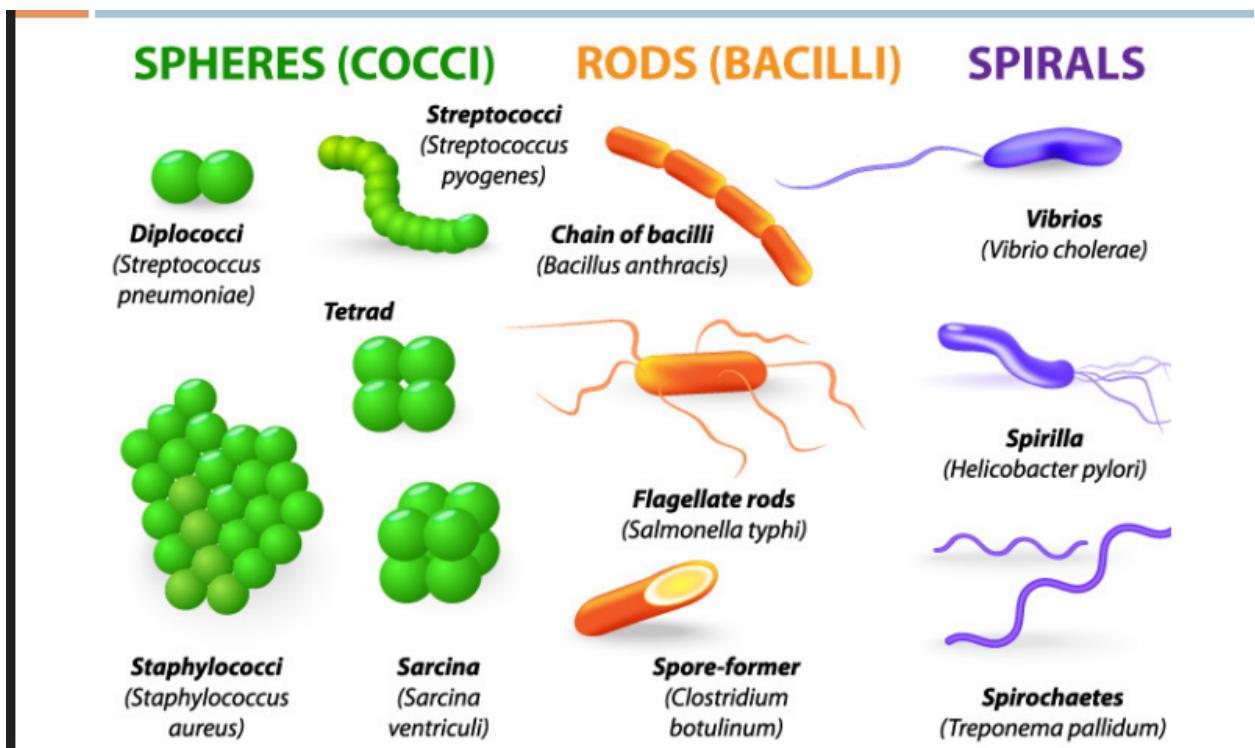


Week 1

- Louis Pasteur- Swan neck experiment, developed vaccines against fowl chol, rabies
- Antonie Van Leeuwenhoek- ‘animalcules’, invention of microscope
- Robert Koch - Germ theory of disease, Koch’s postulates
- John Tyndall - Sterilisation
- Flemming - discovery of penicillin

Week 2



- Bacterial plasma membrane: It is a phospholipid bilayer. Some phospholipids are phosphatidylcholine, phosphatidylethanolamine, sphingomyelin etc.
- Bacterial cell wall: Their cell walls are made of peptidoglycans. Peptidoglycans are made of a structural heteropolymer of NAM and NAG. D amino acids are also found in prokaryotic cell walls.
- For gram positive bacteria, the peptidoglycan layer is thick, with no external lipid layer on top of it. Teichoic acids are unique to gram positive bacteria. Lipoteichoic acids go all the way down to the cell membrane. They help in adhesion. Gram positive bacteria retain crystal violet stain.

- Gram negative bacteria have a very thin peptidoglycan layer (single layered), which has a lipid layer external to it. They contain lipopolysaccharides (LPS). LPS are also termed endotoxins as they trigger immune responses. LPS binds to CDH4/TLR . Based on their location, they can be classified into K antigens (capsule), O antigens and H antigens. Porins can be found in gram negative bacteria. Periplasmic space is also present (which is absent in positive bacteria).
- Gram staining process -> fixation -> crystal violet -> iodine -> alcohol -> counter stain
- Mycoplasma is a bacterial genus without a cell wall.
- Capsule is external to the cell and is found in both positive and negative bacteria. If it is loosely attached it is called a slime layer. It contributes to virulence of bacteria and protects them.
- The flagella of prokaryotes is made up of flagellin, a globular protein that polymerizes to form a hollow tube. The flagella is anchored to the cell using the basal body, which consists of 2 (for gram positive bacteria) or 4 (for gram negative bacteria). The basal body is a modified centriole.
- Small fimbriae help the prokaryotic cell adhere to its surroundings.
- Pili are longer than fimbriae and are used during conjugation.
- Endospore are dormant forms of bacteria, usually formed by gram positive bacteria.

Week 3

1. Endoplasmic Reticulum
 - The general structure of the endoplasmic reticulum is a network of membranes called cisternae. These sac-like structures are held together by the cytoskeleton. The phospholipid membrane encloses the cisternal space (or lumen), which is continuous with the perinuclear space but separate from the cytosol. The functions of the endoplasmic reticulum can be summarized as the synthesis and export of proteins and membrane lipids
 - Ribosomes are not a stable part of this organelle's structure as they are constantly being bound and released from the membrane. A ribosome only binds to the RER once a specific protein-nucleic acid complex forms in the cytosol. This special complex forms when a free ribosome begins translating the mRNA of a protein destined for the secretory pathway. The first 5–30 amino acids polymerized encode a signal peptide, a molecular message that is recognized and bound by a signal recognition particle (SRP). Translation pauses

and the ribosome complex binds to the RER translocon where translation continues with the nascent (new) protein forming into the RER lumen and/or membrane. The protein is processed in the ER lumen by an enzyme (a signal peptidase), which removes the signal peptide. Ribosomes at this point may be released back into the cytosol.

- There is no continuous membrane between the endoplasmic reticulum and the Golgi apparatus, membrane-bound transport vesicles shuttle proteins between these two compartments. Vesicles are surrounded by coating proteins called COPI and COPII. COPII targets vesicles to the Golgi apparatus and COPI marks them to be brought back to the rough endoplasmic reticulum.
- For smooth endoplasmic reticulum, it synthesizes lipids, phospholipids, and steroids. Cells which secrete these products, such as those in the testes, ovaries, and sebaceous glands have an abundance of smooth endoplasmic reticulum. It also carries out the metabolism of carbohydrates, detoxification of natural metabolism products and of alcohol and drugs, attachment of receptors on cell membrane proteins, and steroid metabolism
- Correct folding of newly made proteins is made possible by several endoplasmic reticulum chaperone proteins, including protein disulfide isomerase (PDI), ERp29 (endoplasmic reticulum protein 29) the Hsp70 family member BiP/Grp78, calnexin, calreticulin, and the peptidylpropyl isomerase family.
- Proteins that are destined for places outside the endoplasmic reticulum are packed into transport vesicles and moved along the cytoskeleton toward their destination.

2. Nucleus

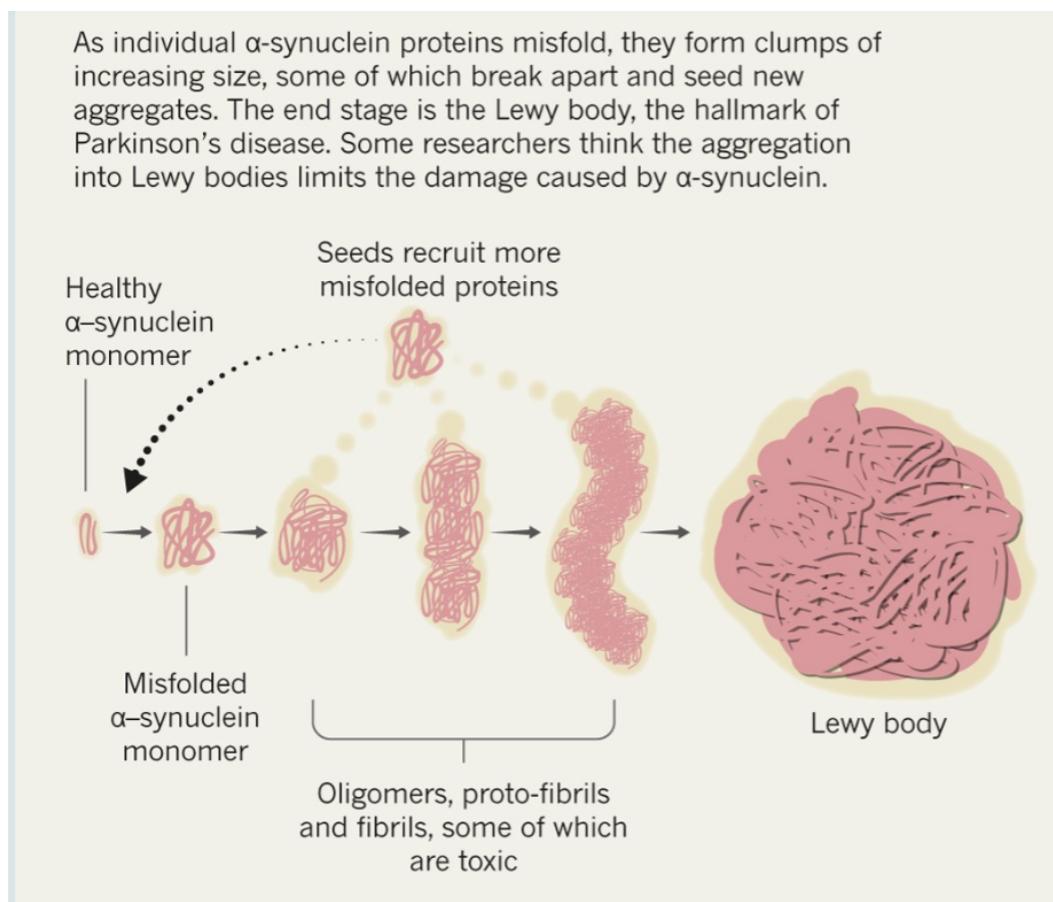
- The nucleus is bound by a double membrane
- The nucleolus is the largest part of the nucleus and is the site of ribosome biogenesis. It forms around the nucleolar organising regions of DNA.
- Types of chromosomal mutations: inversion, translocation (from a non homologous chromosome), deletions and duplications.
- Types of point mutations: insertions, deletions, substitutions.
- Down's syndrome - complete or partial trisomy of the 21st chromosome
- Edward's syndrome - trisomy of the 18th chromosome.
- Patau's syndrome - trisomy of the the 13th chromosome
- Angelman Syndrome - Nonfunctional ubiquitin protein ligase 3 (on 15th chromosome)
- Prader Willi syndrome: deletions in the 15th chromosome

3. Ribosomes

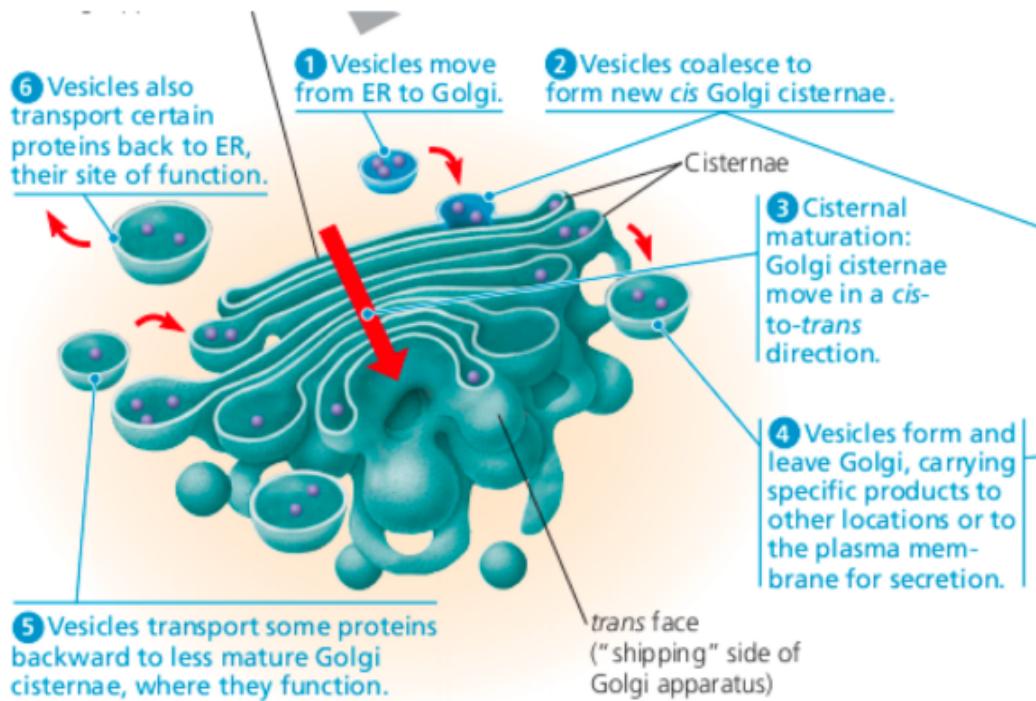
- Prokaryotic ribosomes are 70s and consist of a 30s (made of 16s rRNA) and 50s subunit. Eukaryotic ribosomes are 80s and consist of a 40s (made of 18s rRNA) and 60s subunit.
- During translation, the mRNA is held by the smaller subunit.
- Large and small subunit dimerize when Mg concentration is above 1mM.
- Peptidyltransferase catalyzes the formation of peptide bond.
- Streptomycin and gentamycin attach to the 30 subunit, and erythromycin and chloramphenicol bind to 50s subunit.

Week 4

1. Prion principle of pathological transmission
- Alpha-synuclein is a protein that, in humans, is encoded by the SNCA gene. It is abundant in the brain, while smaller amounts are found in the heart, muscle and other tissues. In the brain, alpha-synuclein is found mainly at the tips of neurons in specialized structures called presynaptic terminals. It is the main constituent of Lewy Bodies



2. Golgi apparatus



- Part of the endomembrane system in the cytoplasm, it packages proteins into membrane-bound vesicles inside the cell before the vesicles are sent to their destination. It resides at the intersection of the secretory, lysosomal, and endocytic pathways. It is of particular importance in processing proteins for secretion, containing a set of glycosylation enzymes that attach various sugar monomers to proteins as the proteins move through the apparatus
- In mammals, a single Golgi apparatus is usually located near the cell nucleus, close to the centrosome. Tubular connections are responsible for linking the stacks together.
- In most eukaryotes, the Golgi apparatus is made up of a series of compartments and is a collection of fused, flattened membrane-enclosed disks known as cisternae (singular: cisterna, also called "dictyosomes"), originating from vesicular clusters that bud off the endoplasmic reticulum. A mammalian cell typically contains 40 to 100 stacks of cisternae. Between four and eight cisternae are usually present in a stack. This collection of cisternae is broken down into *cis*, medial, and *trans* compartments, making up two main networks: the *cis* Golgi network (CGN) and the *trans* Golgi network (TGN). The CGN is the first

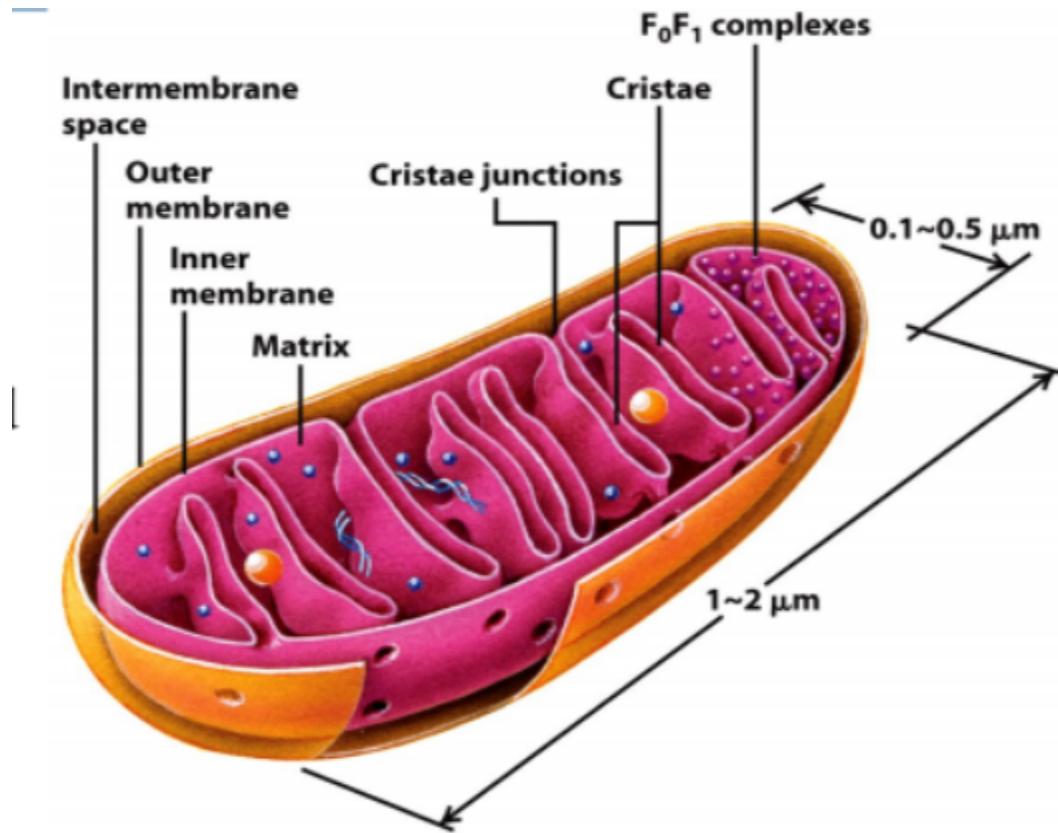
cisternal structure, and the TGN is the final, from which proteins are packaged into vesicles destined to lysosomes, secretory vesicles, or the cell surface.

- Enzymatic reactions within the Golgi stacks occur exclusively near its membrane surfaces, where enzymes are anchored. This feature is in contrast to the ER, which has soluble proteins and enzymes in its lumen. Much of the enzymatic processing is post-translational modification of proteins.
- For example, phosphorylation of oligosaccharides on lysosomal proteins occurs in the early CGN. Cis cisterna are associated with the removal of mannose residues. Removal of mannose residues and addition of N-acetylglucosamine occur in medial cisternae. Addition of galactose and sialic acid occurs in the trans cisternae. Sulfation of tyrosines and carbohydrates occurs within the TGN. Other general post-translational modifications of proteins include the addition of carbohydrates (glycosylation) and phosphates (phosphorylation).
- Protein modifications may form a signal sequence that determines the final destination of the protein. For example, the Golgi apparatus adds a mannose-6-phosphate label to proteins destined for lysosomes. Another important function of the Golgi apparatus is in the formation of proteoglycans. Enzymes in the Golgi append proteins to glycosaminoglycans, thus creating proteoglycans. Glycosaminoglycans are long unbranched polysaccharide molecules present in the extracellular matrix of animals.
-

Types	Description	Example
Exocytic vesicles (constitutive)	Vesicle contains proteins destined for extracellular release. After packaging, the vesicles bud off and immediately move towards the plasma membrane , where they fuse and release the contents into the extracellular space in a process known as constitutive secretion .	Antibody release by activated plasma B cells
Secretory vesicles (regulated)	Vesicles contain proteins destined for extracellular release. After packaging, the vesicles bud off and are stored in the cell until a signal is given for their release. When the appropriate signal is received they move toward the membrane and fuse to release their contents. This process is known as regulated secretion .	Neurotransmitter release from neurons
Lysosomal vesicles	Vesicles contain proteins and ribosomes destined for the lysosome , a degradative organelle containing many acid hydrolases , or to lysosome-like storage organelles. These proteins include both digestive enzymes and membrane proteins. The vesicle first fuses with the late endosome , and the contents are then transferred to the lysosome via unknown mechanisms.	Digestive proteases destined for the lysosome

Week 5

1. Mitochondria

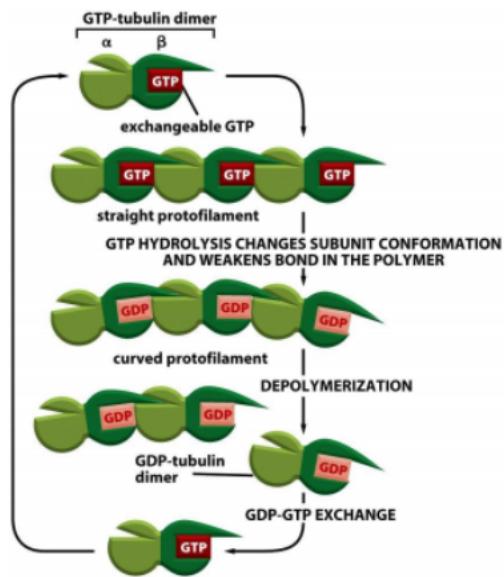


- Krebs cycle takes place in the matrix of mitochondria.
- ETC takes place in the inner membrane.
- Pyruvate molecules produced by glycolysis are actively transported across the inner mitochondrial membrane, and into the matrix where they can either be oxidized and combined with coenzyme A to form CO_2 , acetyl-CoA, and NADH, or they can be carboxylated (by pyruvate carboxylase) to form oxaloacetate.
- In the citric acid cycle, all the intermediates (e.g. citrate, iso-citrate, alpha-ketoglutarate, succinate, fumarate, malate and oxaloacetate) are regenerated during each turn of the cycle.
- Mitochondria contain their own genome. The human mitochondrial genome is a circular DNA molecule of about 16 kilobases. It encodes 37 genes: 13 for subunits of respiratory complexes I, III, IV and V, 22 for mitochondrial tRNA (for the 20 standard amino acids, plus an extra gene for leucine and serine), and 2 for rRNA. One mitochondrion can contain two to ten copies of its DNA

Week 6

1) Microtubules

- They are formed by the polymerization of a dimer of two globular proteins, alpha and beta tubulin into protofilaments that can then associate laterally to form a hollow tube, the microtubule. The most common form of a microtubule consists of 13 protofilaments in the tubular arrangement
- They also make up the internal structure of cilia and flagella. They provide platforms for intracellular transport and are involved in a variety of cellular processes, including the movement of secretory vesicles, organelles, and intracellular macromolecular assemblies (see entries for dynein and kinesin). They are also involved in cell division (by mitosis and meiosis) and are the major constituents of mitotic spindles, which are used to pull eukaryotic chromosomes apart.
- There are many proteins that bind to microtubules, including the motor proteins kinesin and dynein, microtubule-severing proteins like katanin, and other proteins important for regulating microtubule dynamics.
- Typically, microtubules are formed by the parallel association of thirteen protofilament

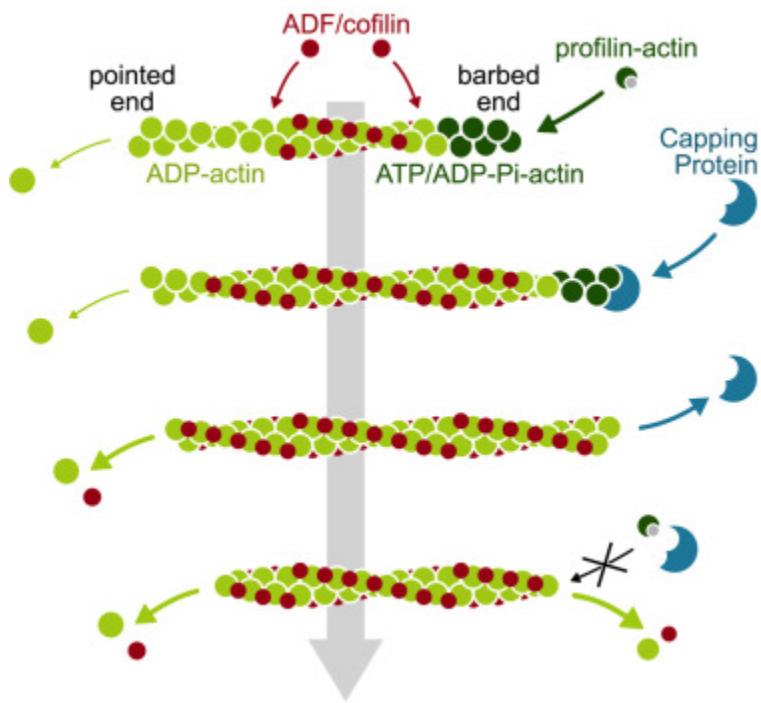


- Therefore, in a protofilament, one end will have the α-subunits exposed while the other end will have the β-subunits exposed. These ends are designated the (-) and (+) ends, respectively.

- Nucleation is the event that initiates the formation of microtubules from the tubulin dimer. Microtubules are typically nucleated and organized by organelles called microtubule-organizing centres (MTOCs). Microtubule growth continues away from the MTOC in the (+) direction
- The centrosome is the primary MTOC of most cell types. However, microtubules can be nucleated from other sites as well. For example, cilia and flagella have MTOCs at their base termed basal bodies.
- The assembly properties of GDP-tubulin are different from those of GTP-tubulin, as GDP-tubulin is more prone to depolymerization. A GDP-bound tubulin subunit at the tip of a microtubule will tend to fall off, although a GDP-bound tubulin in the middle of a microtubule cannot spontaneously pop out of the polymer.
- The centrosome is critical to mitosis as most microtubules involved in the process originate from the centrosome. The minus ends of each microtubule begin at the centrosome, while the plus ends radiate out in all directions. Thus the centrosome is also important in maintaining the polarity of microtubules during mitosis.
- Astral microtubules are a subclass of microtubules which only exist during and around mitosis. They originate from the centrosome, but do not interact with the chromosomes, kinetochores, or with the microtubules originating from the other centrosome. Instead their microtubules radiate towards the cell membrane. Once there they interact with specific motor proteins which create force that pull the microtubules, and thus the entire centrosome towards the cell membrane. As stated above, this helps the centrosomes orient themselves away from each other in the cell.
- Interpolar/Polar microtubules are a class of microtubules which also radiate out from the centrosome during mitosis. These microtubules radiate towards the mitotic spindle
- K fibers/Kinetochoore microtubules Each K fiber is composed of 20–40 parallel microtubules, forming a strong tube which is attached at one end to the centrosome and on the other to the kinetochore.
- As the K fibers shorten the pair chromosomes are pulled apart right before cytokinesis.
- Dynamic instability of microtubules is also required for the migration of most mammalian cells that crawl

2. Microfilaments

- Microfilaments, also called actin filaments, are protein filaments in the cytoplasm of eukaryotic cells that form part of the cytoskeleton. They are primarily composed of polymers of actin, but are modified by and interact with numerous other proteins in the cell
- Microfilaments are usually about 7 nm in diameter and made up of two strands of actin. Microfilament functions include cytokinesis, amoeboid movement, cell motility, changes in cell shape, endocytosis and exocytosis, cell contractility, and mechanical stability.

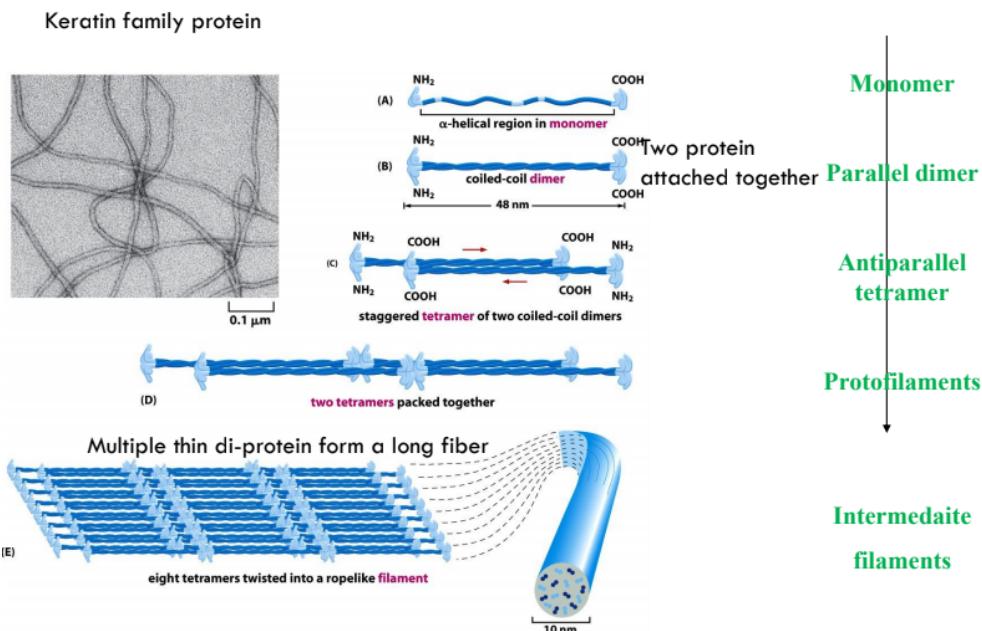


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- Actin filaments are assembled in two general types of structures: bundles and networks. Bundles can be composed of polar filament arrays, in which all barbed ends point to the same end of the bundle, or non-polar arrays, where the barbed ends point towards both ends.
- They are polymers of actin subunits (globular actin, or G-actin), which as part of the fiber are referred to as filamentous actin, or F-actin. Each microfilament is made up of two helical, interlaced strands of subunits. Much like microtubules, actin filaments are polarized. Electron micrographs have provided evidence of their fast-growing barbed-ends and their slow-growing pointed-end.
- In vitro actin polymerization, or nucleation, starts with the self-association of three G-actin monomers to form a trimer. ATP-bound actin then itself binds the barbed end, and the ATP is subsequently hydrolyzed

- Subsequently, ADP-actin dissociates slowly from the pointed end, a process significantly accelerated by the actin-binding protein, cofilin.
- The pointed end is commonly referred to as the minus (-) end and the barbed end is referred to as the plus (+) end.
- At steady-state, the polymerization rate at the barbed end matches the depolymerization rate at the pointed end, and microfilaments are said to be treadmilling. Treadmilling results in elongation in the barbed end and shortening in the pointed-end, so that the filament in total moves. Since both processes are energetically favorable, this means force is generated, the energy ultimately coming from ATP

3. Intermediate filaments

Structure of an intermediate filaments

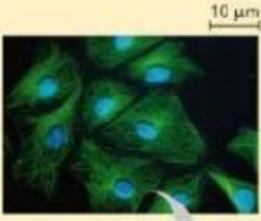
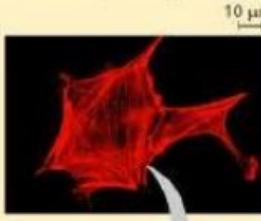
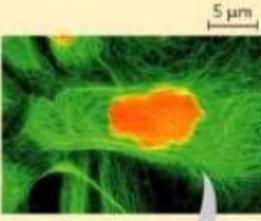
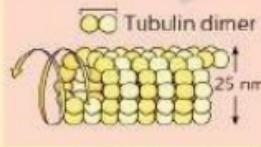
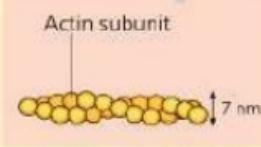
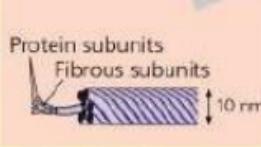


- The central building block of an intermediate filament is a pair of two intertwined proteins that is called a coiled-coil structure. This name reflects the fact that the structure of each protein is helical, and the intertwined pair is also a helical structure.
- Cytoplasmic IFs assemble into non-polar unit-length filaments (ULFs). Identical ULFs associate laterally into staggered, antiparallel, soluble tetramers, which associate head-to-tail into protofilaments that pair up laterally into protofibrils, four of which wind together into an intermediate filament. Part of the assembly

process includes a compaction step, in which ULF tighten and assume a smaller diameter. The reasons for this compaction are not well understood, and IF are routinely observed to have diameters ranging between 6 and 12 nm.

- The N-terminus and the C-terminus of IF proteins are non-alpha-helical regions and show wide variation in their lengths and sequences across IF families.

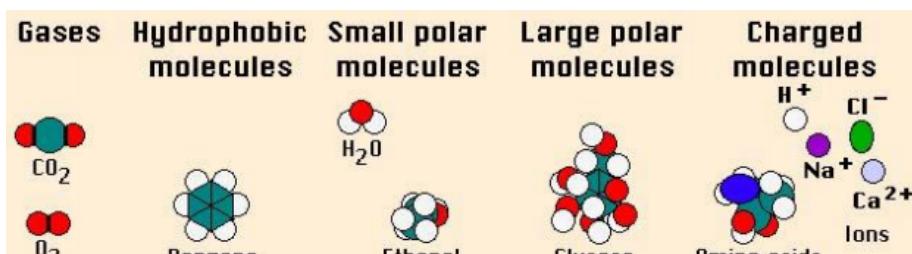
Table 7.2 The Structure and Function of the Cytoskeleton

Property	Microtubules	Microfilaments (Actin Filaments)	Intermediate Filaments
Structure	Hollow tubes; wall consists of 13 columns of tubulin molecules	Two intertwined strands of actin	Fibrous proteins supercoiled into thicker cables
Diameter	25 nm with 15-nm lumen	7 nm	8–12 nm
Protein subunits	Tubulin, consisting of α -tubulin and β -tubulin	Actin	One of several different proteins of the keratin family, depending on cell type
Main functions	Maintenance of cell shape (compression-resisting "girders") Cell motility (as in cilia or flagella) Chromosome movements in cell division Organelle movements	Maintenance of cell shape (tension-bearing elements) Changes in cell shape Muscle contraction Cytoplasmic streaming Cell motility (as in pseudopodia) Cell division (cleavage furrow formation)	Maintenance of cell shape (tension-bearing elements) Anchorage of nucleus and certain other organelles Formation of nuclear lamina
			
			

SOURCE: Adapted from W. M. Becker, L. I. Kleinsmith, and J. Hardin, *The World of the Cell*, 4th ed. (San Francisco, CA: Benjamin Cummings, 2000), p. 753.

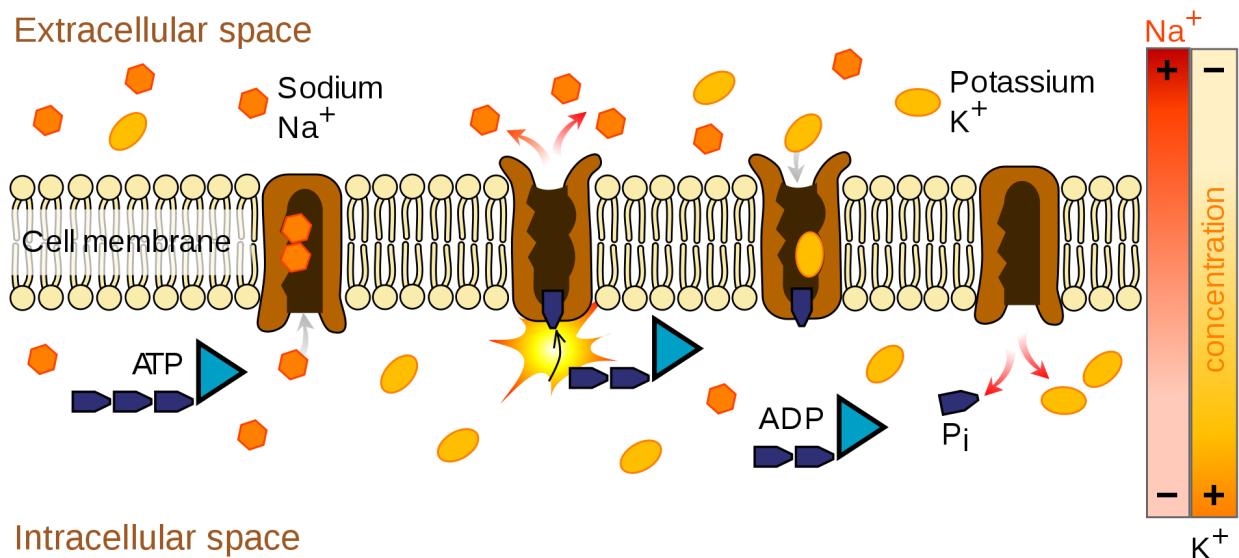
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4. Transport

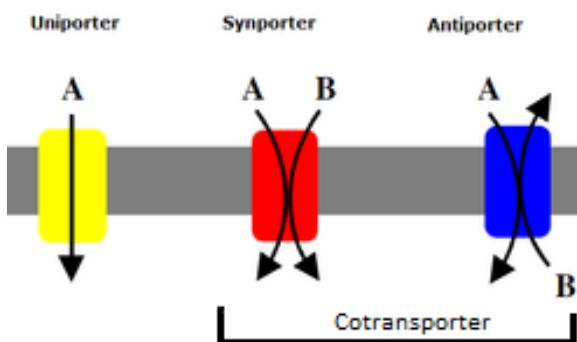


- Water: Water can move across the membrane either through osmosis or via aquaporins.
- Facilitated diffusion (also known as facilitated transport or passive-mediated transport) is the process of spontaneous passive transport (as opposed to active transport) of molecules or ions across a biological membrane via specific transmembrane integral proteins. Being passive, facilitated transport does not directly require chemical energy from ATP hydrolysis in the transport step itself; rather, molecules and ions move down their concentration gradient reflecting its diffusive nature. It uses the natural kinetic energy and entropy of the molecules to transport them.
- Glucose, sodium ions, and chloride ions are just a few examples of molecules and ions that must efficiently cross the plasma membrane but to which the lipid bilayer of the membrane is virtually impermeable. Their transport must therefore be "facilitated" by proteins that span the membrane and provide an alternative route or bypass mechanism. Some examples of proteins that mediate this process are glucose transporters, organic cation transport proteins, urea transporter, monocarboxylate transporter 8 and monocarboxylate transporter 10.
- active transport is the movement of molecules across a cell membrane from a region of lower concentration to a region of higher concentration

- There are two types of active transport: primary active transport that uses adenosine triphosphate (ATP), and secondary active transport that uses an electrochemical gradient.
- Active transport is usually associated with accumulating high concentrations of molecules that the cell needs, such as ions, glucose and amino acids. Examples of active transport include the uptake of glucose in the intestines in humans and the uptake of mineral ions into root hair cells of plants, and sodium potassium pumps.



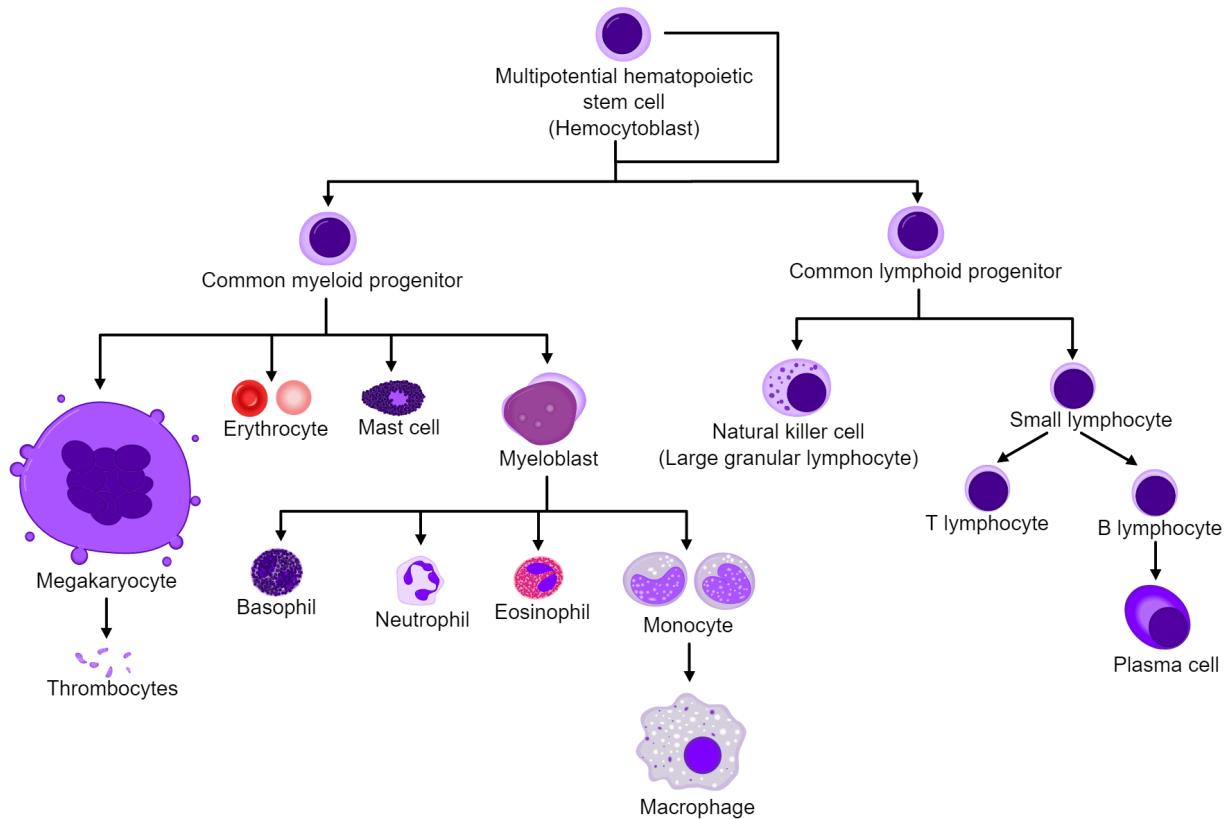
- Intracellular space
- Cotransporters are a subcategory of membrane transport proteins (transporters) that couple the favorable movement of one molecule with its concentration gradient and unfavorable movement of another molecule against its concentration gradient.
- Antiporters and symporters both transport two or more different types of molecules at the same time in a coupled movement.
- $\text{Na}^+/\text{glucose}$ cotransporter (SGLT1) – is also known as sodium-glucose cotransporter 1 and is encoded by the SLC5A1 gene. SGLT1 is an electrogenic transporter as the sodium electrochemical gradient drives glucose uphill into the cells.



Week 7

1. Stem Cells

- Embryonic stem cells (ESCs) are derived from the inner cell of the blastocyst. They have the ability to transform into cells from any of the three germ layers. They are pluripotent i.e they can form any of the embryonic tissue.
- Totipotent stem cells possess the ability to form both embryonic and extraembryonic tissues i.e give rise to an entire new organism. Examples include zygotes and spores.
- Adult stem cells are of varying potencies. Hematopoietic stem cells are multipotent stem cells that can differentiate into different blood cells. Myeloid cells and lymphoid cells are oligopotent. The main difference between myeloid and lymphoid cells is that myeloid cells give rise to red blood cells, granulocytes, monocytes, and platelets whereas lymphoid cells give rise to lymphocytes and natural killer cells.



- Induced pluripotent stem cells (also known as iPS cells or iPSCs) are a type of pluripotent stem cell that can be generated directly from a somatic cell. The introduction of four specific genes (named Myc, Oct3/4, Sox2 and Klf4), collectively known as Yamanaka factors, encoding transcription factors could convert somatic cells into pluripotent stem cells.
2. Cell Signalling
- Signal transduction is the conversion of extracellular signals to intracellular signals.

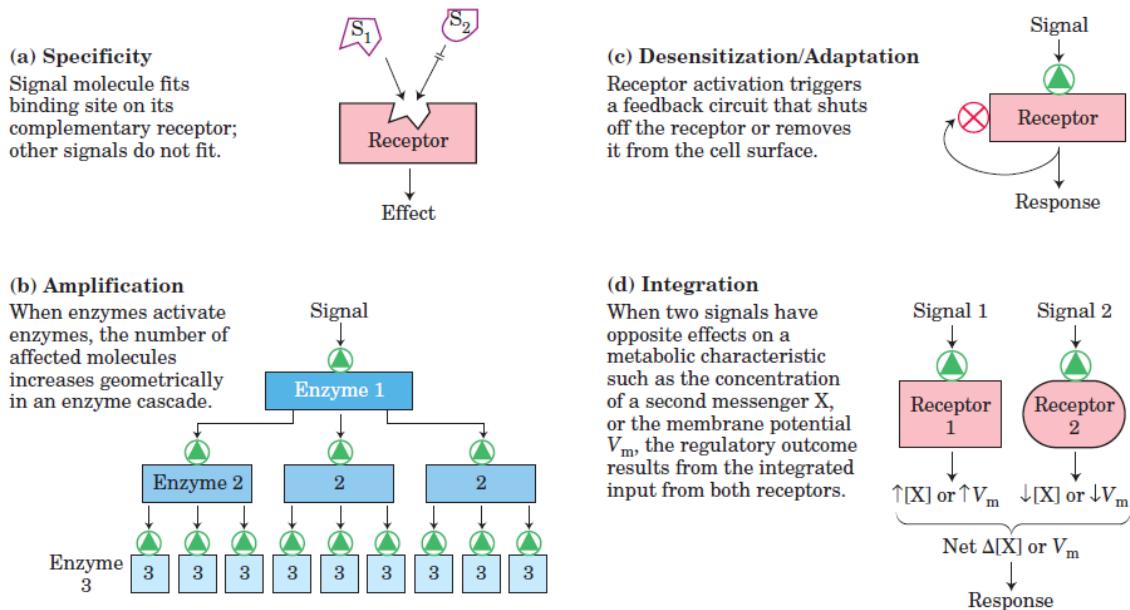
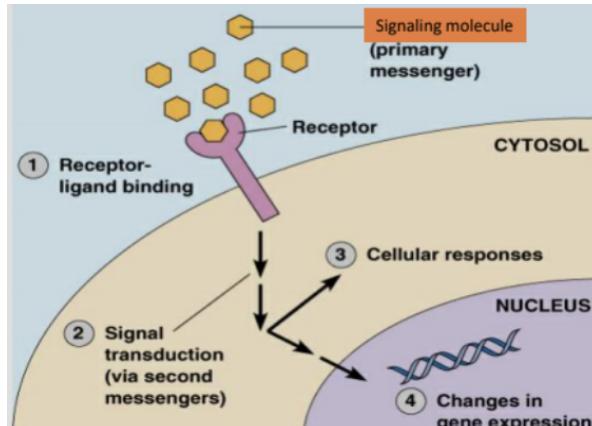


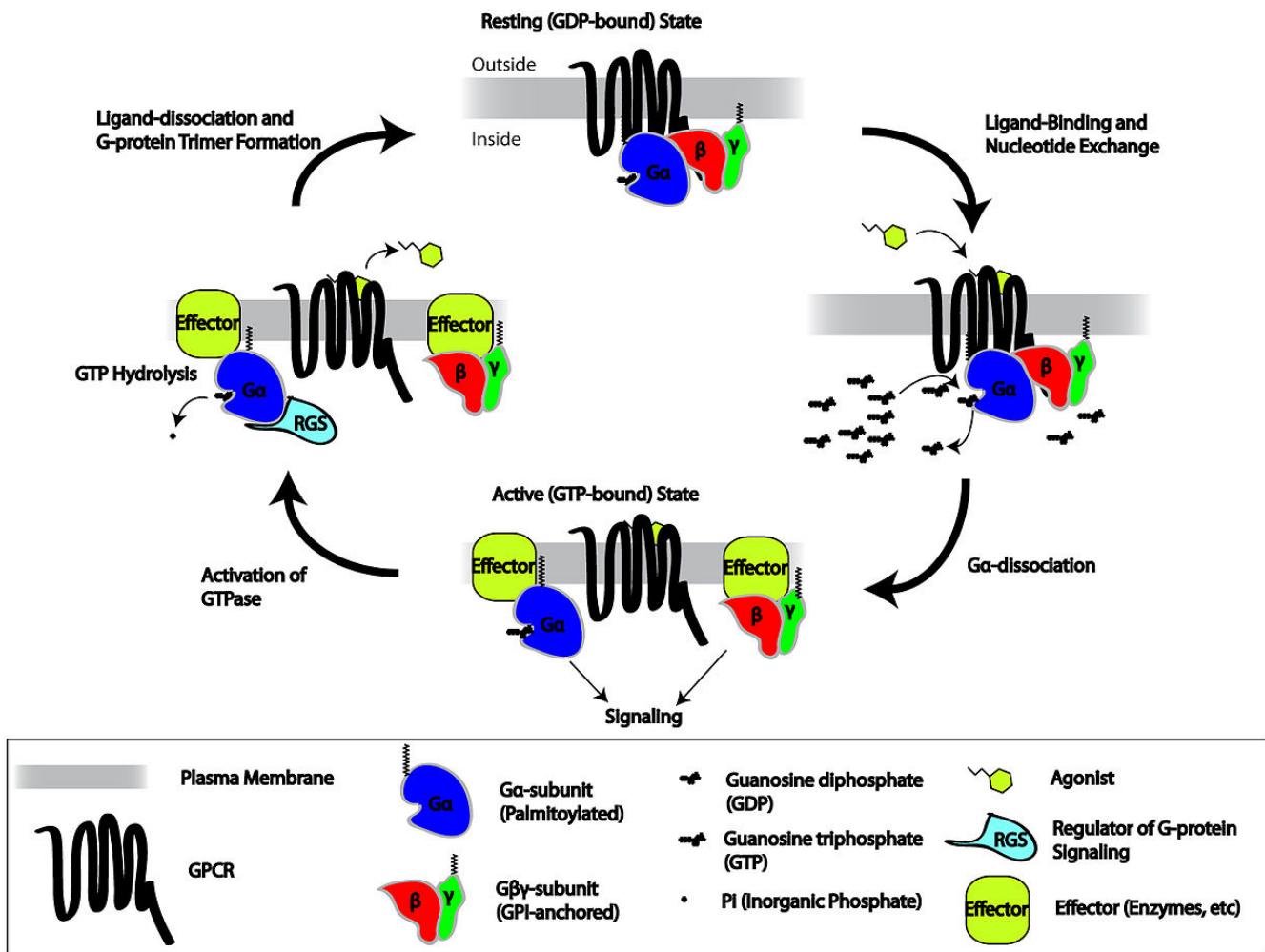
FIGURE 12-1 Four features of signal-transducing systems.



- The components involved in cell signaling are signal molecules, receptors, transducers, amplifiers, effectors. The target of cell signaling can be an enzyme

(to produce a change in metabolism), gene control (for regulation of gene expression) or cytoskeletal components.

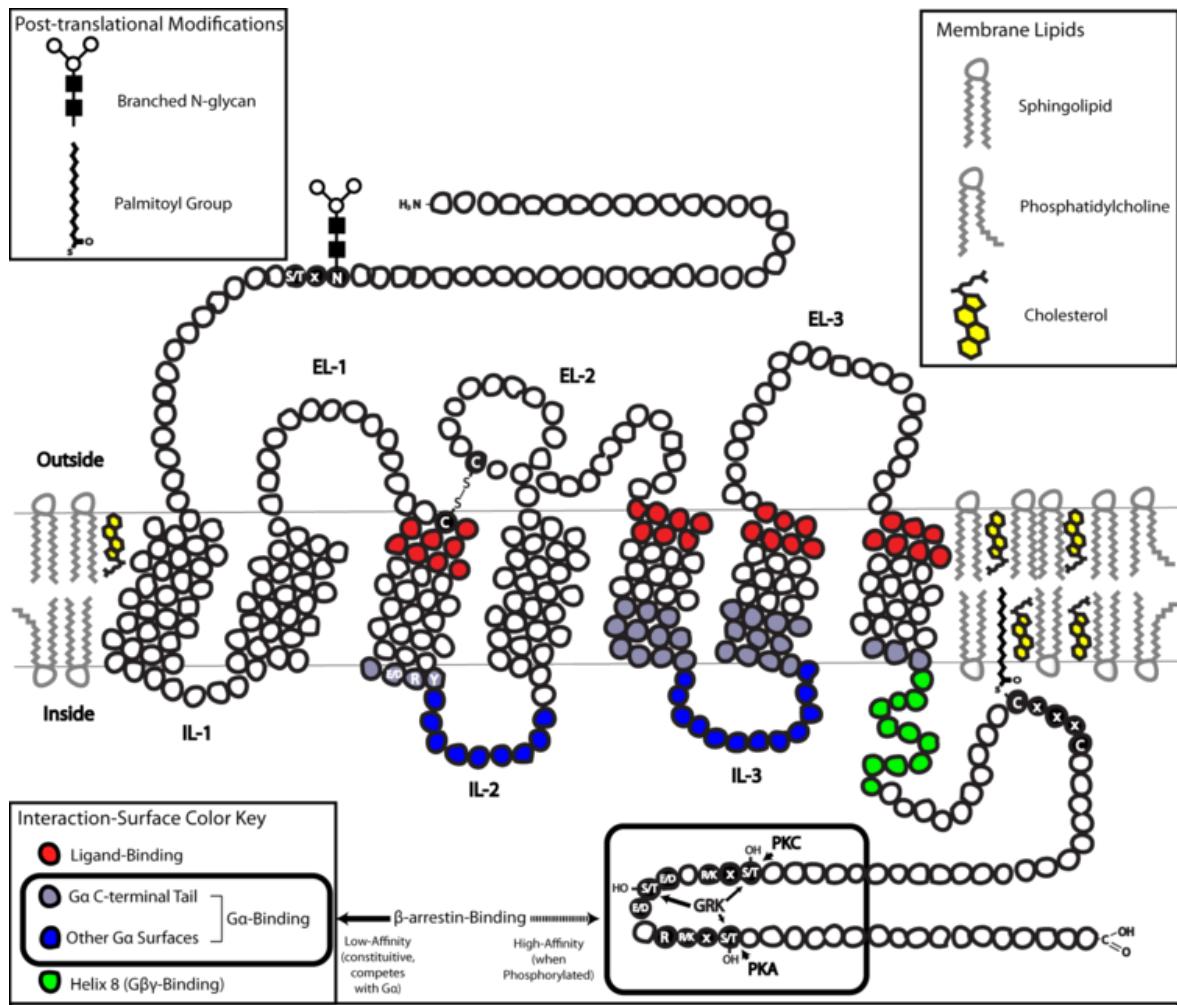
- Signal molecules can be small and hydrophobic, in which case they can simply pass through the cell membrane. Examples are steroid hormones, thyroid hormones and vitamin D.
 - Larger, polar molecules require a receptor on the cell membrane in order to work. Examples are proteins, smaller peptides and other polar molecules.
 - Some gases also work as signal molecules, such as NO and ethylene.
3. GPCR



- G protein coupled receptors (also called serpentine receptors) form a large group of evolutionarily-related proteins that are cell surface receptors that detect molecules outside the cell and activate cellular responses. Coupling with G proteins, they are called seven-transmembrane receptors (7TM) because they

pass through the cell membrane seven times (seven transmembrane alpha helices).

- When a ligand binds to the GPCR it causes a conformational change in the GPCR, which allows it to act as a guanine nucleotide exchange factor (GEF). The GPCR can then activate an associated G protein by exchanging the GDP bound to the G protein for a GTP. The G protein's α subunit, together with the bound GTP, can then dissociate from the β and γ subunits to further affect intracellular signaling proteins or target functional proteins directly depending on the α subunit type.
- An example of GPCR is the beta 2 adrenergic receptor (binds epinephrine).
- In terms of structure, GPCRs are characterized by an extracellular N-terminus, followed by seven transmembrane (7-TM) α -helices (TM-1 to TM-7) connected by three intracellular (IL-1 to IL-3) and three extracellular loops (EL-1 to EL-3), and finally an intracellular C-terminus.



Gated ion channel

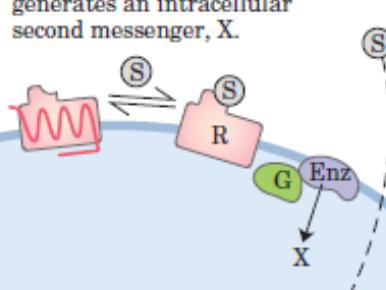
Opens or closes in response to concentration of signal ligand (S) or membrane potential.



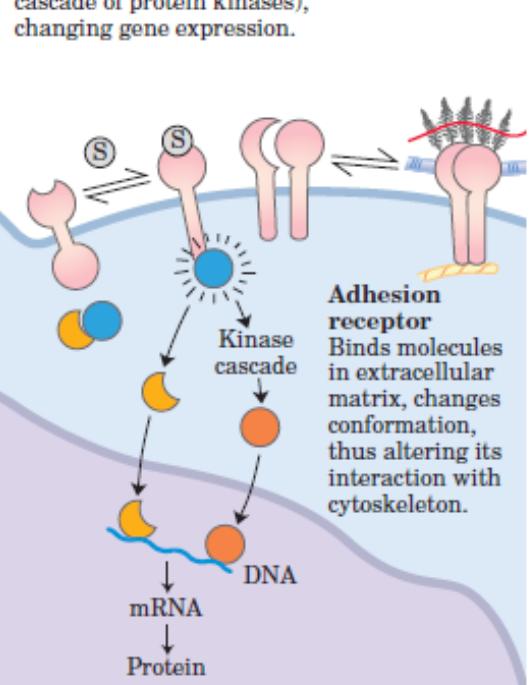
Receptor enzyme
Ligand binding to extracellular domain stimulates enzyme activity in intracellular domain.

Serpentine receptor

External ligand binding to receptor (R) activates an intracellular GTP-binding protein (G), which regulates an enzyme (Enz) that generates an intracellular second messenger, X.

**Receptor with no intrinsic enzymatic activity**

Interacts with cytosolic protein kinase, which activates a gene-regulating protein (directly or through a cascade of protein kinases), changing gene expression.



Steroid receptor
Steroid binding to a nuclear receptor protein allows the receptor to regulate the expression of specific genes.

- Gated ion channel; Acetylcholine receptors
- Receptor enzymes: Insulin receptor
- Serpentine/ GPCR: Beta adrenergic receptors
- Steroid receptors: Estrogen receptors
- Receptor with no intrinsic enzymatic activity: JAK-STAT pathway
- Adhesion receptors: Integrin
- Agonist: Structural analog to ligand that can trigger normal response

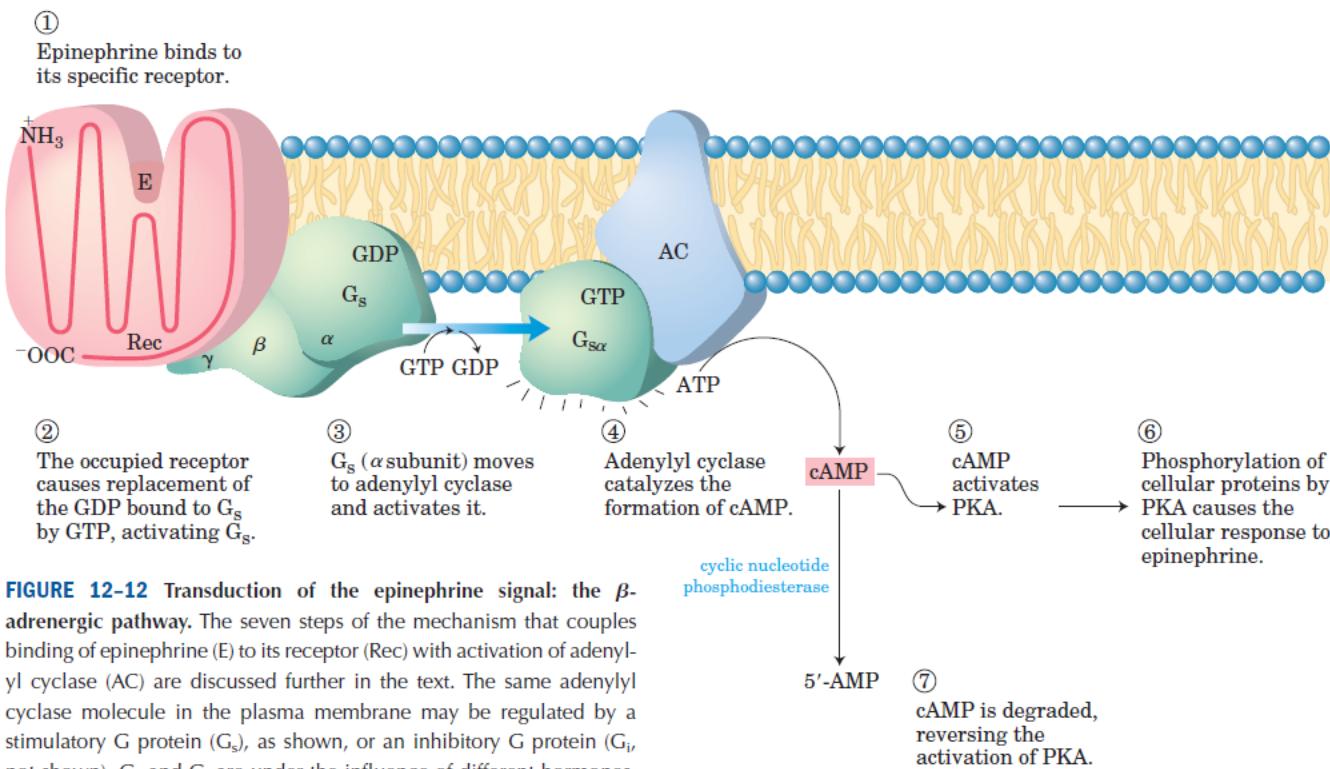


FIGURE 12–12 Transduction of the epinephrine signal: the β -adrenergic pathway. The seven steps of the mechanism that couples binding of epinephrine (E) to its receptor (Rec) with activation of adenyl cyclase (AC) are discussed further in the text. The same adenyl cyclase molecule in the plasma membrane may be regulated by a stimulatory G protein (G_s), as shown, or an inhibitory G protein (G_i , not shown). G_s and G_i are under the influence of different hormones. Hormones that induce GTP binding to G_i cause *inhibition* of adenyl cyclase, resulting in lower cellular [cAMP].

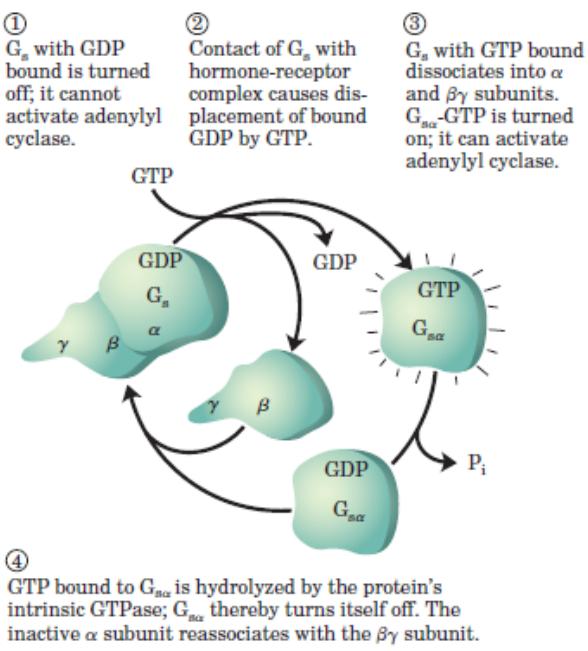
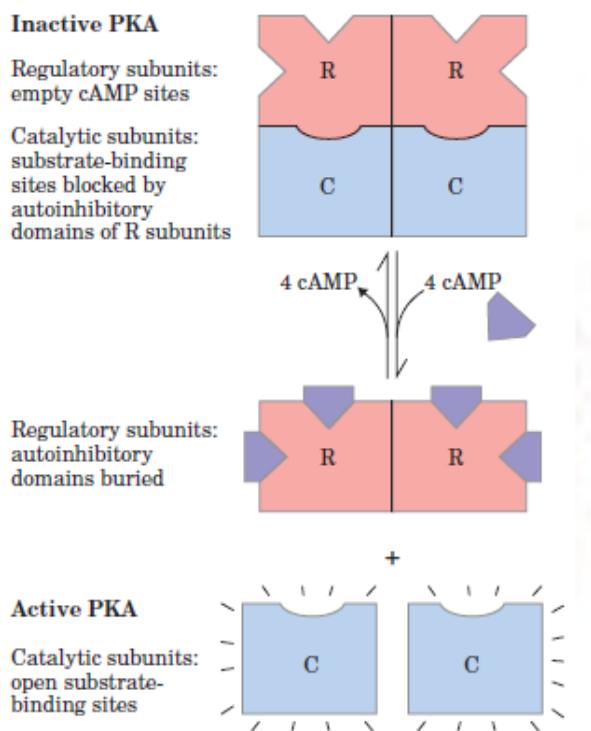


FIGURE 12–14 Self-inactivation of G_s . The steps are further described in the text. The protein's intrinsic GTPase activity, in many cases stimulated by RGS proteins (regulators of G protein signaling), determines how quickly bound GTP is hydrolyzed to GDP and thus how long the G protein remains active.

2. cAMP dependent pathway

- G protein- signal transducer; Adenylyl cyclase- effector; cAMP- secondary messenger. Amplification occurs at each step.
- Active Gs alpha subunit binds to adenylyl cyclase which converts ATP to cAMP. cAMP activates protein kinase A (PKA), which goes on to phosphorylate other enzymes or transcription factors.
- Gs alpha subunit turns itself off. It possesses GTPase activity which hydrolyses its own GTP to form GDP, which allows it to associate with the beta and gamma subunits of the G proteins, readying it again for receiving a new ligand.



- cAMP is degraded by cyclic nucleotide phosphodiesterase to 5' AMP.

TABLE 12-4 Some Signals That Use cAMP as Second Messenger

Corticotropin (ACTH)
Corticotropin-releasing hormone (CRH)
Dopamine [D ₁ , D ₂]*
Epinephrine (β -adrenergic)
Follicle-stimulating hormone (FSH)
Glucagon
Histamine [H ₂]*
Luteinizing hormone (LH)
Melanocyte-stimulating hormone (MSH)
Odorants (many)
Parathyroid hormone
Prostaglandins E ₁ , E ₂ (PGE ₁ , PGE ₂)
Serotonin [5-HT-1a, 5-HT-2]
Somatostatin
Tastants (sweet, bitter)
Thyroid-stimulating hormone (TSH)

TABLE 12-3 Some Enzymes and Other Proteins Regulated by cAMP-Dependent Phosphorylation (by PKA)

Enzyme/protein	Sequence phosphorylated*	Pathway/process regulated
Glycogen synthase	RASCTSSS	Glycogen synthesis
Phosphorylase <i>b</i> kinase		
α subunit	VEFRRLSI	
β subunit	RTKRSGSV	}
Pyruvate kinase (rat liver)	GVLRRASVAZL	Glycogen breakdown
Pyruvate dehydrogenase complex (type L)	GYLRRASV	Glycolysis
Hormone-sensitive lipase	PMRRSV	Pyruvate to acetyl-CoA
		Triacylglycerol mobilization and fatty acid oxidation
Phosphofructokinase-2/fructose 2,6-bisphosphatase	LQRRRGSSIPQ	Glycolysis/gluconeogenesis
Tyrosine hydroxylase	FIGRRQSL	Synthesis of L-DOPA, dopamine, norepinephrine, and epinephrine
Histone H1	AKRKASGPPVS	DNA condensation
Histone H2B	KKAKASRKESYSVWYK	DNA condensation
Cardiac phospholamban (cardiac pump regulator)	AIRRASR	Intracellular $[Ca^{2+}]$
Protein phosphatase-1 inhibitor-1	IRRRRPTP	Protein dephosphorylation
PKA consensus sequence†	XR(R/K)X(S/T)B	Many

3. Inositol triphosphate signalling

- Inositol triphosphate is made by hydrolysis of phosphatidylinositol 4,5-bisphosphate (PIP₂), a phospholipid that is located in the plasma membrane, by phospholipase C (PLC). Together with diacylglycerol (DAG), IP₃ is a second messenger molecule used in signal transduction in biological cells. While DAG stays inside the membrane, IP₃ is soluble and diffuses through the cell, where it binds to its receptor, which is a calcium channel located in the endoplasmic reticulum. When IP₃ binds its receptor, calcium is released into the cytosol, thereby activating various calcium regulated intracellular signals.

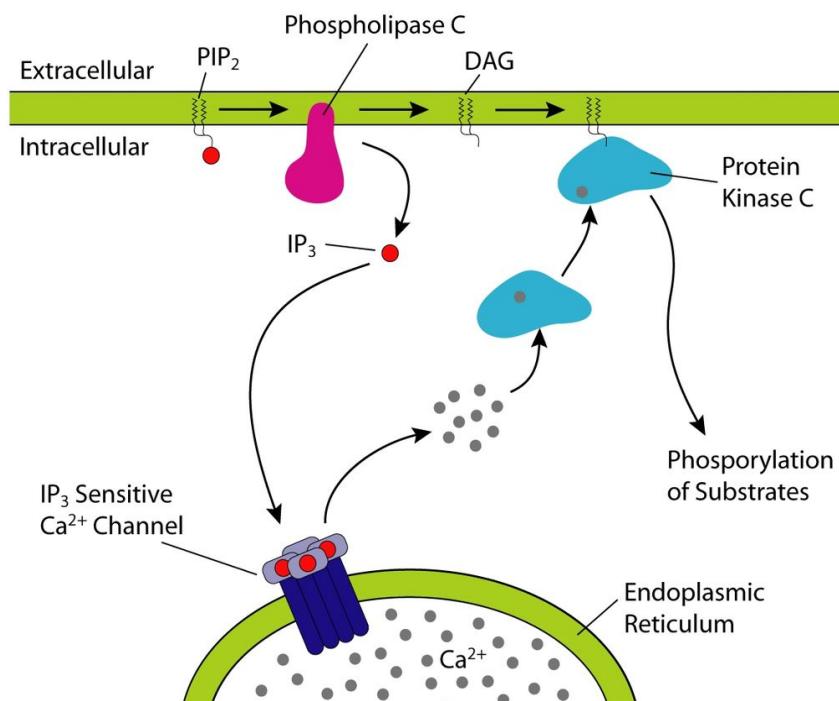


TABLE 12-5 Some Signals That Act through Phospholipase C and IP₃

Acetylcholine [muscarinic M ₁]	Gastrin-releasing peptide	Platelet-derived growth factor (PDGF)
α_1 -Adrenergic agonists	Glutamate	Serotonin [5-HT-1c]*
Angiogenin	Gonadotropin-releasing hormone (GRH)	Thyrotropin-releasing hormone (TRH)
Angiotensin II	Histamine [H ₁]*	Vasopressin
ATP [P _{2x} and P _{2y}]*	Light (<i>Drosophila</i>)	
Auxin	Oxytocin	

- Protein kinase C is activated by elevated concentrations of calcium ions. DAG plays a role in activating PKC. Thus both DAG and IP₃ are secondary messengers. DAG also serves as a precursor for eicosanoids. PKC phosphorylates serine and threonine residues on target proteins, and remains active even after the original Ca²⁺ signal is over. PKC is involved in receptor desensitization, in modulating membrane structure events, in regulating transcription, in mediating immune responses, in regulating cell growth, and in learning and memory.
- Effects of increase in calcium ions: Rearrangement of cytoskeletal components, exocytosis in neurons etc.
- Ca²⁺ rises from 0.1 micromolar to around 1 micromolar.
- More types of cell signalling pathways

TABLE 12-7 Signaling Components Present in Mammals, Plants, or Bacteria

Signaling protein	Mammals	Plants	Bacteria
Ion channels	+	+	+
Electrogenic ion pumps	+	+	+
Two-component His kinases	+	+	+
Adenylyl cyclase	+	+	+
Guanylyl cyclase	+	+	?
Receptor protein kinases (Ser/Thr)	+	+	?
Ca ²⁺ as second messenger	+	+	?
Ca ²⁺ channels	+	+	?
Calmodulin, CaM-binding protein	+	+	—
MAPK cascade	+	+	—
Cyclic nucleotide-gated channels	+	+	—
IP ₃ -gated Ca ²⁺ channels	+	+	—
Phosphatidylinositol kinases	+	+	—
Serpentine receptors	+	+/-	+
Trimeric G proteins	+	+/-	—
PI-specific phospholipase C	+	?	—
Tyrosine kinase receptors	+	?	—
SH2 domains	+	?	?
Nuclear steroid receptors	+	—	—
Protein kinase A	+	—	—
Protein kinase G	+	—	—

Week 8

1. Calmodulin

- Changes in intracellular $[Ca^{2+}]$ are detected by Ca^{2+} -binding proteins that regulate a variety of Ca^{2+} -dependent enzymes. Calmodulin (CaM) is an acidic protein with four high-affinity Ca^{2+} -binding sites. When intracellular $[Ca^{2+}]$ rises to about 1 micromolar the binding of Ca^{2+} to calmodulin drives a conformational change in the protein. Calmodulin associates with a variety of proteins and, in its Ca^{2+} -bound state, modulates their activities.
- In order to activate contraction of smooth muscle, the head of the myosin light chain must be phosphorylated. This phosphorylation is done by myosin light chain (MLC) kinase. This MLC kinase is activated by a calmodulin when it is bound by calcium, thus making smooth muscle contraction dependent on the presence of calcium, through the binding of calmodulin and activation of MLC kinase.
- CAMK, also written as CaMK, is an abbreviation for the Ca^{2+} /calmodulin-dependent protein kinase class of enzymes. CAMKs are activated by increases in the concentration of intracellular calcium ions (Ca^{2+}) and calmodulin. When activated, the enzymes transfer phosphates from ATP to defined serine or threonine residues in other proteins, so they are serine/threonine-specific protein kinases.



(a)



(b)

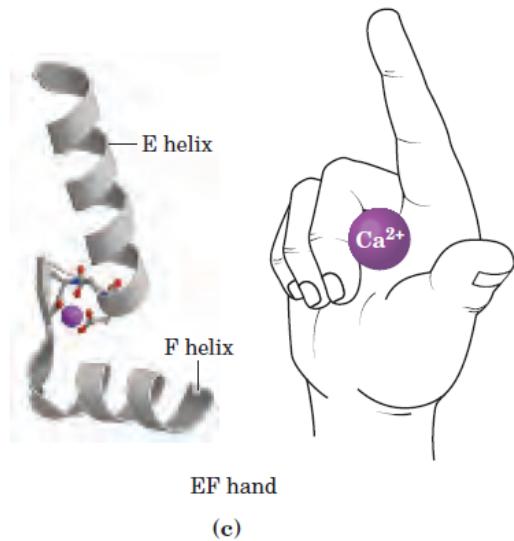


FIGURE 12-21 Calmodulin. This is the protein mediator of many Ca^{2+} -stimulated enzymatic reactions. Calmodulin has four high-affinity Ca^{2+} -binding sites ($K_d \approx 0.1$ to $1 \mu M$). (a) A ribbon model of the crystal structure of calmodulin (PDB ID 1CLL). The four Ca^{2+} -binding sites are occupied by Ca^{2+} (purple). The amino-terminal domain is on the left; the carboxyl-terminal domain on the right. (b) Calmodulin associated with a helical domain (red) of one of the many enzymes it regulates, calmodulin-dependent protein kinase II (PDB ID 1CDL). Notice that the long central α helix visible in (a) has bent back on itself in binding to the helical substrate domain. The central helix is clearly more flexible in solution than in the crystal. (c) Each of the four Ca^{2+} -binding sites occurs in a helix-loop-helix motif called the EF hand, also found in many other Ca^{2+} -binding proteins.

TABLE 12-6 Some Proteins Regulated by Ca^{2+} and Calmodulin

Adenylyl cyclase (brain)
Ca^{2+} /calmodulin-dependent protein kinases (CaM kinases I to IV)
Ca^{2+} -dependent Na^+ channel (<i>Paramecium</i>)
Ca^{2+} -release channel of sarcoplasmic reticulum
Calcineurin (phosphoprotein phosphatase 2B)
cAMP phosphodiesterase
cAMP-gated olfactory channel
cGMP-gated Na^+ , Ca^{2+} channels (rod and cone cells)
Glutamate decarboxylase
Myosin light chain kinases
NAD^+ kinase
Nitric oxide synthase
Phosphoinositide 3-kinase
Plasma membrane Ca^{2+} ATPase (Ca^{2+} pump)
RNA helicase (p68)

- In resting states of the cell, Ca^{2+} concentration is kept low by active transport or cotransport from the cytosol to the exterior or into the ER. There are also proteins that bind to free floating Ca^{2+} .
- CAM kinases have an autoinhibitory domain. Once the CAMK protein is initially activated by calcium or calmodulin, it can, in turn, further activate itself, so it doesn't become inactive even when it is without calcium or calmodulin.

2. Receptor Tyrosine Kinases

- Like GPCRs, enzyme-coupled receptors are transmembrane proteins that display their ligand-binding domains on the outer surface of the plasma membrane (see Figure 16–13C). Instead of associating with a G protein, however, the cytoplasmic domain of the receptor either acts as an enzyme itself or forms a complex with another protein that acts as an enzyme.
- In enzyme-coupled cell surface receptors, ligands bind to the extracellular domains to activate intracellular responses to the membrane bound enzyme receptor.

- Receptor tyrosine kinases (RTKs) are the high-affinity cell surface receptors for many polypeptide growth factors, cytokines, and hormones. There are 20 different classes of RTKs.
- The activated kinases phosphorylate tyrosine residues in target proteins, which in turn can be amplified by subsequent kinase cascades. (PLC, PI3K, MAP kinase)
- RTKs play a role in the cell cycle, cell differentiation, growth and immune responses.
- Defective RTKs have been implicated in cancer. Examples: v-src gene is an oncogenic gene that encodes for a tyrosine kinase which causes uncontrolled cell division. ABL is another tyrosine kinase that is a proto-oncogene.
- Epidermal growth factor receptors (EGFs): Receptor tyrosine-protein kinase erbB-2, also known as CD340 (cluster of differentiation 340), proto-oncogene Neu, Erbb2 (rodent), or ERBB2 (human), is a protein that in humans is encoded by the ERBB2 gene. ERBB is abbreviated from erythroblastic oncogene B, a gene isolated from avian genome. It is also frequently called HER2 (from human epidermal growth factor receptor 2) or HER2/neu.
- Insulin receptors are a type of RTKs.
- Fibroblast growth factor receptors are also RTKs that bind to fibroblast growth factors. Vascular endothelial growth factor (VEGF) is one of the main inducers of endothelial cell proliferation and permeability of blood vessels. Two RTKs bind to VEGF at the cell surface, VEGFR-1 and VEGFR-2.

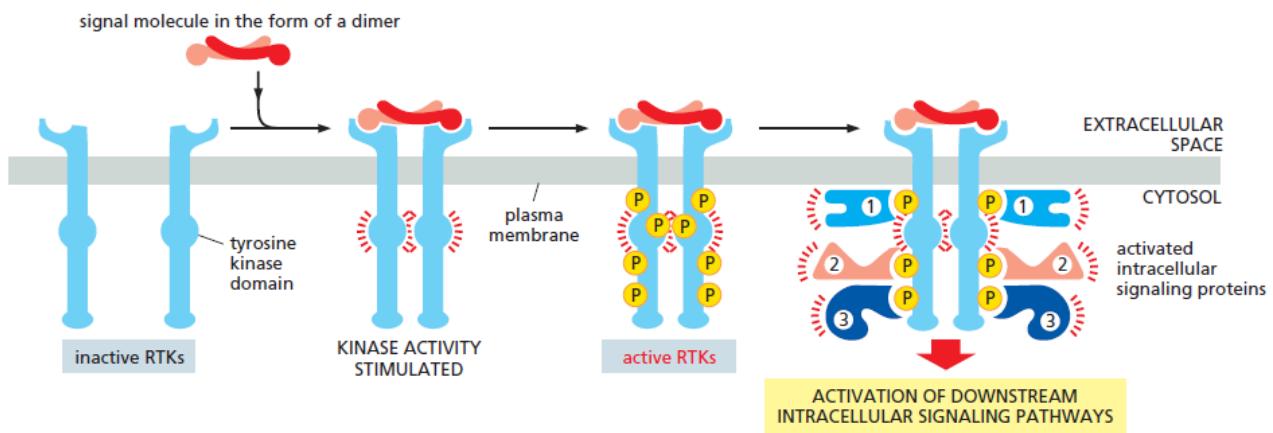


Figure 16–29 Activation of an RTK stimulates the assembly of an intracellular signaling complex. Typically, the binding of a signal molecule to the extracellular domain of an RTK causes two receptor molecules to associate into a dimer. The signal molecule shown here is itself a dimer and thus can physically cross-link two receptor molecules; other signal molecules induce a conformational change in the RTKs, causing the receptors to dimerize (not shown). In either case, dimer formation brings the kinase domain of each cytosolic receptor tail into contact with the other; this activates the kinases to phosphorylate the adjacent tail on several tyrosines. Each phosphorylated tyrosine serves as a specific docking site for a different intracellular signaling protein, which then helps relay the signal to the cell's interior; these proteins contain a specialized interaction domain—in this case, a module called an SH2 domain—that recognizes and binds to specific phosphorylated tyrosines on the cytosolic tail of an activated RTK or on another intracellular signaling protein.

- Platelet derived growth factor receptors are also RTKs.
- To terminate the response in an RTK, tyrosine phosphatases remove the phosphates and return the kinases to their inactive forms.

3. Ras

- Ras is a family of related proteins which is expressed in all animal cell lineages and organs. All Ras protein family members belong to a class of protein called small GTPase, and are involved in transmitting signals within cells.
- Virtually all RTKs activate and recruit Ras for further signalling. It plays a role in cell differentiation, division and growth.
- Ras are monomeric GTPases. They are docked to the cell membrane through a fatty acid tail.

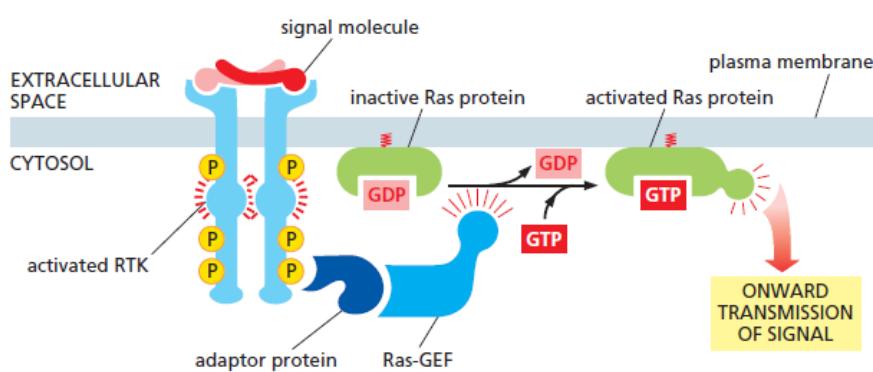


Figure 16–30 RTKs activate Ras. An adaptor protein docks on a particular phosphorytyrosine on the activated receptor (the other signaling proteins that would be bound to the receptor, as shown in Figure 16–29, have been omitted for simplicity). The adaptor recruits a Ras guanine nucleotide exchange factor (Ras-GEF) that stimulates Ras to exchange its bound GDP for GTP. The activated Ras protein can now stimulate several downstream signaling pathways, one of which is shown in Figure 16–31. Note that the Ras protein contains a covalently attached lipid group (red) that helps anchor the protein to the inside of the plasma membrane.

- The GTP bound state of Ras is the active form, while the GDP bound state is the inactive form. Ras also has GTPase activity to shut itself off.
- Ras initiates MAP kinase cascade reaction, which affects cell proliferation.

4. PI3K

- Another pathway that is activated by RTKs is the phosphatidylinositol 3-kinase (PI3K) pathway. The phosphorylated lipids then serve as docking sites for other intracellular signaling molecules.
- One of these is Akt, also called protein kinase B. Akt phosphorylates serine/threonine residues in target proteins. Akt inactivates protein Bad, which otherwise promotes apoptosis. Thus Akt promotes cell survival.
- Akt activates another protein Tor which in turns inhibits protein degradation and promotes protein synthesis, which leads to cell growth.

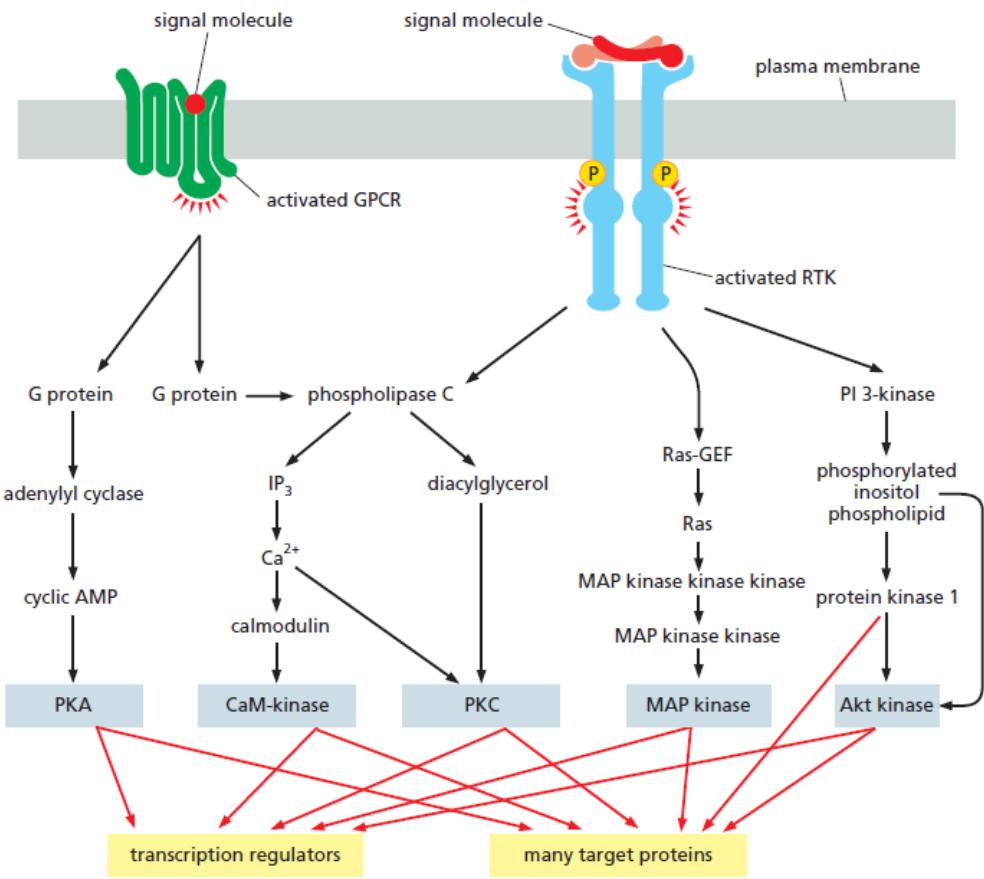


Figure 16–35 Both GPCRs and RTKs activate multiple intracellular signaling pathways. The figure reviews five of these pathways: two leading from GPCRs—through adenyl cyclase and through phospholipase C—and three leading from RTKs—through phospholipase C, Ras, and PI 3-kinase. Each pathway differs from the others, yet they use some common components to transmit their signals. Because all five eventually activate protein kinases (gray boxes), it seems that each is capable in principle of regulating practically any process in the cell.

Mitosis and the Cell Cycle

1. Cell cycle control and CDKs
 - Cell cycle control is done via several biochemical binary switches (either off or on, no in between).
 - There is a start checkpoint prior to the S phase, then a G₂/M checkpoint and a metaphase-anaphase.
 - Cyclin-dependent kinases (CDKs), in conjunction with cyclins are responsible for controlling the cell cycle. Their enzymatic activities rise and fall throughout the cell cycle. CDKs require to be tightly bound with their respective cyclins in order to be active.
 - There are four types for cyclins:
 - G₁/S cyclins: They begin their activity in late G₁ phase and trigger progression into the S phase, resulting in a commitment to cell division.

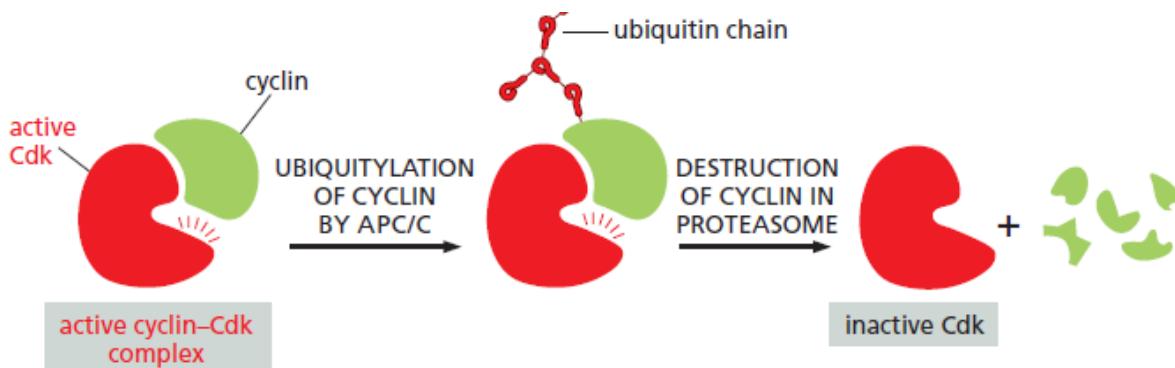
- S cyclins: They bind CDKs after the start of the S phase and remain active into early mitosis, and also regulate early mitotic events.
- M cyclins: M cyclins trigger entry into mitosis, and are shortly destroyed thereafter.
- G1 cyclins: They assist G1/S cyclins in late G1.

TABLE 18–2 THE MAJOR CYCLINS AND CDKS OF VERTEBRATES

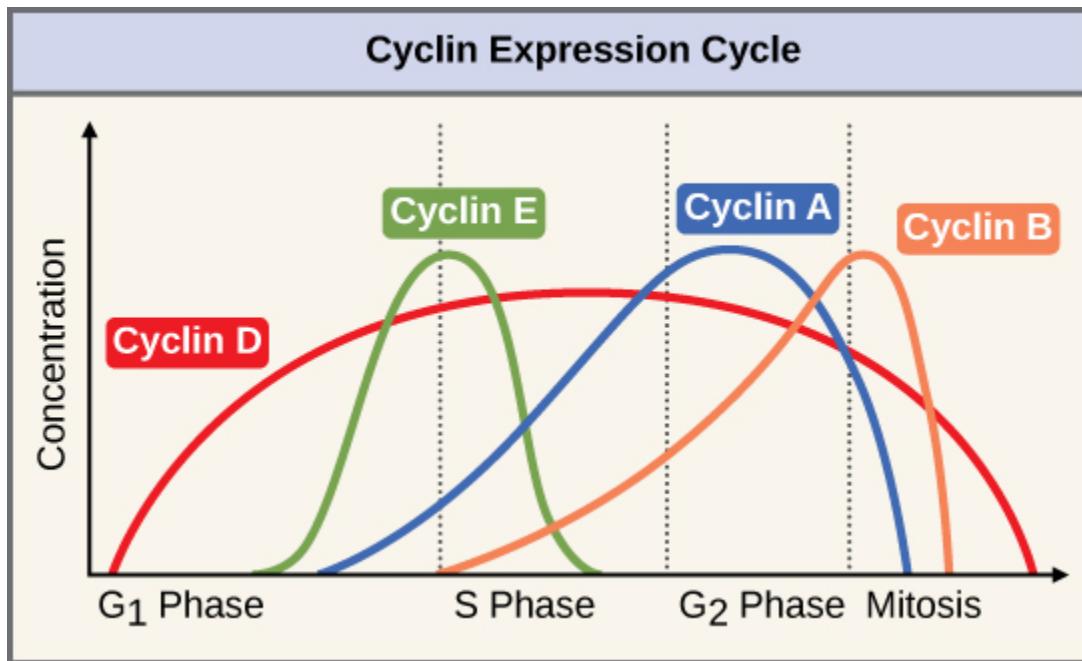
Cyclin–Cdk Complex	Cyclin	Cdk Partner
G1-Cdk	cyclin D*	Cdk4, Cdk6
G1/S-Cdk	cyclin E	Cdk2
S-Cdk	cyclin A	Cdk2
M-Cdk	cyclin B	Cdk1

*There are three forms of cyclin D in mammals (cyclins D1, D2, and D3).

- CDKs require both their cyclins and the activity of CDK activating kinase (CAK) to become fully active.
- The activity of the CDKs is largely dependent on the rise and fall of cyclins during the cell cycle but other regulatory mechanisms also exist.
- Wee1, a kinase, phosphorylates residues in the CDK to inactivate it, while Cdc25, a phosphatase dephosphorylates the CDK to activate it.
- Progression through the start and the G2/M checkpoint happens through phosphorylation/dephosphorylation.
- The metaphase-anaphase checkpoint is regulated by the anaphase-promoting complex, or cyclosome C, (APC/C). APC/C catalyses the ubiquitylation and proteolysis of securin, a protein that plays a role in holding the sister chromatids.
- APC/C also destroys S and M cyclins.



- APC/C remains active throughout mitosis and into G1, and finally inactivated by G1/S cyclins.
- CDK inhibitor proteins are also used to inactivate CDKs during G1. Example: p27 and p21 inactivate G1/S and S CDK-cyclin complexes in case the process needs to halt.
- Upon external and internal cues, G1 CDK is activated, which drives G1/S and S cyclin synthesis. G1/S CDK activity promotes S CDK activity. M CDK activation triggers progression into the M phase. APC/C formation, along with its activator Cdc20, destroys securin and other cyclins, which promotes separation of sister chromatids.

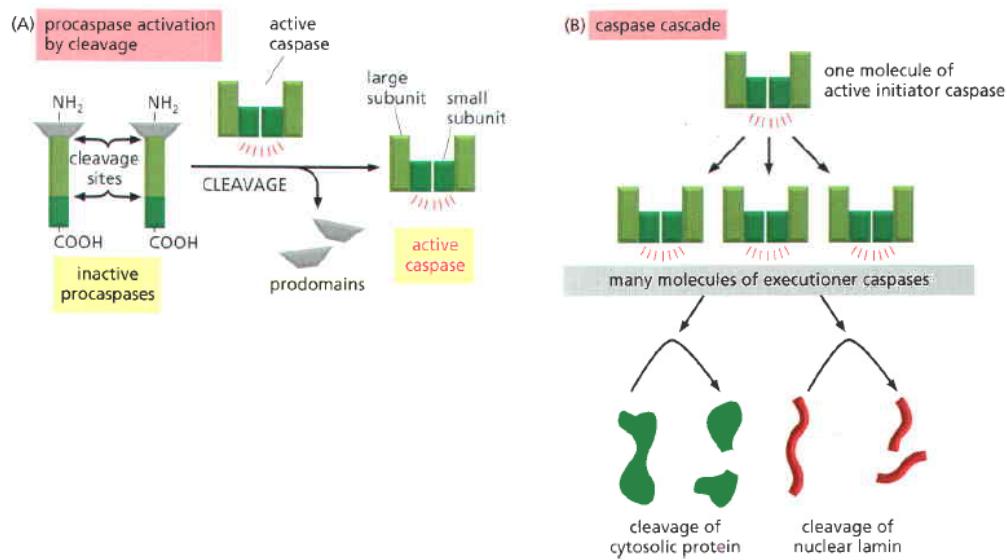


Week 9

1. Apoptosis
 - The process by which cells kill themselves in a controlled manner is called programmed cell death.
 - Apoptosis is a type of programmed cell death (and is not the only one) but is the most common pathway.
 - Apoptotic cells possess characteristic morphology. They shrink and condense, the cytoskeleton collapses, nuclear membrane disassembles, chromatin condenses and breaks into pieces. Cell blebs and larger cells can break up into smaller membrane bound bodies called apoptotic bodies. There is loss of

mitochondrial membrane potential and proteins such as cytochrome c are relocated from

- During apoptosis, endonucleases cleave the DNA into many small fragments which are seen in a ladder pattern on an agarose gel.
- Phosphatidylserine which is usually present on the inner membrane of the lipid bilayer of cell membranes flips to the outer membrane and serves as a signal for macrophages to engulf it.
- Apoptosis depends on a family of caspases (cysteine-aspartic acid proteases). They are synthesized in their inactive form of procaspases. They are activated by their cleavage at aspartic acid residues to form a heterodimer. Two heterodimers associate to form the active tetramer.
- Activated caspases can activate other procaspases, resulting in an amplifying cascade. Initiator caspases activate executioner procaspases which activate other executioner caspases and act on target proteins.
- Some target proteins include nuclear lamins (filament proteins that are a part of the nuclear envelope) and lead to nuclear membrane degradation.
- They also act on other cytoskeletal proteins, cell-cell adhesion proteins (to allow the cell to free itself of its neighbours).

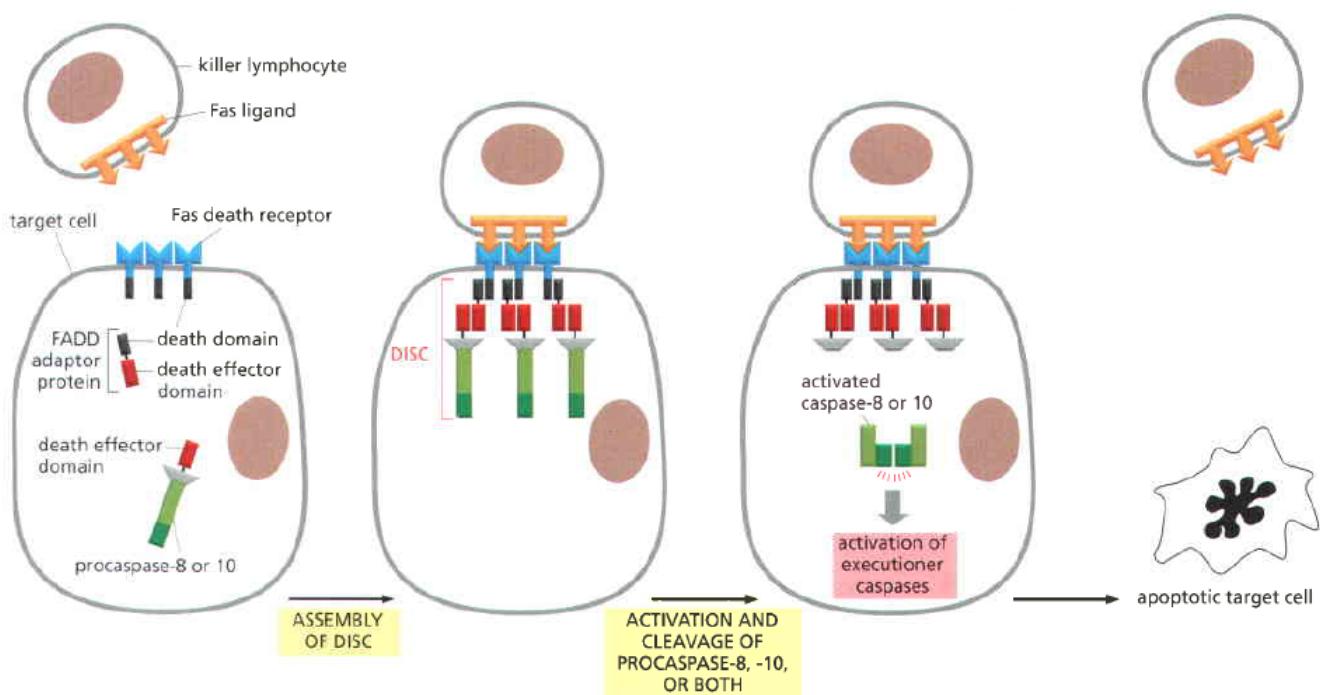


- Initiator procaspases have a long prodomain, which contains a caspase recruitment domain (CARD) that enables them to assemble with adaptor proteins into activation complexes when the cell receives a signal to undergo apoptosis. Once incorporated into such a complex, the initiator

procaspases are brought into close proximity, which is sufficient to activate them; they then cleave each other to make the process irreversible

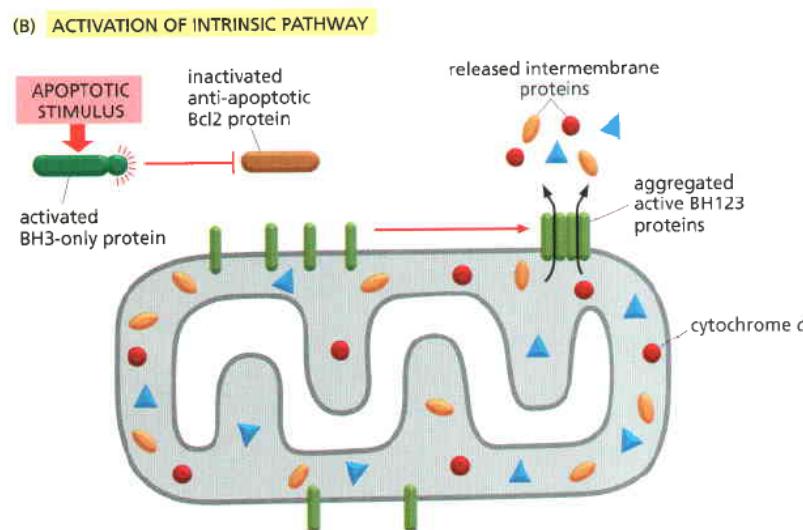
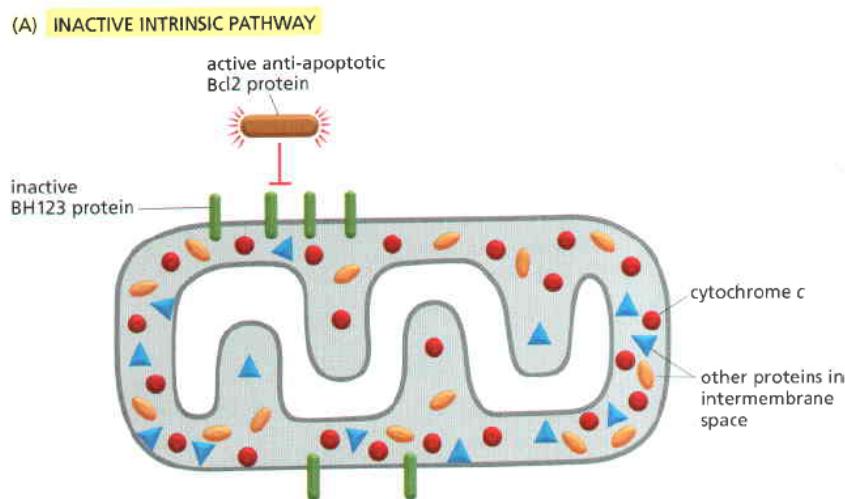
2. Extrinsic Apoptotic Pathway

- In the extrinsic pathway, external signals bind to death receptors on the cell surface. Death receptors are cell receptors that contain an extracellular ligand binding domain, a transmembrane domain and an intracellular death domain. They are homotrimers and are part of the tumour necrosis factor receptor family. The ligands that activate the death receptors are also homotrimers.
- A killer lymphocyte with Fas ligands binds to the Fas death receptors. This causes the intracellular domains of the Fas receptors to recruit adaptor proteins FADD (Fas associated death domains) which in turn recruit initiator procaspases (procaspase 8 or 10) forming a DISC (death inducing signalling complex). The DISC activates the procaspases which initiates the downstream amplification.



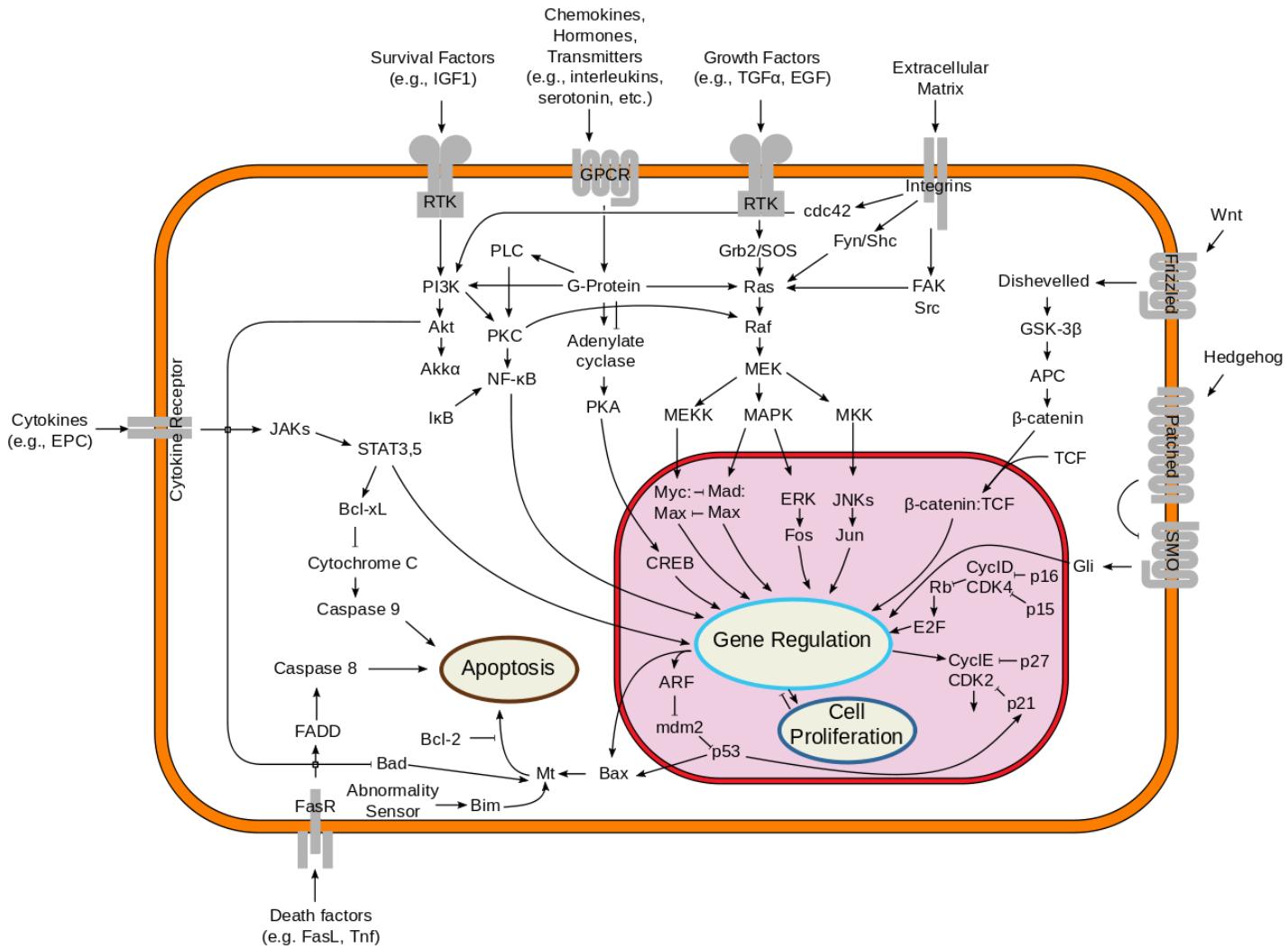
Intrinsic Apoptotic pathway

- Cells can also activate apoptosis from inside the cell.
- In this pathway, cytochrome c is released from the mitochondria into the cytosol. It binds to pro caspase activating adaptor protein Apaf1 (apoptotic protease activating factor 1) causing it to oligomerise into a wheel shaped heptamer called an apoptosome. The apoptosome recruits and activates procaspase 9. Pro caspase 9 activates executioner caspases downstream.
- The extrinsic pathway recruits and activates the intrinsic pathway to amplify the process of apoptosis.
- Bcl2 family of proteins regulate apoptosis and are highly conserved across species. They mainly control the release of proteins such as cytochrome c from the mitochondria. They can be either pro or anti apoptotic.
- Bax and Bak (BH123) are types of proapoptotic proteins that promote the transport of cytochrome c out of the mitochondria. Bcl2 and Bcl-XL are anti apoptotic. They inhibit apoptosis by inhibiting pro apoptotic proteins like Bax. Other pro apoptotic proteins are Bad, Bim, Puma and Noxa (BH3 proteins)



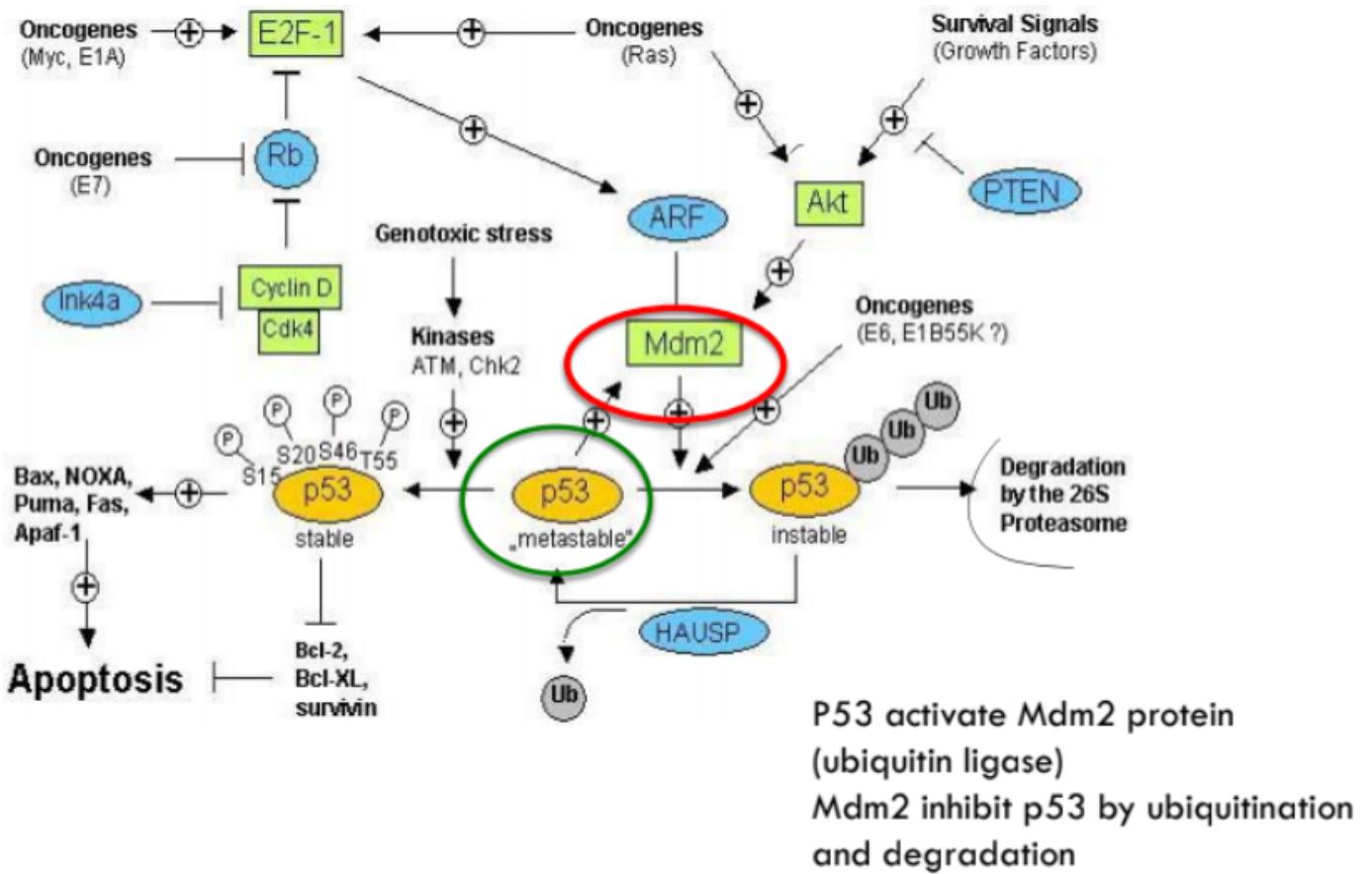
- External signals activate certain pro apoptotic proteins such as Bad and Bim (BH3 only), which in turn suppress anti apoptotic Bcl2 proteins which allows the proapoptotic Bax and Bak to function.

p53



- Tumour protein p53 encoded by the TP53 is a tumour suppressor.
- p53 becomes activated in response to myriad stressors, including but not limited to DNA damage (induced by either UV, IR, or chemical agents such as hydrogen peroxide), oxidative stress, osmotic shock, ribonucleotide depletion, and deregulated oncogene expression.

- Activation is marked by two major events. First, the half-life of the p53 protein is increased drastically, leading to a quick accumulation of p53 in stressed cells. Second, a conformational change forces p53 to be activated as a transcription regulator in these cells. The critical event leading to the activation of p53 is the phosphorylation of its N-terminal domain. The N-terminal transcriptional activation domain contains a large number of phosphorylation sites and can be considered as the primary target for protein kinases transducing stress signals



- p53 then activates pro apoptotic factors such as Bax, Noxa, Fas etc. which in turn trigger the intrinsic pathway.
- In unstressed cells, levels of p53 are kept low by Mdm2. Mdm2 (also called HDM2 in humans), binds to p53, preventing its action and transports it from the nucleus to the cytosol. Mdm2 also acts as an ubiquitin ligase and covalently attaches ubiquitin to p53 and thus marks p53 for degradation by the proteasome.
- p21 is a potent cyclin-dependent kinase inhibitor (CKI). The p21 (CIP1/WAF1) protein binds to and inhibits the activity of cyclin-CDK2, -CDK1, and -CDK4/6

complexes, and thus functions as a regulator of cell cycle progression at G1 and S phase.

- p53 activates p21 which mediates downstream cell cycle arrest.
- Certain viral proteins can also function as pro or anti apoptotic factors.

Week 10

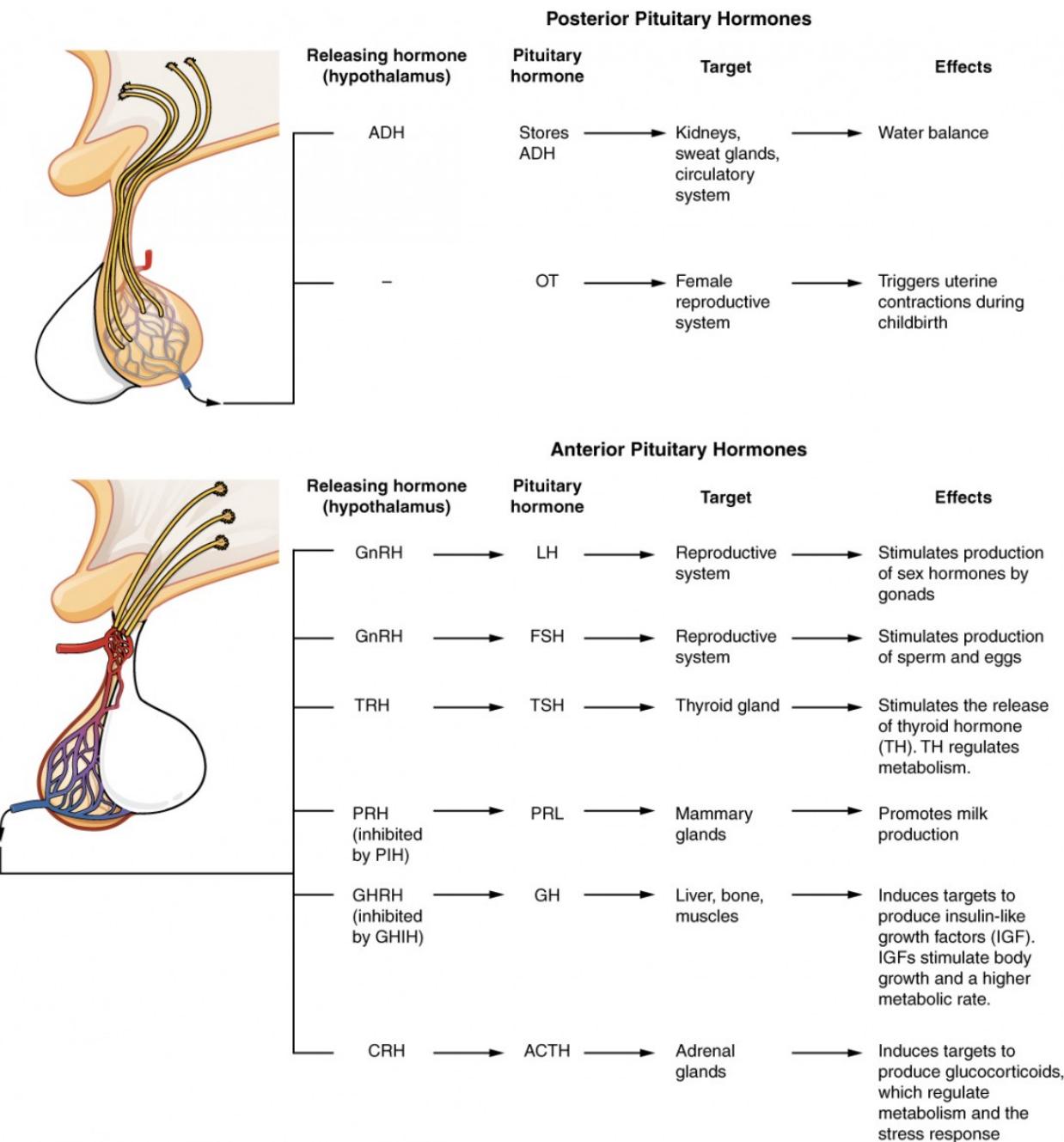
1. Hormones

- Hormones are biologically active molecules that are produced by endocrine glands, transported through the blood to their target tissues where they bring about some change.

TABLE 17.5 Hormones from Sources Other than the Hypothalamus and Pituitary (continued)

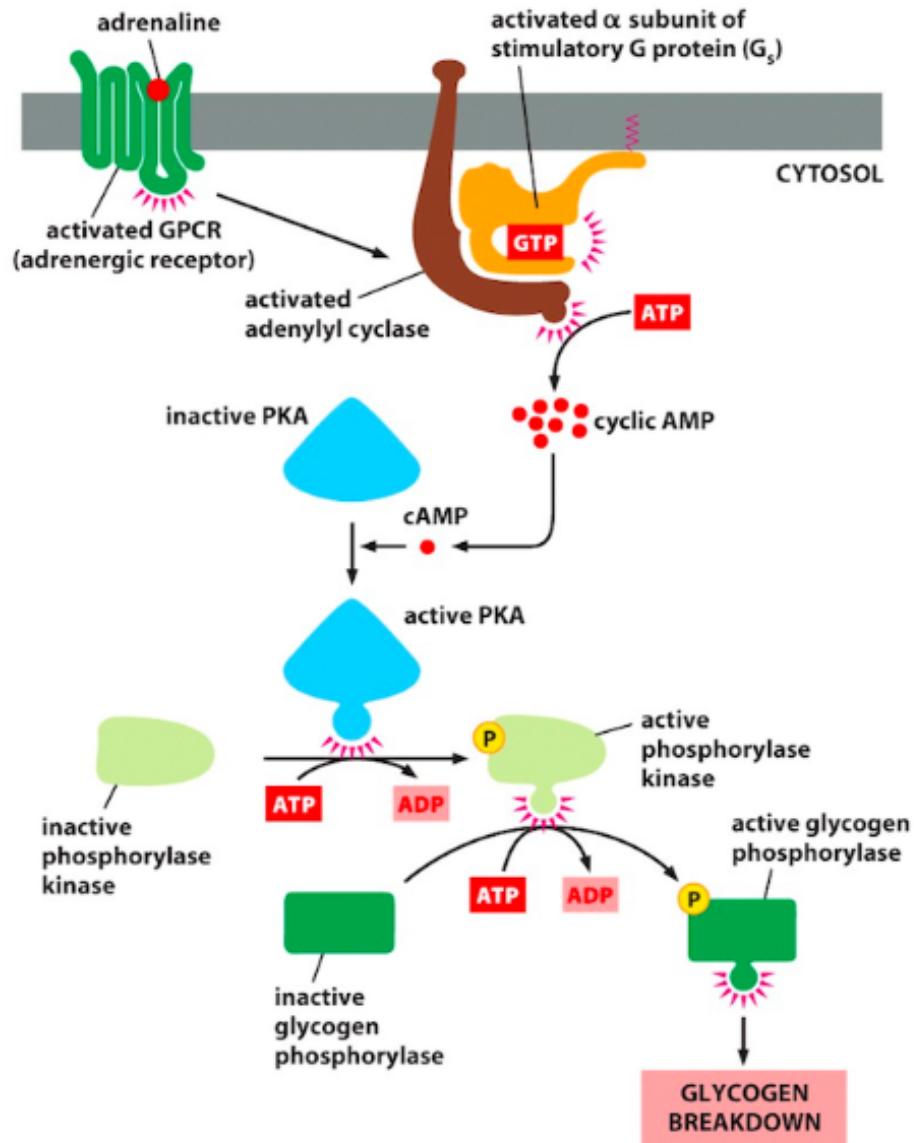
Source	Hormone	Target Organs and Tissues	Principal Effects
Ovaries	Estradiol	Many tissues	Stimulates female reproductive development and adolescent growth; regulates menstrual cycle and pregnancy; prepares mammary glands for lactation
	Progesterone	Uterus, mammary glands	Regulates menstrual cycle and pregnancy; prepares mammary glands for lactation
	Inhibin	Anterior pituitary	Inhibits FSH secretion
Testes	Testosterone	Many tissues	Stimulates fetal and adolescent reproductive development, musculoskeletal growth, sperm production, and libido
	Inhibin	Anterior pituitary	Inhibits FSH secretion
Skin	Cholecalciferol	—	Precursor of calcitriol (see kidneys)
Liver	Calcidiol	—	Precursor of calcitriol (see kidneys)
	Angiotensinogen	—	Precursor of angiotensin II (see kidneys)
	Erythropoietin	Red bone marrow	Promotes red blood cell production, increases oxygen-carrying capacity of blood
	Hepcidin	Small intestine, liver	Regulates plasma iron level
	Insulin-like growth factor I	Many tissues	Prolongs and mediates action of growth hormone
Kidneys	Angiotensin I	—	Precursor of angiotensin II, a vasoconstrictor
	Calcitriol	Small intestine	Increases blood calcium level mainly by promoting intestinal absorption of Ca^{2+}
	Erythropoietin	Red bone marrow	Promotes red blood cell production, increases oxygen-carrying capacity of blood
Heart	Natriuretic peptides	Kidney	Lower blood volume and pressure by promoting Na^+ and water loss
Stomach and small intestine	Cholecystokinin	Gallbladder, brain	Bile release; appetite suppression
	Gastrin	Stomach	Stimulates acid secretion
	Ghrelin	Brain	Stimulates hunger, initiates feeding
	Peptide YY	Brain	Produces sense of satiety, terminates feeding
	Other enteric hormones	Stomach, intestines	Coordinate secretion and motility in different regions of digestive tract
Adipose tissue	Leptin	Brain	Limits appetite over long term
Osseous tissue	Osteocalcin	Pancreas, adipose tissue	Stimulates pancreatic beta cells to multiply, increases insulin secretion, enhances insulin sensitivity of various tissues, and reduces fat deposition
Placenta	Estrogen, progesterone	Many tissues of mother and fetus	Stimulate fetal development and maternal bodily adaptations to pregnancy; prepare mammary glands for lactation

- Endocrine- secreted inside body, exocrine - secreted outside body, autocrine - acts on self, paracrine - acts on cells that are nearby.



- Hormones either directly regulate gene expression or mediate it via a secondary messenger.
- There are three types of receptors for hormones
- Nuclear receptors (estrogen)

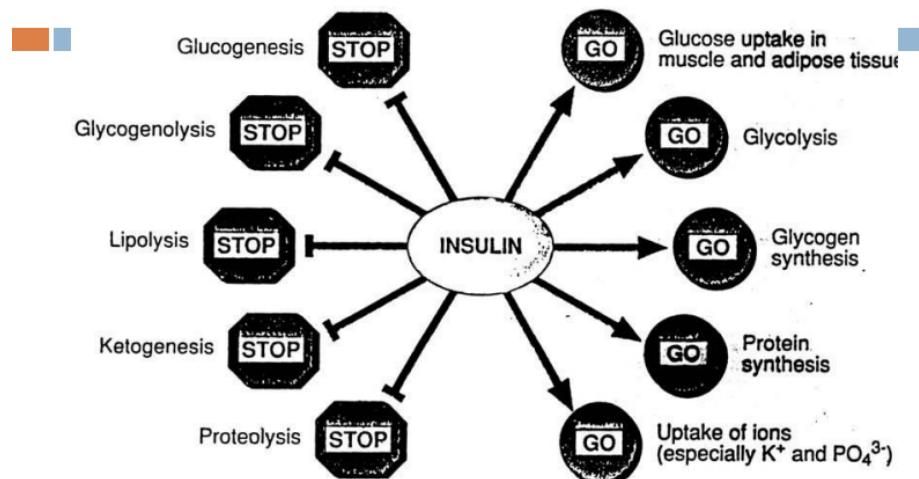
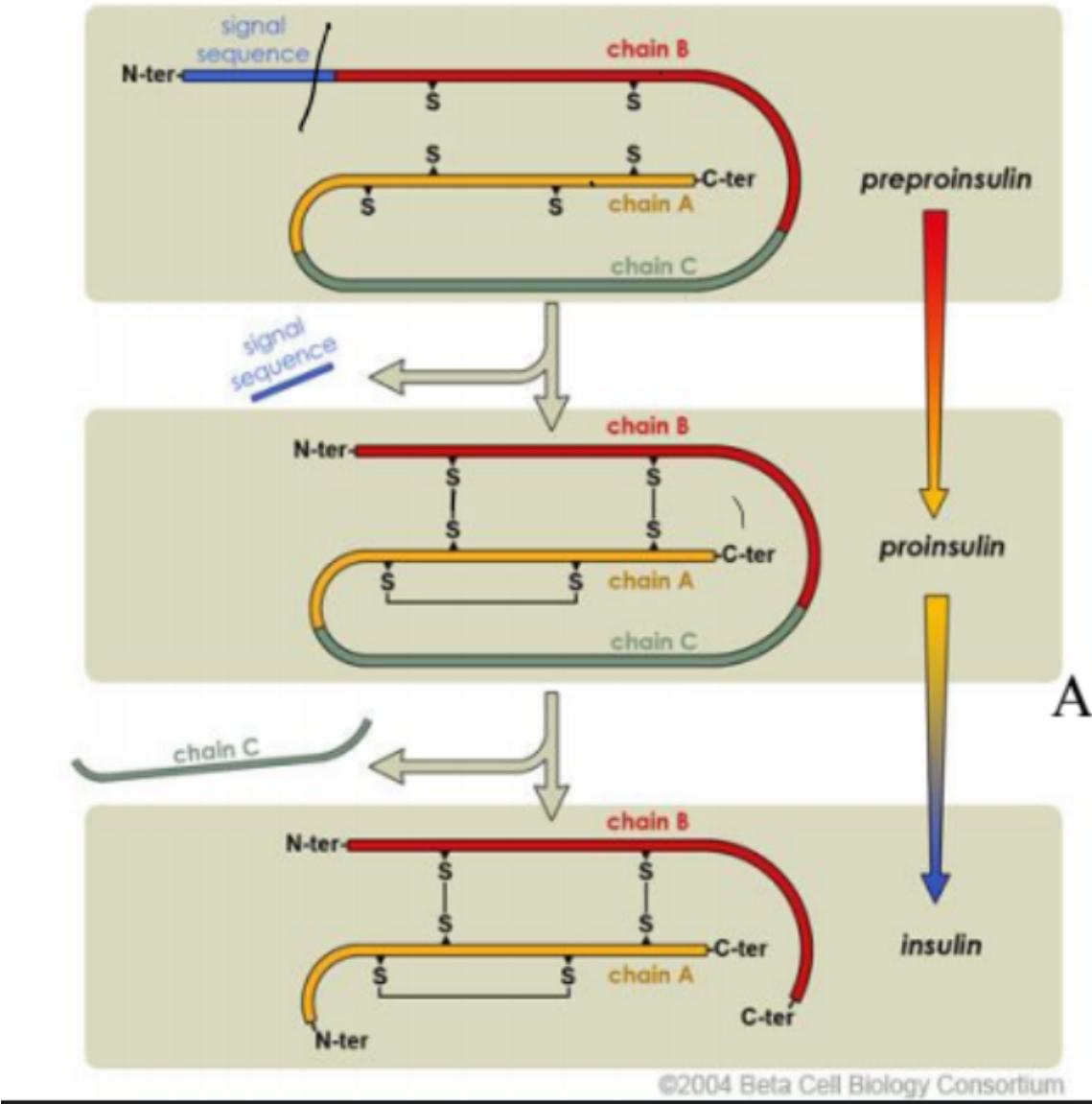
- Cytoplasmic receptors (testosterone, steroid hormones and thyroid hormones)
- Membrane bound receptors (GPCRs RTKs)



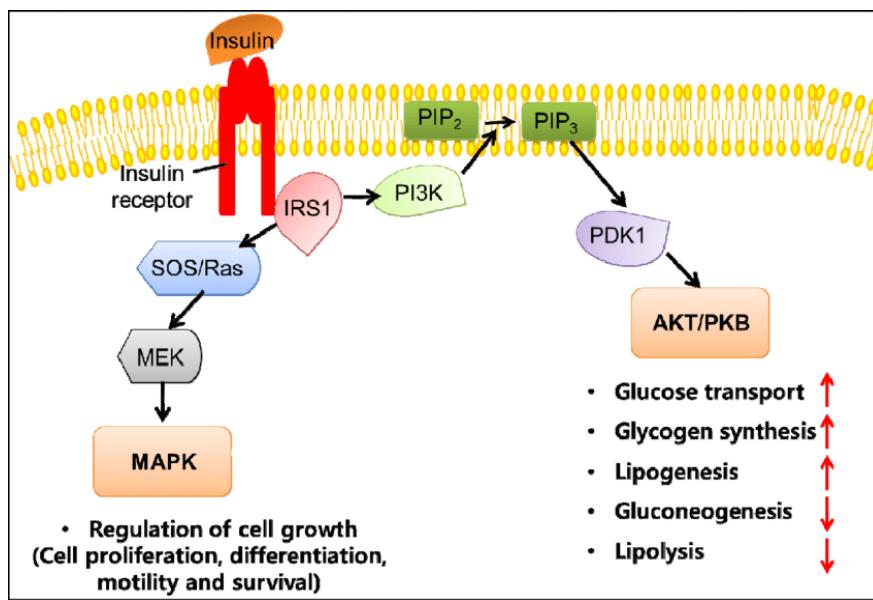
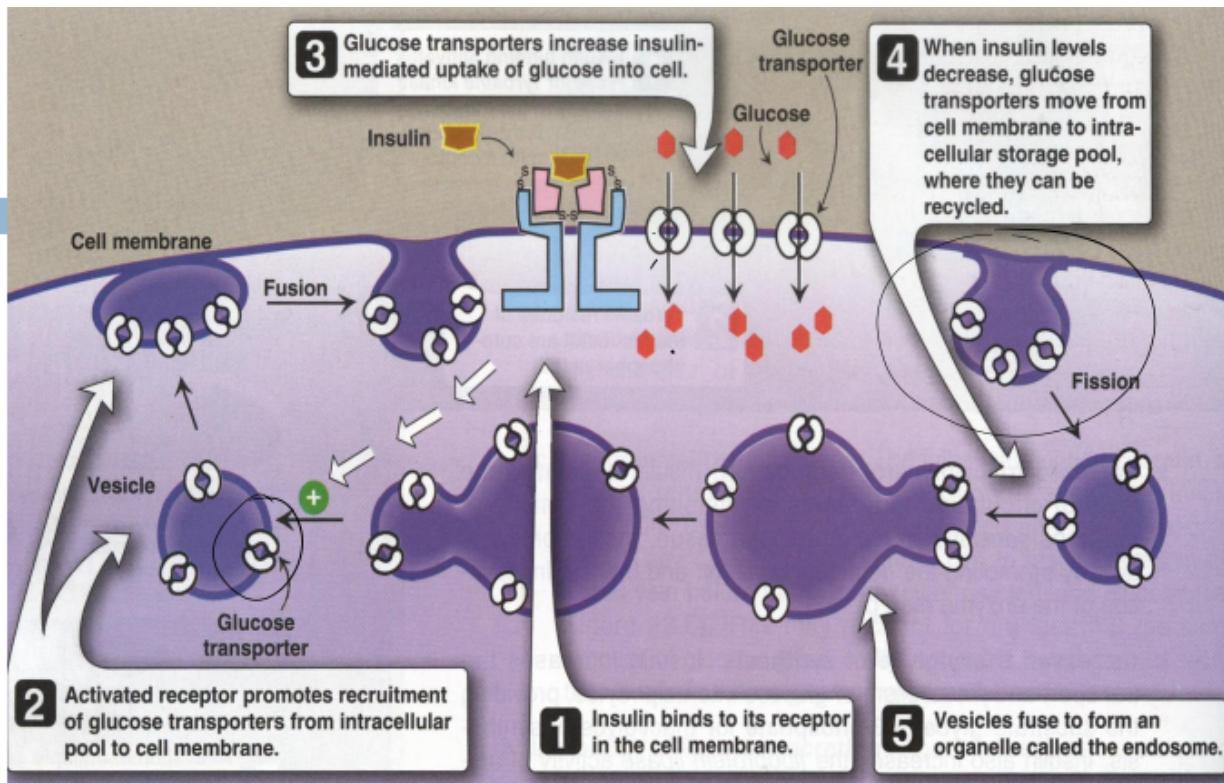
2. Insulin

- Insulin is a peptide hormone produced by beta cells of the pancreatic islets; it is considered to be the main anabolic hormone of the body.

- It consists of two chains with a total of 51 amino acids. These A and B chains are linked by disulphide bonds.
- It is converted from preproinsulin, to proinsulin to its active form insulin.



- Glucagon has the opposite effect of insulin and is produced by alpha cells of the pancreas. It is activated by hypoglycemia and works to increase blood sugar levels. It acts on GPCRs that produce cAMP.
- Insulin production is stimulated by the ‘fed state’ i.e hyperglycemia, intake of amino acids etc. Its production decreases during states of stress.
- Other gastrointestinal hormones can also affect insulin production.

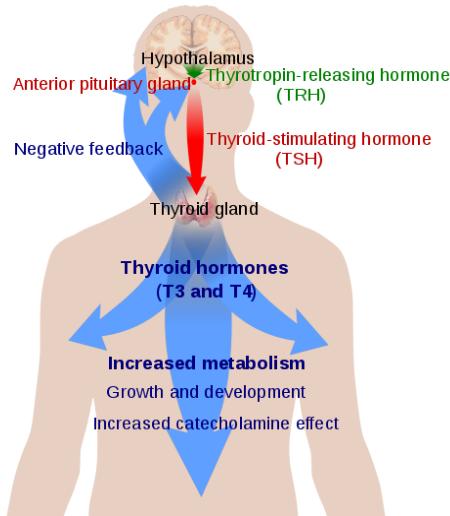


- IRS is the insulin receptor substrate. PKB is the protein kinase B
- In the liver, insulin inhibits gluconeogenesis and glycogenolysis, and promotes glycogenesis.
- In muscle and adipose tissue it promotes synthesis of triglycerides.
- It also inhibits breakdown of triglycerides.

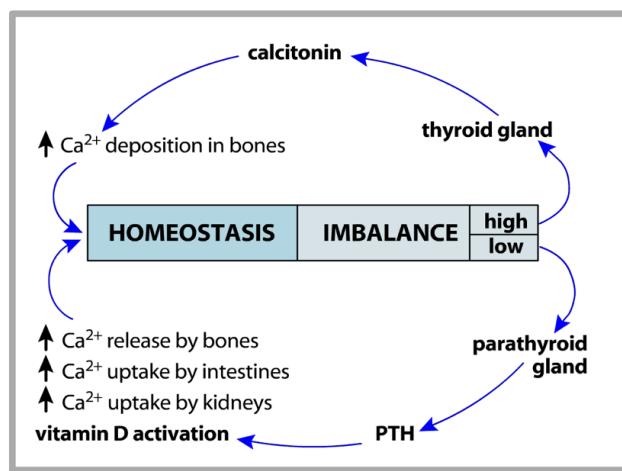
3. Thyroid hormones

- The thyroid gland produces two different types of hormones; triiodothyronine (T3) and thyroxine (T4).
- These are tyrosine based hormones.
- T3 can be produced from T4 by deiodination.
- TSH acts on GPCRs in the thyroid gland.

Thyroid system



4. parathyroid hormone



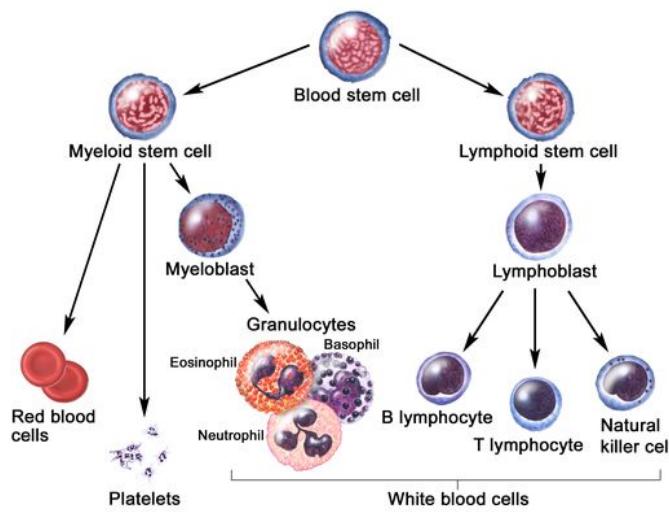
Week 11

1. Blood

- The different types of blood cells are neutrophils, eosinophils, basophils, lymphocytes (T and B cells) and monocytes.

Subtype	Nucleus	Function	Example
Neutrophil	Multi-Lobed	Bacterial or fungal infection. These are the most common first responders to microbial infection.	
Eosinophil	Bi-Lobed	Parasitic infections and allergic reactions (inflammatory).	
Basophil	Bi/Tri-Lobed	Allergic and antigen response (releases histamine causing vasodilation).	
Lymphocyte	Deep Staining, Eccentric	Include B cells, CD4+ helper T cells, and CD8+ cytotoxic T cells. Operate primarily in the lymphatic system.	
Monocyte	Kidney Shaped	Phagocytosis of pathogens. Presentation of antigens to T cells. Eventually, they become tissue macrophages, which remove dead cell debris and attack microorganisms.	

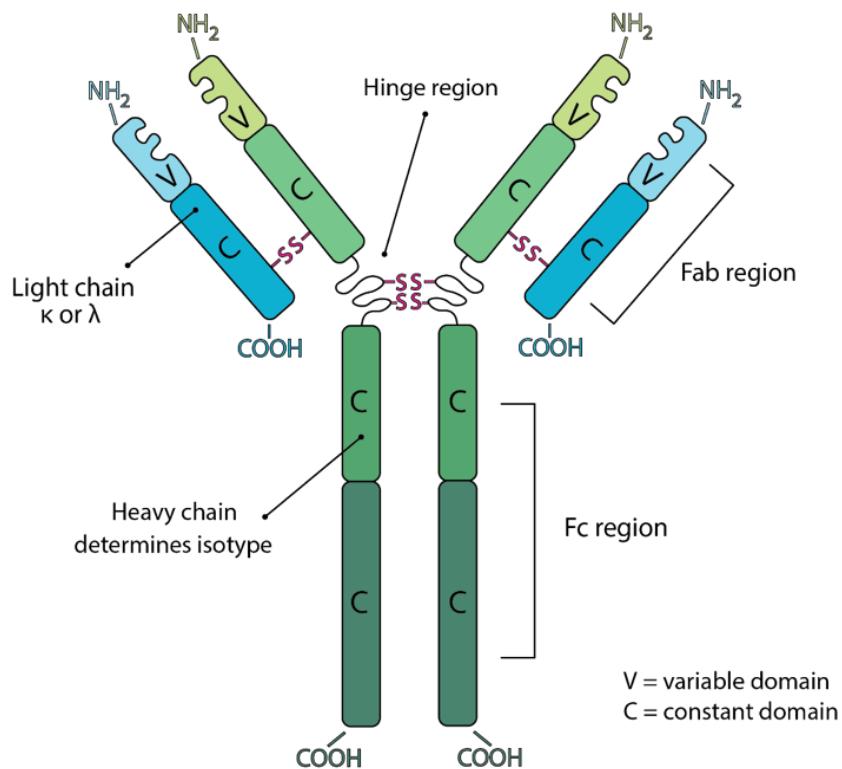
- Platelets are formed from fragments of megakaryocytes. Their lifespan is a few days.



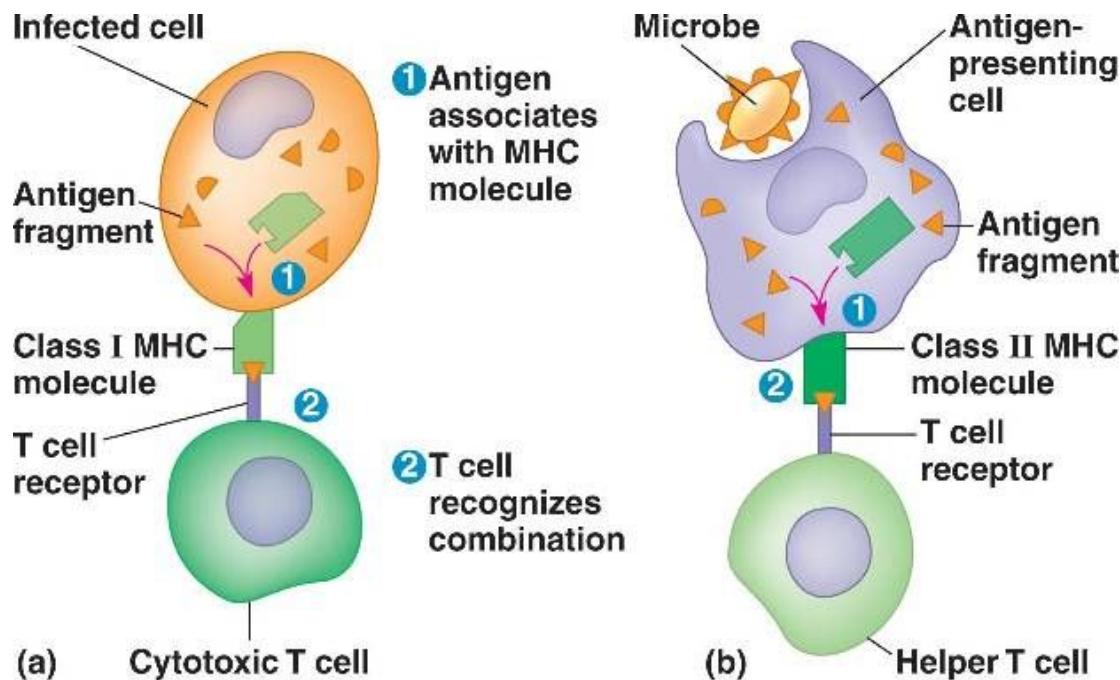
- Myeloid- refers to origin in bone marrow. They also produce dendritic cells and macrophages.
- Innate immune system- nonspecific, acts immediately. Includes physical barriers and macrophages (monocytes and neutrophils), antigen presenting cells(APCs) and NK cells.
- Adaptive immune system is acquired, specific and takes time. Includes lymphocytes.
- Dendritic cells remain inactivated in tissue and are activated by pathogens/injury. They act as APCs and present antigens on their surfaces to lymphocytes.
- NK cells are activated by cytokine signals from macrophages. They secrete granzymes and perforins that lyse pathogenic cells and kill them.
- T cells are matured in the thymus. The two major phenotypic versions are CD4 (helper T cells) and CD8 (killer T cells).
- B cells are matured in the bone marrow itself. They transform into plasma cells and then produce antibodies.

2. Antigens

- Antigen regions that are recognised by the host immune cells are called epitopes. One antigen can have more than one epitope. Epitopes can be amino acids, sugars, fatty acids etc.
- B and T lymphocytes have receptors on their cell surfaces that bind to antigens. They are highly specific.



- Fab - Antigen binding fragment, Fc - crystalline fragment. Hypervariable regions are domains on immunoglobulin heavy and light chains variable regions that are in direct contact with antigen and are frequently mutated to allow diverse antigenic specificities to be recognized.
 - A monoclonal antibody (mAb or moAb) is an antibody made by cloning a unique white blood cell. All subsequent antibodies derived this way trace back to a unique parent cell. Monoclonal antibodies can have monovalent affinity, binding only to the same epitope (the part of an antigen that is recognized by the antibody).
3. Immune system
- First line - barriers, traps, elimination, unfavourable environment, lysozyme
 - Second line - NK cells, macrophages, complement system, inflammation
 - Third line - true acquired adaptive immunity, B and T cells
 - The major histocompatibility complex (MHC) binds an antigen derived from self-proteins, or from pathogens, and binding the antigen presentation to the cell surface for recognition by the appropriate T-cells. MHC is the tissue-antigen that allows the immune system (more specifically T cells) to bind to, recognize, and tolerate itself (autorecognition). MHC is also the chaperone for intracellular peptides that are complexed with MHCs and presented to T cell receptors (TCRs) as potential foreign antigens.



- Macrophages can also act as APCs along with dendritic cells.

- Humoural immunity is mediated by antibodies from B cells and cellular immunity is through T cells.
- Opsonization is the molecular mechanism whereby molecules, microbes, or apoptotic cells are chemically modified to have stronger interactions with cell surface receptors on phagocytes and antibodies.
- Antibodies contribute to immunity by opsonization, neutralization by binding to active sites, agglutination, precipitation of soluble antigens and activation of complement system.
- Plasma cells produce antibodies while memory B cells remain in the body with memory of antibodies and antigens.
- Secondary humoural immune response is faster and more intense than primary response.
- Helper T cells recruit B cells and cytotoxic T cells.

Week 12

1. Cytokines

- Cytokines are a broad and loose category of small proteins important in cell signaling. Cytokines are peptides and cannot cross the lipid bilayer of cells to enter the cytoplasm. Cytokines have been shown to be involved in autocrine, paracrine and endocrine signaling as immunomodulating agents.
- Autocrine (act on same self), paracrine (act on adjacent cells) and endocrine (act on distant target).
- Cytokines include chemokines, interferons, interleukins, lymphokines, and tumour necrosis factors.
- NK cells are unique, however, as they have the ability to recognize and kill stressed cells in the absence of antibodies and MHC, allowing for a much faster immune reaction.
- NK cells are cytotoxic; small granules in their cytoplasm contain proteins such as perforin and serine proteases known as granzymes. Upon release in close proximity to a cell slated for killing, perforin forms pores in the cell membrane of the target cell, creating an aqueous channel through which the granzymes and associated molecules can enter, inducing either apoptosis or osmotic cell lysis.
- NK cells are activated by cytokines such as interleukins and interferons.
- NK cells work to control viral infections by secreting IFN γ (interferon gamma) and TNF α (tumour necrosis factor alpha). IFN γ activates macrophages for phagocytosis and lysis, and TNF α acts to promote direct NK tumor cell killing.

- Some cytokines are pro-inflammatory and some are anti-inflammatory.
 - Mononuclear phagocytes (monocytes, macrophages and dendritic cells) are the primary sources of cytokines in innate immunity.
 - T lymphocytes are the primary sources of cytokines in acquired immunity.
 - Pleiotropic action of cytokines- when one cytokine produces more than one effect in different cells.
 - Redundant action of cytokines - When two or more cytokines produce the same effect because they act on the same receptors and pathways.
 - Synergistic action of cytokines - When two or more cytokines combine to produce an increased effect
 - Antagonist effect - when a cytokine blocks a receptor site
2. Toll-like receptors
- TLRs are considered to be pattern recognition receptors. Pattern Recognition Receptors (PRRs) are proteins capable of recognizing molecules frequently found in pathogens (the so-called Pathogen-Associated Molecular Patterns—PAMPs), or molecules released by damaged cells (the Damage-Associated Molecular Patterns—DAMPs). They emerged phylogenetically prior to the appearance of the adaptive immunity and, therefore, are considered part of the innate immune system.
 - They are single-pass membrane-spanning receptors usually expressed on sentinel cells such as macrophages and dendritic cells. They are found on the cell membrane and on the nuclear membrane (which detect nucleic acids)
 - There are 14 TLRs. TLR2 forms a heterodimer with TLR1 or TLR6. Others form homodimers. Different TLRs recognise different pathogen patterns.
 - For example. TLR4 is activated by lipopolysaccharides. TLRs 3,7,8 detect viral nucleic acids. Their TIR domains are in the cytoplasm while the receptor domains lie inside the nucleus.
 - The Toll/interleukin-1 receptor (TIR) homology domain is an intracellular signaling domain found in MyD88 (protein) interleukin-1 receptors, Toll receptors and many plant R proteins. It contains crucial proline residues.
 - After ligand binding, all TLRs apart from TLR3, interact with adaptor protein MyD88. Another adaptor protein, which is activated by TLR3 and TLR4, is called TIR domain-containing adaptor inducing IFN- β (TRIF). Subsequently, these proteins activate other transcription factors.
 - MyD88 adaptor recruits IRAK-1, IRAK-4 (interleukin receptor associated kinase) and TRAF-6 (TNF receptor associated factor)

- NF-κB is a protein complex that controls transcription of DNA, cytokine production and cell survival.

