes of cellular functions. Some of the key functions are summarized as below :

- Biocatalysis- Almost all the biological reactions are catalyzed by the enzymes. These are substrate specific and carry out reactions at very high rates under mild physiological conditions. Several thousand enzymes have been identified to date.

- Membrane are constitute of lipoprotein and some proteins are integral part of membrane. Receptors found on the membrane are also protein in nature.

- Transport and storage proteins - small molecules are often carried by proteins in the physiological setting e.g. haemoglobin is responsible for the transport of oxygen to tissues.

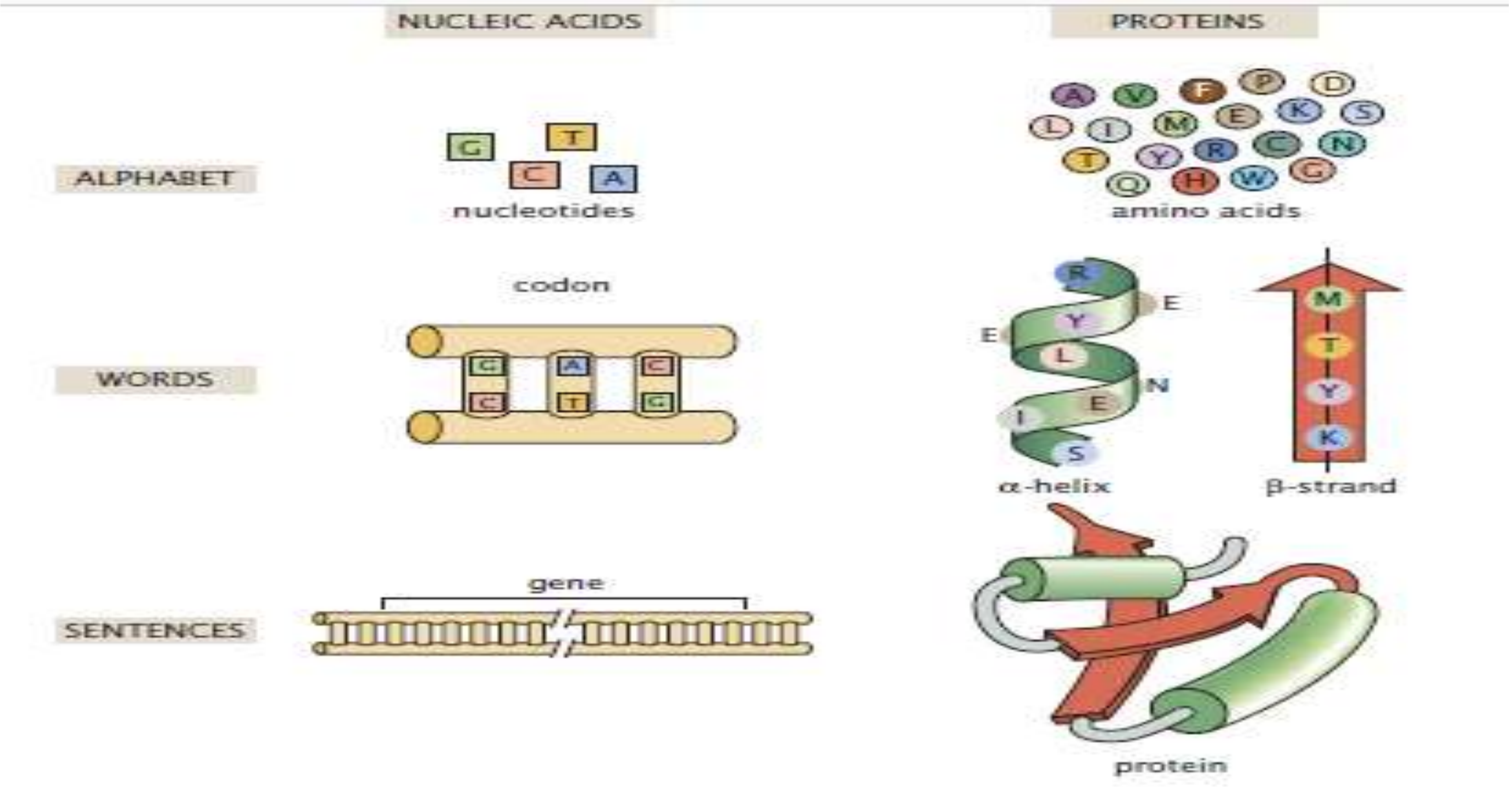
- Muscle are made up of proteins and their contraction is done by actin and myosin protein.

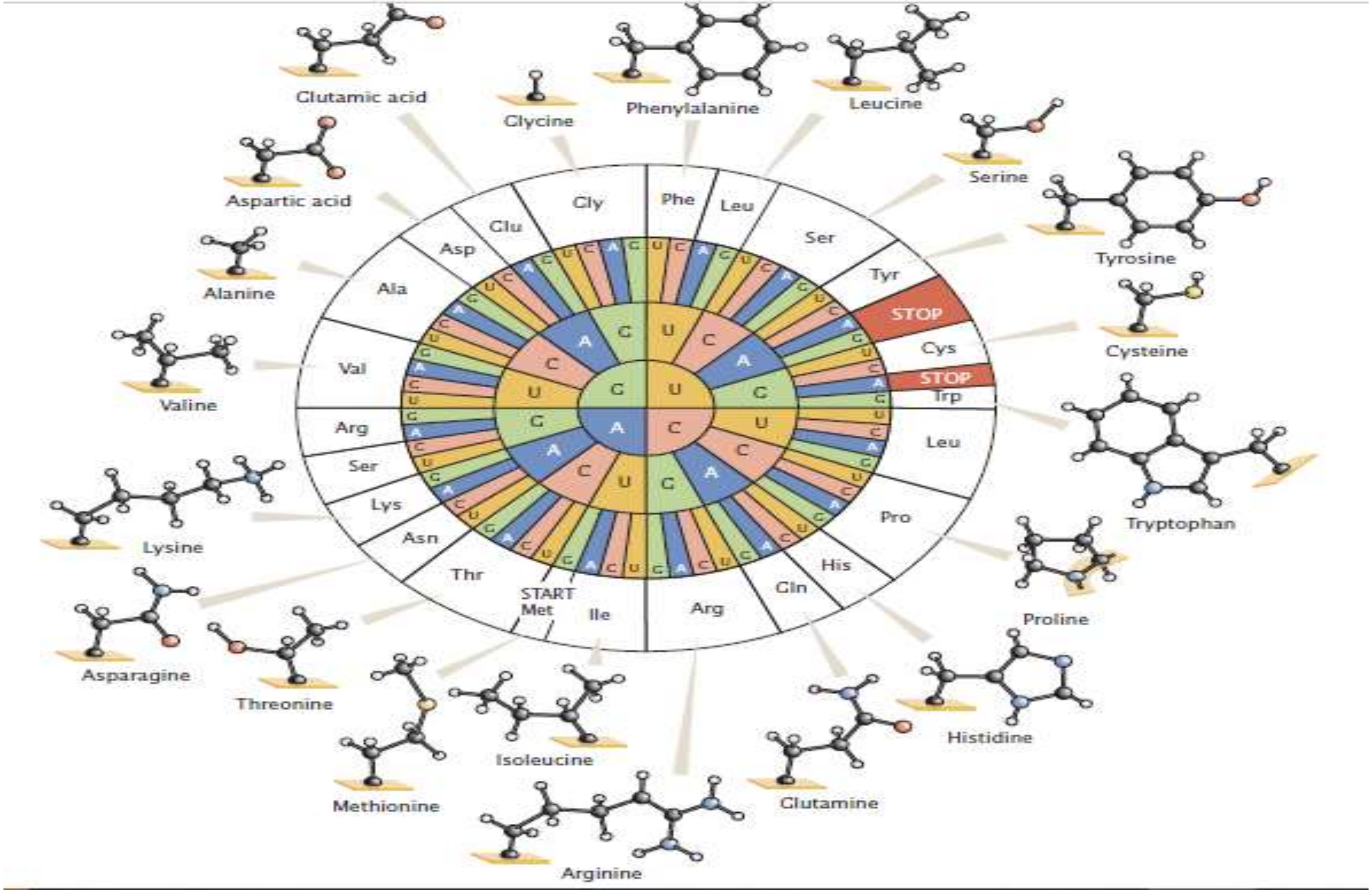
- Mechanical support - skin and bone are strengthened by the protein collagen.

- Antibodies of immune system are protein structures.

- Many of the hormones and growth factors such as insulin or thyroid stimulating hormone are proteins.

Nucleic Acids and Proteins Are Polymer Languages with Different Alphabets

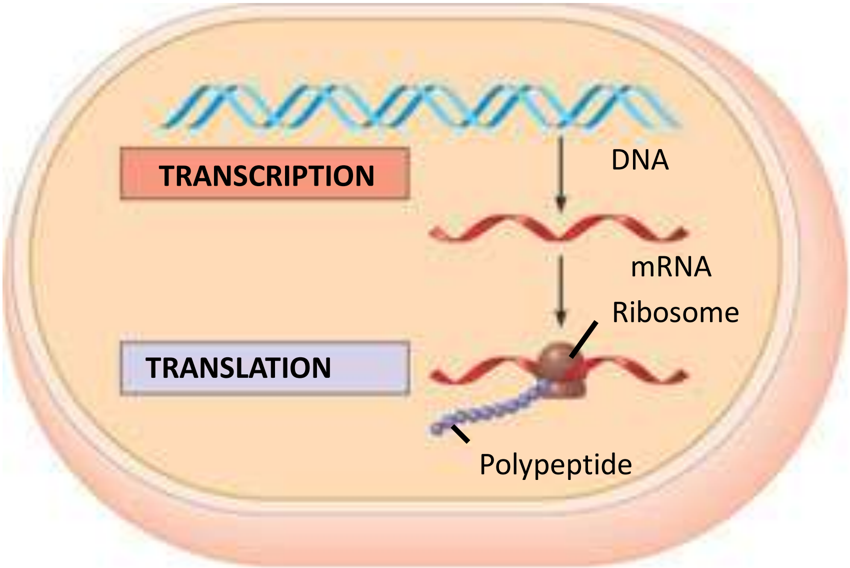



Glutamic acid
Glycine
Phenylalanine
Leucine
Serine
Tyrosine
Cysteine
Tryptophan
Proline
Histidine
Glutamine
Arginine
Isoleucine
Methionine
Threonine
Asparagine
Lysine
Valine
Alanine
Aspartic acid
Gly
Phe
Leu
Ser
Tyr
STOP
Cys
STOP
Trp
Leu
Pro
His
Gln
Arg
Ile
START
Met
Thr
Asn
Lys
Ser
Arg
Val
Ala
Asp
Glu

Basic Principles of Transcription and Translation

- Transcription
  - Is the synthesis of RNA under the direction of DNA
  - Produces messenger RNA (mRNA)
- Translation
  - Is the actual synthesis of a polypeptide, which occurs under the direction of mRNA
  - Occurs on ribosomes

- In prokaryotes
  - Transcription and translation occur together



(a) **Prokaryotic cell.** In a cell lacking a nucleus, mRNA produced by transcription is immediately translated without additional processing.

Figure 17.3a

- In eukaryotes
  - RNA transcripts are modified before becoming true mRNA

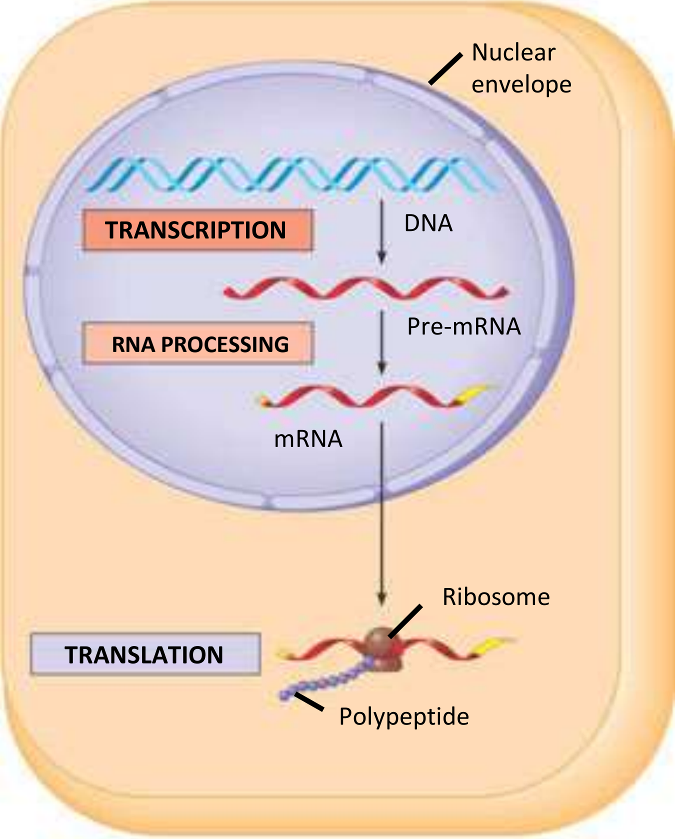


Figure 17.3b

(b) Eukaryotic cell. The nucleus provides a separate compartment for transcription. The original RNA transcript, called pre-mRNA, is processed in various ways before leaving the nucleus as mRNA.

- Cells are governed by a cellular chain of command
  - DNA $\rightarrow$ RNA $\rightarrow$ protein

The Genetic Code

Codons: Triplets of Bases

- Genetic information
  - Is encoded as a sequence of nonoverlapping base triplets, or codons

- During transcription
  - The gene determines the sequence of bases along the length of an mRNA molecule

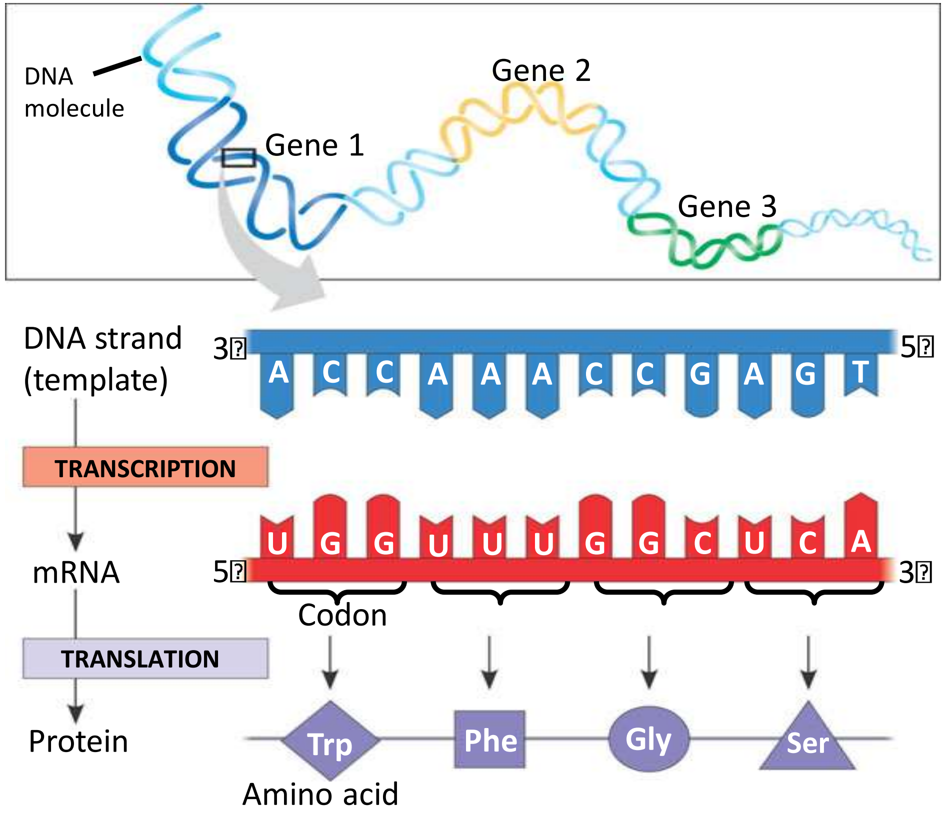


Figure 17.4

Cracking the Code

- A codon in messenger RNA
  - Is either translated into an amino acid or serves as a translational stop signal

First mRNA base (5′ end)	Second mRNA base: U	Second mRNA base: C	Second mRNA base: A	Second mRNA base: G	Third mRNA base (3′ end)
U	UUU, UUC: Phe UUA, UUG: Leu	UCU, UCC, UCA, UCG: Ser	UAU, UAC: Tyr UAA: Stop UAG: Stop	UGU, UGC: Cys UGA: Stop UGG: Trp	U C A G
C	CUU, CUC, CUA, CUG: Leu	CCU, CCC, CCA, CCG: Pro	CAU, CAC: His CAA, CAG: Gln	CGU, CGC, CGA, CGG: Arg	U C A G
A	AUU, AUC, AUA: Ile AUG: Met or start	ACU, ACC, ACA, ACG: Thr	AAU, AAC: Asn AAA, AAG: Lys	AGU, AGC: Ser AGA, AGG: Arg	U C A G
G	GUU, GUC, GUA, GUG: Val	GCU, GCC, GCA, GCG: Ala	GAU, GAC: Asp GAA, GAG: Glu	GGU, GGC, GGA, GGG: Gly	U C A G

Figure 17.5

- Codons must be read in the correct reading frame
    - For the specified polypeptide to be produced

Evolution of the Genetic Code

- The genetic code is nearly universal
  - Shared by organisms from the simplest bacteria to the most complex animals

How cells are constructed?

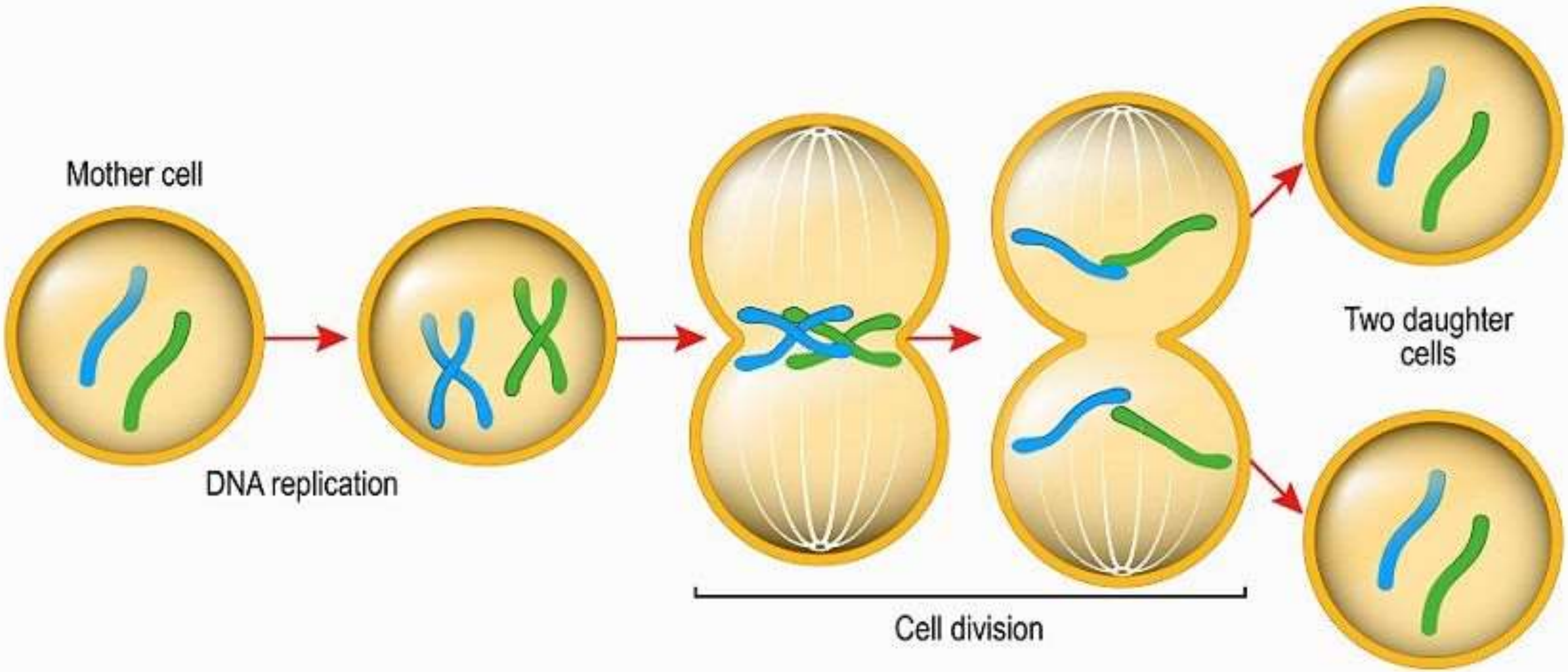
- New cells are created from existing cells through a process referred to as the cell cycle. One cell can make a copy of itself and form two new daughter cells.

- There are two major tasks that have to happen every cell cycle. First, cells have to make an exact copy of their DNA. DNA is like the instruction manual for a cell. It encodes genes for characteristics and dictates things like eye color and blood type.

- The second major task of every cell cycle is for the replicated chromosomes to be organized and separated into opposite sides of the cell. This happens during mitosis, or M phase of the cell cycle.

- The cell then grows longer, further separating those masses of chromosomes. The middle of the cell then pinches off in a process known as cytokinesis, splitting the cell into two cells. A new cell has been created and that completes the cell cycle.

MITOSIS


Mother cell
DNA replication
Cell division
Two daughter cells

Mitosis

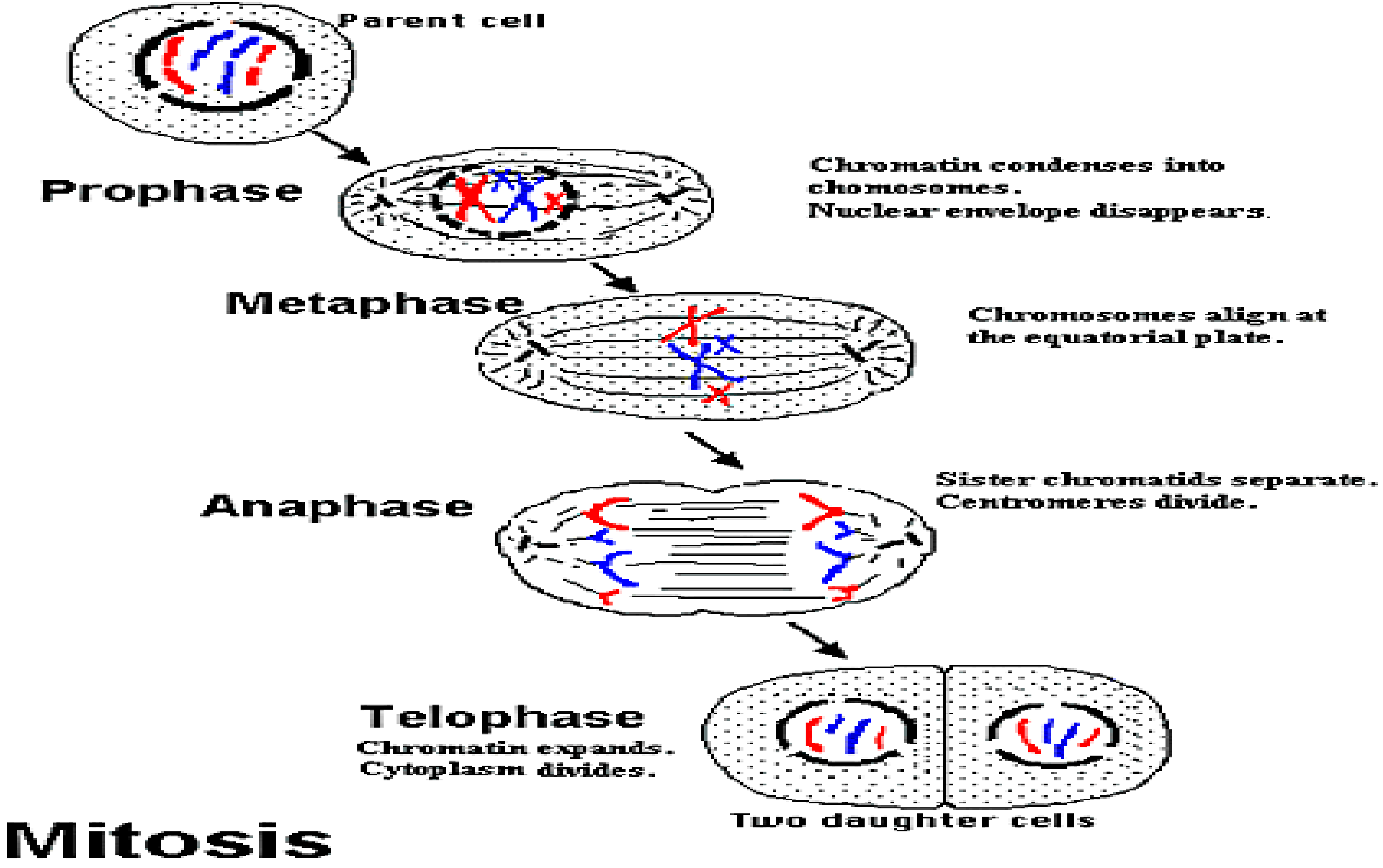
Mitosis is a process of cell division in which each of two identical daughter cells receives a diploid complements of chromosomes same as the diploid complement of the parent cell. It is usually followed by cytokinesis in which the cell itself divides to yield two identical daughter cells.

The basics in mitosis include:

1. Each chromosome is present as a duplicated structure at the beginning of nuclear division (2n).

2. Each chromosome divides longitudinally into identical halves and become separated from each other.

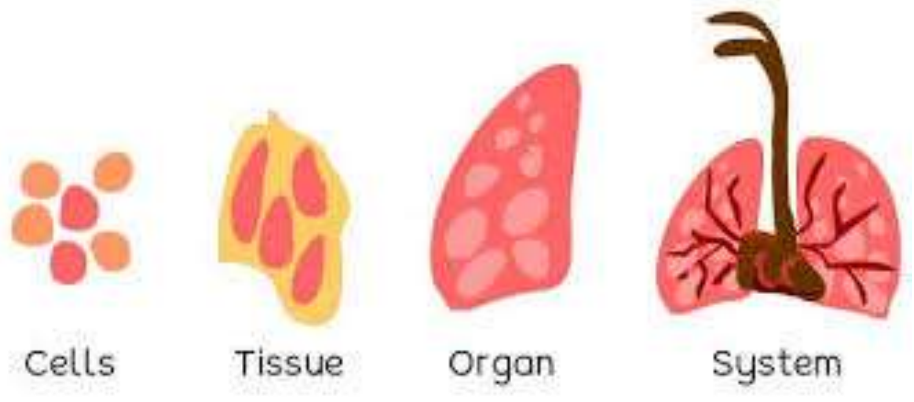
3. The separated chromosome halves move in opposite directions, and each becomes included in one of the two daughter nuclei that are formed.

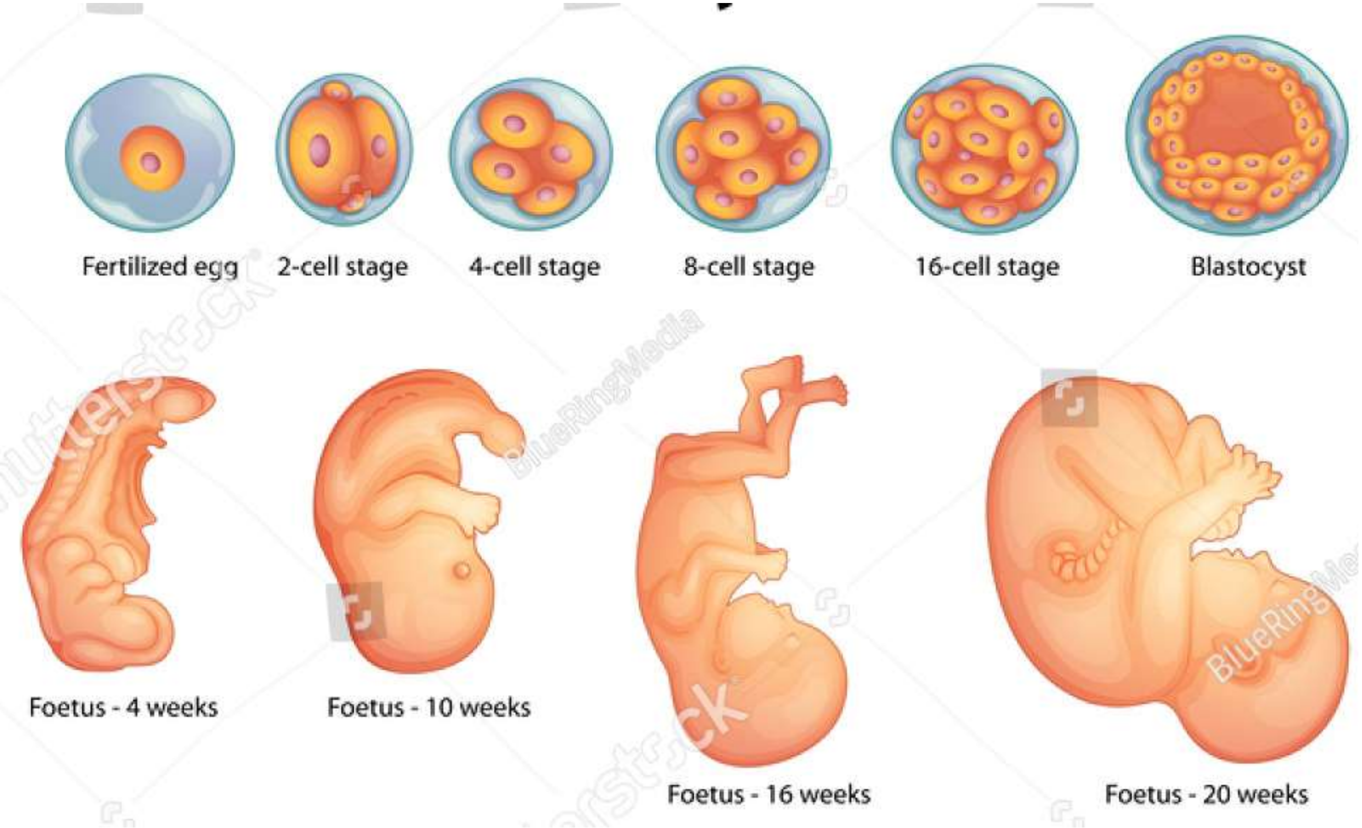


Parent cell
Prophase
Chromatin condenses into chomosomes.
Nuclear envelope disappears.
Metaphase
Chromosomes align at the equatorial plate.
Anaphase
Sister chromatids separate.
Centromeres divide.
Telophase
Chromatin expands.
Cytoplasm divides.
Two daughter cells
Mitosis

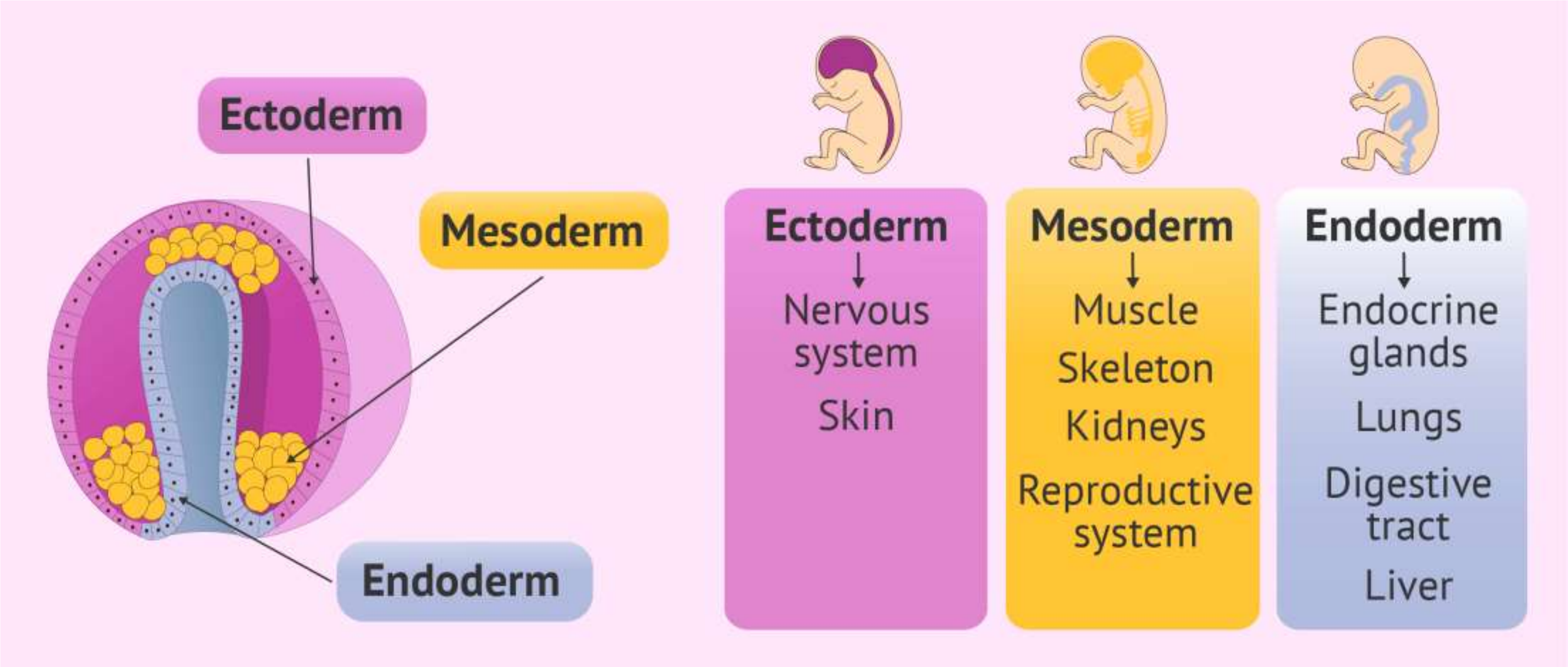
How cells build Organisms ?

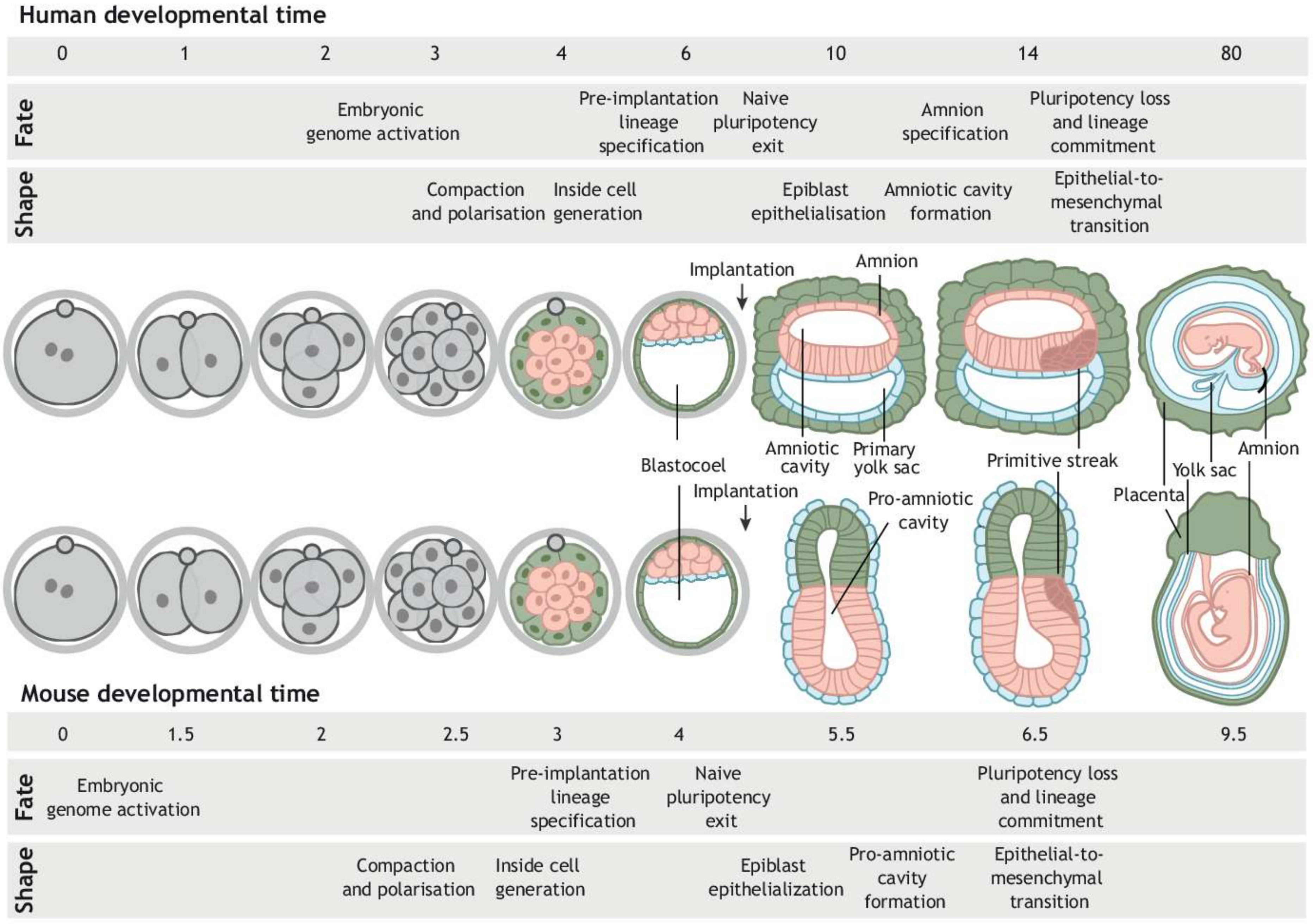
Organizational control mechanism allows cells to form tissues and anatomical structures in the developing embryo



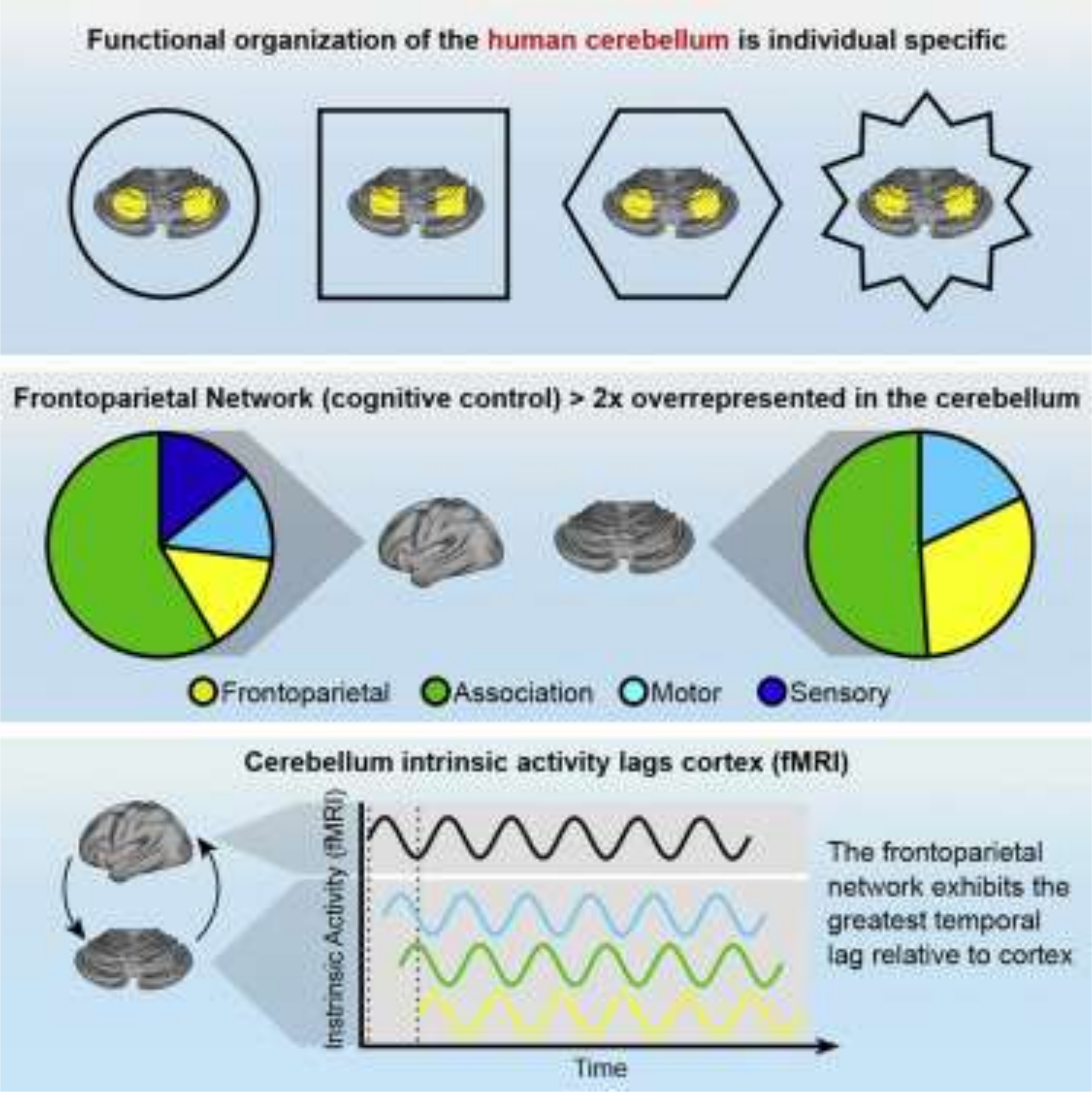


Spatial and Temporal organization





Human developmental time
0
1
2
3
4
6
10
14
80
Fate
Embryonic genome activation
Pre-implantation lineage specification
Naive pluripotency exit
Amnion specification
Pluripotency loss and lineage commitment
Shape
Compaction and polarisation
Inside cell generation
Epiblast epithelialisation
Amniotic cavity formation
Epithelial-to-mesenchymal transition
Implantation
Amnion
Blastocoel
Amniotic cavity
Primary yolk sac
Primitive streak
Yolk sac
Amnion
Placenta
Implantation
Pro-amniotic cavity
Mouse developmental time
0
1.5
2
2.5
3
4
5.5
6.5
9.5
Fate
Embryonic genome activation
Pre-implantation lineage specification
Naive pluripotency exit
Pluripotency loss and lineage commitment
Shape
Compaction and polarisation
Inside cell generation
Epiblast epithelialization
Pro-amniotic cavity formation
Epithelial-to-mesenchymal transition



- Individual-specific functional brain networks can be elucidated in the cerebellum

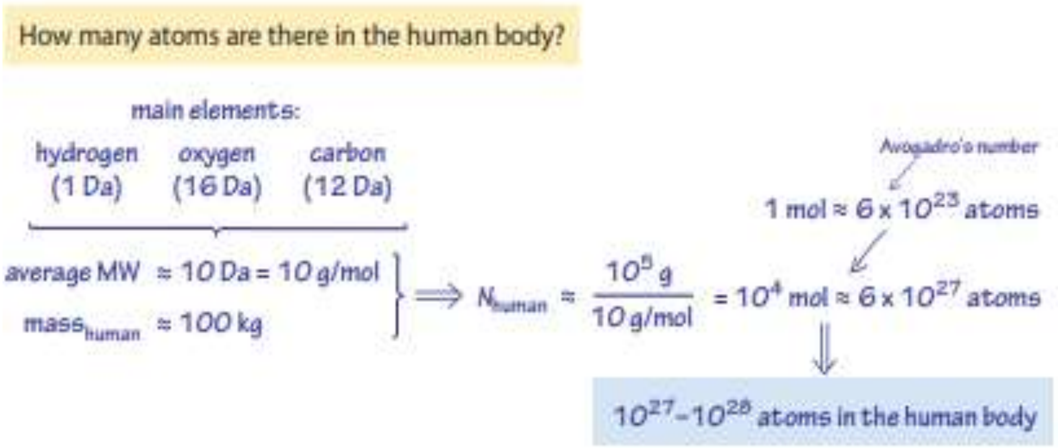
- Precision functional mapping of individuals revealed that functional networks in the cerebral cortex exhibit measurable individual specificity.

What is the elemental composition of a cell?

Living chemistry is largely built around carbon, oxygen, nitrogen, and hydrogen, with these elemental components serving as the key building blocks making up the cell’s dry weight.

The dry weight of E. coli contains, for every nitrogen atom, about two oxygen atoms, seven hydrogen atoms, and four carbon atoms. Hence, the empirical composition can be approximated as C4:H7:O2:N1.

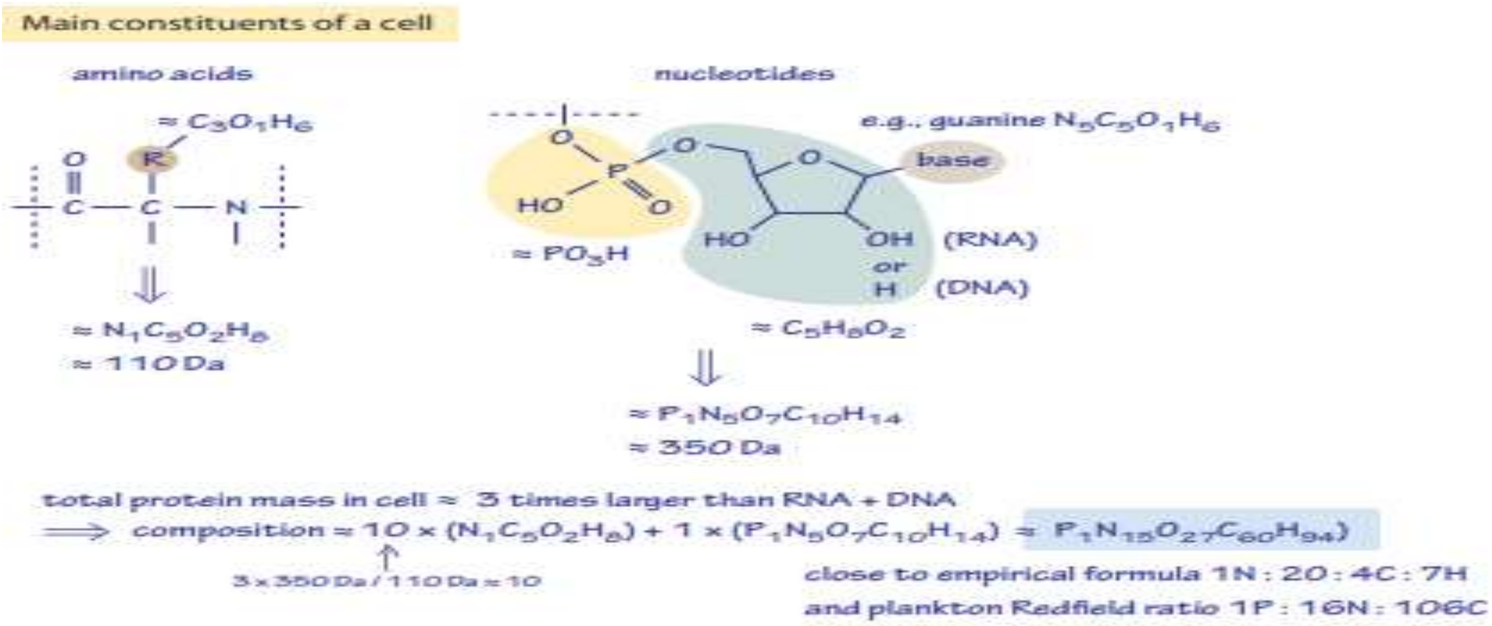
$$H_{2.5E9}O_{9.7E8}C_{4.9E8}N_{4.7E7}P_{9.0E6}Ca_{8.9E6}K_{2.0E6}Na_{1.9E6}S_{1.6E6}Cl_{1.3E6}$$
$$Mg_{3.0E5}Fe_{5.5E4}F_{5.4E4}Zn_{1.2E4}Si_{9.1E3}Cu_{1.2E3}B_{7.1E2}Cr_{98}Mn_{93}Ni_{87}Se_{65}Sn_{64}I_{60}Mo_{19}Co_{17}V_{1}.$$



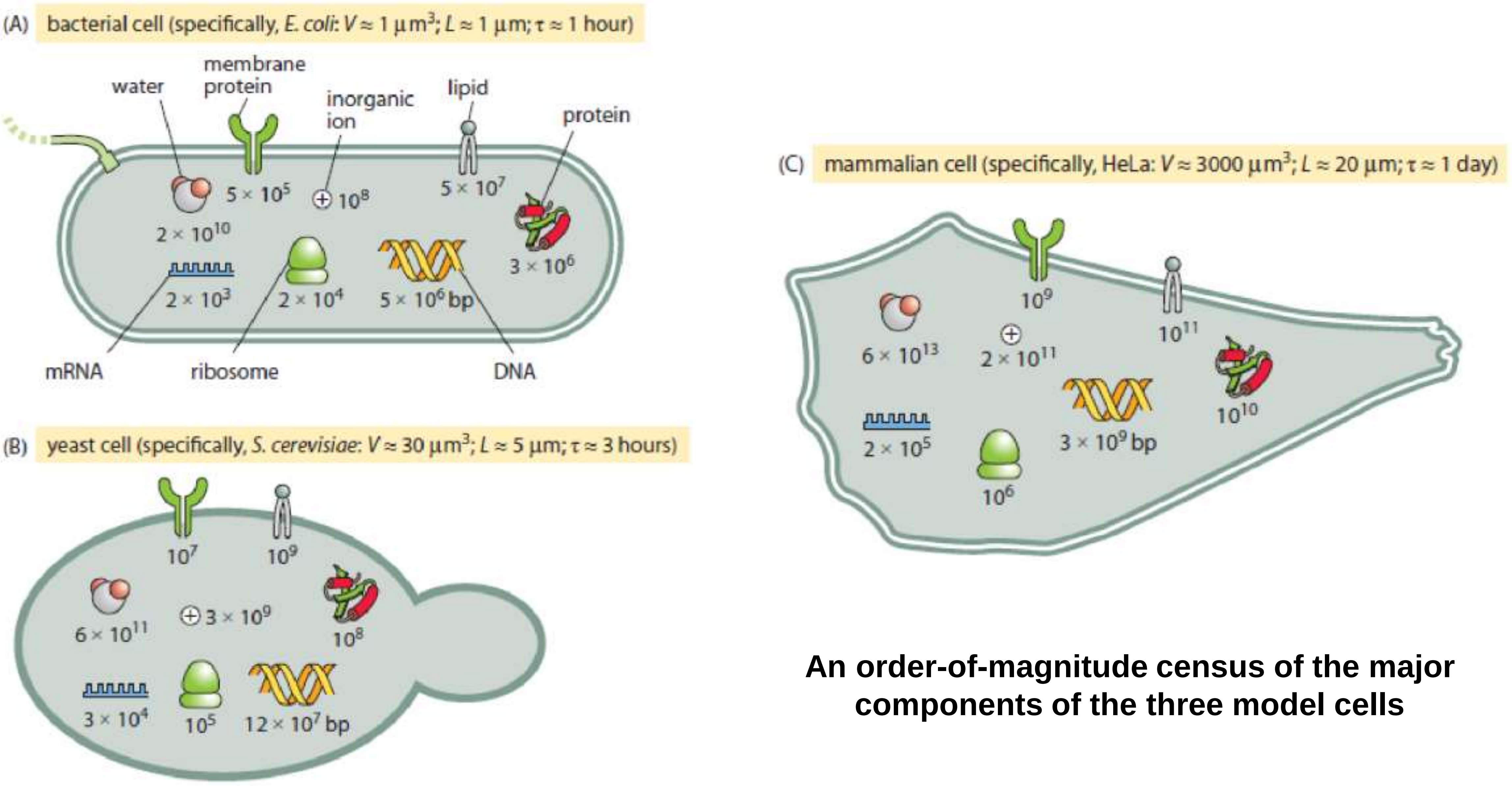
Composition of cell

A bacterial cell is made up of about 55% protein, 20% nucleic acids, 10% lipids, and another 15% of various other components Exploiting the fact that the mass ratio of proteins to nucleic acids is about 3:1.

A nucleotide is composed of a phosphate (PO4) and ribose (C5H8O2) backbone and a base (~N5C5O1H6, using guanine as our representative example). Thus, the total chemical composition is P1N5O7C10H14, with a total mass of about 350 Da (BNID 104886). An amino acid consists of a backbone with a peptide bond–RC(O)NH–,



Cell Census



An order-of-magnitude census of the major components of the three model cells

property	*E. coli*	budding yeast	mammalian (HeLa line)
cell volume	0.3–3 μm^3	30–100 μm^3	1000–10,000 μm^3
proteins per μm^3 cell volume		$2–4 \times 10^6$	
mRNA per cell	$10^3–10^4$	$10^4–10^5$	$10^5–10^6$
proteins per cell	$\sim 10^6$	$\sim 10^8$	$\sim 10^{10}$
mean diameter of protein		4–5 nm	
genome size	4.6 Mbp	12 Mbp	3.2 Gbp
number protein coding genes	4300	6600	21,000
regulator binding site length	10–20 bp	5–10 bp	
promoter length	~100 bp	~1000 bp	$\sim 10^4–10^5$ bp
gene length	~1000 bp	~1000 bp	$\sim 10^4–10^6$ bp (with introns)
concentration of one protein per cell	~1 nM	~10 pM	~0.1–1 pM
diffusion time of protein across cell ($D \approx 10\ \mu m^2/s$)	~0.01 s	~0.2 s	~1–10 s
diffusion time of small molecule across cell ($D \approx 100\ \mu m^2/s$)	~0.001 s	~0.03 s	~0.1–1 s
time to transcribe a gene	<1 min (80 nts/s)	~1 min	~30 min (incl. mRNA processing)
time to translate a protein	<1 min (20 aa/s)	~1 min	~30 min (incl. mRNA export)
typical mRNA lifetime	3 min	30 min	10 h
typical protein lifetime	1 h	0.3–3 h	10–100 h
minimal doubling time	20 min	1 h	20 h
ribosomes/cell	$\sim 10^4$	$\sim 10^5$	$\sim 10^6$
transitions between protein states (active/inactive)		1–100 μs	
time scale for equilibrium binding of small molecule to protein (diffusion limited)		1–1000 ms (1 μM–1 nM affinity)	
time scale of transcription factor binding to DNA site		~1 s	
mutation rate		$10^{-8}–10^{-10}$/bp/replication	

Importance of cell census

- Realistic physical picture of any biological phenomenon demands a precise, quantitative understanding of the individual molecules involved and the distance between them
- You will find the cell interior is extremely crowded in contrast to the dilute and homogeneous environment of the biochemical test tube.
- We will see that the mean spacing between protein molecules within a typical cell is less than 10 nm.
- This is extremely useful to estimate the rates of macromolecular synthesis during the cell cycle.

E Coli: a model organism which has led to astounding discoveries

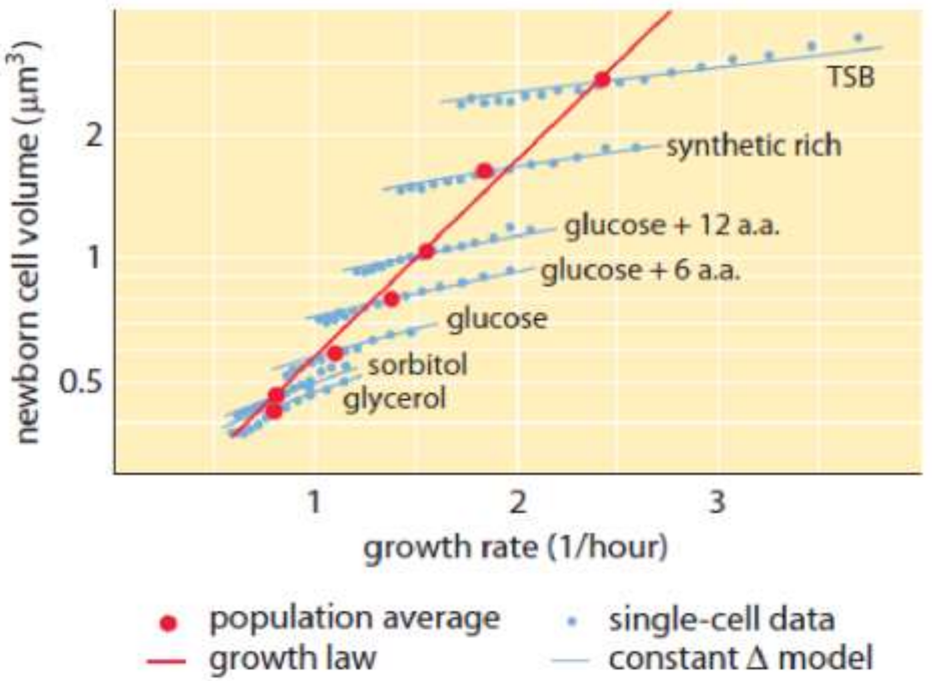
- Is easy to isolate present in human fecal matter
- E. coli is able to grow well in the presence of oxygen
- Easy to culture in lab, has high growth rate
- Genome has been sequenced 1997
- It carries plasmids extra-chromosomal DNA which can be manipulated easily by molecular biology techniques.
- Molecular biology techniques are easy to apply for creation of mutants
- Often, we will have recourse to *E. coli* because of particular experiments that have been performed on this organism.
- Further, even when we speak of experiments on other cells or organisms, often E. coli will be behind the scenes coloring our thinking.

Size of an *E. coli cells and molecular composition*

- E. coli. are made up of an array of different macromolecules as well as small molecules and ions. To estimate the number of proteins in an E. coli cell
- We begin by noting that with its 1 fL volume, the mass of such a cell is roughly 1 pg, where we have assumed that the density of the cell is that of water which is 1 g/mL. Measurements reveal that the dry weight of the
- Cell is roughly 30 percent of its total and half of that mass is protein.
- As a result, the total protein mass within the cell is roughly 0.15 pg
- We can also estimate the number of carbon atoms in a bacterium on the grounds that roughly half the dry mass comes from the carbon content of these cells, a figure that implies 1010 carbon atoms per cell
- Revealing the extent of crowding within a bacterium, we can estimate the number of proteins by assuming a mean protein of 300 amino acids with each amino acid having a characteristic mass of 100 Da.
- Using these rules of thumb, we find that the mean protein has a mass of 30,000 Da.
- Using the conversion factor that 1 Da 1.6×10^{-24} g, we have that our typical protein has a mass of 5×10^{-20} g. The number of proteins per E. coli cell

How big is an *E. coli* cell ?

- The size of a typical bacterium such as *E. coli* serves as a convenient standard ruler for characterizing length scales in molecular and cell biology
- Diameter ≈1μm, a length of ≈2μm, and a volume of ≈1μm3
- The shape can be approximated as a spherocylinder—that is, a cylinder with hemispherical caps.
- Inferences can vary with cell types under various conditions.



Relation between cell volume and growth rate. Using microscopy and microfluidic devices, cell volume can be measured at the single-cell level under various conditions, confirming that the average cell volume grows exponentially
with growth rate.

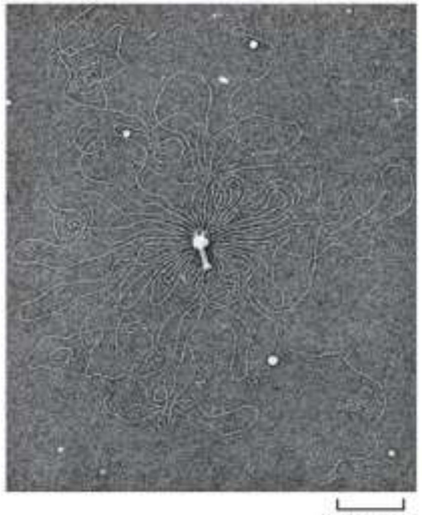


Figure 1.13 Physical Biology of the Cell (© Garland Science 2009)

	Quantity of interest	Symbol	Rule of thumb
E. coli	Cell volume	$V_{E.\ coli}$	$\approx 1\ \mu m^3$
	Cell mass	$m_{E.\ coli}$	≈ 1 pg
	Cell cycle time	$t_{E.\ coli}$	≈ 3000 s
	Cell surface area	$A_{E.\ coli}$	$\approx 6\ \mu m^2$
	Genome length	$N_{bp}^{E.\ coli}$	$\approx 5 \times 10^6$ bp
	Swimming speed	$v_{E.\ coli}$	$\approx 20\ \mu m/s$
Yeast	Volume of cell	V_{yeast}	$\approx 60\ \mu m^3$
	Mass of cell	m_{yeast}	≈ 60 pg
	Diameter of cell	d_{yeast}	$\approx 5\ \mu m$
	Cell cycle time	t_{yeast}	≈ 200 min
	Genome length	N_{bp}^{yeast}	$\approx 10^7$ bp
Organelles	Diameter of nucleus	$d_{nucleus}$	$\approx 5\ \mu m$
	Length of mitochondrion	l_{mito}	$\approx 2\ \mu m$
	Diameter of transport vesicles	$d_{vesicle}$	≈ 50 nm
Water	Volume of molecule	V_{H_2O}	$\approx 10^{-2}\ nm^3$
	Density of water	ρ	$1\ g/cm^3$
	Viscosity of water	η	≈ 1 centipoise (10^{-2} g/(cm s)) $=10^{-3}$ Pa·sec
	Hydrophobic embedding energy	$\approx E_{hydr}$	25 cal/(mol Å^2)
DNA	Length per base pair	l_{bp}	$\approx 1/3$ nm
	Volume per base pair	V_{bp}	$\approx 1\ nm^3$
	Charge density	λ_{DNA}	2 e/0.34 nm
	Persistence length	ξ_P	50 nm =147bp
Amino acids and proteins	Radius of "average" protein	$r_{protein}$	≈ 2 nm
	Volume of "average" protein	$V_{protein}$	$\approx 25\ nm^3$
	Mass of "average" amino acid	M_{aa}	≈ 100 Da
	Mass of "average" protein	$M_{protein}$	$\approx 30{,}000$ Da
	Protein concentration in cytoplasm	$c_{protein}$	≈ 300 mg/mL
	Characteristic force of protein motor	F_{motor}	≈ 5 pN
	Characteristic speed of protein motor	v_{motor}	≈ 200 nm/s
	Diffusion constant of "average" protein	$D_{protein}$	$\approx 100\ \mu m^2/s$
Lipid bilayers	Thickness of lipid bilayer	d	≈ 5 nm
	Area per molecule	A_{lipid}	$\approx \frac{1}{2}\ nm^2$
	Mass of lipid molecule	m_{lipid}	≈ 800 Da

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1 Da = (mass of one carbon-12)/12

Water is 70 % of the cell mass $(m_{E.Coli} = 1\text{pg})$

Dry mass of the cell (30% of 1pg) = 0.3 pg

Half of the dry mass (=0.15 pg) = proteins

1 Da = mass of a hydrogen atom $= \frac{1}{6 \times 10^{23}} g = 1.6 \times 10^{-24} g$

1 amino acid = 100 Da

average protein size = 300 a.a. → 30,000 Da

$$N_{prot} = \frac{0.15\, pg}{30,000\, Da} = \frac{0.15\, pg}{30,000 \times 1.6 \times 10^{-24} g} \approx 3,000,000$$

$$= \begin{cases} \frac{1}{3} N_{prot} \rightarrow \text{membrane proteins} \\ \frac{2}{3} N_{prot} \rightarrow \boxed{\text{cytoplasmic proteins}} \end{cases}$$

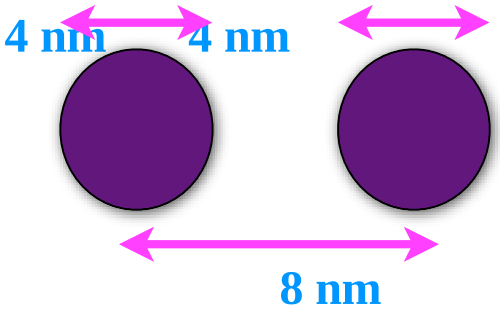
$m_{water} = 0.7\, pg$

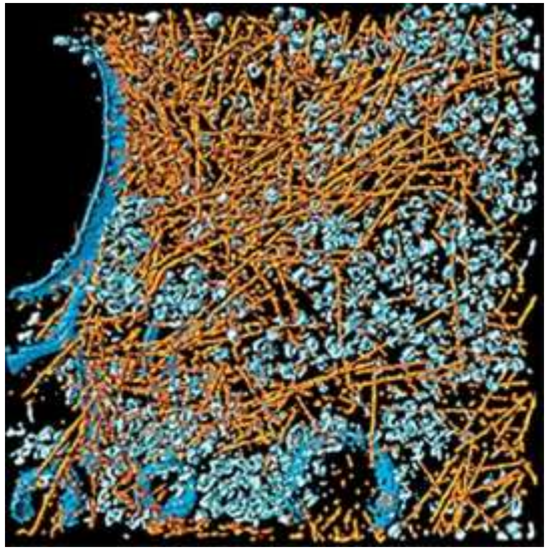
$$\rightarrow N_{water} = \frac{0.7\, pg}{18 Da \times (1.6 \times 10^{-24} g / Da)} \approx 2 \times 10^{10}$$

There are 2×10^{6} proteins in cytoplasm

$$c_{prot} = 2 \times 10^{6} / 1\mu m^{3}$$

$$d_{prot-prot} = c^{-1/3} = \left(\frac{(10^{3}\, nm)^{3}}{2 \times 10^{6}} \right)^{1/3} = (500 nm)^{1/3} \approx 8nm$$





Mean spacing between the macromolecules in cell

~

size of macromolecules themselves

Cell is very crowded ...

Membrane

Surface area of *E.Coli*

$$A_{E.Coli} \approx (2\pi R) \times L \approx 6\mu m^2$$

E. coli has double (inner and outer) membranes and each membrane is made of bilayer.

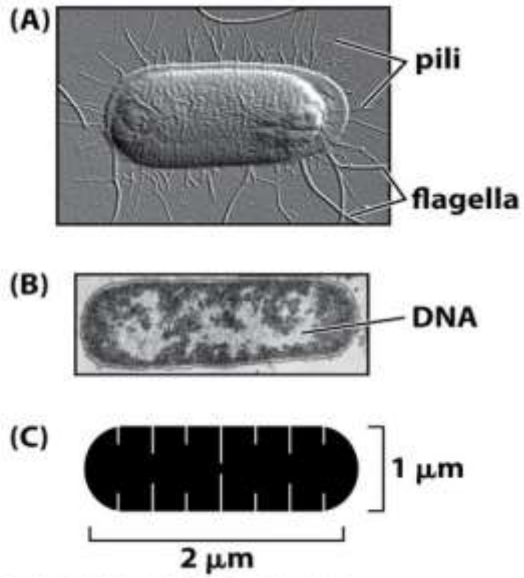


Figure 2.1 Physical Biology of the Cell (© Garland Science 2009)

Half of the surface area is covered with membrane proteins

$$N^{lipid}_{E.Coli} \approx \frac{4 \times 0.5 \times 6\mu m^2}{0.5 nm^2} \approx 2 \times 10^7$$

Taking the molecular census to set criteria for the judgement

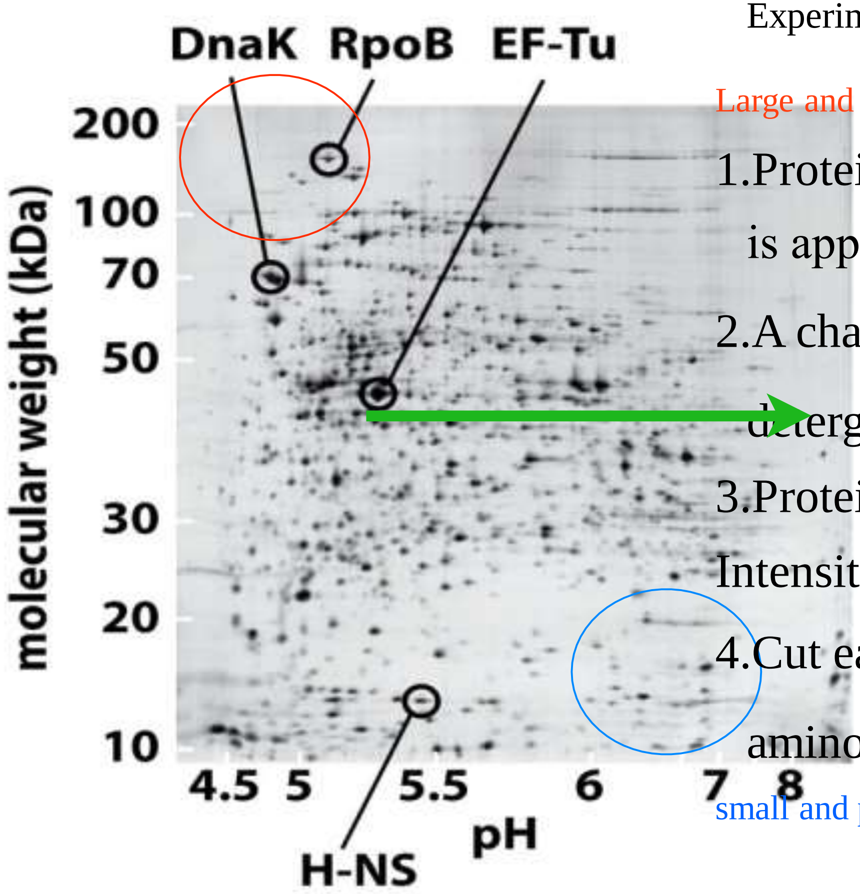


Figure 2.3 Physical Biology of the Cell (© Garland Science 2009)

Measurement of protein census of *E. Coli* using 2D polyacrylamide gel electrophoresis

Experimental determination of biomolecular content

Large and negatively charged proteins

1.Protein mixture loaded at one end of the gel and an electric field is applied across the gel. (F=qE=ζv)

2.A charged detergent binding to proteins is added. (charge of detergent ~ protein size; q ~ R~v)

3.Proteins are stained using dye. Conc ~ Intensity of the spot.

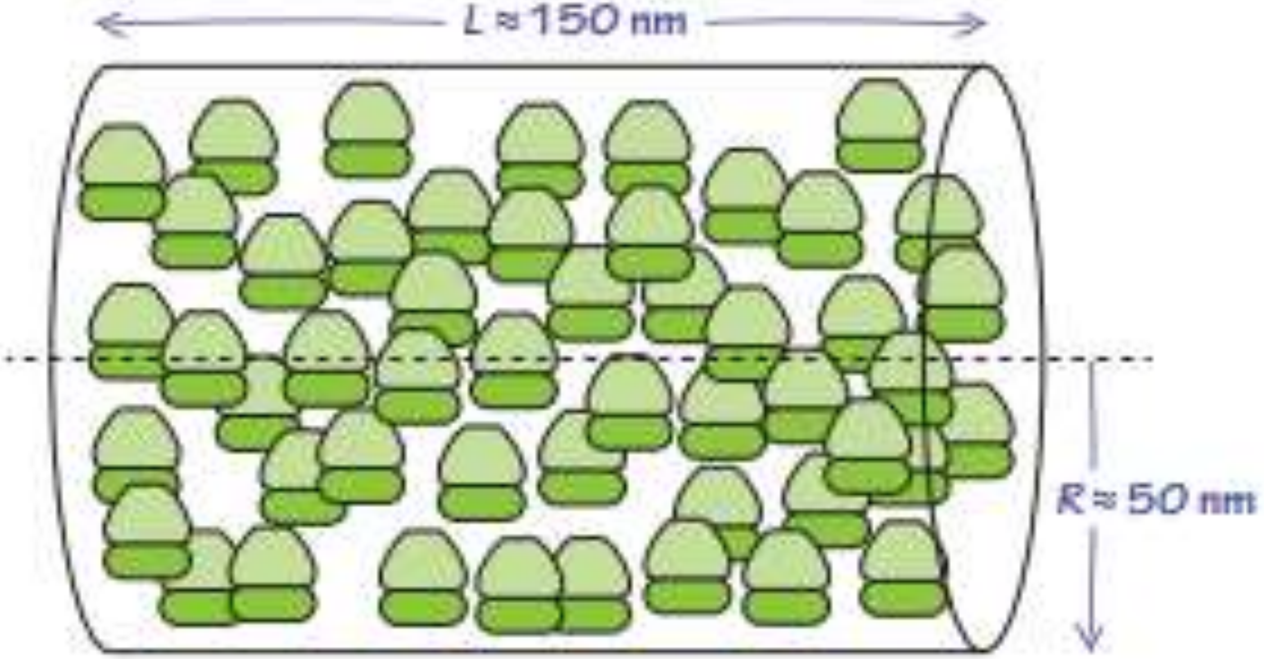
4.Cut each spot, elute the proteins and determine the size and amino acid content using mass spectroscopy.

small and positively charged proteins

How many ribosomes are in a cell?

- One of the familiar refrains in nearly all biology textbooks is that proteins are the workhorses of the cell. As a result, cells are deeply attentive to all the steps between the readout of the genetic information hidden within DNA and the expression of active proteins. One of the ways that the overall rhythm of protein production is controlled is through tuning the number of ribosomes. Ribosomes are one of the dominant constituents in cells especially in rapidly dividing cells.

How many ribosomes in a cellular volume?



cellular volume $\approx \pi R^2 L \approx 3 \times (50\ \text{nm})^2 \times 150\ \text{nm} \approx 10^6\ \text{nm}^3 \approx 10^{-3}\ \mu\text{m}^3$

ribosome density $\approx \dfrac{50\ \text{ribosomes}}{10^{-3}\ \mu\text{m}^3} \approx \boxed{50{,}000\ \text{ribosomes}/\mu\text{m}^3}$

Substance	% of total dry weight	Number of molecules
Macromolecule		
Protein	55.0	2.4×10^6
RNA	20.4	
23S RNA	10.6	19,000
16S RNA	5.5	19,000
5S RNA	0.4	19,000
Transfer RNA (4S)	2.9	200,000
Messenger RNA	0.8	1,400
Phospholipid	9.1	22×10^6
Lipopolysaccharide	3.4	1.2×10^6
DNA	3.1	2
Murein	2.5	1
Glycogen	2.5	4,360
Total macromolecules	**96.1**	
Small molecules		
Metabolites, building blocks, etc.	2.9	
Inorganic ions	1.0	
Total small molecules	**3.9**	

Table 2.1 Observed macromolecular census of an *E. coli* cell. (Data from F. C. Neidhardt et al., Physiology of the Bacterial Cell, Sunderland, Sinauer Associates Inc., 1990 and M. Schaechter et al., Microbe, Washington DC, ASM Press, 2006.)

Table 2.1 Physical Biology of the Cell (© Garland Science 2009)

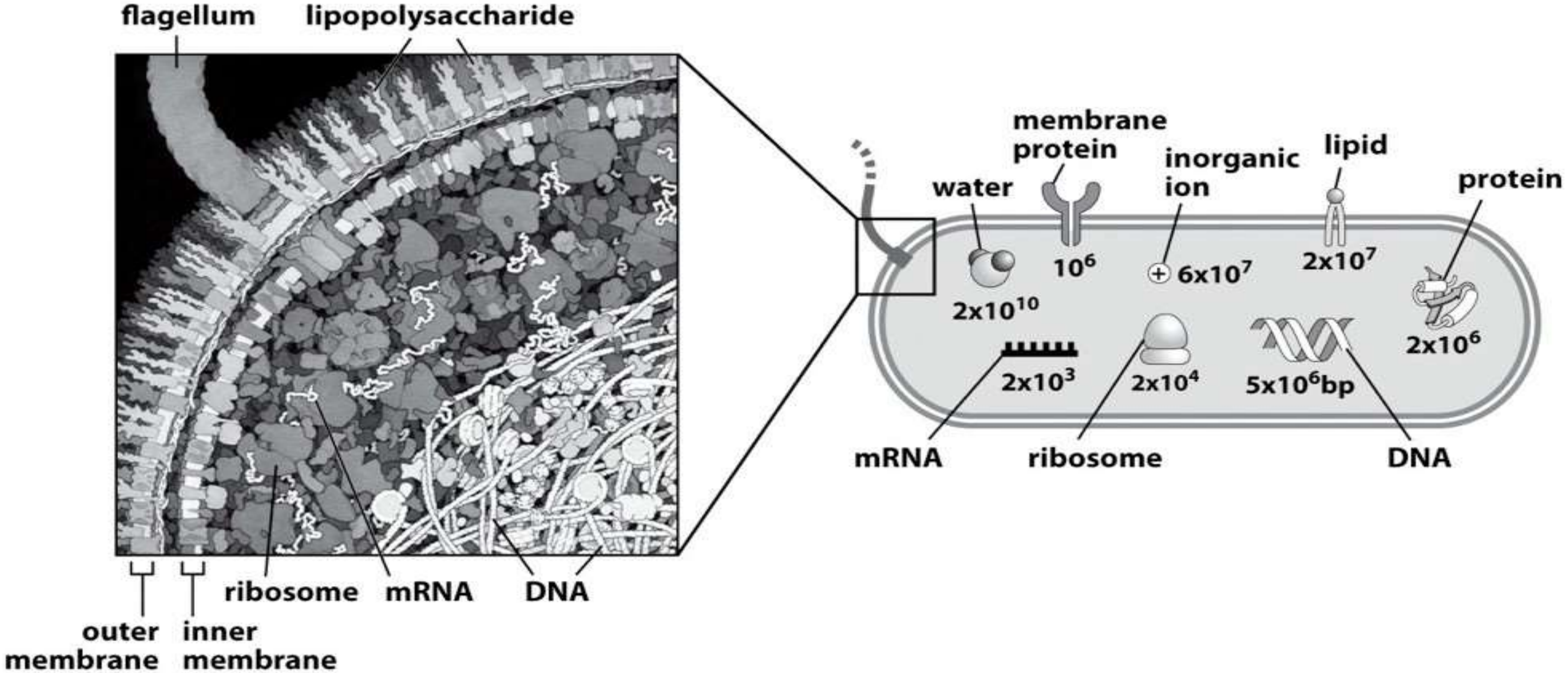
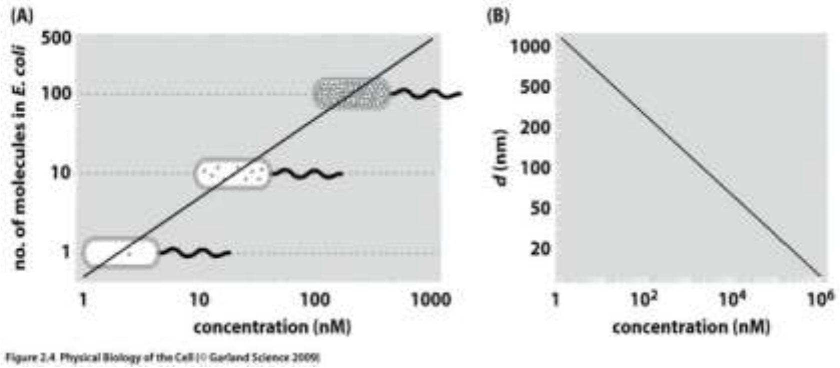
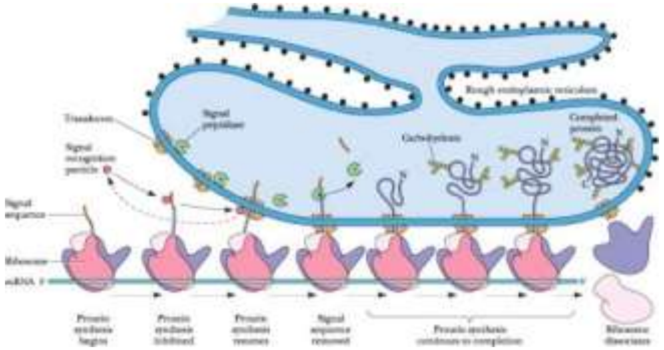


Figure 2.2 Physical Biology of the Cell (© Garland Science 2009)

Conversion : Number ⇨ Concentration ⇨ Average distance

* 1 molecule in a *bacterium* ~ 2 nM.



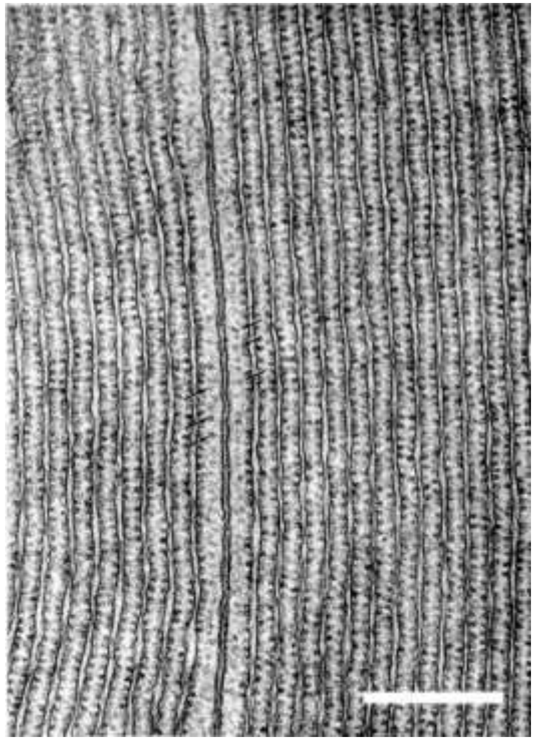


Example : Ribosome $1L = 10^{-3}\,m^3$

no. of ribosome = 19,000 (Table 2.1)

Concentration = 19,000/1fL ~ 32 μM

Average distance ~ 37 nm.



Cellular crowding and its implications

- The Cellular Interior Is Highly Crowded With Mean Spacings Between Molecules That Are Comparable to Molecular Dimensions
- Increase in the effective concentration of macromolecules alters the rates and equilibrium constants of their reactions
- Alters dissociation constants by favoring the association of macromolecules, such as when multiple proteins come together to form protein complexes, or when DNA-binding proteins bind to their targets in the genome
- Crowding may also affect enzyme reactions involving small molecules if the reaction involves a large change in the shape of the enzyme.[10]
- The size of the crowding effect depends on both the molecular mass and shape of the molecule involved,

Cellular crowding and its implications

- the increase in the strength of interactions between proteins and DNA[5] is importance in processes such as transcription and DNA replication
- involved in processes as diverse as the aggregation of hemoglobin in sickle-cell disease, and the responses of cells to changes in their volume.[4]
- the crowding effect can accelerate the folding process,
- crowding can reduce the yield of correctly folded protein by increasing protein aggregation.[
- increase the effectiveness of chaperone proteins such as GroEL in the cell,[17]
- Crystallins fill the interior of the lens. These proteins have to remain stable and in solution for the lens to be transparent; precipitation or aggregation of crystallins causes cataracts
- Crystallins are present in the lens at extremely high concentrations, over 500 mg/ml, and at these levels crowding effects are very strong.

- The large crowding effect adds to the thermal stability of the crystallins, increasing their resistance to denaturation
- This effect may partly explain the extraordinary resistance shown by the lens to damage caused by high temperatures.[22]
- Crowding may also play a role in diseases that involve protein aggregation, such as sickle cell anemia alzheimer's disease,

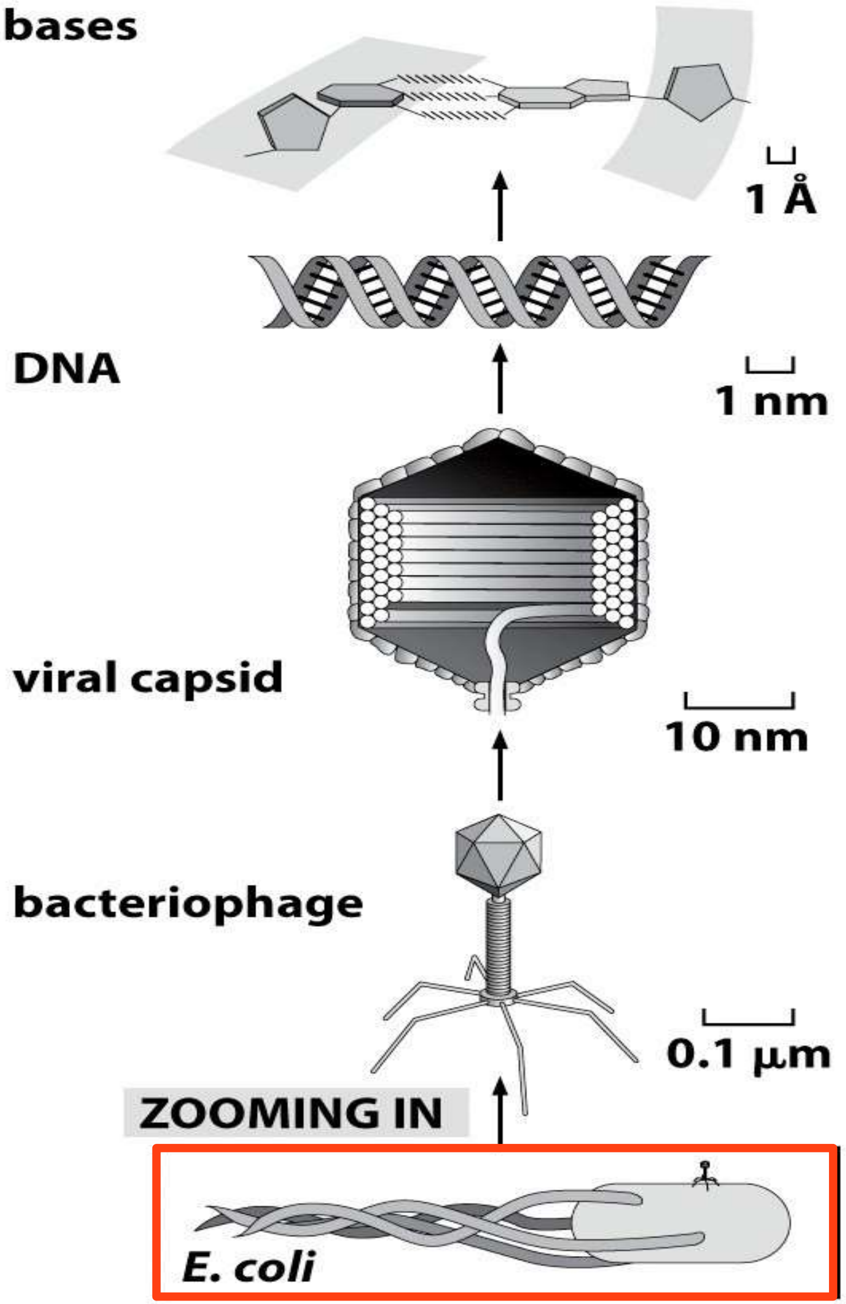


Figure 2.7 (part 1) Physical Biology of the Cell (© Garland Science 2009)

Biological Structures exist over a huge range of scales

Hierarchy of spatial scales

Number of proteins in an E.coli cell

3,000,000

Number of ribosomes in an E.coli cell

20,000

Number of lipids in an E.coli cell

20,000,000

Size of genome in an E.coli cell

5,000,000 bp

Figure 1-17 Molecular Biology of the Cell 5/e (© Garland Science 2008)

yeast cell : useful representative to study eukaryotes

Tremendous diversity in living cells ...

Protist

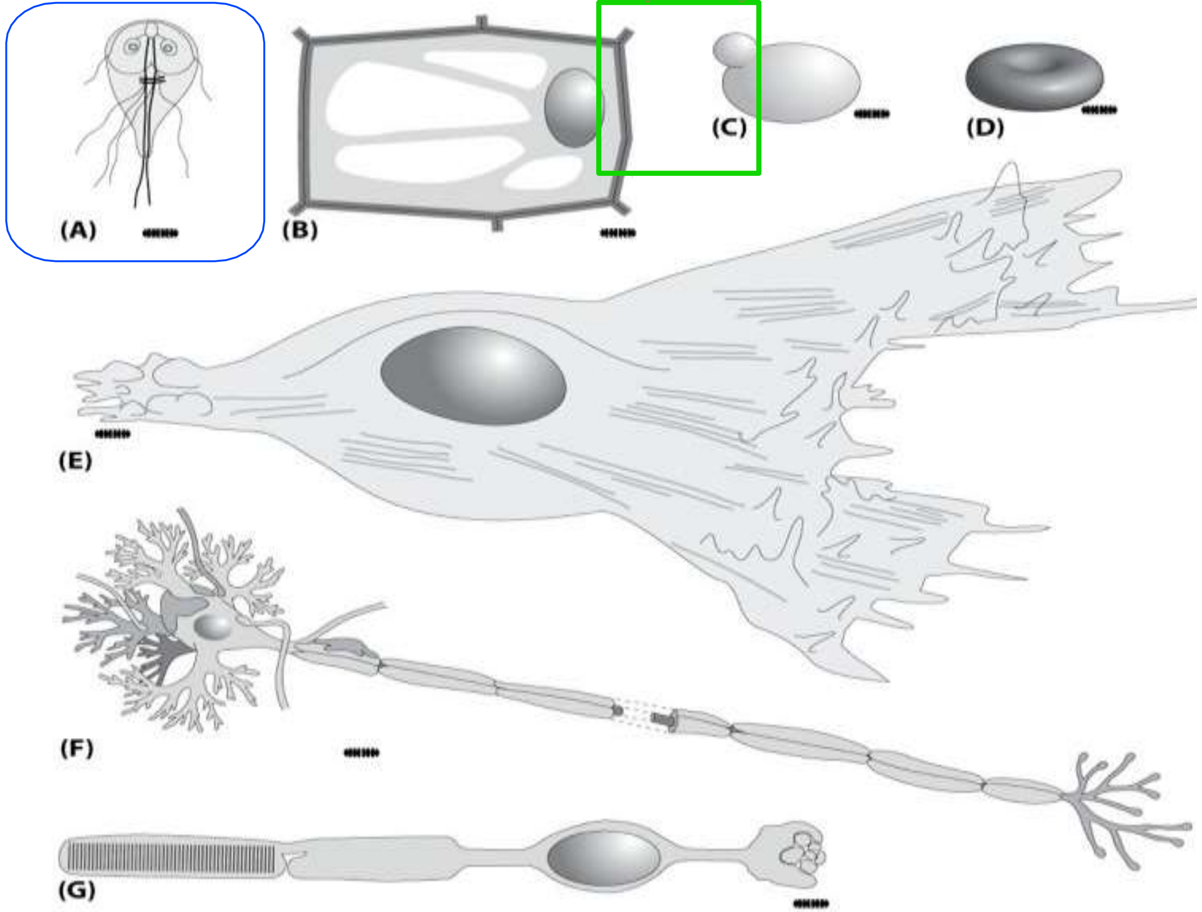


Figure 2.8 Physical Biology of the Cell (© Garland Science 2009)

Cells

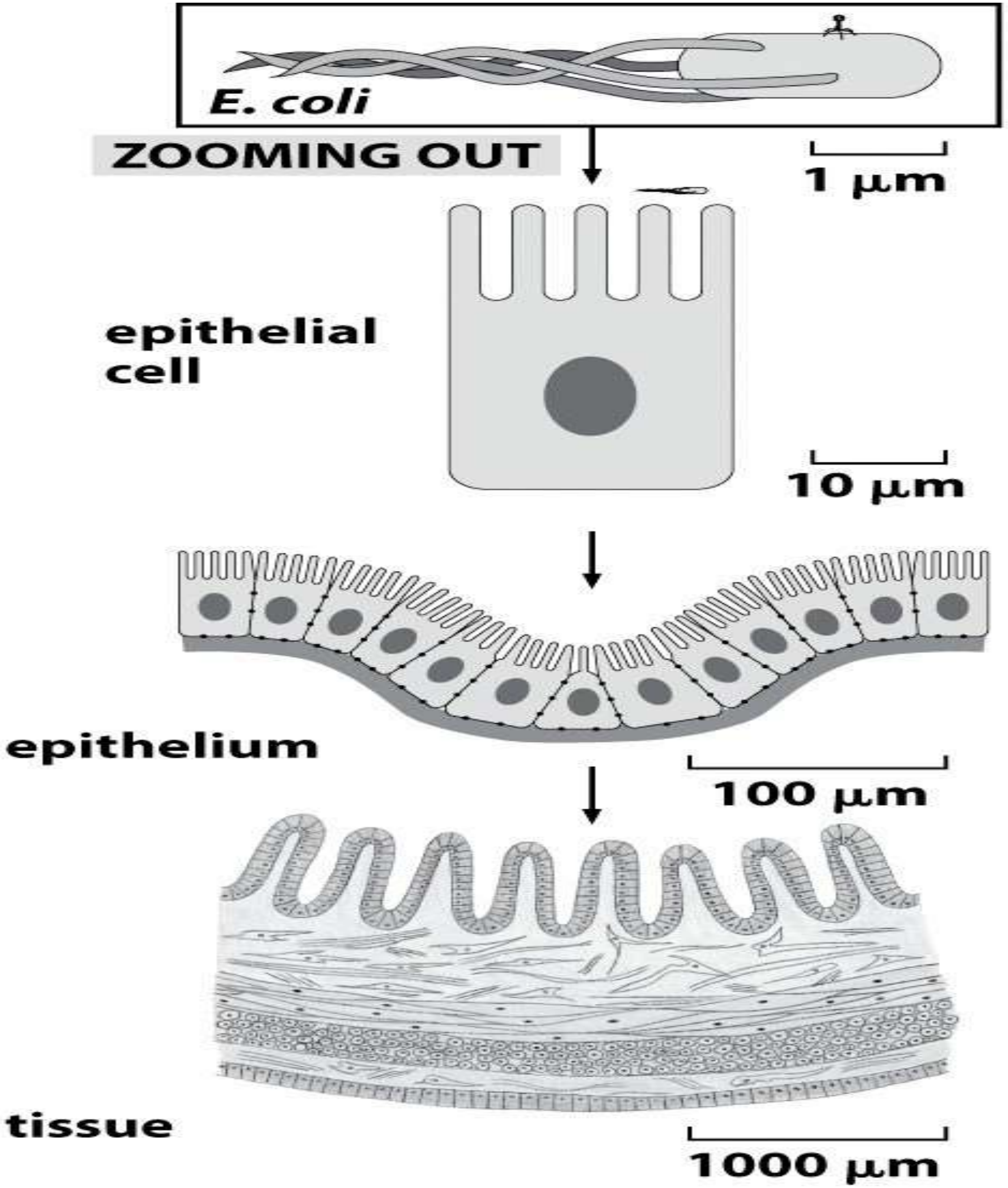


Figure 2.7 (part 2) Physical Biology of the Cell (© Garland Science 2009)

Biological Structures exist over a huge range of scales

Hierarchy of spatial scales

yeast cell : model system to study a single eukaryote cell

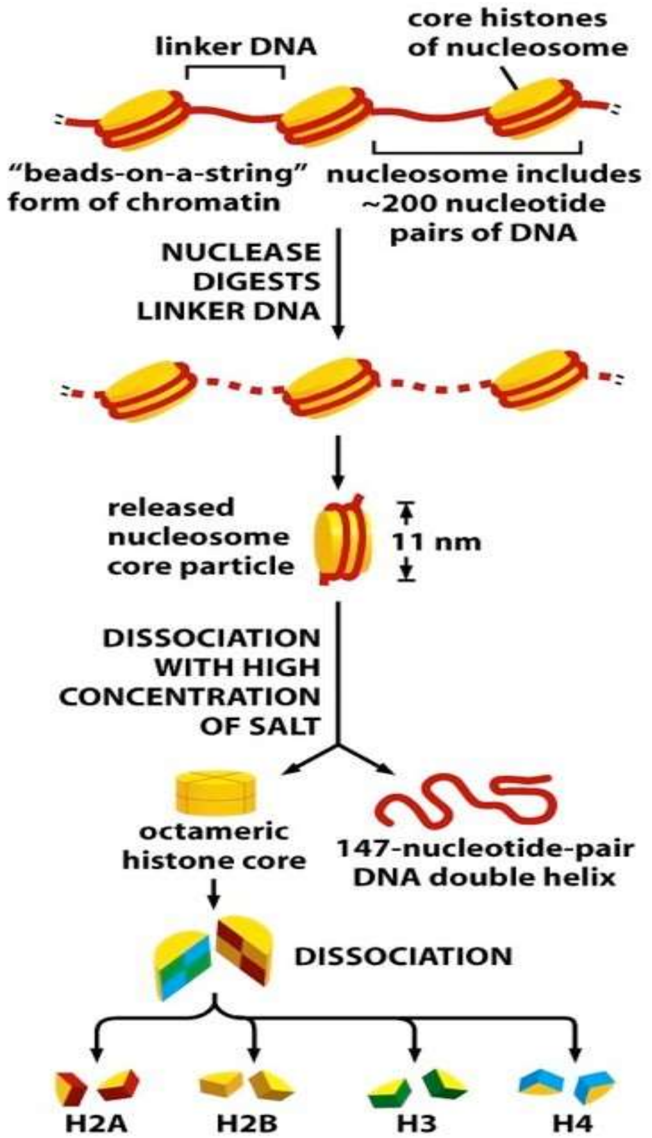


Figure 4-23 Molecular Biology of the Cell 5/e (© Garland Science 2008)

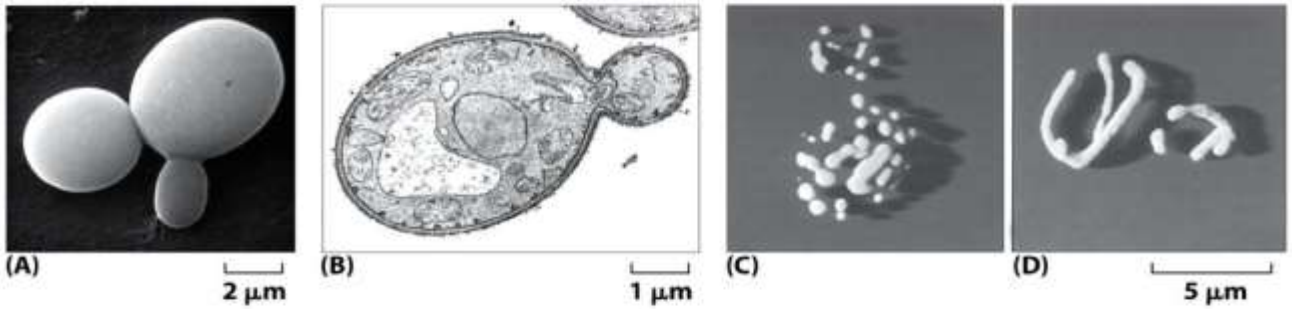


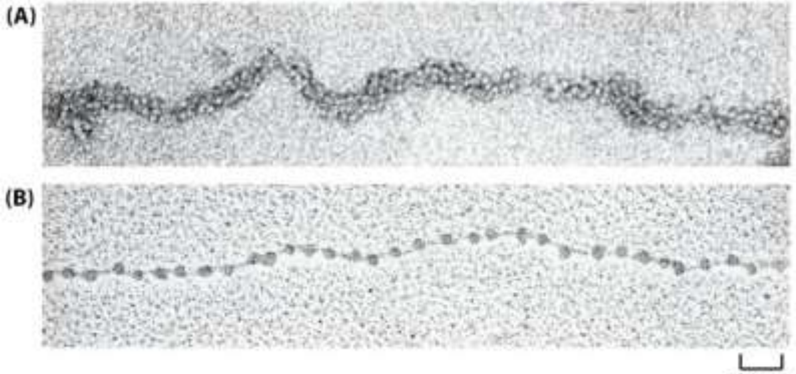
Figure 2.9 Physical Biology of the Cell (© Garland Science 2009)

$$L_{yeast} \approx 5\mu m \qquad V_{yeast} = \frac{4}{3}\pi (2.5\mu m)^3 \approx 60\mu m^3 \approx 60 V_{E.Coli}$$

$$N^{Yeast}_{protein} \approx 60 \times N^{E.Coli}_{protein}$$

$$N^{Yeast}_{lipid} \approx \frac{2 \times 0.5 \times (80\mu m^2)}{0.5 nm^2} \approx 2 \times 10^8$$

$$N_{genome} \sim 1.2 \times 10^7 bp \qquad N_{nucleosome} \approx \frac{1.2 \times 10^7 bp}{200 bp / nucleosome} = 60,000$$



Video resources

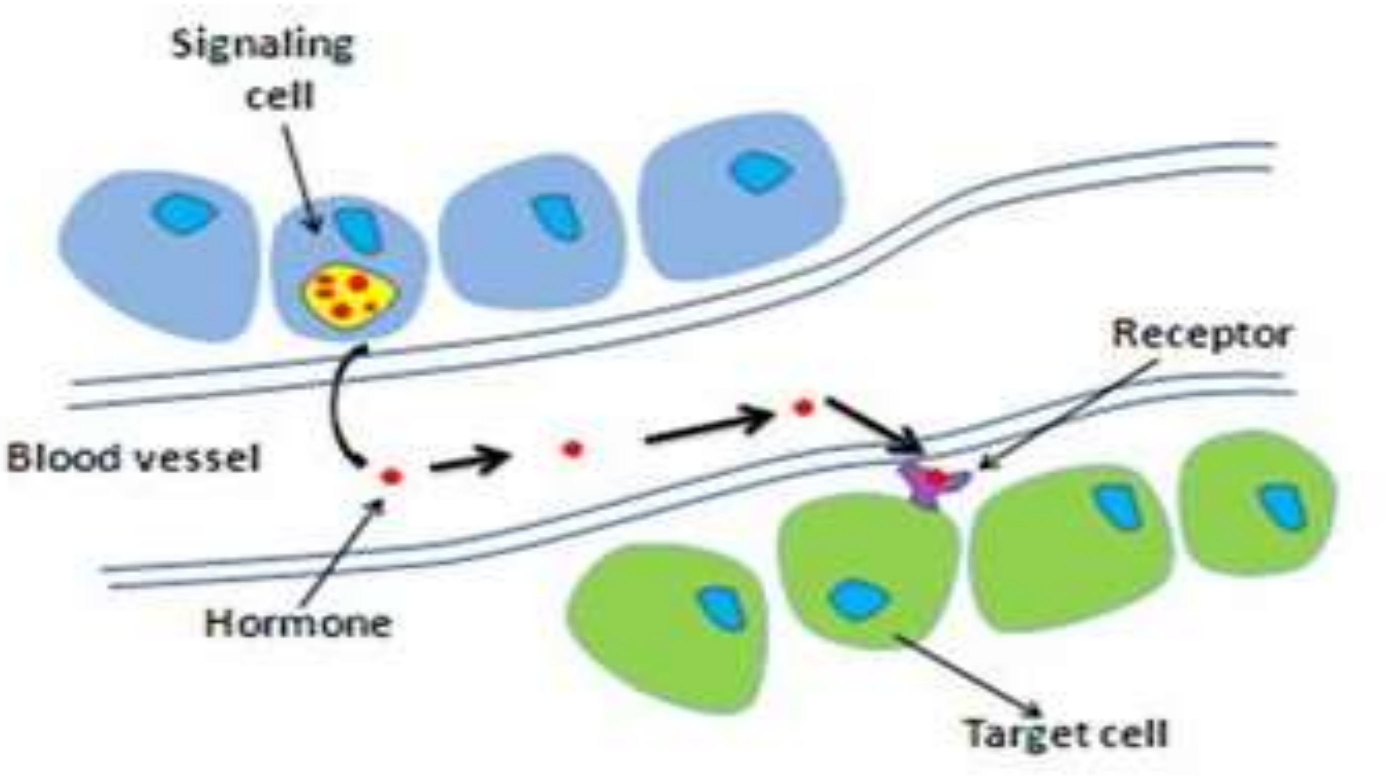
https://www.youtube.com/watch?v=URUJD5NEXC8

https://dnalc.cshl.edu/resources/3d/08-how-dna-is-packaged-advanced.html

https://www.youtube.com/watch?v=jOhNyVjkChM

Machines and signals: Key model factors, molecules and organisms

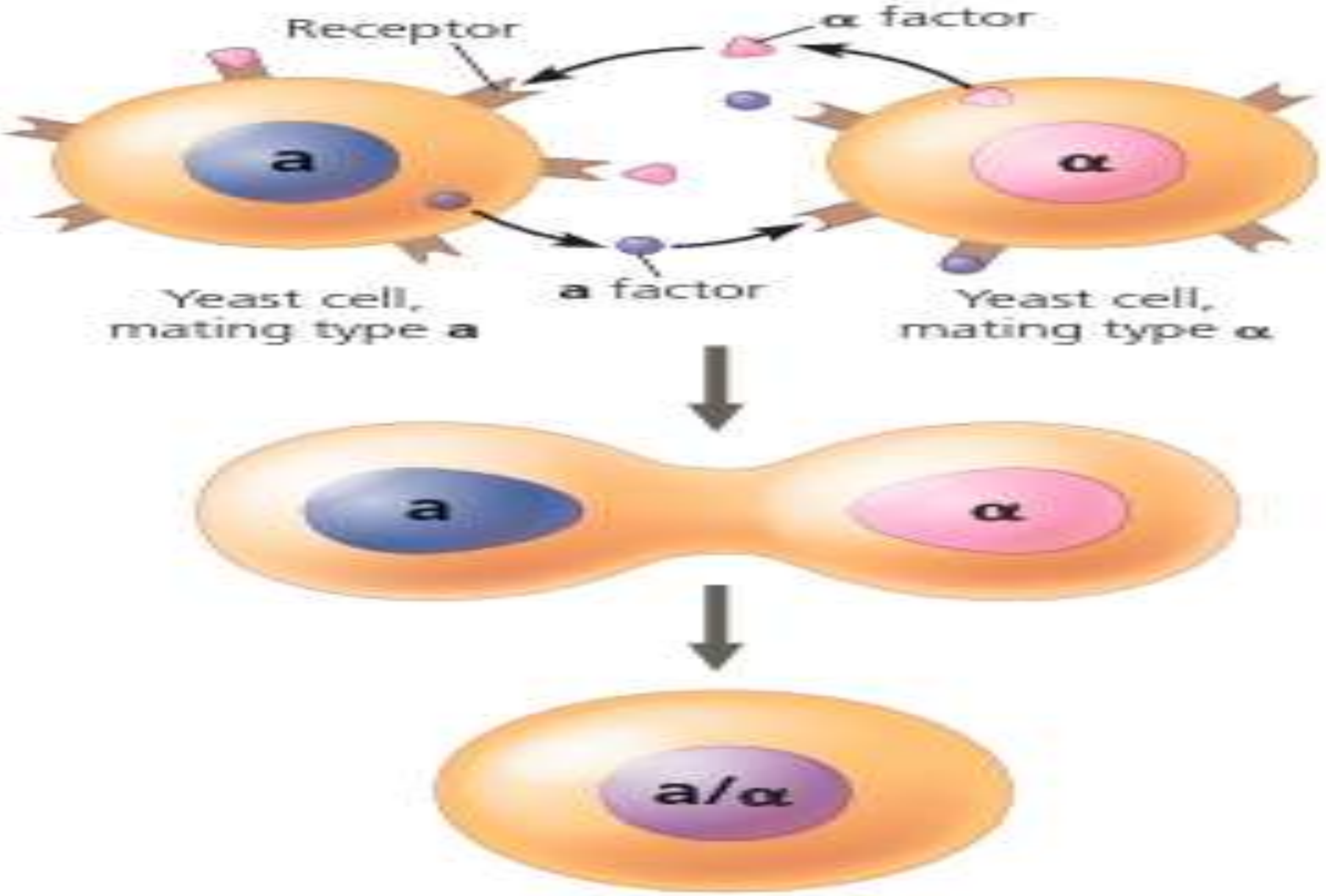
As living organisms we are constantly receiving and interpreting signals from our environment. These signals can be light, heat, odours, touch or sound. The cells of our bodies are also constantly receiving signals from other cells.



1 Exchange of mating factors. Each cell type secretes a mating factor that binds to receptors on the other cell type.

2 Mating. Binding of the factors to receptors induces changes in the cells that lead to their fusion.

3 New a/α cell. The nucleus of the fused cell includes all the genes from the **a** and **α** cells.

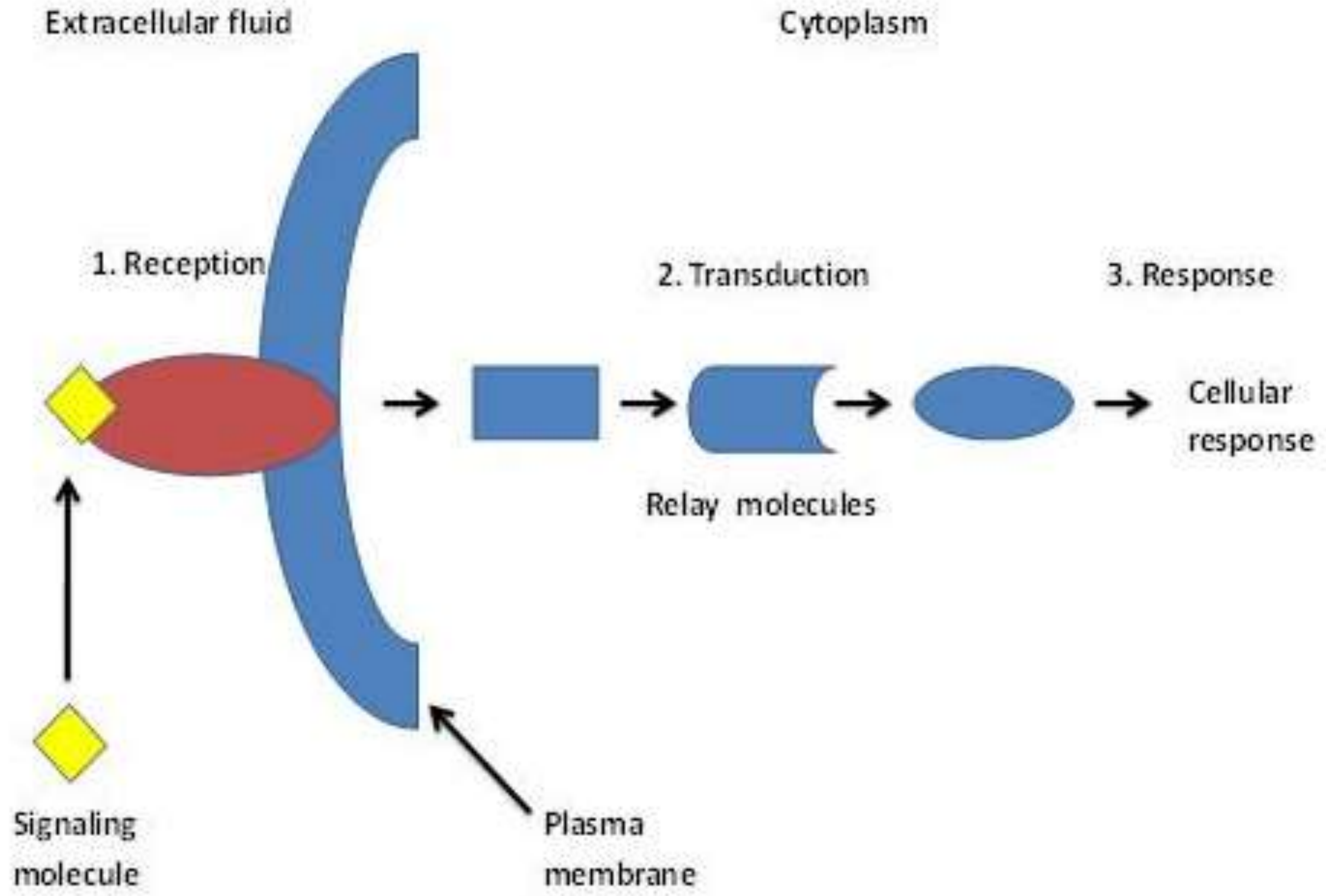


▲ **Figure 11.2 Communication between mating yeast cells.** *Saccharomyces cerevisiae* cells use chemical signaling to identify cells of opposite mating type and initiate the mating process. The two mating types and their corresponding chemical signaling molecules, or mating factors, are called **a** and **α**.

Cell signaling can be divided into 3 stages:

- **1. Reception :** A cell detects a signaling molecule from the outside of the cell. A signal is detected when the ligand binds to a receptor protein on the surface of the cell or inside the cell.
- **2. Transduction :** When the signaling molecule binds to the receptor, it changes the receptor protein. This change initiates the process of transduction. Each relay molecule in the signal transduction pathway changes the next molecule in the pathway.
- **3. Response :** Finally, the signal triggers a specific cellular response

Reception: A signaling molecule binds to a receptor protein, causing it to change shape

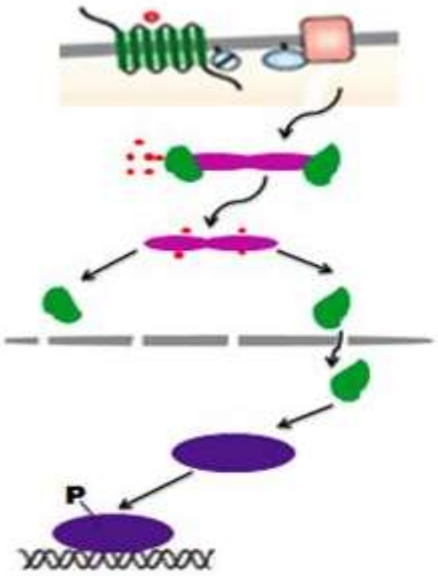


Transduction: Cascades of molecular interactions relay signals from receptors to target molecules in the cell

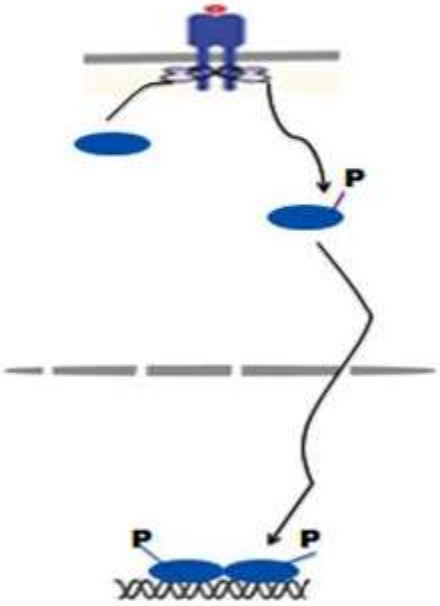
Response: Cell signaling leads to regulation of transcription or cytoplasmic activities

Receptor

A receptor is a protein molecule found on the surface of a cell which receives chemical signals originating externally from the cell. Binding of specific signalling molecules to a receptor directs a cell to allow certain molecules to enter or exit or directs a cell to divide or die.



G protein-coupled receptor

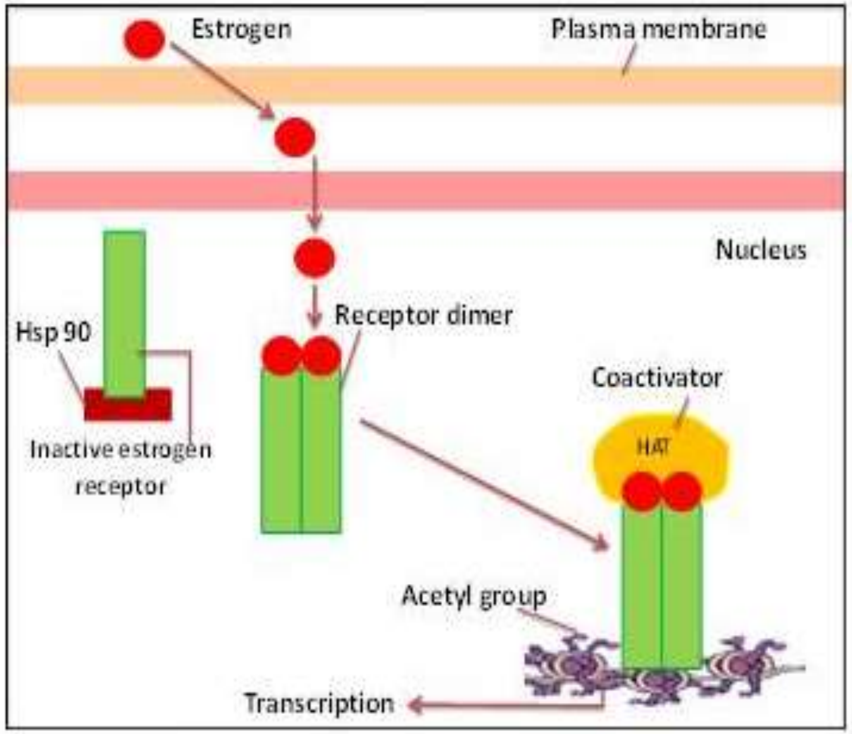


Cytokine receptor

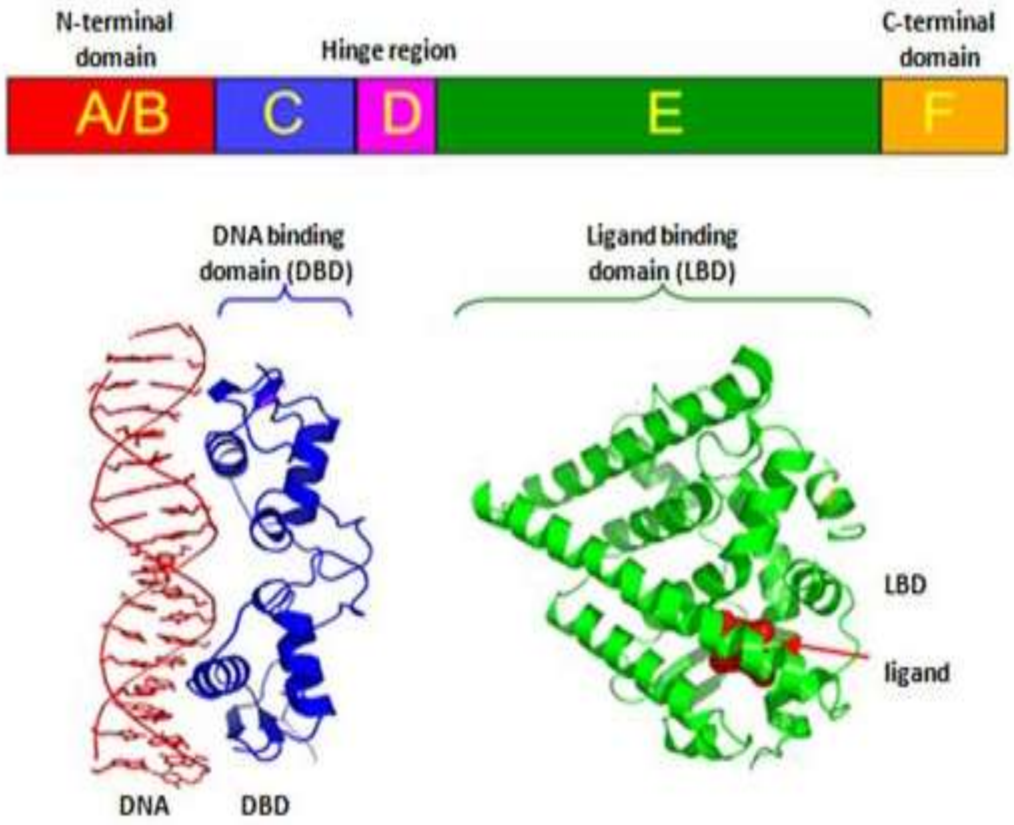
Receptor types based on cellular location:

There are mainly three types of receptors present in the cell based on their location in the cell. They are:

- Cytosolic receptors
- Nuclear receptors
- Membrane bound receptors

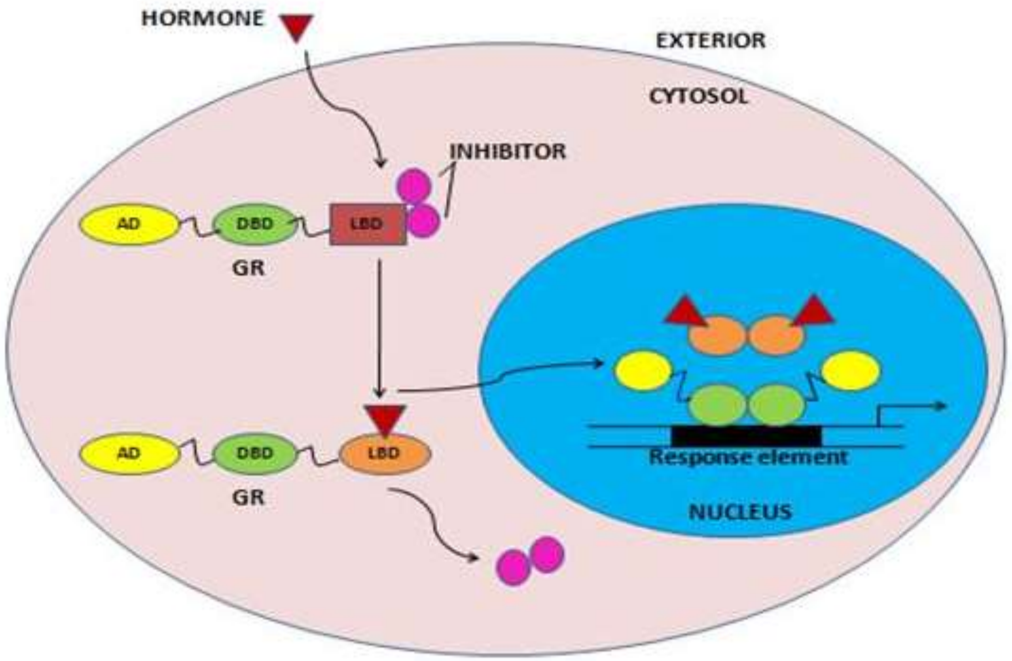


Estrogen receptor action



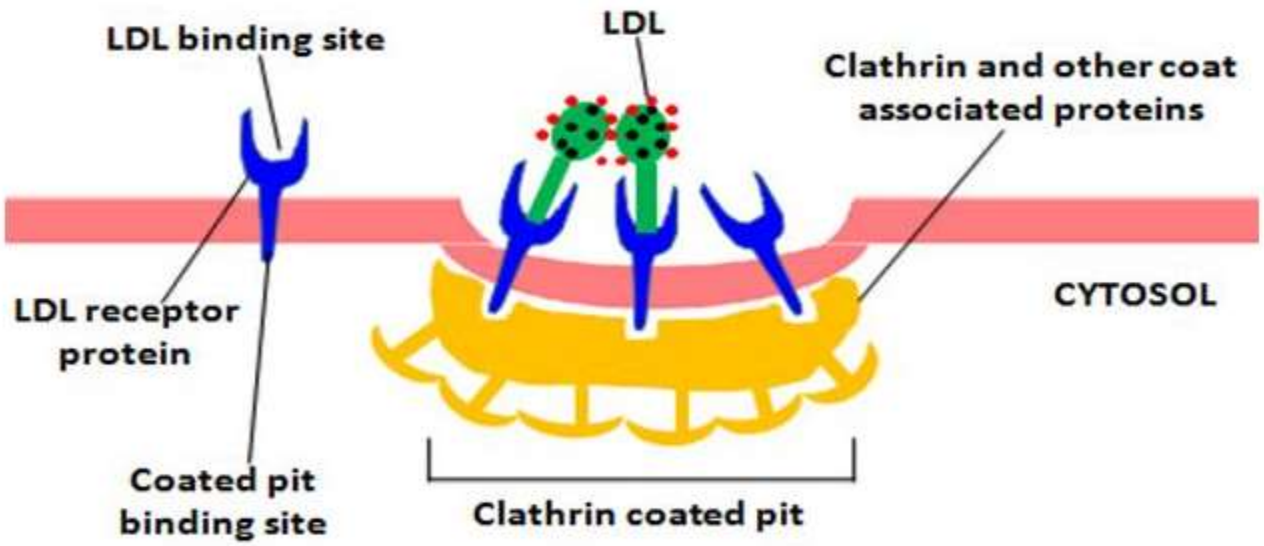
Structural Organization of Nuclear Receptors (estrogen receptor)

Mechanism of action: The intracellular nuclear receptors respond to small hydrophobic signaling molecules that diffuse readily across the plasma membrane. These molecules bind to the receptors and a conformational change takes place in the receptor. This is followed by a series of intracellular signal transduction cascade.



Membrane bound receptors

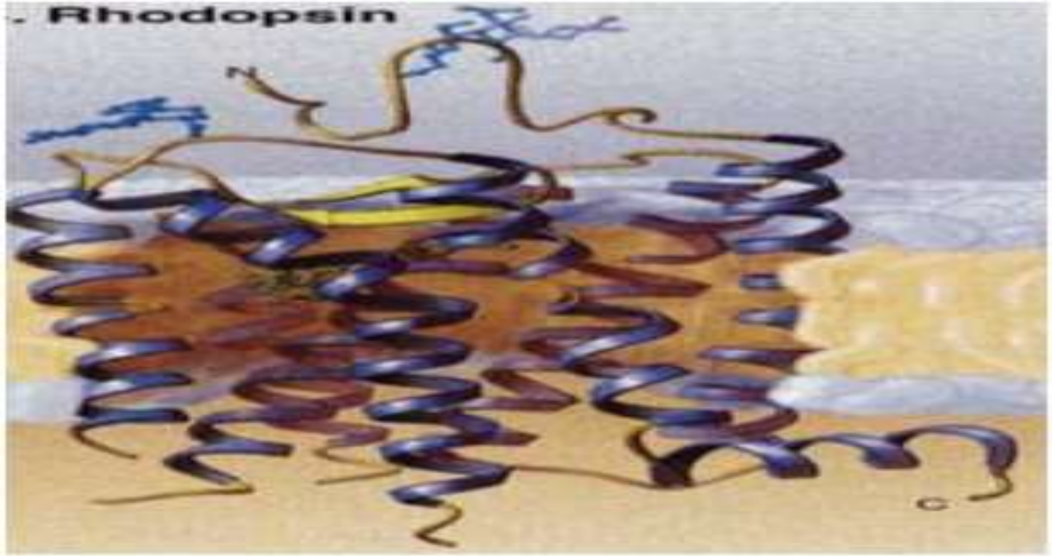
Membrane bound receptors are proteins that are associated with the cell membrane . They can span across the membrane and can transmit a signal from outside the cell to inside the cell. Outside the cell, a ligand (e.g. Hormone) will bind to the receptor . A few chemical stimuli, including steroid hormones and the gas nitric oxide cross the plasma membrane and bind receptors inside the cell.



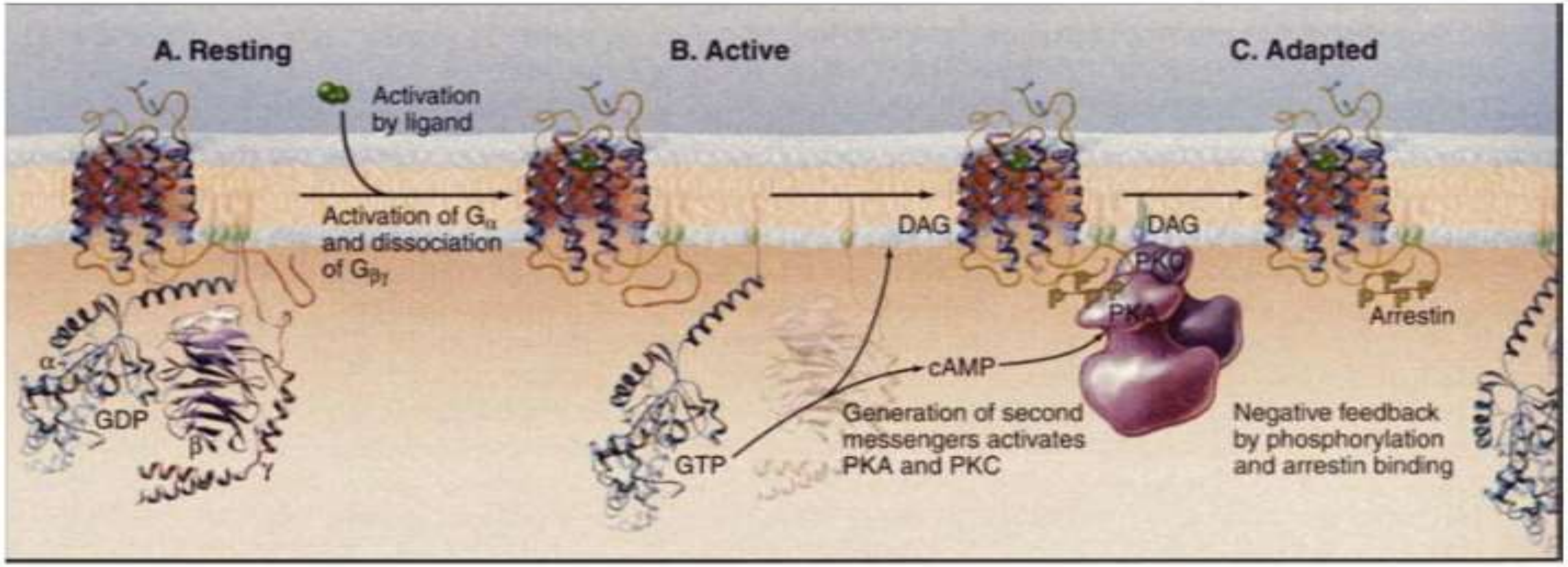
LDL receptor proteins binding to a coated pit in the plasma membrane of a cell

The seven major classes of cell surface receptors are:

- G protein-coupled receptors
- Cytokine receptors
- Receptor tyrosine kinases
- TGFβ receptors
- Hedgehog receptors
- Wnt receptors
- Notch receptor



Atomic structure of seven helix receptor of bovine rhodopsin, the light activated protein in vertebrate eye



Cyclic AMP

cAMP is an important second messenger involved in a plethora of cellular effects and biological roles by regulating various metabolic process and mediating the effects of many hormones that binds to a specific receptor on the cell membrane of target cells including catecholamines, ACTH, and vasopressin. It also plays imperative role in the transcription of some genes.

- Some of the hormones that achieve their effects through cAMP as a second messenger:
- Adrenaline
- Glucagon
- Luteinizing hormone (LH)

- Cyclic AMP is synthesized from ATP by the action of the enzyme adenylyl cyclase .
- cAMP decomposition into AMP is catalyzed by the enzyme phosphodiesterase .
- cAMP and its associated kinases function in several biochemical processes, including the regulation of glycogen, sugar, and lipid metabolism.

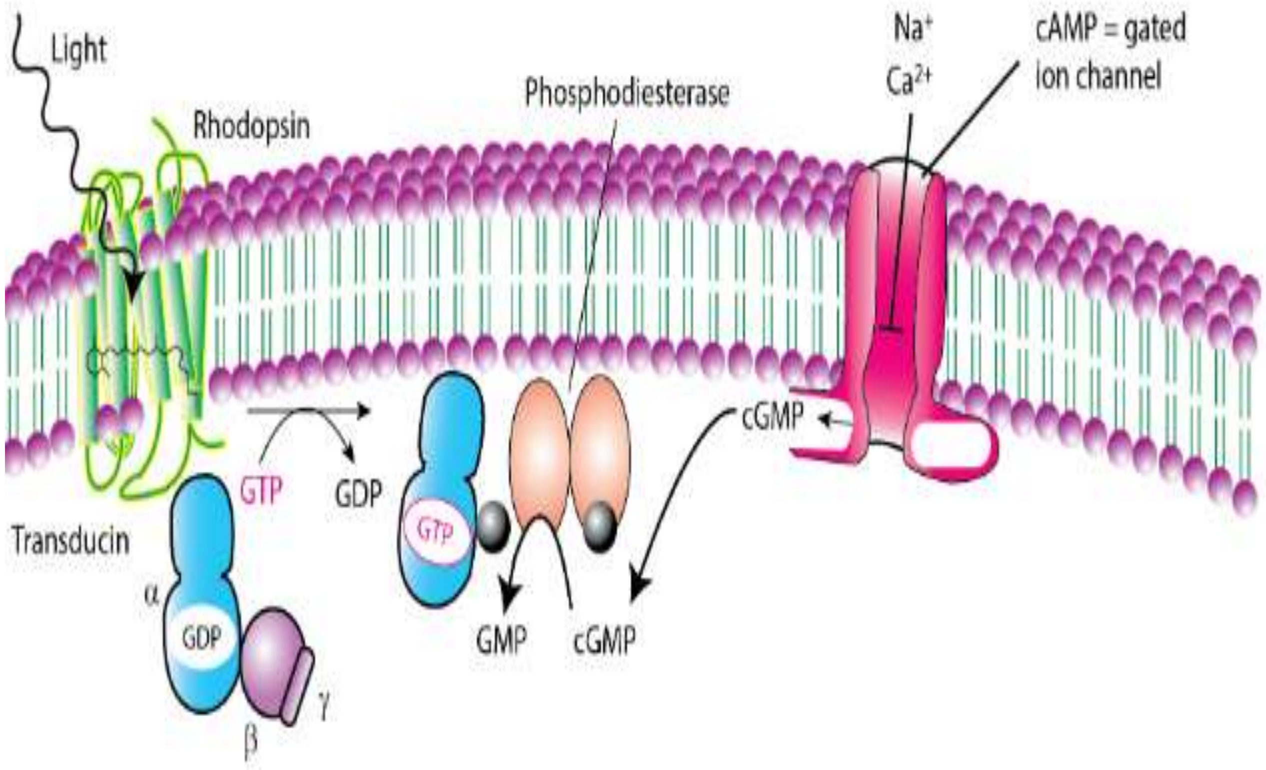
Cyclic Guanosine monophosphate

Cyclic Guanosine monophosphate or cGMP, is a cyclic nucleotide derived from guanosine triphosphate(GTP). cGMP is a multi-functional second messenger molecule, similar in action to cAMP but generally producing opposite effects on cell function.

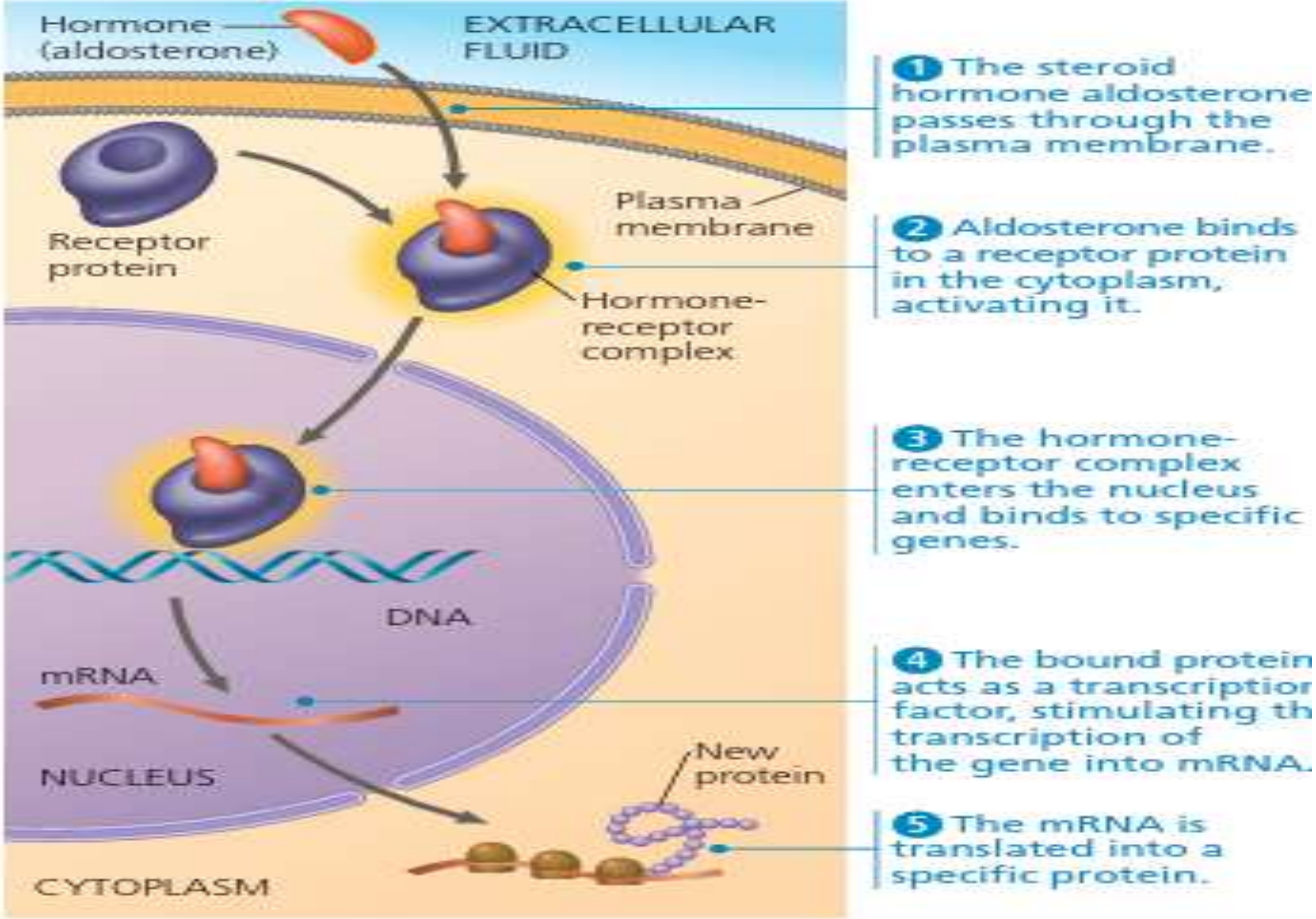
1. cGMP is an important molecule of the cell that takes part in various activities in cellular system. When guanylyl cyclase stimulation leads to elevated levels of cGMP, it then mediates biological responses, such as blood vessel dilation which increases blood flow.

2. The action of cGMP is regularly facilitated by stimulation of cGMP dependent protein kinases, although cGMP is a common regulator of ion channel conductance, glycogenolysis, cellular apoptosis and phosphodiesterases.

3. Another well-known role of cGMP is in the vertebrate eye, where it serves as the second messenger responsible for converting the visual signals received as light to nerve impulses. The photoreceptor in rod cells of the retina is a G protein-coupled receptor called rhodopsin.



isual Signal Transduction. The light-induced activation of rhodopsin leads to the hydrolysis of cGMP, which in turn leads to ion channel closing and the initiation of an action potential.



▲ **Figure 11.9** **Steroid hormone interacting with an intracellular receptor.**

Ion-channel linked receptors

- All nerve impulses are generated via ion-channel linked receptors
  - The release of neurotransmitter causes the ion-channel on the target neuron to allow the passage of ions (which?) into the cell. This action is propagated through the nerve cell along its axon.

Calcium ion flux

- Calcium ions are also important intracellular messengers. In fact, calcium ions are probably the most widely used intracellular messengers. Calcium (Ca^{2+}) plays an essential role in the physiology and biochemistry of organisms and the cell. It plays role in common signalling mechanism because once it enters the cytoplasm it exerts allosteric regulatory affects on many enzymes and proteins. Calcium is a second messenger produced by indirect signal transduction pathways such as G-protein coupled receptors. Calcium ions (Ca^{2+}) impact nearly every aspect of cellular life.

Role of Calcium in cell signalling:

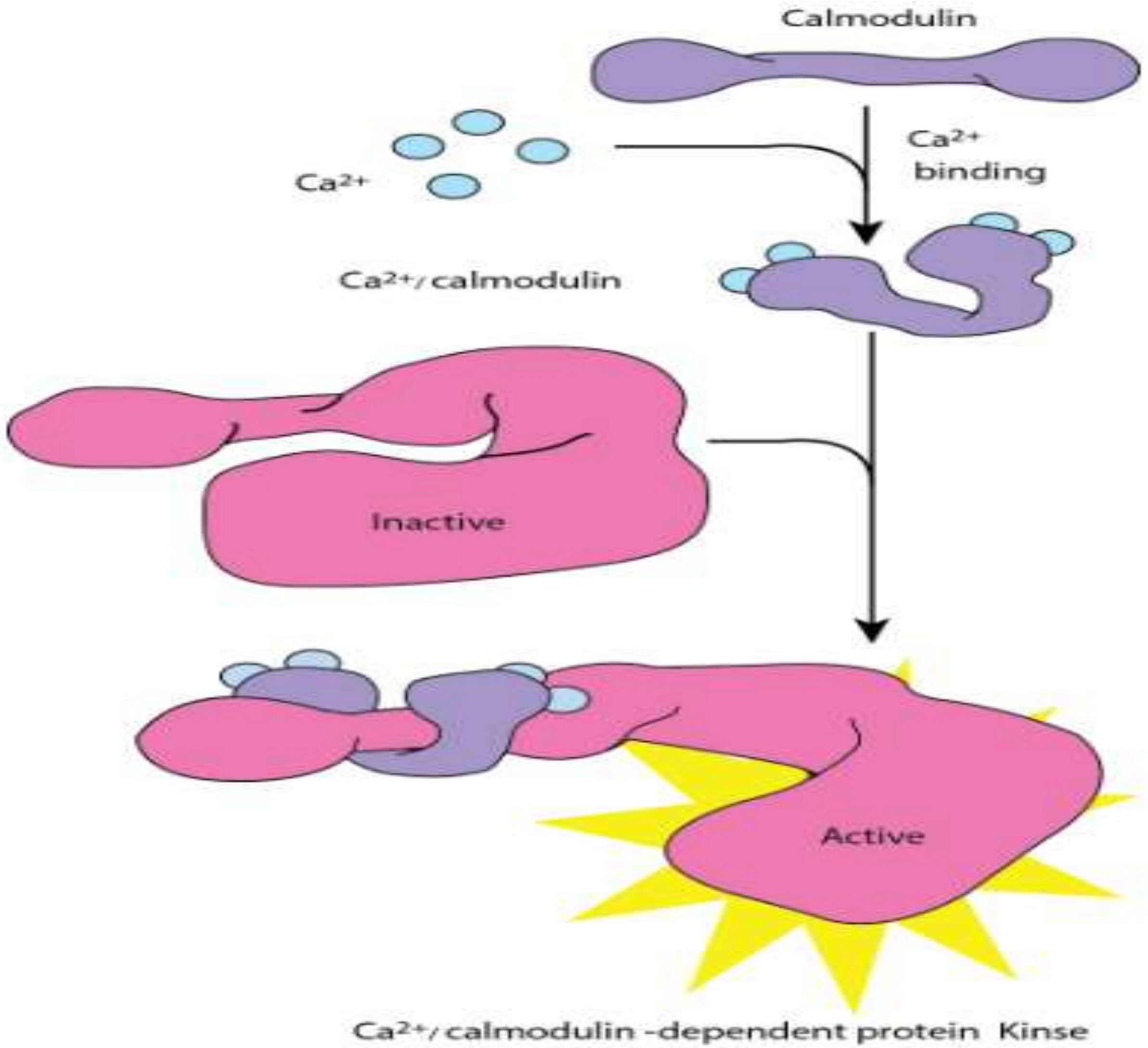
- In response to many different signals, a rise in the concentration of Ca^{2+} in the cytosol triggers many types of events such as:
- Muscle contraction
- Exocytosis

a) Release of neurotransmitters at synapses (and essential for the long-term synaptic changes that produce Long-Term Potentiation (LTP) and Long-Term Depression (LTD)

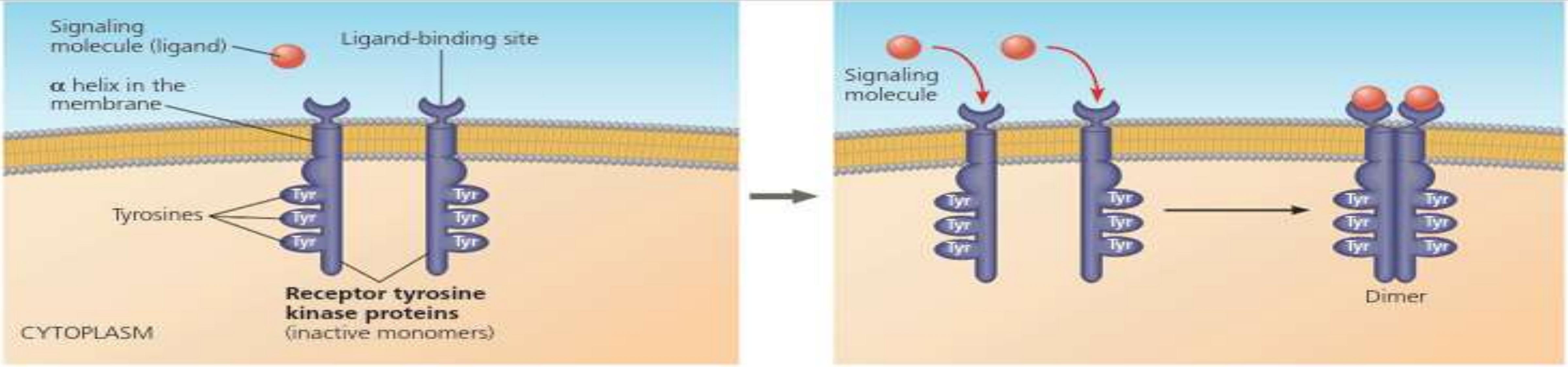
b) Secretion of hormones like insulin

- Activation of T cells and B cells when they bind antigen with their antigen receptors (TCRs and BCRs respectively)
- Adhesion of cells to the extracellular matrix (ECM)
- Apoptosis
- A variety of biochemical changes mediated by P rotein K inase C (PKC)

- Calcium ions are probably the most widely used intracellular messengers.
- Normally, the level of calcium in the cell is very low (~100 nM).
- Getting Ca^{2+} into (and out of) the cytosol is via Voltage-gated channels.

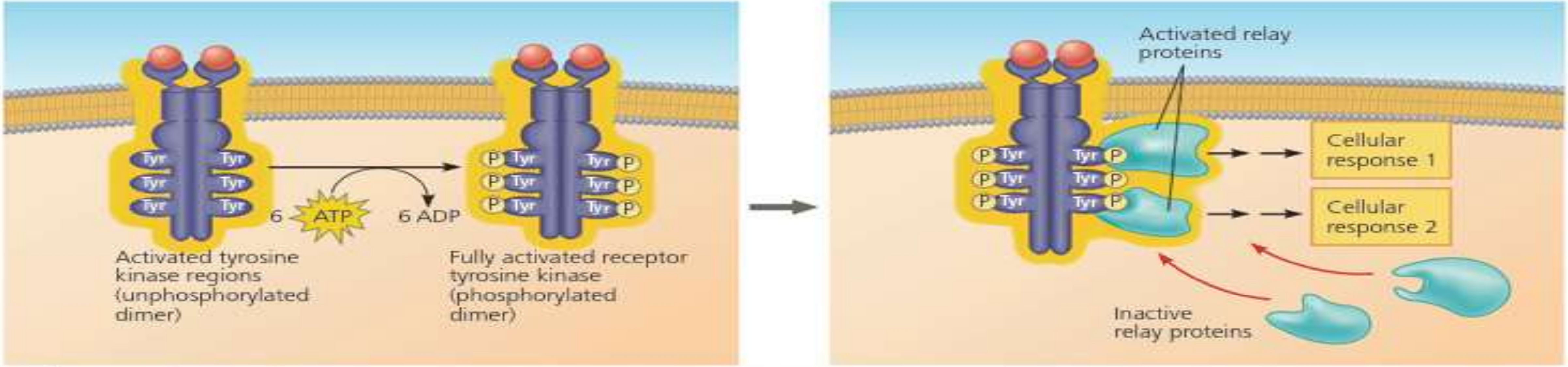


Calcium ion dependent enzyme- calmodulin and Ca^{2+}/calmodulin-dependent protein kinases



1. Many receptor tyrosine kinases have the structure depicted schematically here. Before the signaling molecule binds, the receptors exist as individual units referred to as monomers. Notice that each has an extracellular ligand-binding site, an α helix spanning the membrane, and an intracellular tail containing multiple tyrosines.

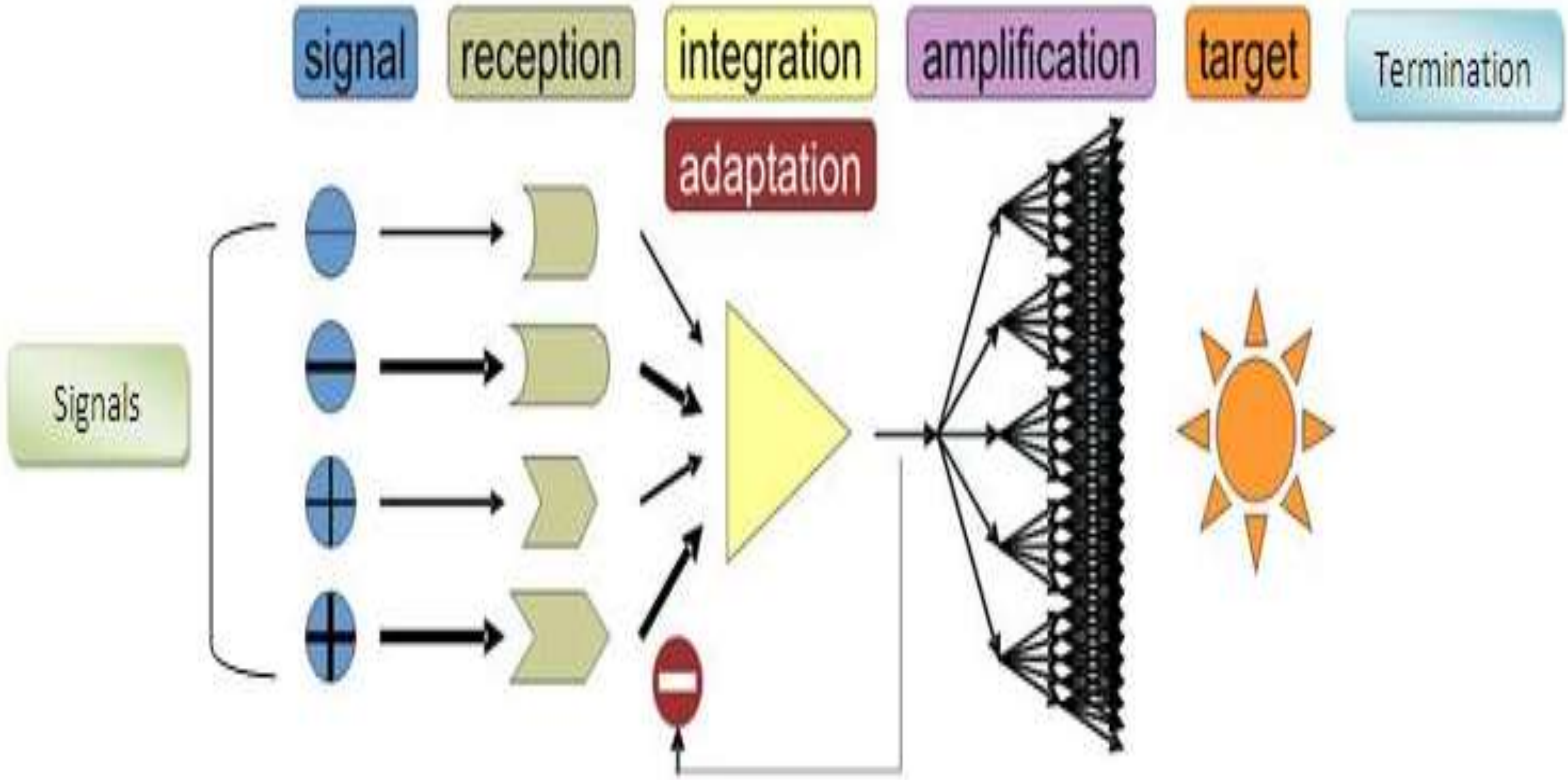
2. The binding of a signaling molecule (such as a growth factor) causes two receptor monomers to associate closely with each other, forming a complex known as a dimer in a process called dimerization. (In some cases, larger clusters form. The details of monomer association are a focus of current research.)



Signal Transduction

Signal transduction is phenomenon which involves in the transfer of signal from extracellular to intracellular environment through the cell surface receptor protein that stimulate intracellular target enzymes, which may be either directly linked or indirectly coupled to receptors by G proteins.

- Signal transduction is the combination of following phenomenon:
- Signal reception
- Integration
- Amplification
- A target that is affected
- Termination



signal
reception
integration
adaptation
amplification
target
Termination
Signals

SIGNAL TRANSDUCTION

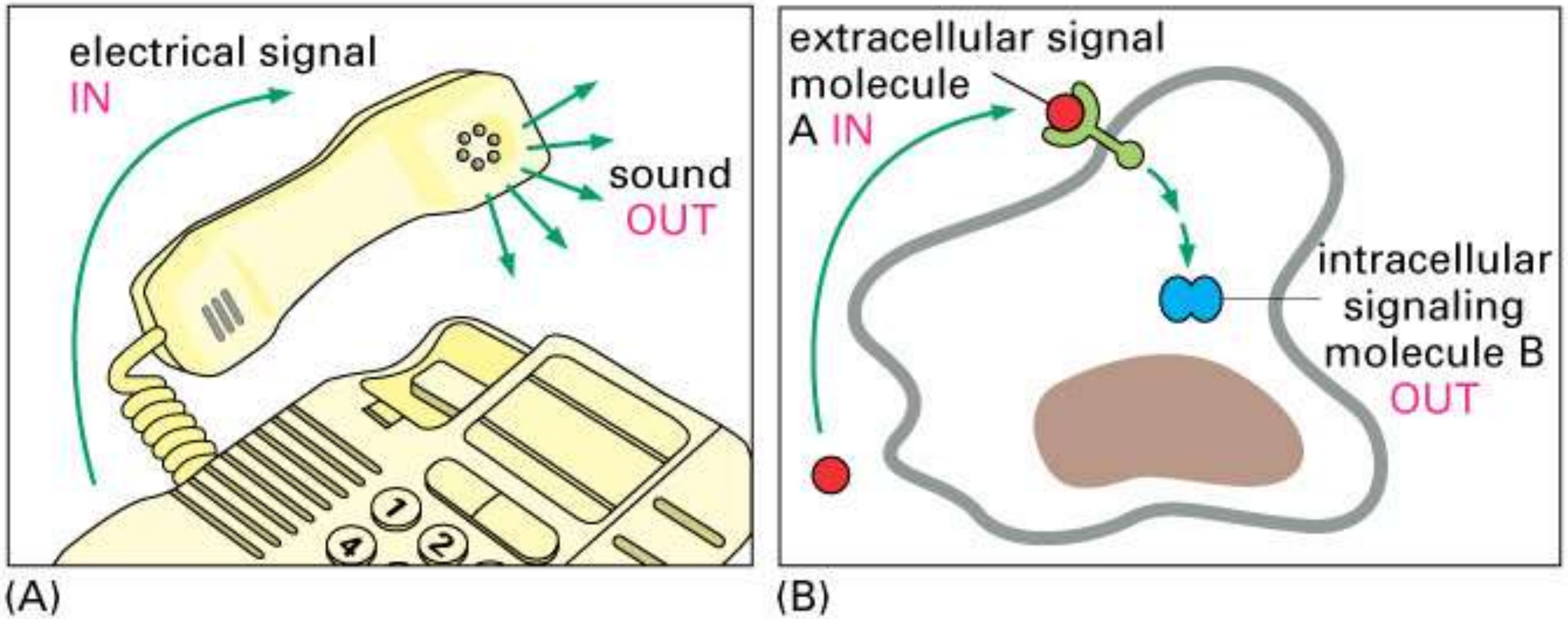
- Cells can exist as single celled organisms or be part of a multi-cellular organism
- How do they know what is happening around them?
- Cells do not have ‘eyes’, ‘noses’, or ‘ears’

SIGNAL TRANSDUCTION

Cells communicate with others and have mechanisms to sense their environments using a variety of methods as we will uncover - whichever method is used it involves a very important principle called

Signal Transduction

The conversion of a signal, of some type, from one physical form to another.



Electrical impulses are converted to sound waves that we hear

Signal molecules are received by target cells via receptors and converted to other intracellular forms

Figure 16-2 Essential Cell Biology, 2/e. (© 2004 Garland Science)

Cell Signaling types

- Endocrine - hormones, long distance
- Paracrine - local vicinity
- Neuronal - very short distances
- Contact-dependent - physical contact
- Autocrine - act on self

Endocrine (hormonal) signaling. Specialized endocrine cells secrete hormones into body fluids, often blood. Hormones reach virtually all body cells, but are bound only by some cells.

Paracrine signaling. A secreting cell acts on nearby target cells by secreting molecules of a local regulator (a growth factor, for example).

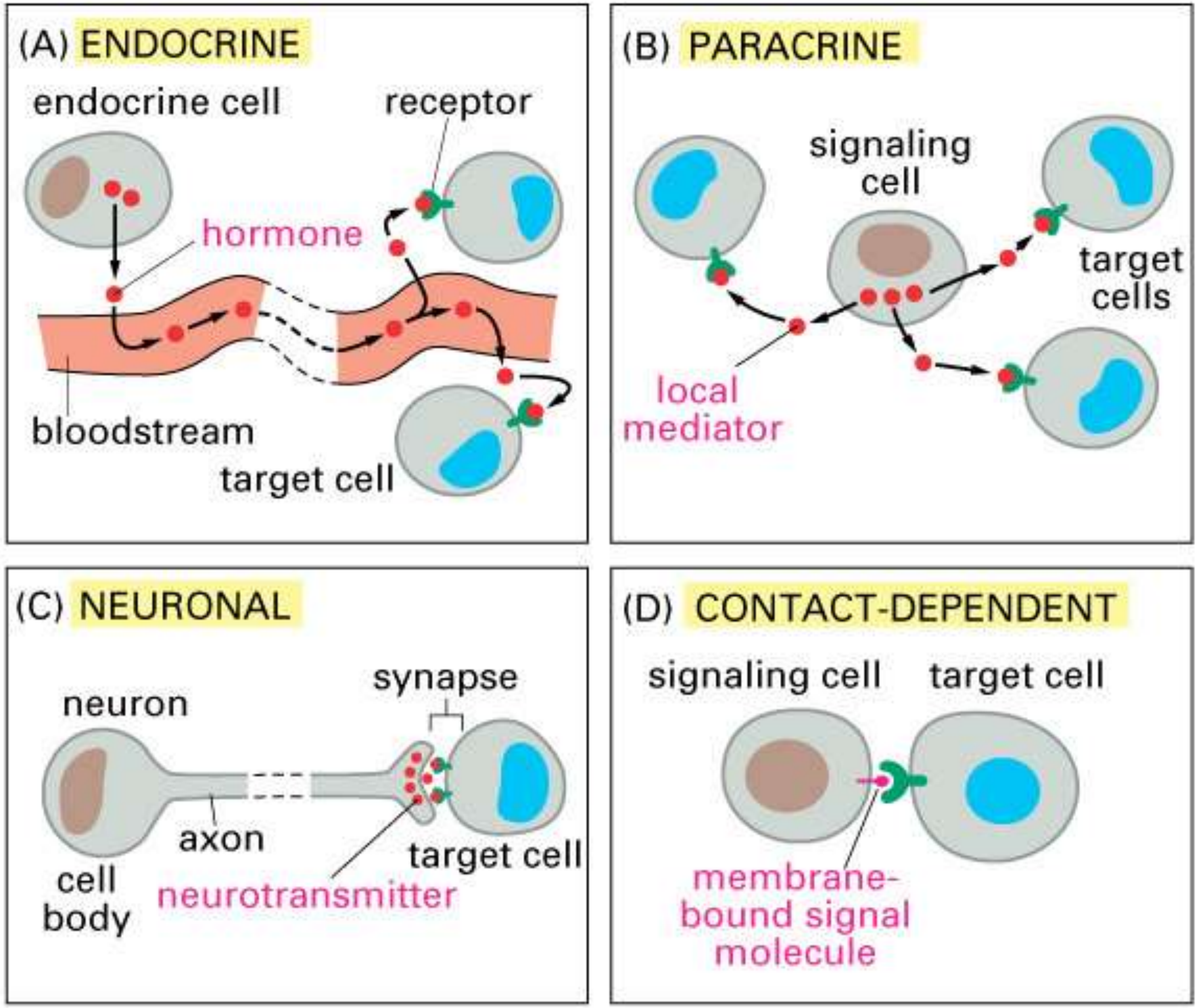
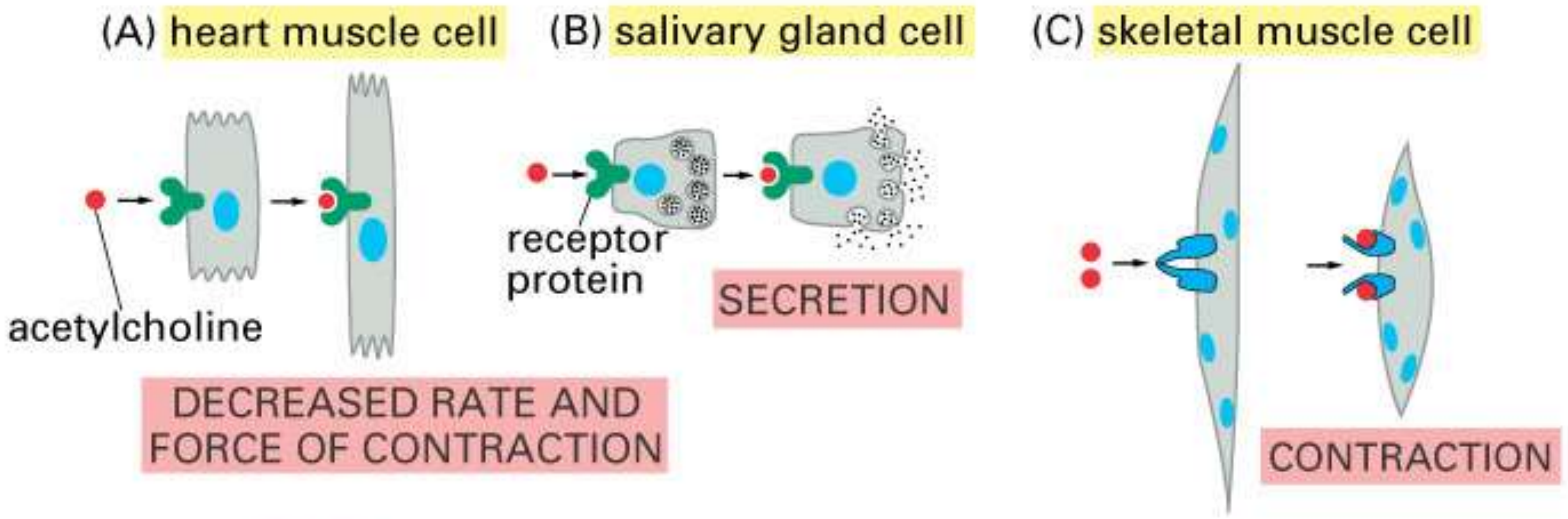


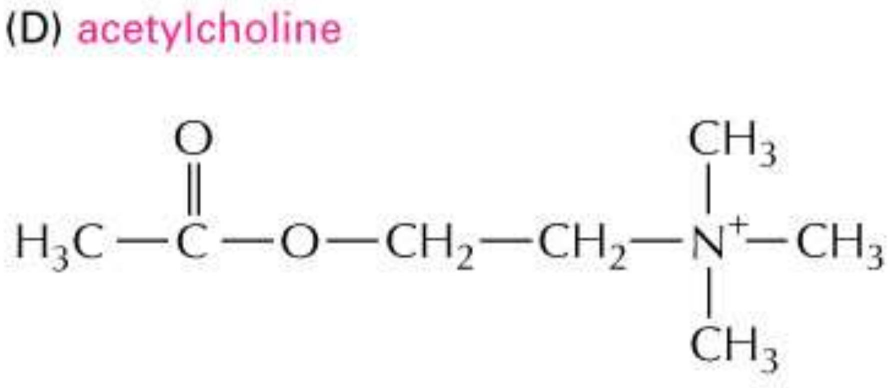
Figure 16-3 Essential Cell Biology, 2/e. (© 2004 Garland Science)

Synaptic signaling. A nerve cell releases neurotransmitter molecules into a synapse, stimulating the target cell, such as a muscle or nerve cell.

Cell-cell recognition. Two cells in an animal may communicate by interaction between molecules protruding from their surfaces.

The same signal molecule may interact with different cells with entirely different effects. Here is an example of acetylcholine



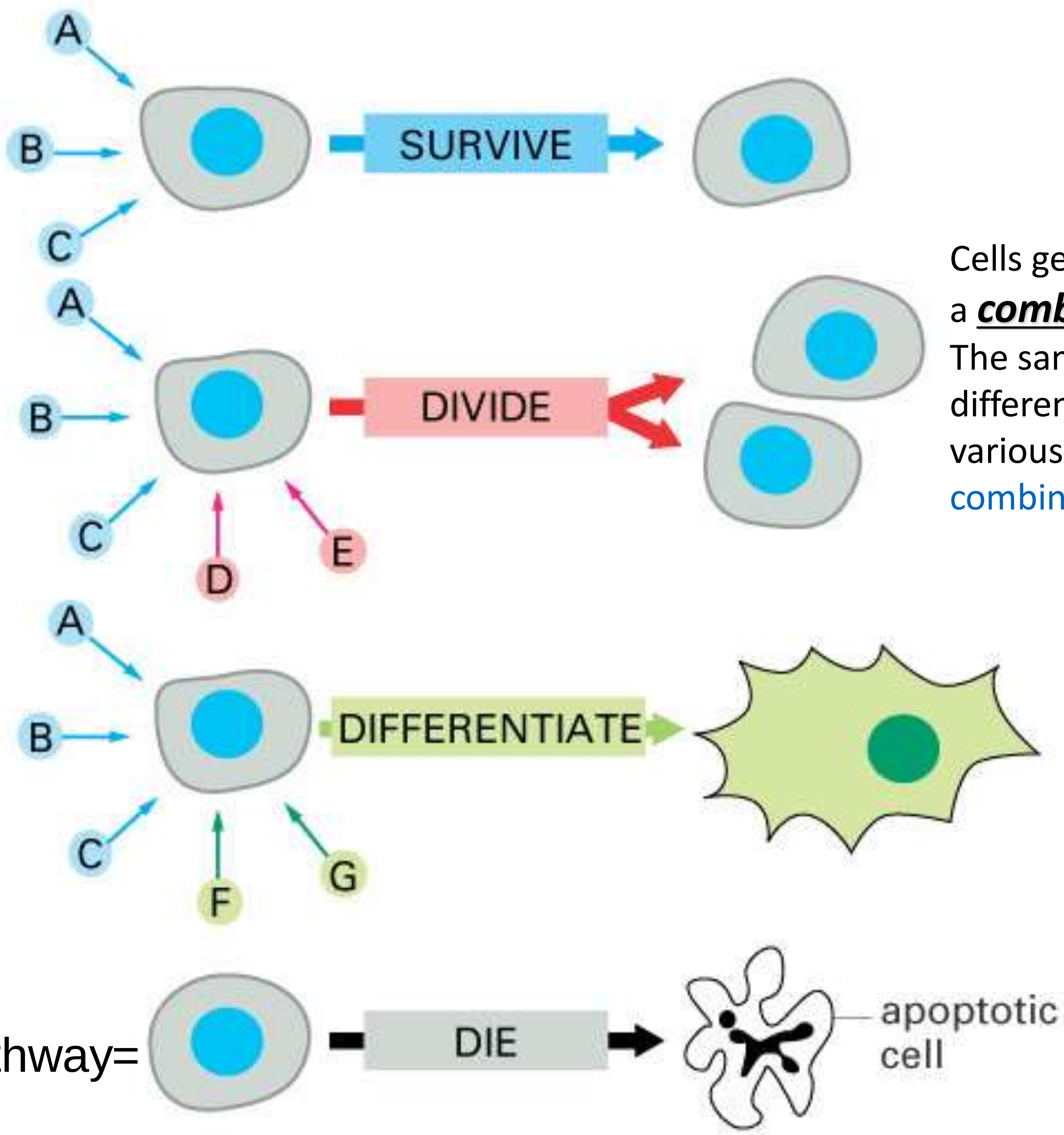


Acetylcholine has a role in both branches of your nervous system

It has a half-life of about 2 minutes.

Figure 16-5 Essential Cell Biology, 2/e. (© 2004 Garland Science)

Cells generally respond to a ***combination*** of signals. The same cell may have different outcomes to various signal combinations



The default pathway=

Cells that DO NOT RECEIVE SIGNALS **DIE**

Figure 16-6 Essential Cell Biology, 2/e. (© 2004 Garland Science)

How do these signals work

At which level?

Where?

How many?

General Plan of Action

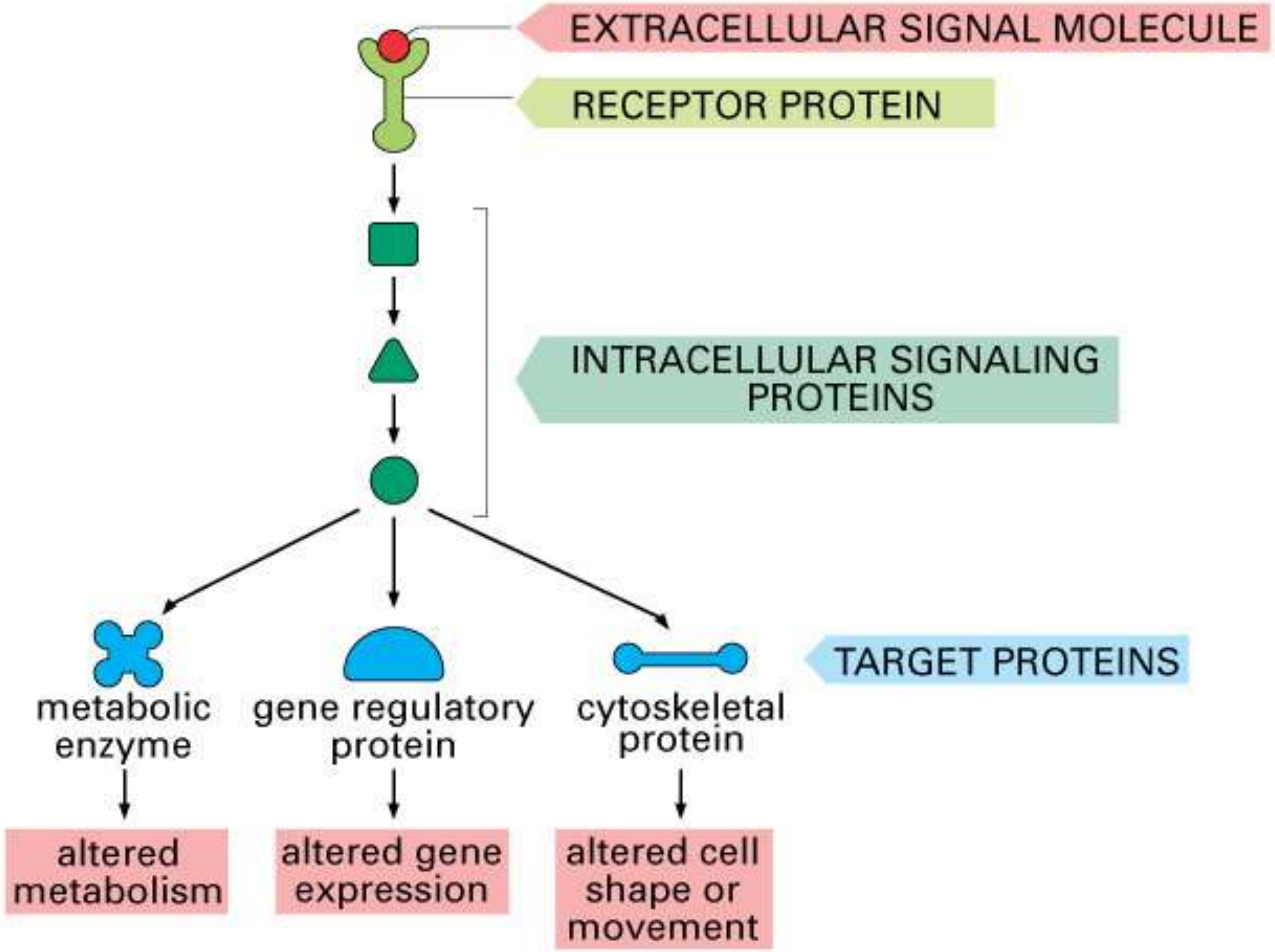


Figure 16-7 Essential Cell Biology, 2/e. (© 2004 Garland Science)

- Each cell responds to a limited set of signals - why?

- These signals change the activity of internal cellular proteins which chances the behavior of the cell

- These signals follow a chain of events known as the signal cascade
  - A system of relaying information from the site of reception to the point of action
  - Normally the signal is amplified too - a small input is quickly converted to a large response

General Overview 2

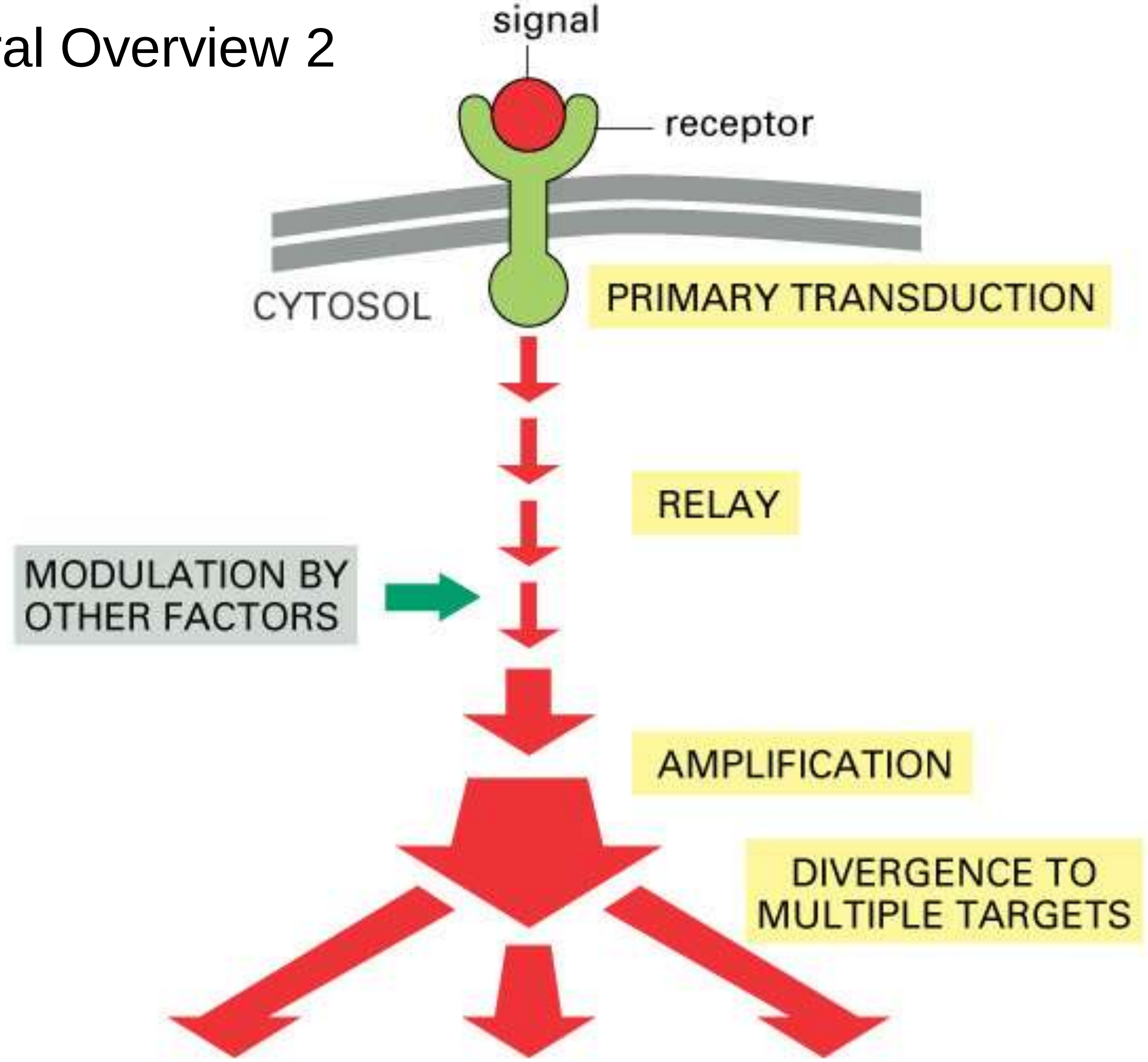
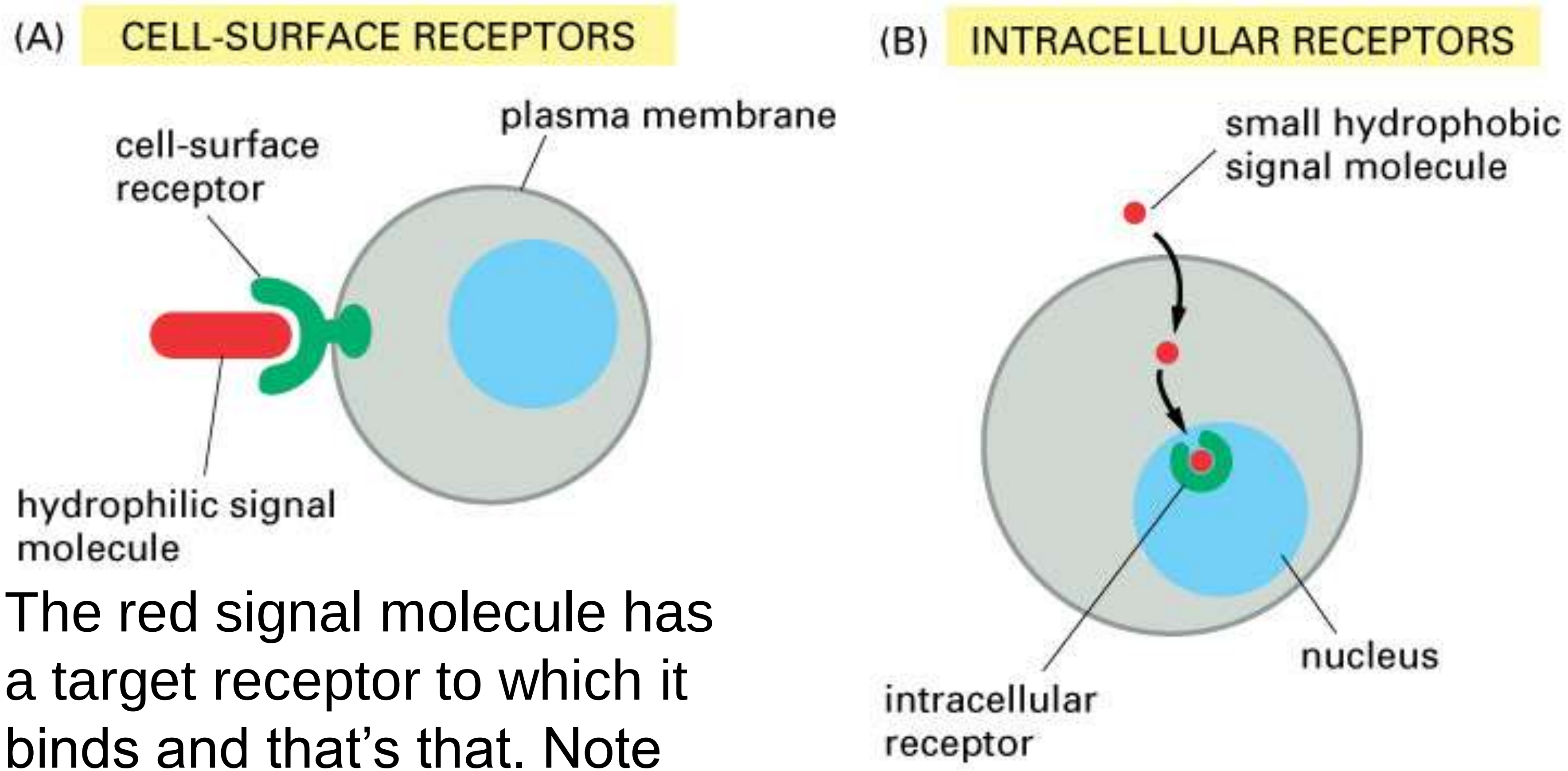


Figure 16-8 Essential Cell Biology, 2/e. (© 2004 Garland Science)

Some signal molecules act at the cell surface whilst others can enter the cell readily and act inside such as steroids.



The red signal molecule has a target receptor to which it binds and that's that. Note that it is usually hydrophilic.

Other receptors enter the cell. If they must pass through the membrane without P's they are..

Figure 16-9 Essential Cell Biology, 2/e. (© 2004 Garland Science)

A simple example of how a steroid works.

-The signal can enter the cell through the membrane and bind to its target protein.

-This is now able to enter through the nuclear pore and control transcription directly of certain target genes

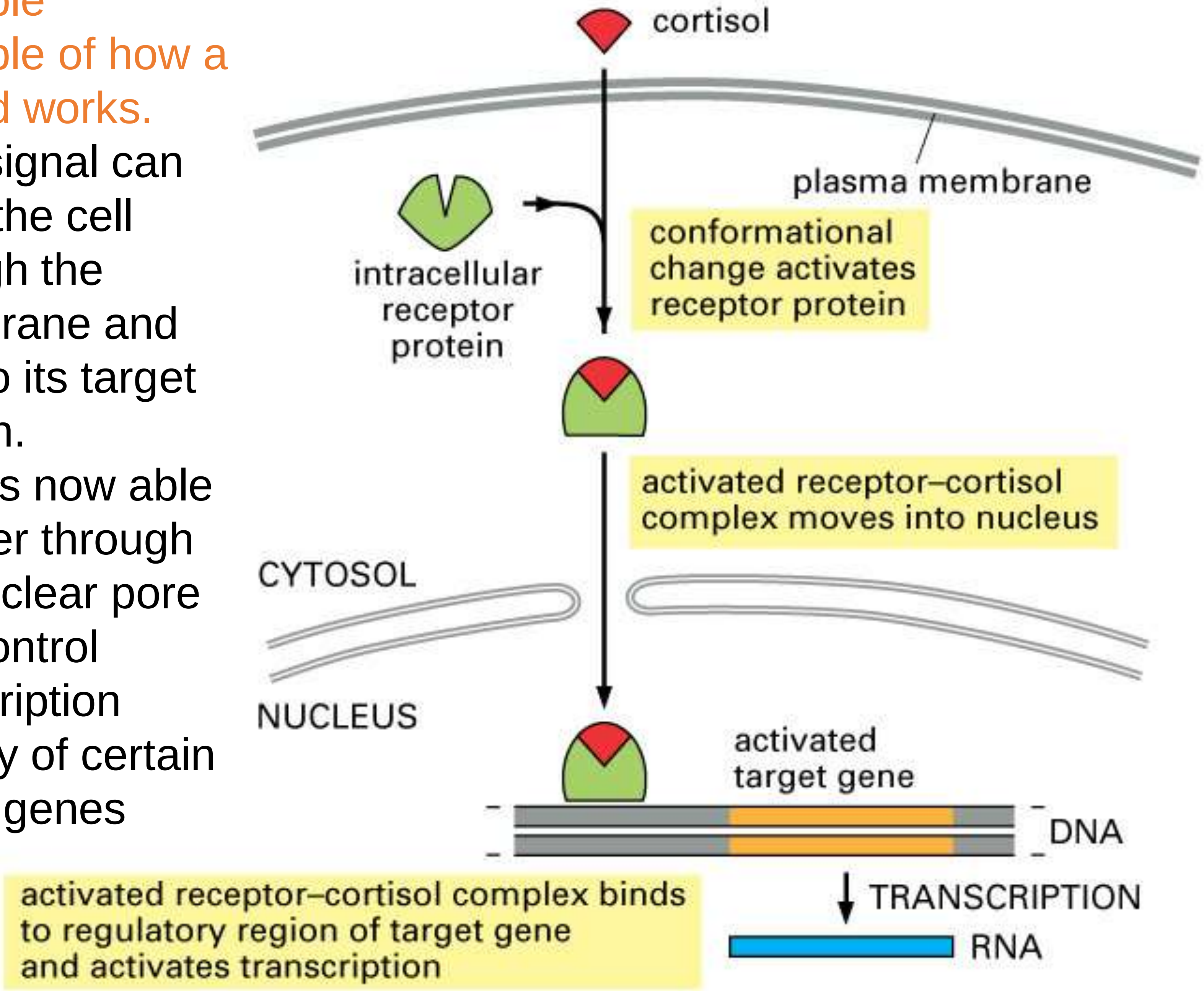


Figure 16-12 Essential Cell Biology, 2/e. (© 2004 Garland Science)

Some cellular responses are quick, whilst others are slow.

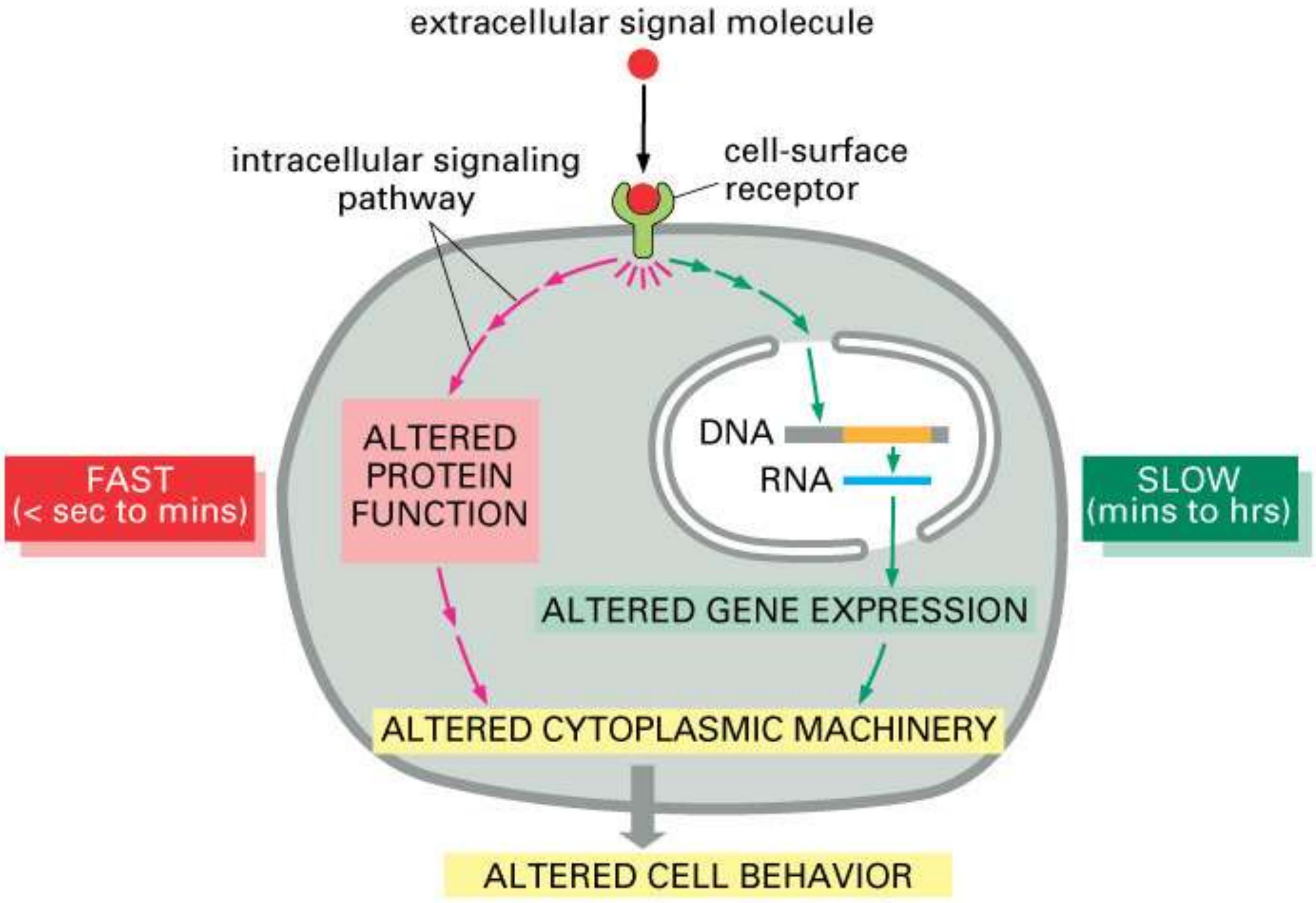


Figure 16-23 Essential Cell Biology, 2/e. (© 2004 Garland Science)

Many interactions taking place within the cell act to turn **on** or **off** proteins. These are known as molecular switches.

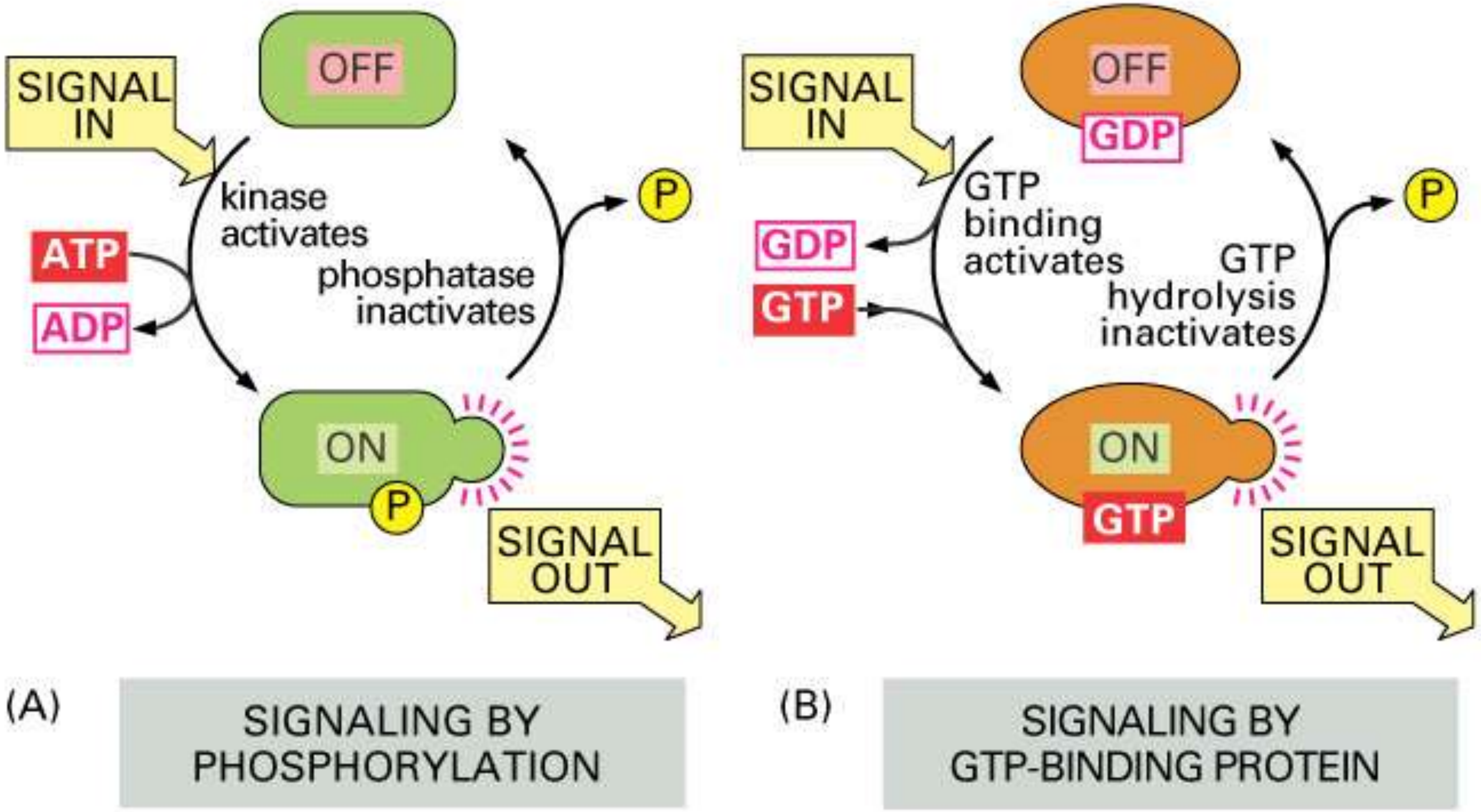
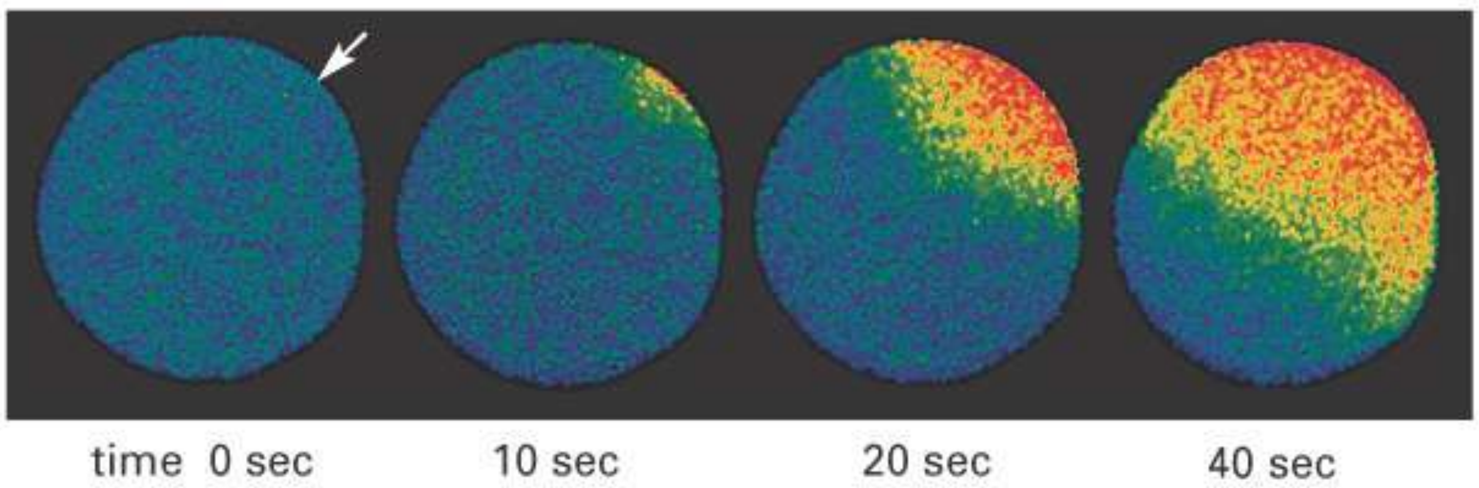


Figure 16-15 Essential Cell Biology, 2/e. (© 2004 Garland Science)

16-

Calcium has a very important role to play as an intercellular messenger.

As we know the concentration of calcium is extremely low in the cytoplasm of a typical cell, compared to the outside and to that of the ER.



In this example fertilization results in the wave of receptors opening up to permit the influx of calcium into the cell. This results in a change in the cell surface which both initiates cell division and prevents other sperm from entering the cell.

Figure 16-26 Essential Cell Biology, 2/e. (© 2004 Garland Science)

16-

The speed at which signaling cascades operate is clearly illustrated by the photoreceptors of the eye.

The human eye has two forms of receptors - rods and cones

The cones are further divided depending on the wavelength of light they respond to - red, green, and blue

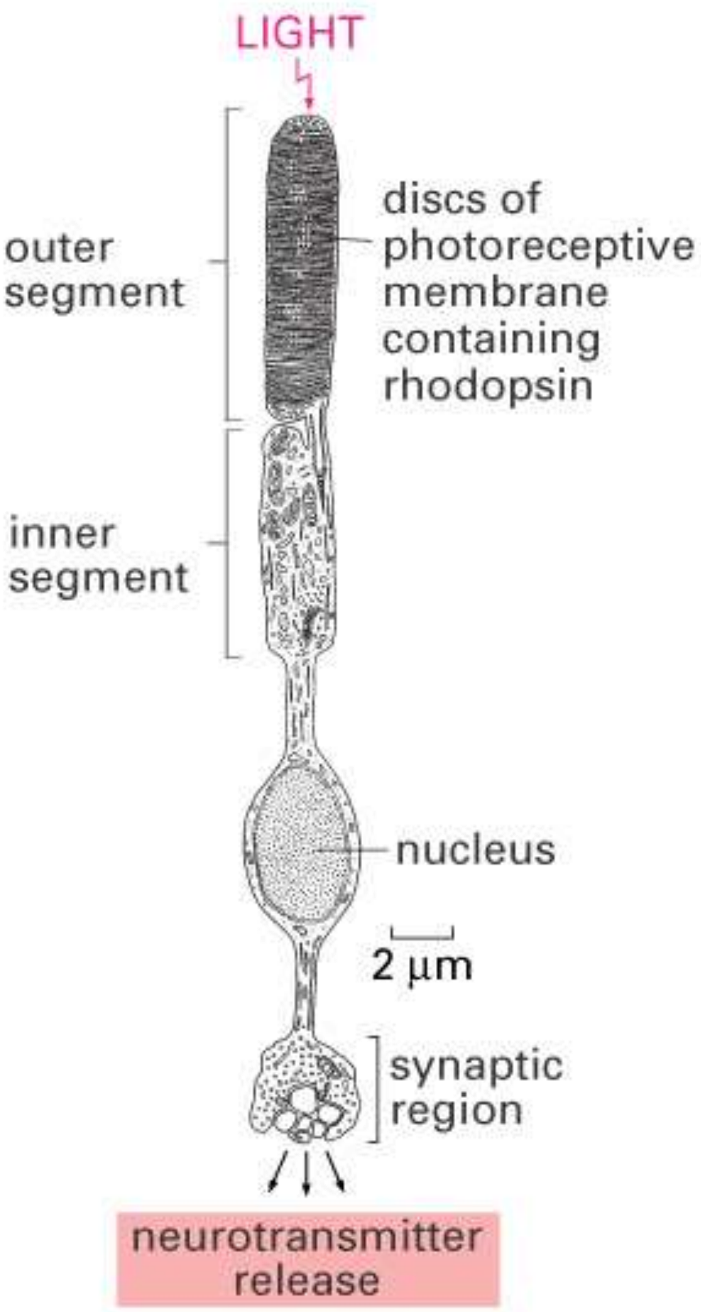


Figure 16-28 Essential Cell Biology, 2/e. (© 2004 Garland Science)

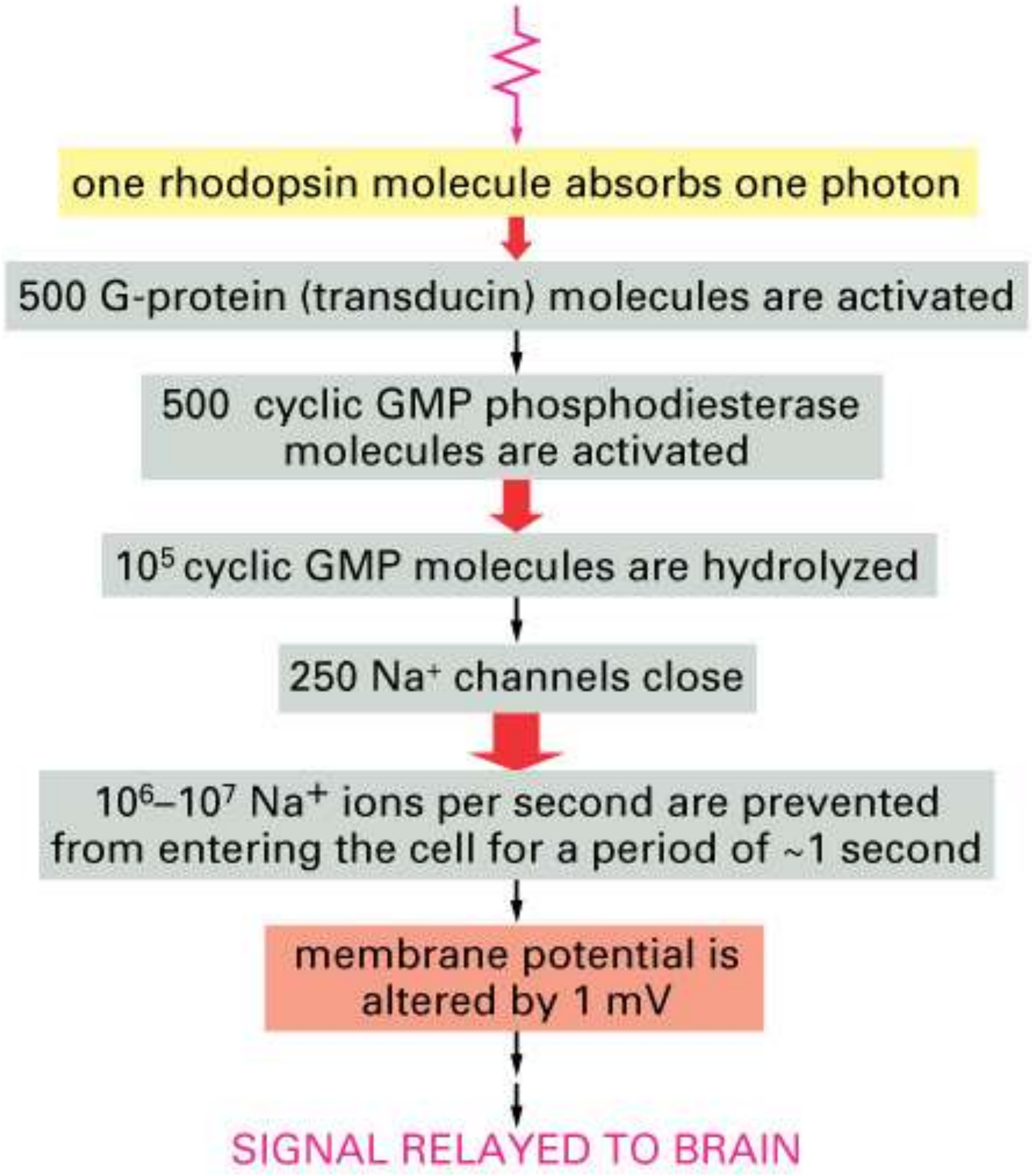
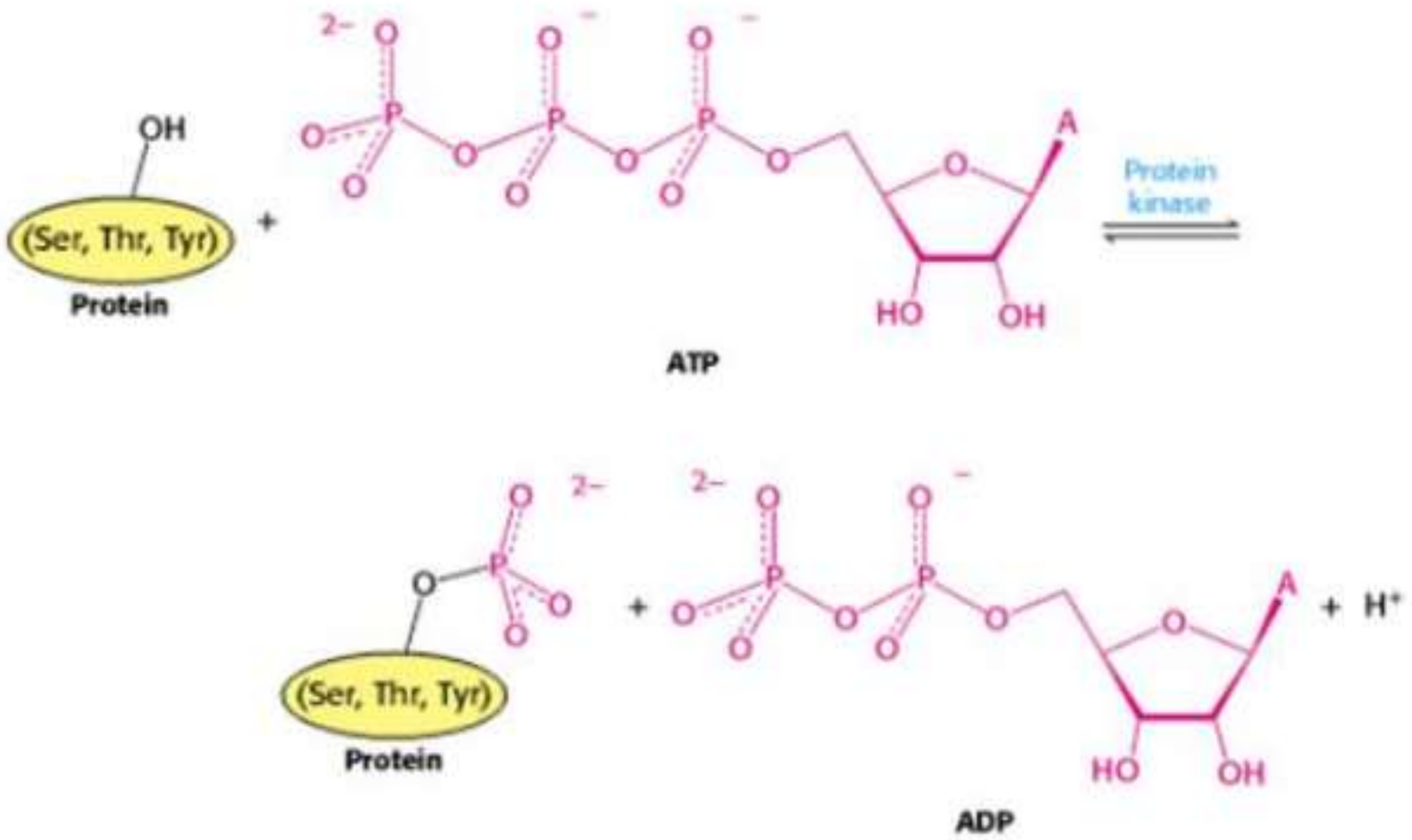


Figure 16-29 Essential Cell Biology, 2/e. (© 2004 Garland Science)

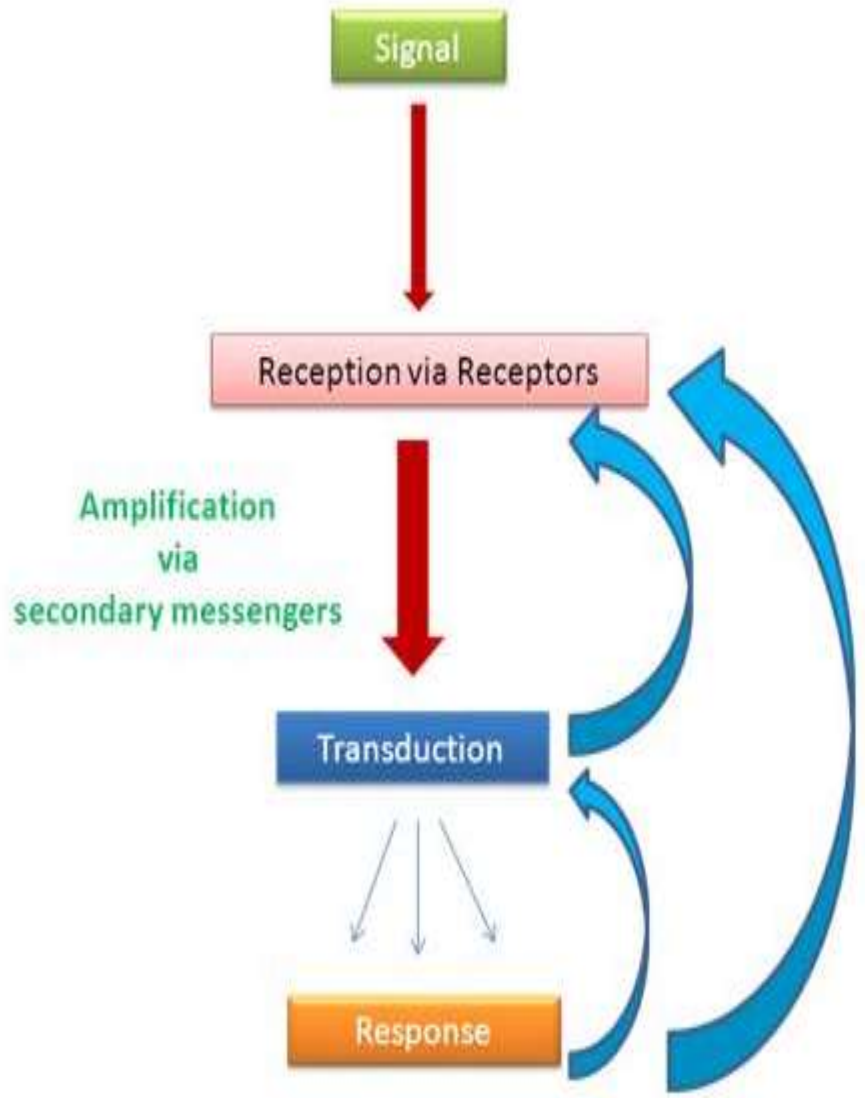
Signal transduction pathways act similar to molecular circuit. This pathway depends on following factors during transformation of signal from extracellular environment to intracellular.

1. Second messengers
2. Signal reception by cell membrane receptor
3. Protein phosphorylation
4. Signal termination by protein phosphatase


OH
(Ser, Thr, Tyr)
Protein
ATP
Protein kinase
(Ser, Thr, Tyr)
Protein
ADP
+ H+

Signal amplification

Signal amplification is phenomenon in which when receptor proteins interact with the signal molecules at the surface of the cell, in most cases signals are relayed to the cytoplasm or the nucleus by second messengers which influences the activity of one or more enzymes or genes inside the cell. However, most signalling molecules are found in such a low concentration that their effect in cytoplasm would be minimal unless the signal was amplified.



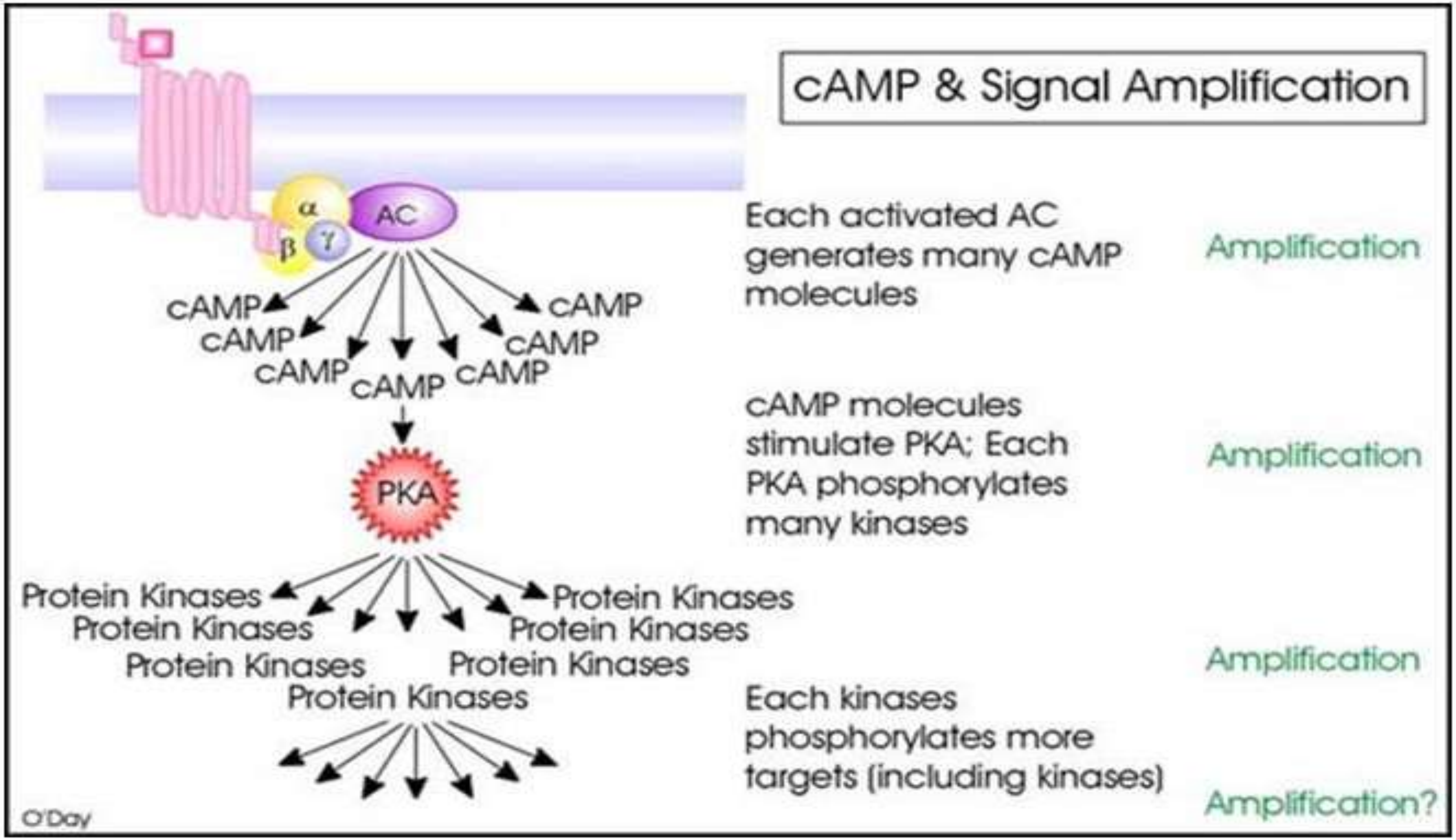
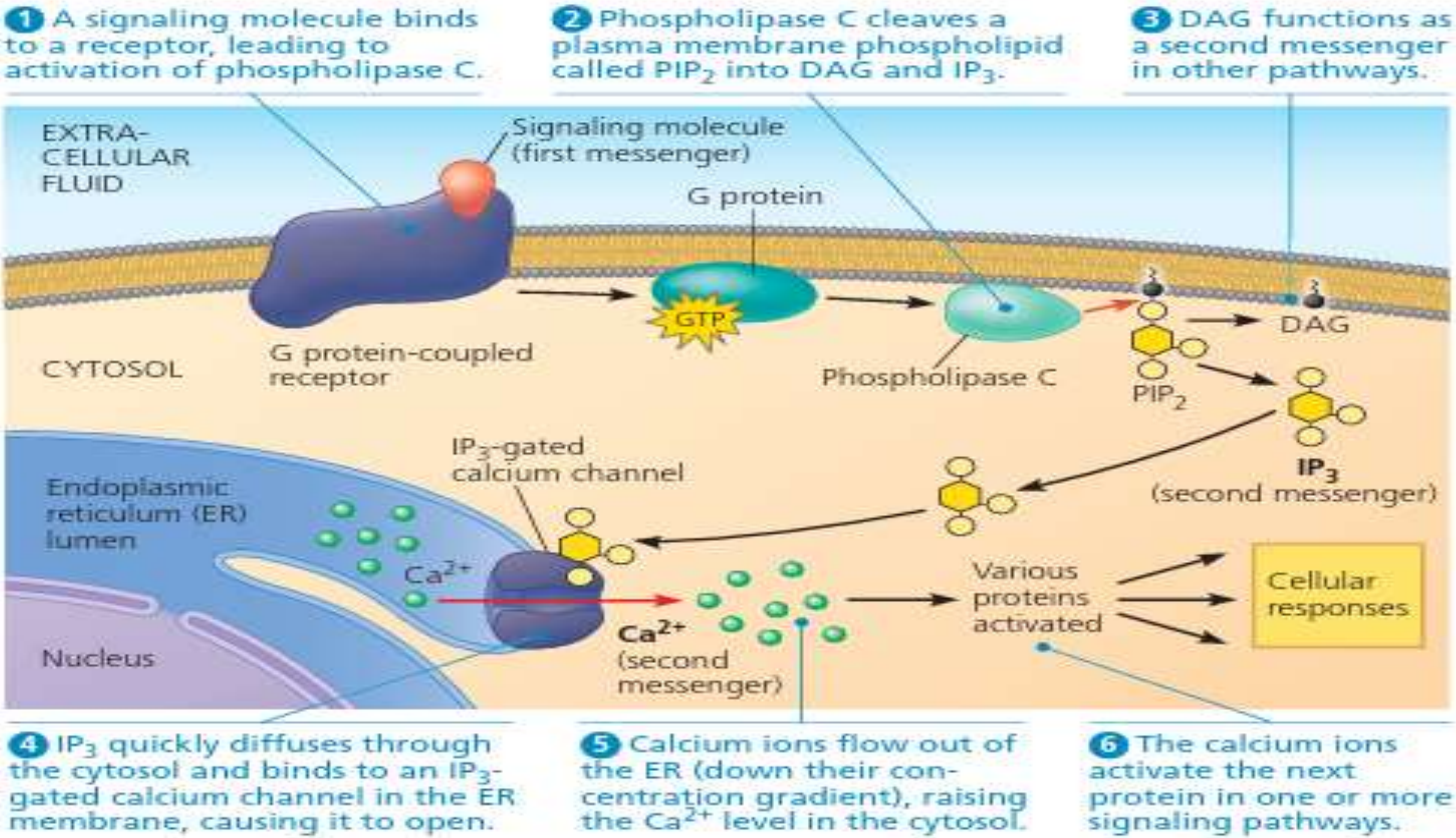

cAMP & Signal Amplification
α
β
γ
AC
cAMP
cAMP
cAMP
cAMP
cAMP
cAMP
cAMP
PKA
Protein Kinases
Protein Kinases
Protein Kinases
Protein Kinases
Protein Kinases
Protein Kinases
Protein Kinases
Each activated AC generates many cAMP molecules
Amplification
cAMP molecules stimulate PKA; Each PKA phosphorylates many kinases
Amplification
Amplification
Each kinases phosphorylates more targets (including kinases)
Amplification?
O'Day

Table 1: Example of hormone induced response mediated by cAMP

Tissue	Hormones	Response
Liver	Epinephrine and glucagon	Glycogen breakdown, glucose synthesis (glucogenesis), inhibition of glycogen synthesis
Skeletal muscle	Epinephrine	Glycogen breakdown, inhibition of glycogen synthesis
Cardiac muscle	Epinephrine	Increase contractility
Adipose	Epinephrine, ACTH and glucagon	Triacyglycerol catabolism
Kidney	Vasopressin(ADH)	Increase permeability of epithelial cells to water
Thyroid	TSH	Secretion of thyroid hormones
Bone	Parathyroid hormone	Increase calcium resorption
Ovary	LH	Increase secretion of steroid hormones
Adrenal cortex	ACTH	Increase secretion of glucocorticoids

There are 3 major classes of second messengers:

- Cyclic nucleotides (**cAMP** and **cGMP**)
- Inositol trisphosphate (**IP_3**) and diacylglycerol (**DAG**)
- Calcium ions (**Ca^{2+}**)


1 A signaling molecule binds to a receptor, leading to activation of phospholipase C.
2 Phospholipase C cleaves a plasma membrane phospholipid called PIP_2 into DAG and IP_3.
3 DAG functions as a second messenger in other pathways.
EXTRA-CELLULAR FLUID
Signaling molecule (first messenger)
G protein
GTP
CYTOSOL
G protein-coupled receptor
Phospholipase C
DAG
PIP_2
IP_3 (second messenger)
IP_3-gated calcium channel
Endoplasmic reticulum (ER) lumen
Ca^{2+}
Various proteins activated
Cellular responses
Ca^{2+} (second messenger)
Nucleus
4 IP_3 quickly diffuses through the cytosol and binds to an IP_3-gated calcium channel in the ER membrane, causing it to open.
5 Calcium ions flow out of the ER (down their concentration gradient), raising the Ca^{2+} level in the cytosol.
6 The calcium ions activate the next protein in one or more signaling pathways.

G-Protein: G-proteins (guanine nucleotide-binding proteins) are a family of proteins involved in transmitting chemical signals outside the cell, and causing changes inside the cell. They communicate signals from many hormones, neurotransmitters, and other signaling factors.

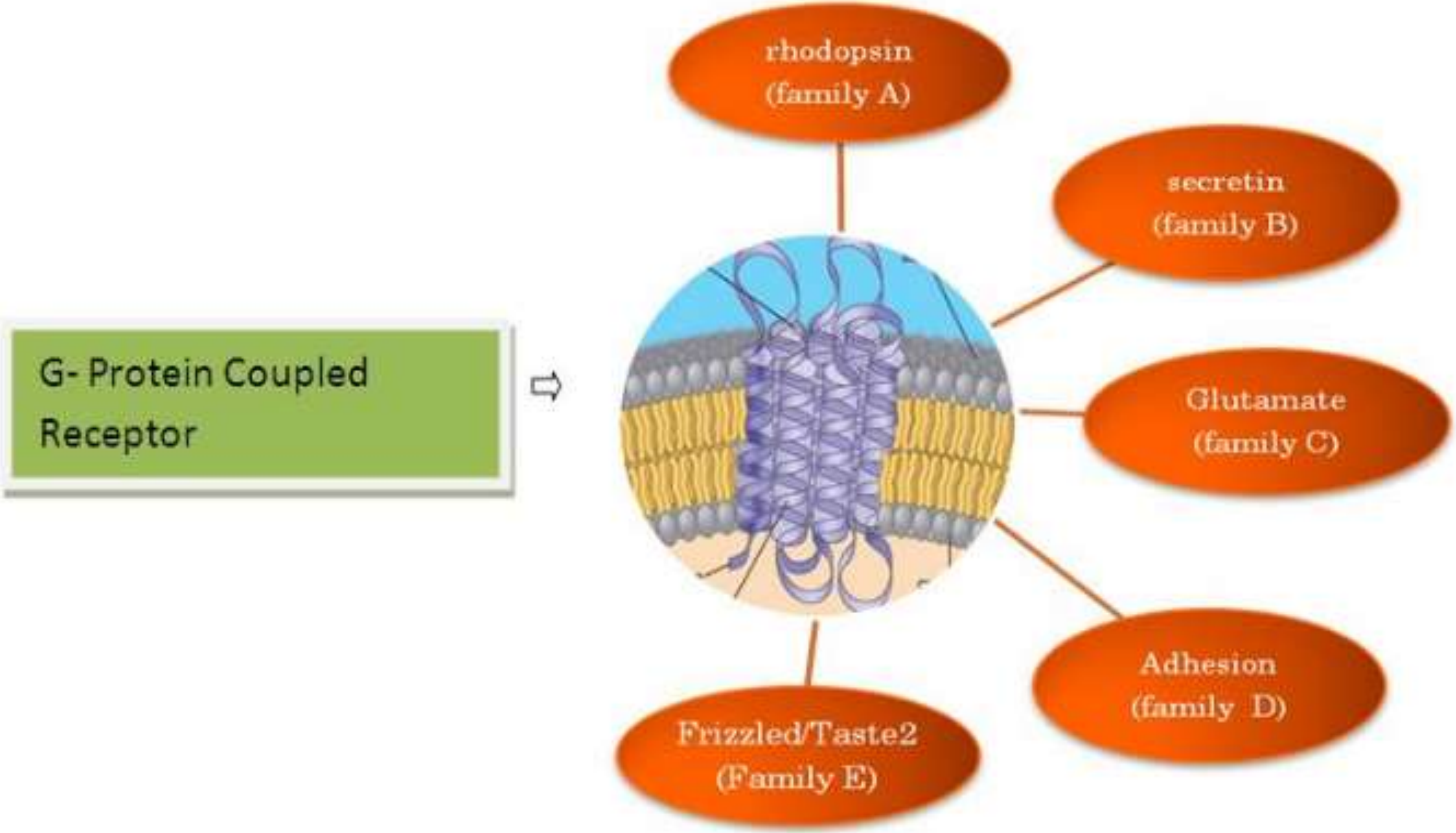
Type of G protein:

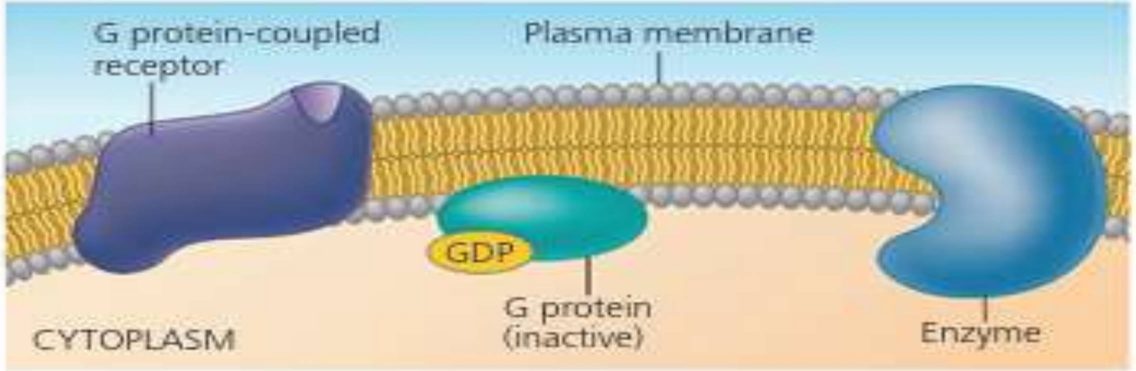
G-protein can refer to two distinct families of proteins.

- **Heterotrimeric G-proteins:** sometimes also known as the large G-proteins that are activated by G protein-coupled receptors and made up of alpha (α), beta (β), and gamma (γ) subunits.

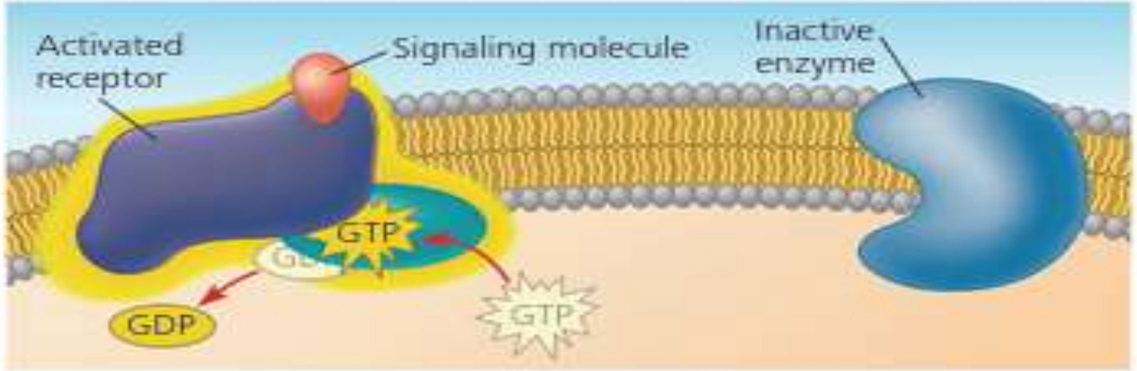
- **Small G-proteins:** They are proteins of 20-25kDa that belong to the Ras superfamily of small GTPases. These proteins are homologous to the alpha (α) subunit found in heterotrimers, and are in fact monomeric. However, they also bind GTP and GDP and are involved in signal transduction.

- G-proteins are molecular switches that use GDP to control their signaling cycle. G-protein is inactive when GDP bounds. To activate the protein, the GDP is replaced with GTP, and then G-protein will deliver its signal.
- The G-protein system plays a central role in many signalling tasks, so it became sensitive target for many drugs and toxins.
- The diversity of GPCRs is observed not only by the multiplicity of stimuli to which they respond, but also by the variety of intracellular signaling pathways they activate

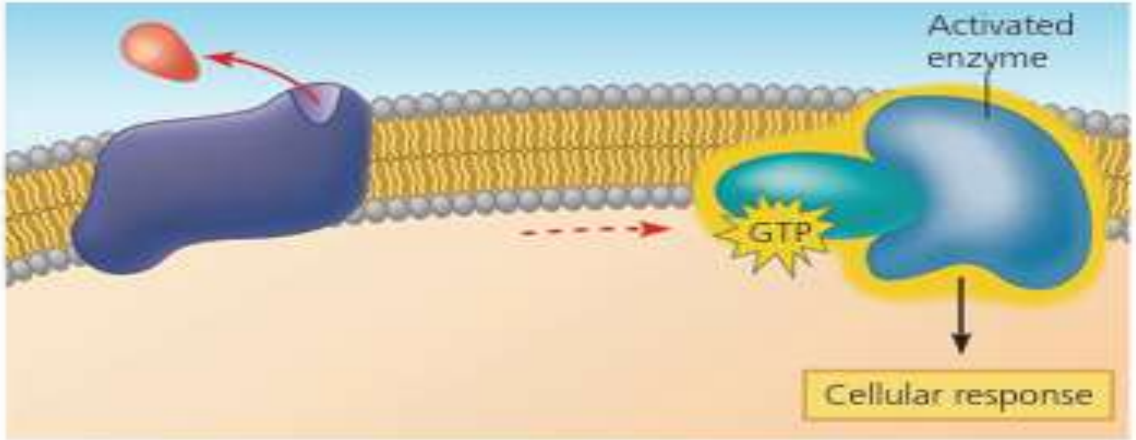

G- Protein Coupled Receptor
rhodopsin (family A)
secretin (family B)
Glutamate (family C)
Adhesion (family D)
Frizzled/Taste2 (Family E)



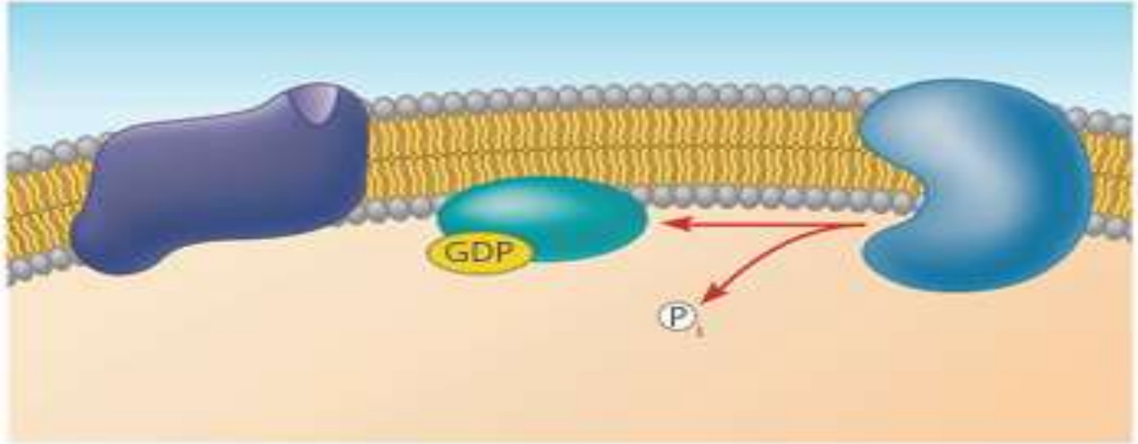
1 Loosely attached to the cytoplasmic side of the membrane, the G protein functions as a molecular switch that is either on or off, depending on which of two guanine nucleotides is attached, GDP or GTP—hence the term *G protein*. (GTP, or guanosine triphosphate, is similar to ATP.) When GDP is bound to the G protein, as shown above, the G protein is inactive. The receptor and G protein work together with another protein, usually an enzyme.



2 When the appropriate signaling molecule binds to the extracellular side of the receptor, the receptor is activated and changes shape. Its cytoplasmic side then binds an inactive G protein, causing a GTP to displace the GDP. This activates the G protein.



3 The activated G protein dissociates from the receptor, diffuses along the membrane, and then binds to an enzyme, altering the enzyme's shape and activity. Once activated, the enzyme can trigger the next step leading to a cellular response. Binding of signaling molecules is reversible: Like other ligands, they bind and dissociate many times. The ligand concentration outside the cell determines how often a ligand is bound and causes signaling.

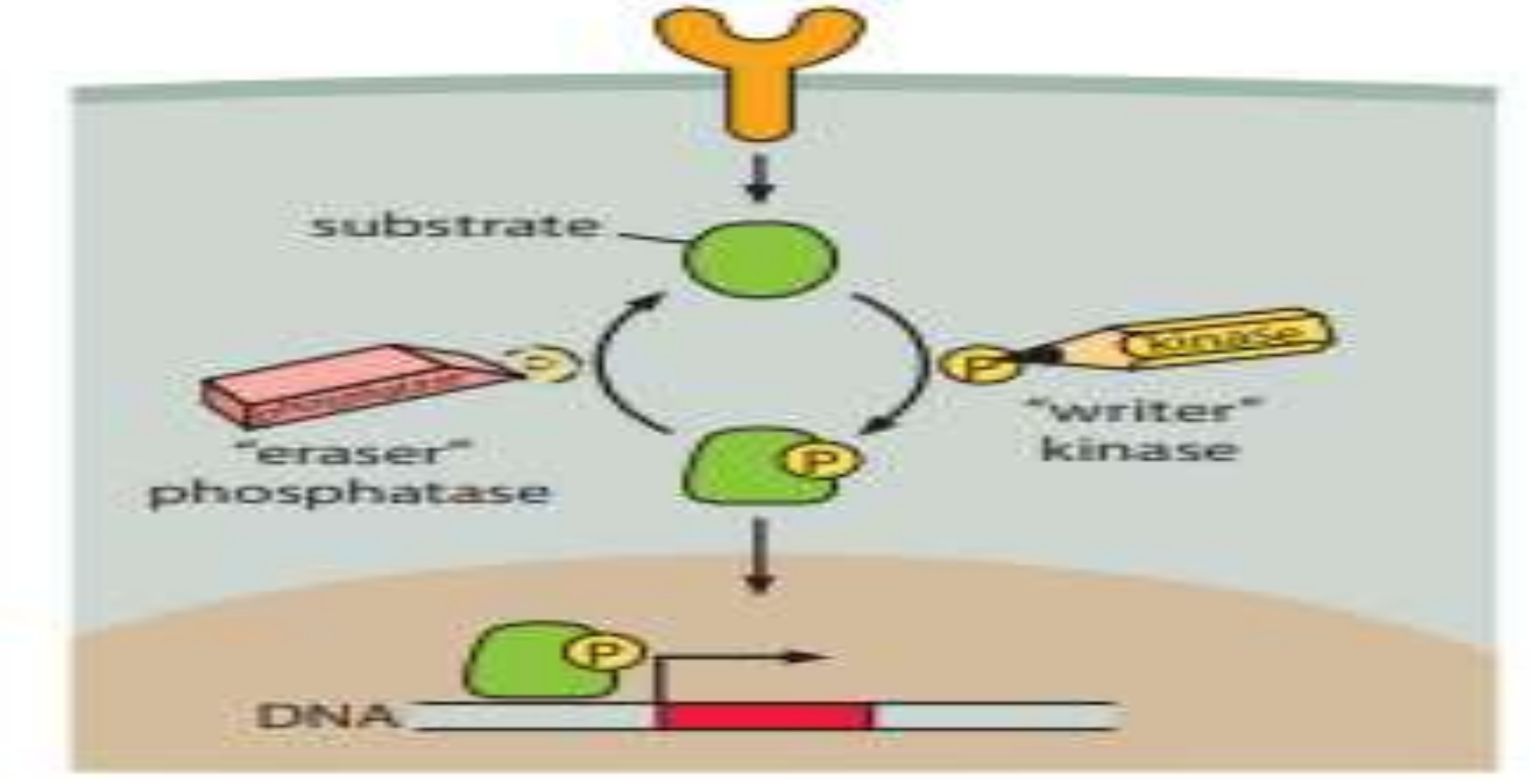


4 The changes in the enzyme and G protein are only temporary because the G protein also functions as a GTPase enzyme—in other words, it then hydrolyzes its bound GTP to GDP and P_i. Now inactive again, the G protein leaves the enzyme, which returns to its original state. The G protein is now available for reuse. The GTPase function of the G protein allows the pathway to shut down rapidly when the signaling molecule is no longer present.

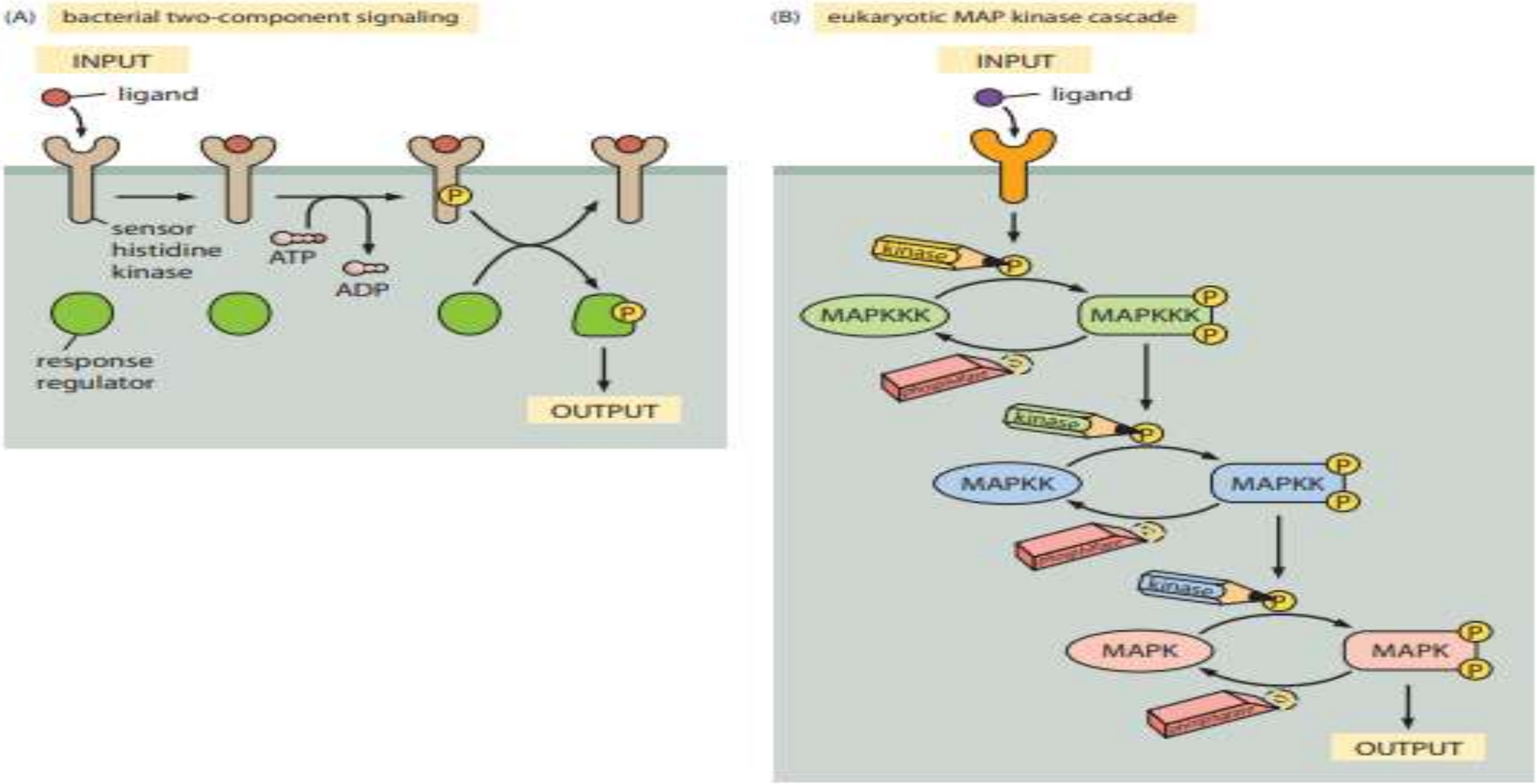
- **Role of G-protein coupled receptor:** GPCRs are involved in a wide variety of physiological processes. Some examples of their physiological roles are as follows:
- The visual sense:
- The sense of smell:
- Behavioral and mood regulation:
- Regulation of immune system activity and inflammation :
- Autonomic nervous system transmission:
- Cell density sensing:.
- Homeostasis modulation (water balance)

What are the absolute numbers of signaling proteins?

- One of the defining characteristics of signaling proteins is that depending upon environmental conditions, the concentration of the relevant signaling molecule, or of the active form, can vary dramatically. As a result, the very feature of these proteins that makes them most interesting stands in the way of giving a precise and definitive answer to the question of the “generic” number of such signaling proteins within cells.



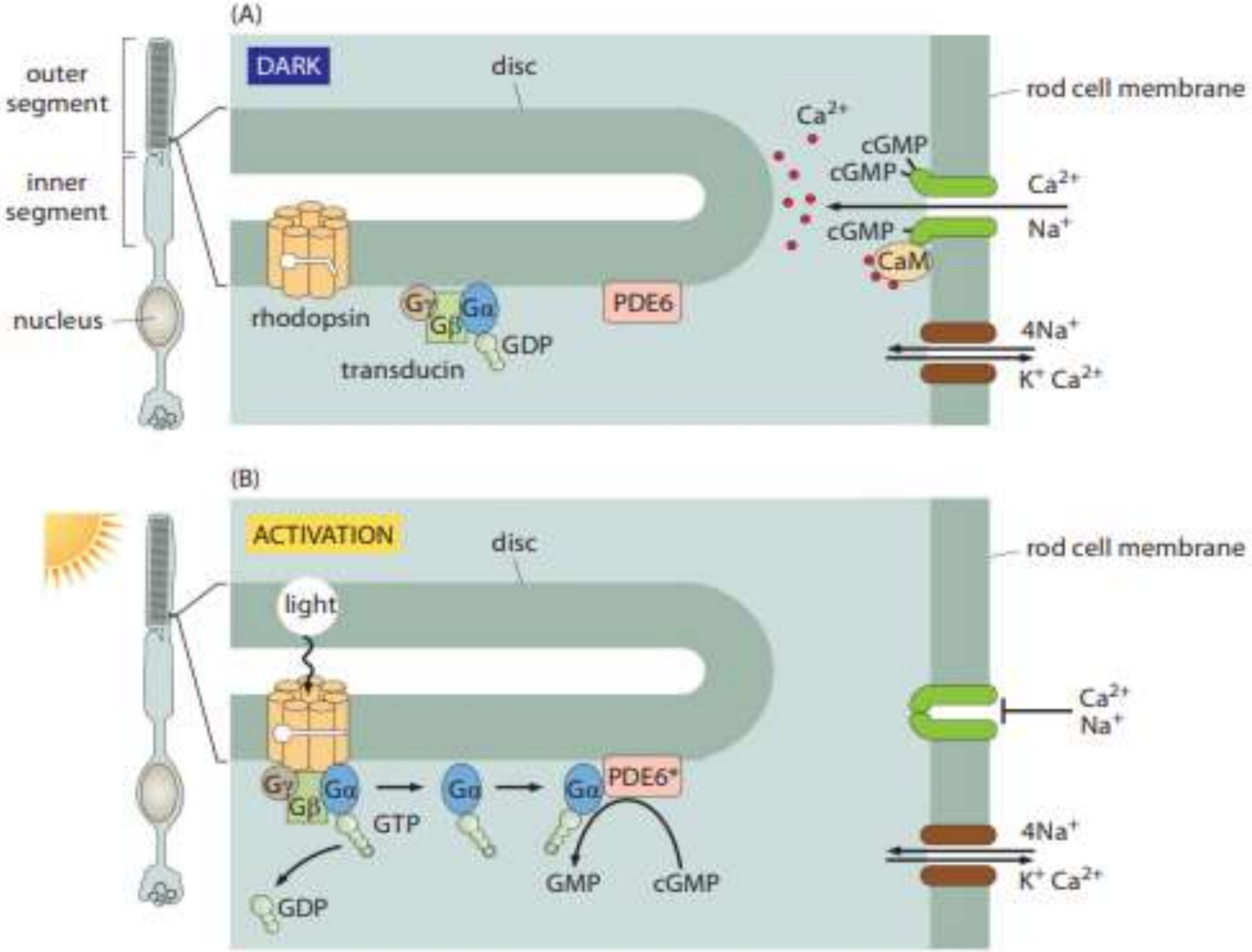
Schematic of a generic signaling network. A membrane receptor at the cell surface (orange) releases a substrate. The substrate is modified by the addition of a phosphate group by a kinase. The addition of the phosphate group localizes the protein to the nucleus (brown), where it then acts as a transcription factor. Removal of the phosphate group is mediated by a phosphatase.


(A) bacterial two-component signaling
INPUT
ligand
sensor histidine kinase
ATP
ADP
P
response regulator
OUTPUT
(B) eukaryotic MAP kinase cascade
INPUT
ligand
kinase
MAPKKK
MAPKKK
MAPKK
MAPKK
MAPK
MAPK
P
OUTPUT

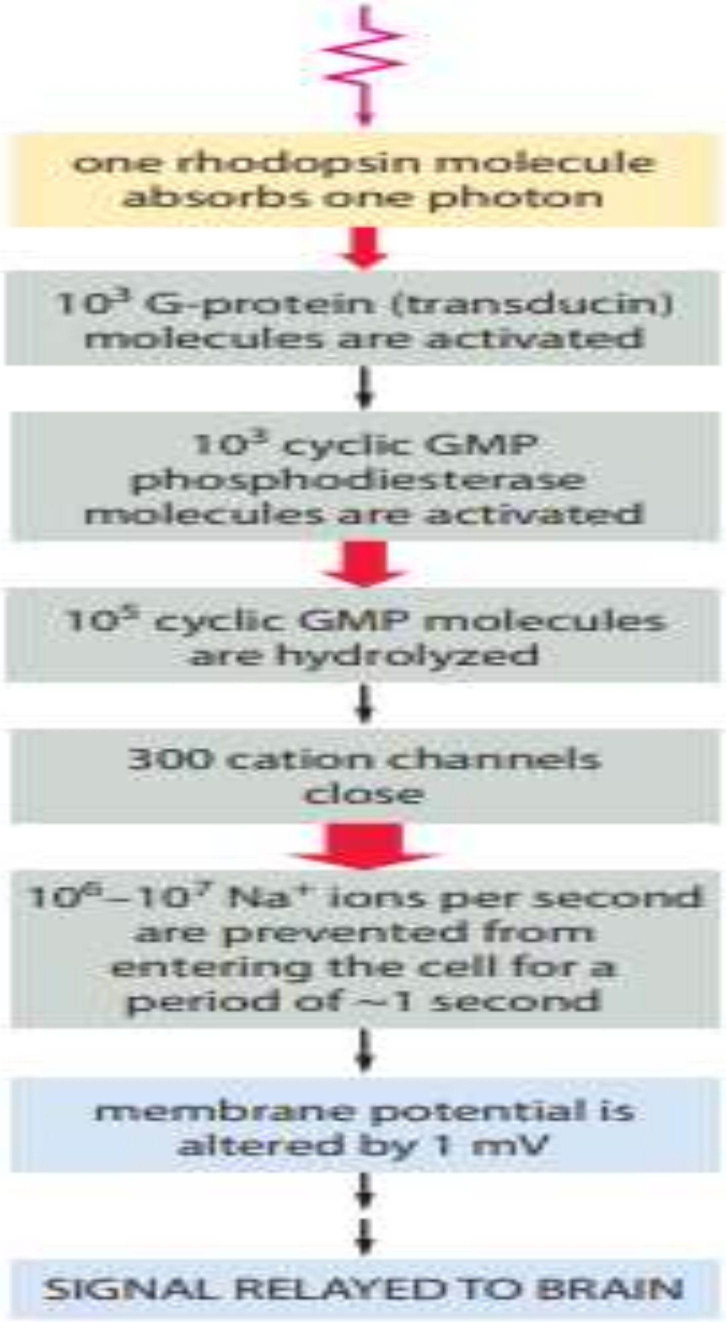
protein	name	molecules/cell	standard error	concentration (nM)
G protein-coupled receptor	Ste2	7000	400	400
G-α	Gpa1	2000	300	130
G-β	Ste4	2000	100	110
PAK kinase	Ste20	4000	500	200
scaffold	Ste5	500	60	30
MAPKKK binding partner	Ste50	1000	100	70
MAPKKK	Ste11	4000	90	200
MAPKK	Ste7	900	70	50
MAPK	Fus3	20,000	3000	1100
MAPK	Kss1	20,000	2000	1200
MAPK	Hog1	6000	400	300
scaffold/MAPKK	Pbs2	2000	200	140
MAPK phosphatase	Msg5	40	3	2
cell cycle inhibitor	Far1	200	20	14
transcriptional activator	Stw12	1400	40	80
transcriptional repressor	Dig1	5000	500	300
transcriptional repressor	Dig2	1000	80	70

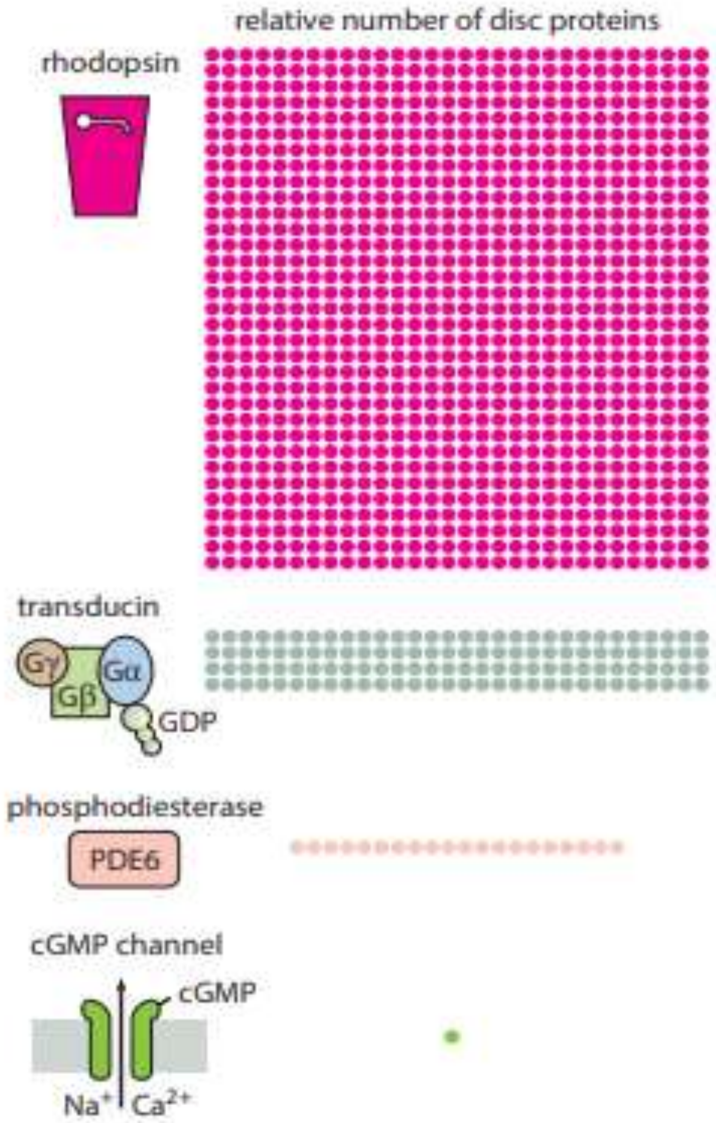
How many rhodopsin molecules are in a rod cell?

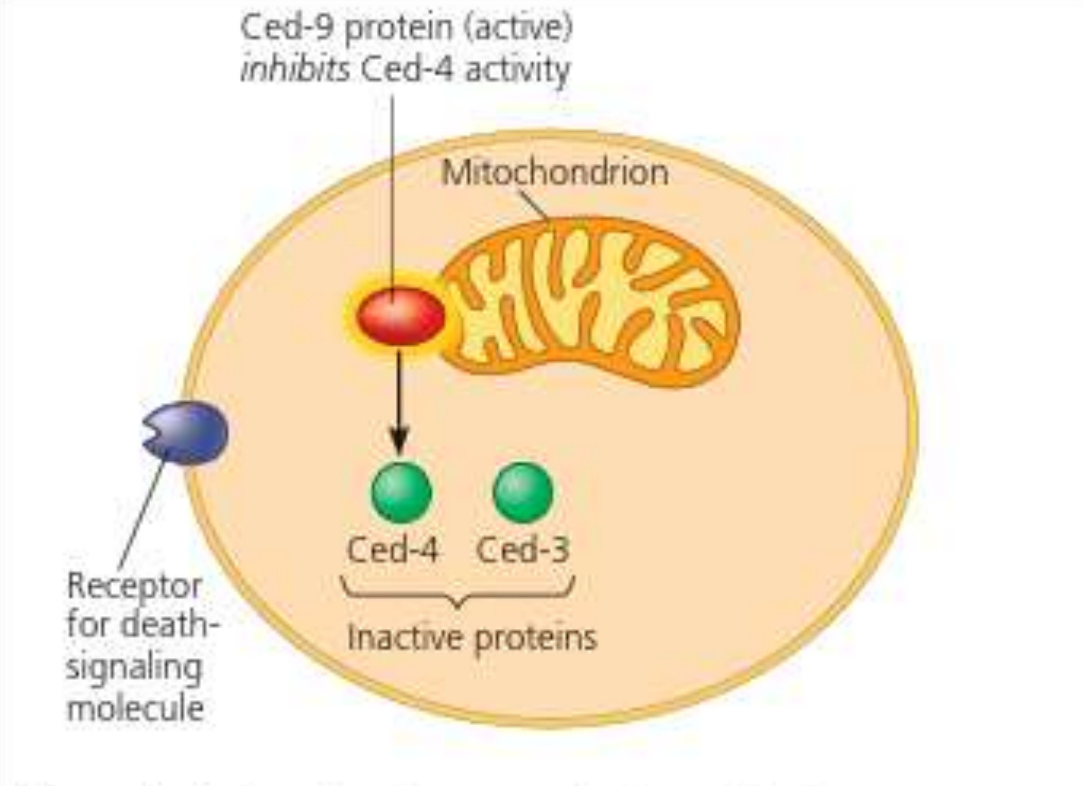
- Responses in signaling pathways depend critically upon how many molecules there are to respond to the signal of interest. The concentrations of molecules, such as rhodopsin in photoreceptor cells, determine the light intensity that can be detected in vertebrate eyes. Beyond this, the number of rhodopsins also helps us understand how frequently a given rod cell will spontaneously fire in the dark.



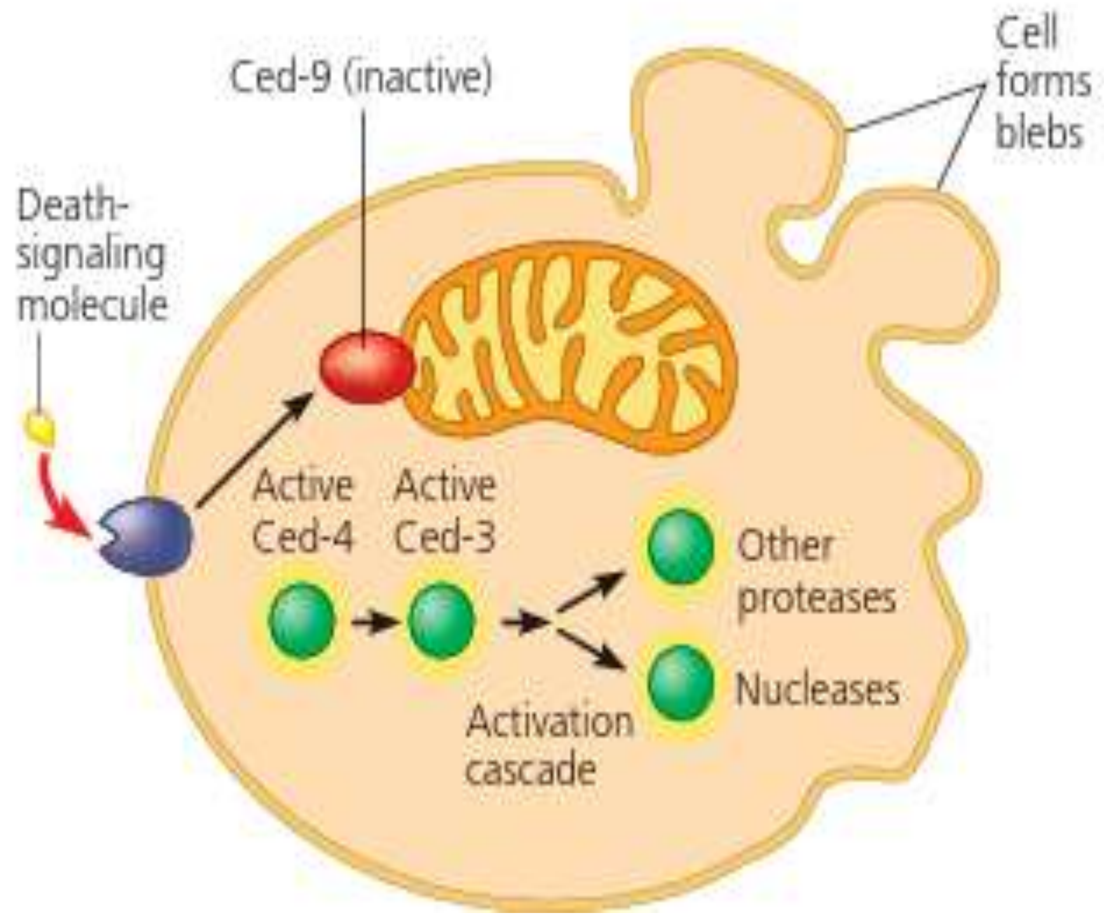
(A)
DARK
outer segment
inner segment
nucleus
disc
rod cell membrane
Ca^{2+}
cGMP
cGMP
Ca^{2+}
cGMP
Na^{+}
CaM
rhodopsin
Gγ
Gβ
Gα
GDP
transducin
PDE6
$4Na^{+}$
K^{+} Ca^{2+}
(B)
ACTIVATION
disc
rod cell membrane
light
Ca^{2+}
Na^{+}
Gγ
Gβ
Gα
GTP
Gα
Gα
PDE6*
GMP
cGMP
GDP
$4Na^{+}$
K^{+} Ca^{2+}


one rhodopsin molecule absorbs one photon
10^3 G-protein (transducin) molecules are activated
10^3 cyclic GMP phosphodiesterase molecules are activated
10^5 cyclic GMP molecules are hydrolyzed
300 cation channels close
10^6–10^7 Na^+ ions per second are prevented from entering the cell for a period of ~1 second
membrane potential is altered by 1 mV
SIGNAL RELAYED TO BRAIN


relative number of disc proteins
rhodopsin
transducin
Gγ
Gβ
Gα
GDP
phosphodiesterase
PDE6
cGMP channel
cGMP
Na^+
Ca^{2+}



(a) No death signal. As long as Ced-9, located in the outer mitochondrial membrane, is active, apoptosis is inhibited, and the cell remains alive.



(b) Death signal. When a cell receives a death signal, Ced-9 is inactivated, relieving its inhibition of Ced-3 and Ced-4. Active Ced-3, a protease, triggers a cascade of reactions leading to activation of nucleases and other proteases. The action of these enzymes causes the changes seen in apoptotic cells and eventual cell death.