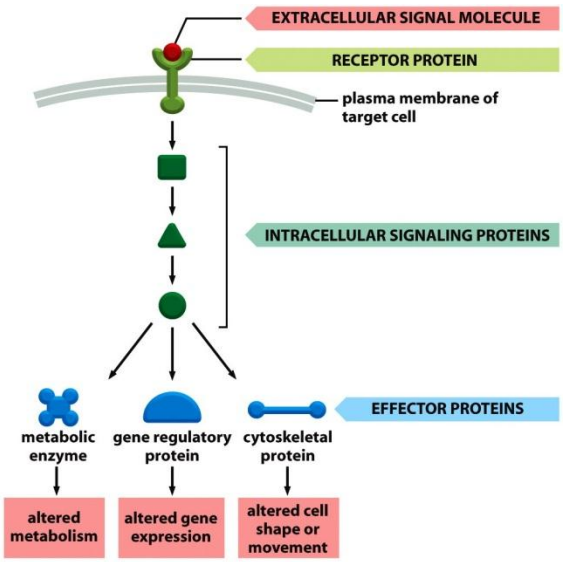
Topic 1

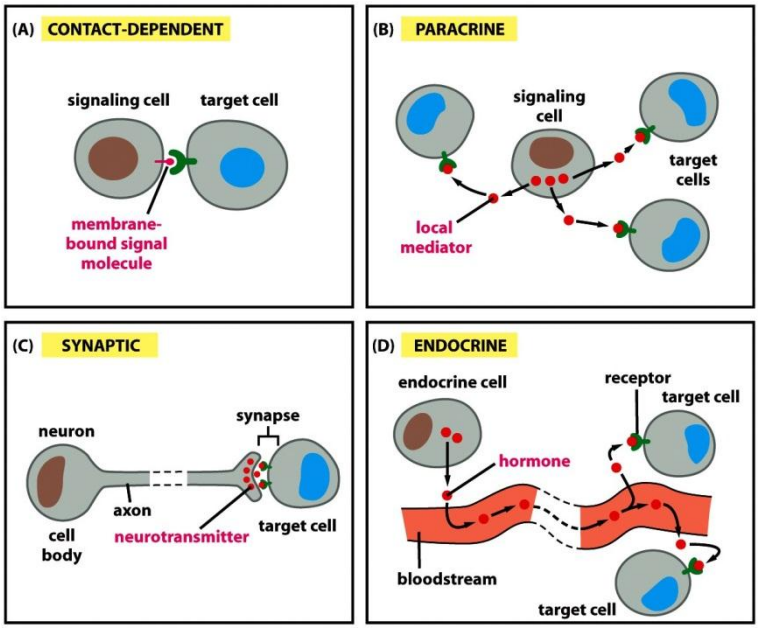
- **What is at cell, a bacterium, a virus**
  - *Cell:* The functional basic unit of life. Genome sequence, expression of a set of genes, reaction to external triggers.
  - *Bacterium:* No nucleus or organelles (prokaryotic), cell wall, flagellum
  - *Virus:* A small infectious agent that can replicate only inside the living cells of organisms. Have genes but no metabolism or cellular structure. “Organisms at the edge of life”.
- **What are cellular components and compartments**
  - *Cellular compartment:* Comprise all of the closed parts within the cytosol of a eukaryotic cell. E.g. most organelles
  - *Cellular component:* Unique, highly organized substances of which cells are composed. E.g. membranes, organelles, proteins, nucleic acids…
- **Proteins**
  - Consists of 20 types of amino acids in long chains also called polypeptides. The core of the polypeptide chain is referred to as the polypeptide backbone. Attached to this are the side chains with different properties like polarity, charge etc.. Because of these they fold into different shapes and get different functions. They can act as proteins, hormones etc. Everything we are is because of proteins.

Topic 2

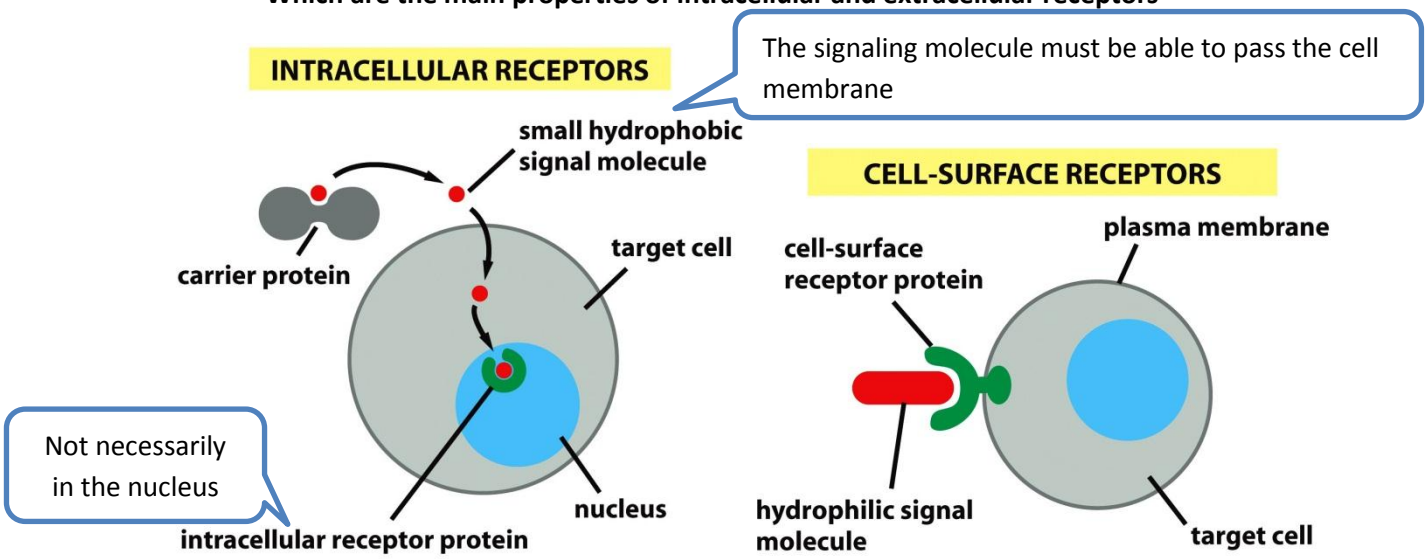
- **What are the different effects of signals**
  - The effects are:
    - Altered metabolism
    - Altered gene expression
    - Altered cell shape or movement



- **What are the main modes of signal transmission**
  - The four main modes of transmission are:
    - Contact-dependent
    - Paracrine
    - Synaptic
    - Endocrine

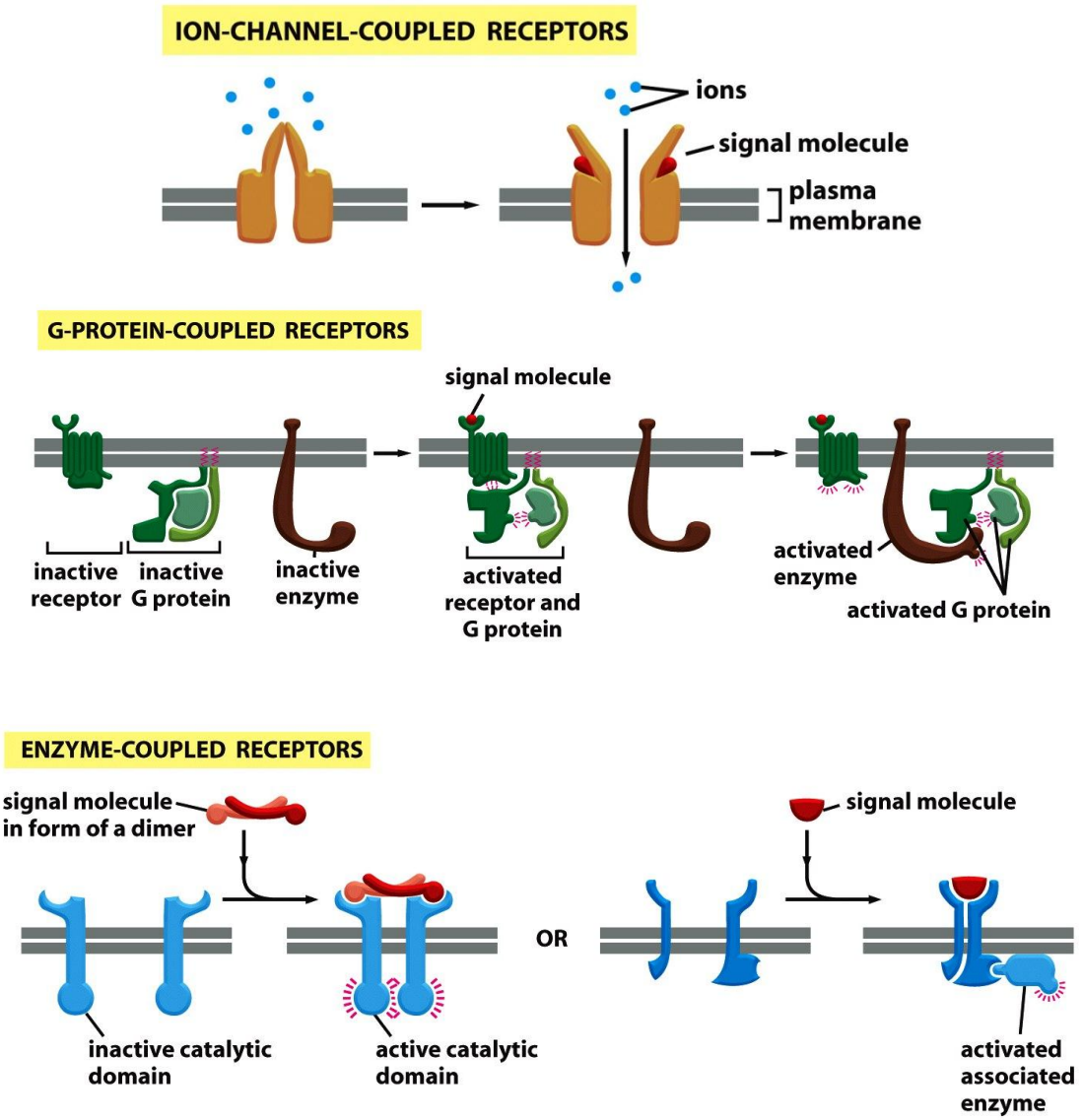


- **Importance of stability of signal molecule**
  - In paracrine signaling the signal must not go too far = signaling molecules are degraded or taken up quickly by neighboring cells. Short half-life of the signaling molecule and its intracellular transducers allow quick on/off. They are destroyed by extracellular enzymes or immobilized by the extracellular matrix.
- **Which are the main properties of intracellular and extracellular receptors**

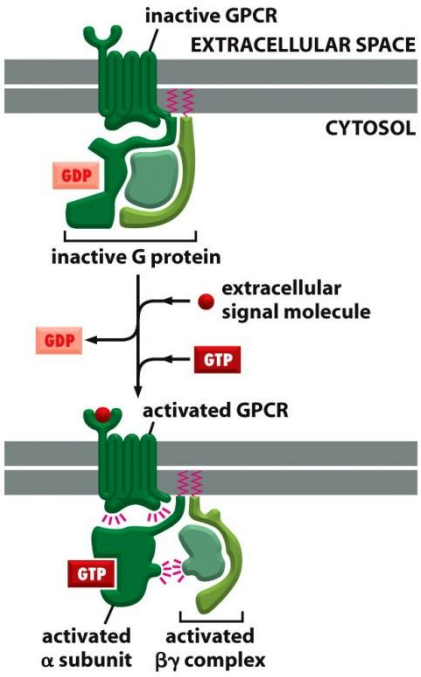


- **Each of the two different types of intracellular receptor/signal molecules**
  - 1: Nitric oxide NO, Carbon Monoxide CO
  - 2: Hydrophobic molecules (e.g. steroid hormones) Not necessarily in the nucleus

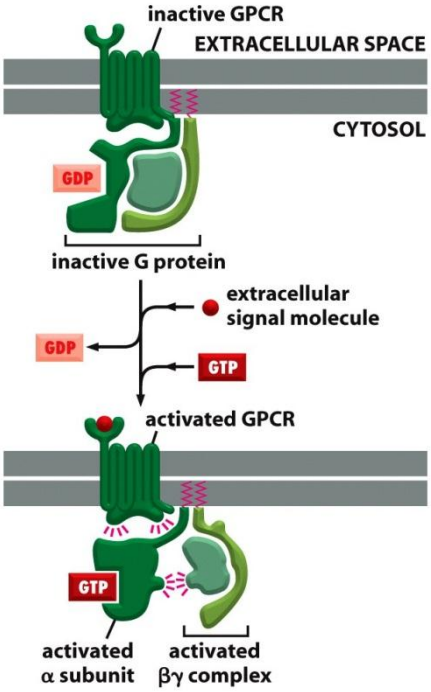
        - Bind to the respective receptor proteins and alter their ability to control transcription of specific genes.
- **Each of the three main classes of cell surface receptors**
    - *Ion –channel-coupled receptors*
        - Also called *transmitter-gated ion channels* or *ionotropic receptors.* They are involved in rapid synaptic signaling between nerve cells and other electrically excitable target cells such as nerve and muscle cells. This type of signaling is mediated by a small number of neurotransmitters that transiently open or close an ion channel formed by the protein to which they bind, briefly changing the permeability of the membrane of the plasma membrane and thereby the excitability of the postsynaptic target cell.
    - *G-protein-coupled receptors*
        - Act by indirectly regulating the activity if a separate plasma-membrane bound target protein, which is generally either an enzyme or an ion channel. A *trimeric GTP-binding protein (G protein)* mediates the interaction between the activated receptor and this target protein. The activation of the target protein can change the concentration of one or more small intracellular mediators (if the target protein is an enzyme), or it can change the ion permeability of the plasma membrane (if the target protein is an ion channel). The small intracellular mediators act in turn to alter the behavior of yet other signaling proteins in the cell. All of the G-protein-coupled receptors belong to a large family of homologous, multipass transmembrane proteins. 50% of all known drugs target these receptors.
    - *Enzyme-coupled receptors*
        - Either function directly as enzymes or associate directly with enzymes that they activate. They are usually single pass transmembrane proteins that have their ligand-binding site inside. Enzyme coupled receptors are heterogeneous in structure compared with the other two classes. The great majority, however, are either protein kinases or associate with protein kinases, which phosphorylate specific sets of proteins in the target cell when activated.

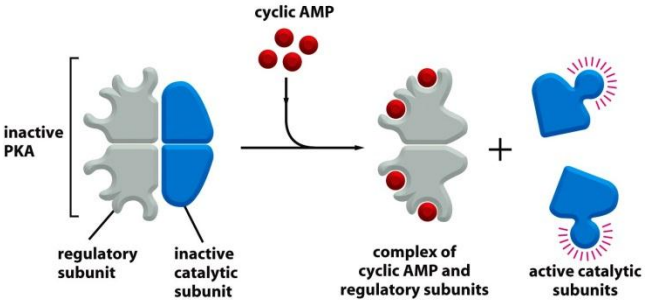


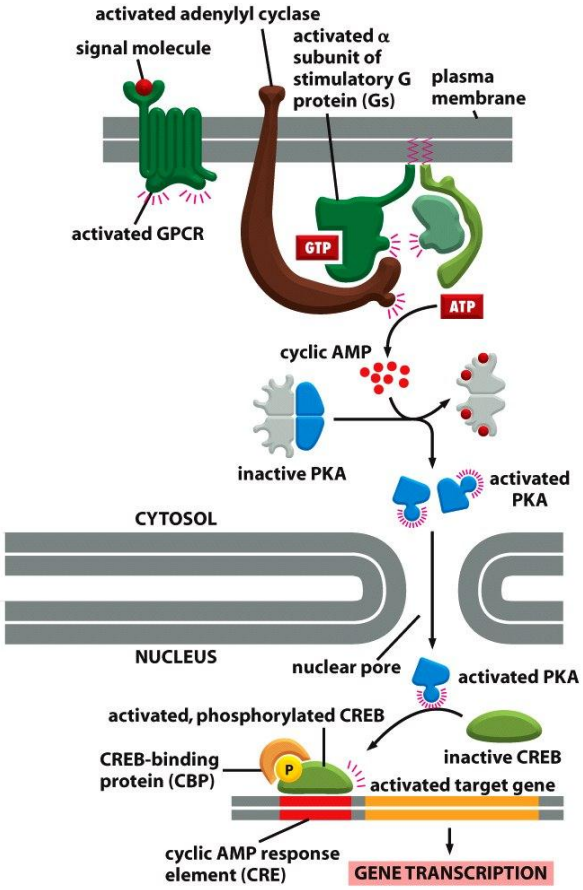
- **Mode of action of trimeric G proteins**
  - All eukaryotes use *G-protein-coupled receptors (GPCRs)*. These form the largest family of cell-surface receptors, and they mediate most responses to signals from the external world, as well as signals from other cells, including hormones, neurotransmitters, and local mediators. When an extracellular signal molecule binds to a GPCR, the receptor undergoes a conformational change that enables it to activate a trimeric *GTP-binding protein (G protein)*. The G protein is attached to the cytoplasmic face of the plasma membrane. There are various types of G proteins, each specific for a particular set of GPCRs and for a particular set of target proteins in the plasma membrane. They all have similar structure however and operate similarly. G proteins are composed of three different subunits α, β and γ. In the unstimulated state, the α subunit has GDP bound and the G protein is inactive. When a GPCR is activated, it acts like a guanine nucleotide exchange factor (GEF) and induces the α subunit to release its bound GDP, allowing GTP to bind in its place. This exchange causes a conformational change that changes the G protein, which activates it. GPCRs activate various intracellular signaling pathways, one example is the cAMP pathway.



- **cAMP pathway, mode of functioning of PKA**
  - *Cyclic AMP (cAMP)* acts as a small intracellular mediator in all prokaryotic and animal cells that have been studied. Its normal concentration in the cytosol is about 10^{-7} M, but an extracellular signal can increase this concentration more than twentyfold in seconds. GPCRs that act by increasing cyclic AMP are coupled to a *stimulatory G protein (G_s)*, which activates adenyl cyclase and thereby increases cyclic AMP concentration. Another G protein called *inhibitory G protein (G_i)*, inhibits adenyl cyclase, but it acts mainly by directly regulating ion channels. In most animal cells, cyclic AMP exerts its effects by activating *cyclic AMP-dependent protein kinase (PKA)*. This kinase phosphorylates specific proteins and effector proteins, thereby regulating their activity. In the inactive state, PKA consists of a complex of two catalytic subunits and two regulatory subunits. The binding of cyclic AMP to the regulatory subunits alters their conformation, causing them to dissociate from the complex. The released catalytic subunits are thereby activated to phosphorylate specific target proteins.


inactive GPCR
EXTRACELLULAR SPACE
CYTOSOL
GDP
inactive G protein
extracellular signal molecule
GDP
GTP
activated GPCR
GTP
activated α subunit
activated βγ complex

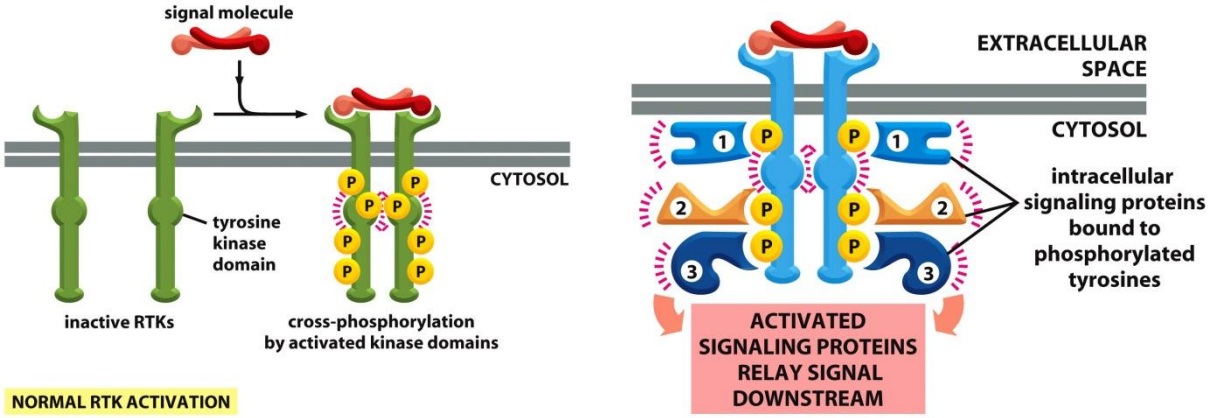

cyclic AMP
inactive PKA
regulatory subunit
inactive catalytic subunit
complex of cyclic AMP and regulatory subunits
active catalytic subunits


activated adenylyl cyclase
signal molecule
activated α subunit of stimulatory G protein (Gs)
plasma membrane
activated GPCR
GTP
ATP
cyclic AMP
inactive PKA
activated PKA
CYTOSOL
NUCLEUS
nuclear pore
activated PKA
activated, phosphorylated CREB
inactive CREB
CREB-binding protein (CBP)
P
activated target gene
cyclic AMP response element (CRE)
GENE TRANSCRIPTION

- **Other types of second messengers (without knowing specific mechanisms)**

Molecule	Produced by	Produced from	Acts on
Inisitol triphosphate (IP_3)	Phospholipase C-β (PLCβ)	Phosphatidylinositol bisphosphate (PIP_2)	ER Ca^{++} channels
Diacylglycerol	Phospholipase C-β (PLCβ)	Phosphatidylinositol bisphosphate (PIP_2)	Protein Kinase C (PKC)
Ca^{++}	ER Ca^{++} channels	ER	Calmodulin and many others

- **Mode of action of Receptor-tyrosine kinases**
  - Many extracellular signal proteins act through *receptor tyrosine kinases (RTKs)*. For many RTKs, ligand binding causes the receptor chains to dimerize, bringing the kinase domains of two receptor chains together so that they can become activated and cross-phosphorylate each other on multiple tyrosines, a process referred to as *transautophosphorylation*. The cross-phosphorylation of adjacent cytosolic tails of RTKs contributes to the receptor activation process in two ways. First, phosphorylation of tyrosines within the kinase domain increases the activity of the enzyme. Second, phosphorylation of tyrosines outside the kinase domain creates high affinity docking sites for the binding specific intracellular signaling proteins. Each of the signaling proteins bind to specific phosphorylated sites on the activated receptors because it contains specific phosphotyrosine-binding domain that recognizes surrounding features of the polypeptide chain in addition to the phophotyrosine. Once bound to the activated RTK, a signaling protein may itself become phosphorylated on tyrosines and thereby be activated. In many cases, however, the binding alone may be sufficient to activate the docked signaling protein, by either inducing a conformational change in the protein or simply bringing it near the protein that is next to the signaling pathway. Thus, transautophosphorylation serves as a switch to trigger the transient assembly of an intracellular signaling complex, which can then relay the signal onward, often along multiple routes, to various destinations in the cell.



Topic 3

- **What is a tissue, what are the mammalian tissues**
  - Collection of cells (not necessarily identical) coming from the same origin and having together a specific role
  1. **Epithelial tissue:** Flat sheets of closely packed cells lining the surface of the body (part of skin) and inner surfaces and organs. Derived from:
     a. Ectoderm- skin, mouth, and nasal linings
     b. Mesoderm- mesothelia (pleura, peritoneum and pericardium) and endothelia (inner lining of the heart and vessels)
     c. Endoderm- GI and urinary tract, vagina, exocrine glands
  2. **Muscle tissue**
     a. Skeletal muscle
     b. Smooth muscle
     c. Cardiac muscle
  3. **Connective tissue**
     a. Supportive tissues: cartilage and bone
     b. Dense connective tissue: tendons and ligaments
     c. Loose connective tissue: fascia (collagen and elastin sheets)
     d. Adipose tissue: WAT and BAT
  4. **Nerve tissue**
     a. Nerve cells- neurons
     b. Glial cells- glia (Schwann cells, oligodendrocytes, astrocytes) (microglia)
  5. **Blood**
     a. Erythrocytes- RBC
     b. Leukocytes- white blood cells
     c. Thrombocytes- platelets
- **What is an organ, what are the mammalian organs and organ systems**
  - Organum/organon = instrument, tool
  - Collection of cells and tissues (can be several types) united into a functional structure

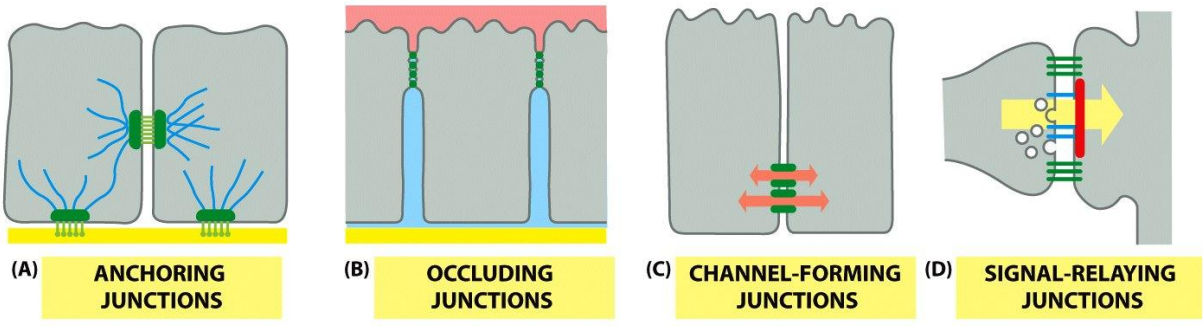
Organ system	Role	Components
1. Skeletal s.	Support locomotion (body) + protection, attachment (organs)	Bones, cartilages, tendonds, ligaments
2. Muscular s.	Movement (body, organs)	Muscles
3. Circulatory s.	Transport (nutrients, waste, gases, hormones)	Heart, blood, vessels
4. Nervous s.	Transmission of electrical signals that control physiology	Brain, spinal cord, nerves
5. Respiratory s.	Exchange of gases	Upper respiratory ducts, lungs
6. Digestive s.	Breakdown and adsorption of nutrients and water	Mouth, esophagus, stomach, small and large intestines
7. Excretory s.	Removal of waste molecules from circulation	Kidneys, ureters, bladder and urethra
8. Endocrine s.	Transmission of chemical signals (hormones)	Hypothalamus, pituitary, thyroid, pancreas, adrenal glands

9. Reproductive s.	Production of reproductive cells and embryonic/fetal development	F: ovaries, oviducts, uterus, vagina and mammary glands. M: testes, seminal vesicles and penis
10. Lymphatic and immune s.	Identification, destruction and removal of non-self	Lymph, lymph nodes and vessels, white blood cells, T- and B-cells.
11. Integumentary s.	Protection, regulation of temperature, sensory receptors	Skin and appendages (hair, nails)

- **Cell junctions- 4 types: what they are, how they are made, what proteins are making these structures and how they work together, what are their roles**

Table 19–1 A Functional Classification of Cell Junctions

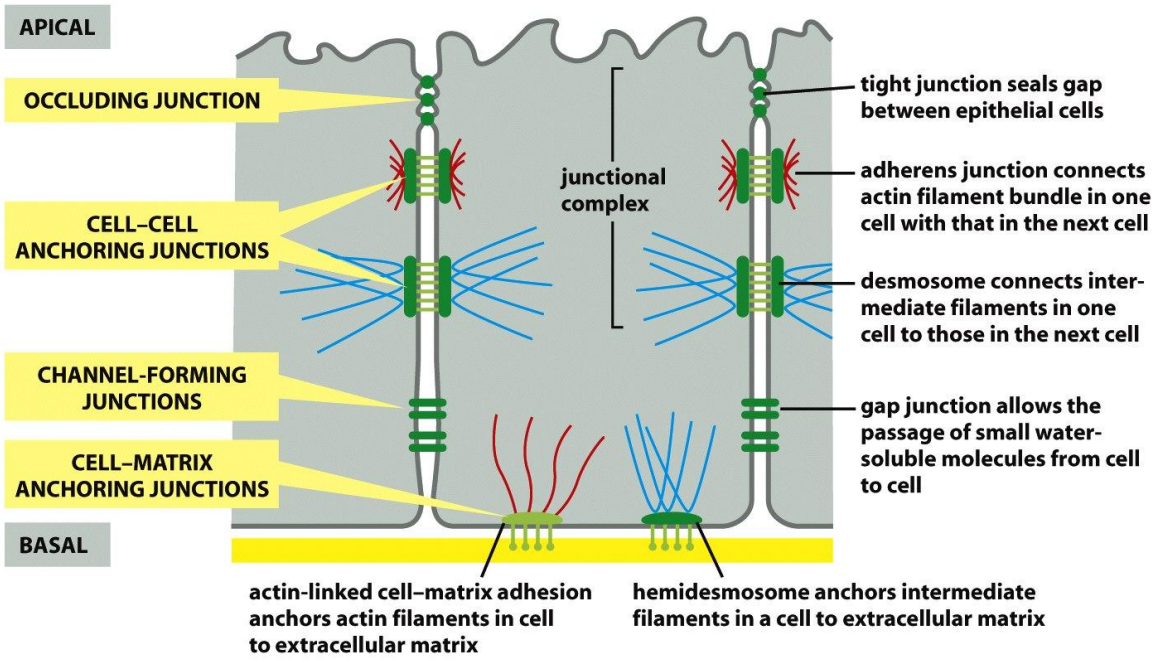
ANCHORING JUNCTIONS
Actin filament attachment sites
1. cell–cell junctions (adherens junctions)
2. cell–matrix junctions (actin-linked cell–matrix adhesions)
Intermediate filament attachment sites
1. cell–cell junctions (desmosomes)
2. cell–matrix junctions (hemidesmosomes)
OCCLUDING JUNCTIONS
1. tight junctions (in vertebrates)
2. septate junctions (in invertebrates)
CHANNEL-FORMING JUNCTIONS
1. gap junctions (in animals)
2. plasmodesmata (in plants)
SIGNAL-RELAYING JUNCTIONS
1. chemical synapses (in the nervous system)
2. immunological synapses (in the immune system)
3. transmembrane ligand–receptor cell–cell signaling contacts (Delta-Notch, ephrin-Eph, etc.). Anchoring, occluding, and channel-forming junctions can all have signaling functions in addition to their structural roles



(A) Anchoring junctions link cell to cell (typically via transmembrane *cadherine* proteins. (B) Occluding junctions (involving *claudin* proteins) seal gaps between epithelial cells. (C) Channel-forming junctions (composed of *connexin* or *innexin* proteins) form passageways for small molecules and ions

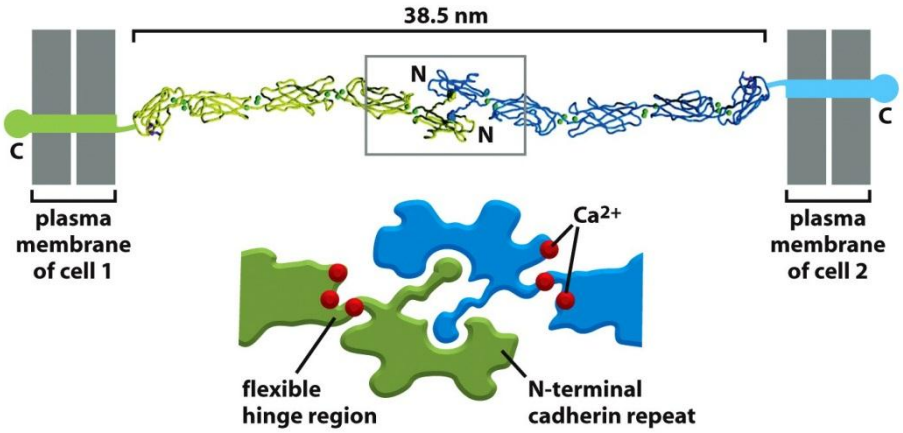
to pass from cell to cell. (D) Signal-relaying junctions are complex structures, typically involving anchorage proteins alongside proteins mediating signal transduction

Closest to the apex lie occluding junctions, preventing molecules from leaking across the epithelium through gaps between the cells. Below these are two types of cell-cell adhesions. **Adherens junctions** are anchorage sites for actin filaments; **desmosome junctions** are anchorage sites for intermediate filaments. Still lower, often mingled with additional desmosome junctions, lie channel-forming junctions called *gap junctions*.



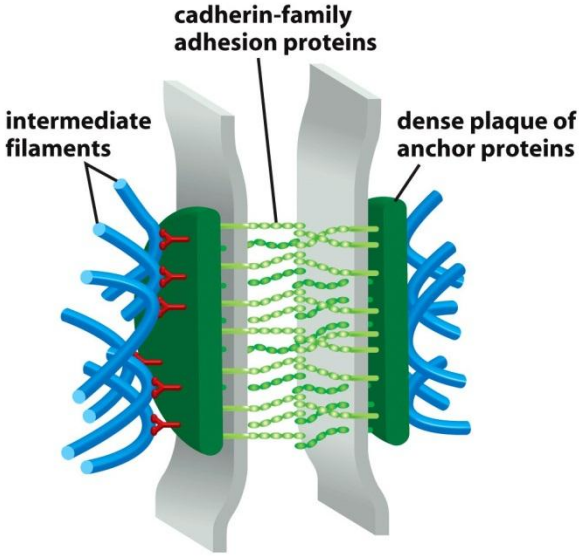
At each of the four types of anchoring junctions, the central role is played by **transmembrane adhesion proteins** that span the membrane, with one end linking to the cytoskeleton inside the cell and the other end linking to other structures outside it. These cytoskeleton-linked membrane molecules fall neatly into two superfamilies, corresponding to the two basic kinds of external attachment. Proteins of the **cadherin** superfamily chiefly mediate attachment of cell to cell. Proteins of the **integrin** family chiefly mediate attachment of cells to matrix. The cadherins take their name from their dependence on Ca^{2+} ions: removing Ca^{2+} from the extracellular medium causes adhesions mediated by cadherins to come adrift.

Anchoring junctions between cells are usually symmetrical: if the linkage is to actin, for example, in the cell on one side of the junction, it will be actin in the cell on the other side also. Unlike receptors for soluble signal molecules, which bind their specific ligand with high affinity, cadherins (and most other cell-cell adhesion proteins) typically bind to their partners with relatively low affinity. Strong attachments result from the formation of many such weak bonds in parallel. Cadherins form specific homophiilic attachments, and this explains why there are so many different family members. Cadherins are not like glue, making cell surfaces generally sticky. Rather, they mediate high selective recognition, enabling cells of a similar type to stick together and to stay segregated from other types of cells.

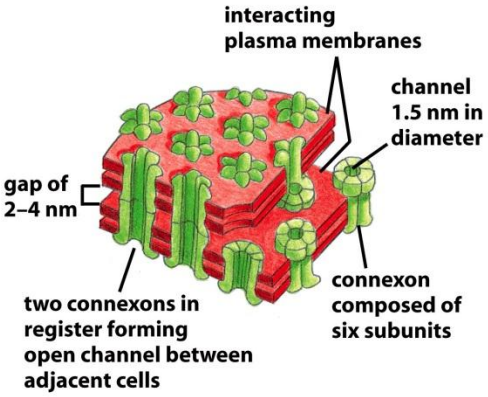


Adherens junctions are an essential part of the machinery for modeling the shapes of multicellular structures in the animal body. By indirectly linking the actin filaments in one cell to those in its neighbors, they enable the cells on the tissue to use their actin cytoskeletons in a coordinated way.

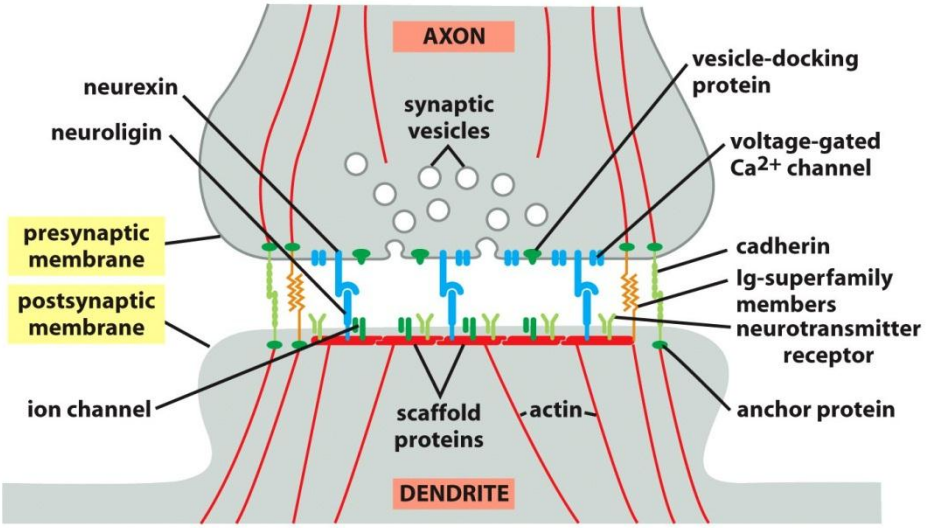
Desmosome junctions are structurally similar to adherens junctions but link to intermediate filaments instead of actin. Their main function is to provide mechanical strength.



Gap junctions are bridging gaps between cells, allowing small water-soluble molecules (ions, metabolites) to diffuse between the cytoplasm of neighboring cells. Channels are made of *connexin* and *innexins.*

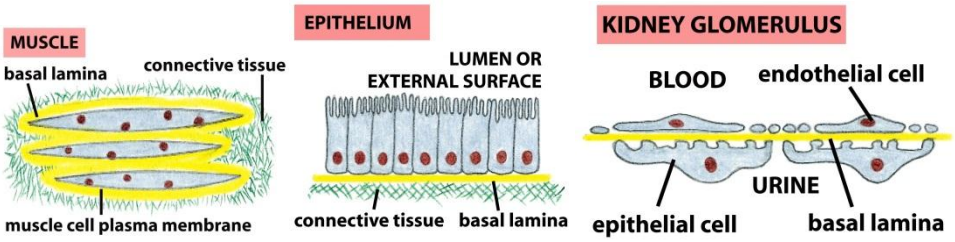


Cells of the nervous system rely on complex systems of adhesion molecules. Thus, cadherins are generally present, concentrated at spots around the periphery of the synapse and within it, and various other types of adhesion molecules. **Scaffold proteins** are thought to have a central role in recruiting all the components for the synapse and holding them in place. One domain of a scaffold proteins may attach to a cell-cell adhesion protein, while another latches onto a ligand-gated ion channel or to another scaffold protein. In this way the cell can assemble a mat of proteins, with all the components that are needed at the synapse woven into its fabric.



- **Basal lamina- Role, structure, function, what is it made of and how**
  - 40-120 nm thick
  - Surrounds individual muscle cells, adipocytes and Schwann cells
  - Can function as selective filter
  - Determine cell polarity, influence cell metabolism, organize proteins in the cell membrane, promote cell survival, proliferation and differentiation, influence cell migration

The basal lamina is synthesized by the cells on each side of it: the epithelial cells contribute to one set of basal lamina components, while the cells of the underlying bed of connective tissue contribute another.

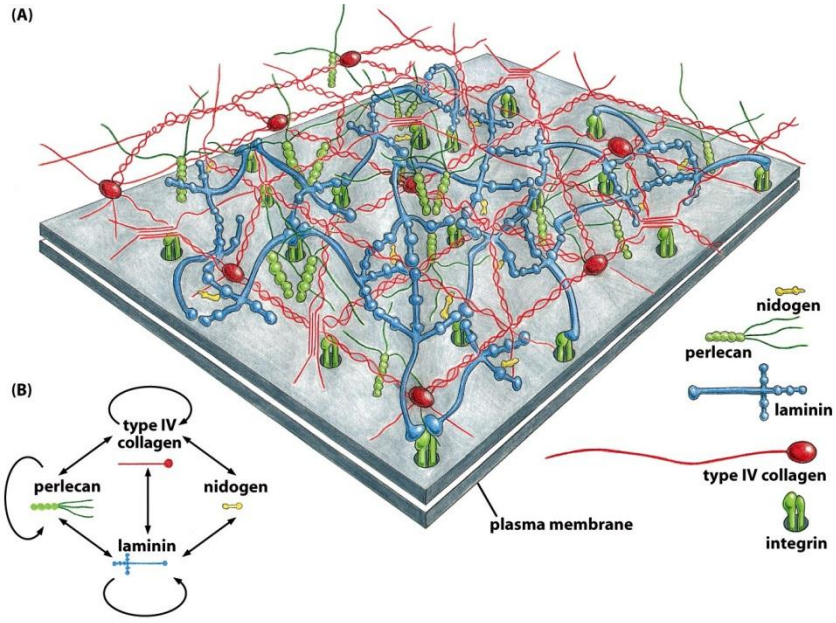


BL is made of 2 classes of extracellular macromolecules:

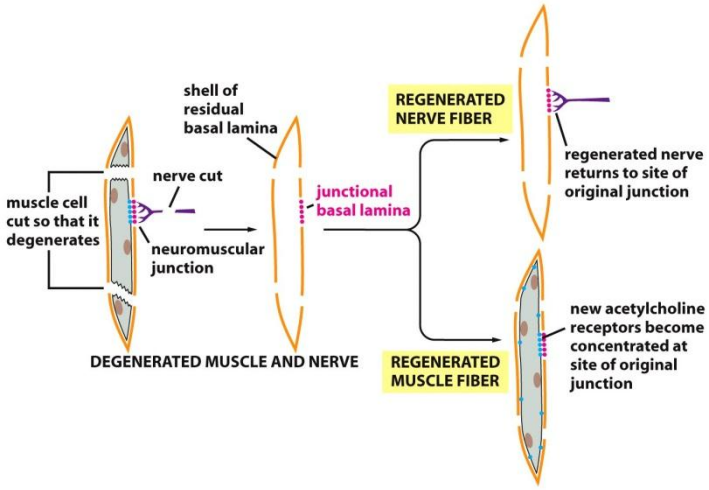
1. Fibrous glycoproteins – long proteins with shirt oligosaccharide side chains
   a. Laminin - α, β, γ chains held by S-S bonds
   b.

c. Nidogen

2. Glycosaminoglycans (GAG) linked to core proteins, forming **proteoglycans**
    a. **Perlecan**



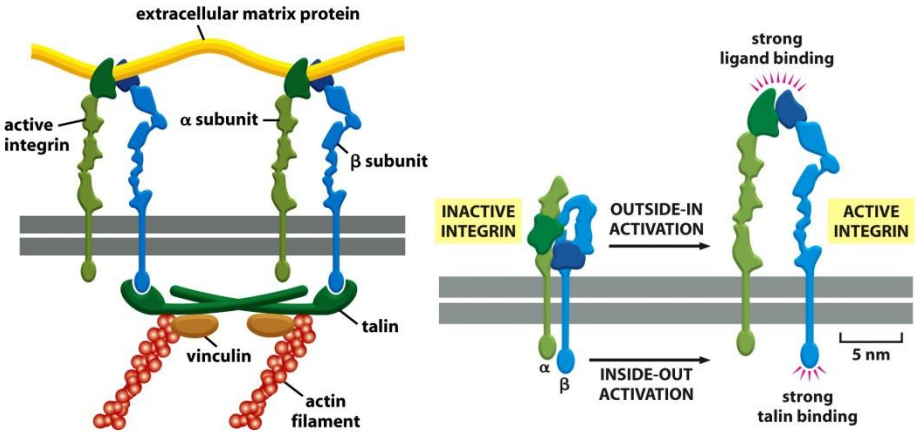
- Selective sieve for molecules and cells: Fibroblasts cannot move from connective tissues to the epithelium but macrophages can, as well as lymphocytes or nerve endings, cutting through it with special enzymes.
- Direction of regeneration



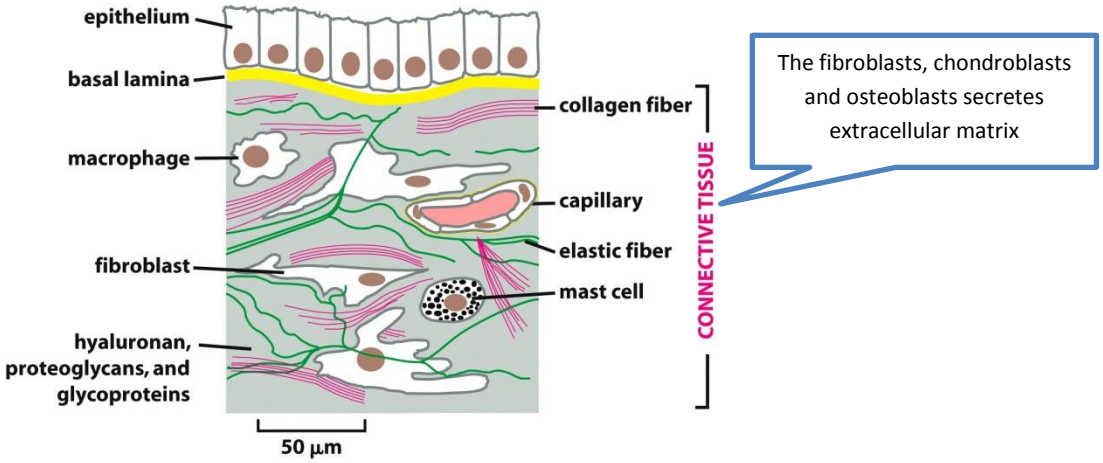
- **Integrins**
    - Cells interact with basal lamina via integrins

24 types in human, all similar

α and β glycoprotein subunits, noncovalently associated, cinformational changes make the two arms work like a “clamp”



- **Extracellular matrix – what is it, who makes it, what is it made of, what is its role**
  - Cells secrete proteins and polysaccharides
  - Connective tissue: a lot of matrix, a few cells , (bone, tendon), collagen



Consists of: Proteoglycans (GAG linked to core proteins) and proteins (collagen, elastin) + filling with **hyaluronan**

- **GAG make hydrated gels**
  - Glycoaminoglycans: unbranched polysaccharide chains, made of repeating disaccharide units (amino sugar + uronic acid)
  - Highly negatively charged (polyanion): most anionic molecules produced by animal tissues
  - Linear, extended → take a lot of volume
  - Hydrophilic → bind water → make gels

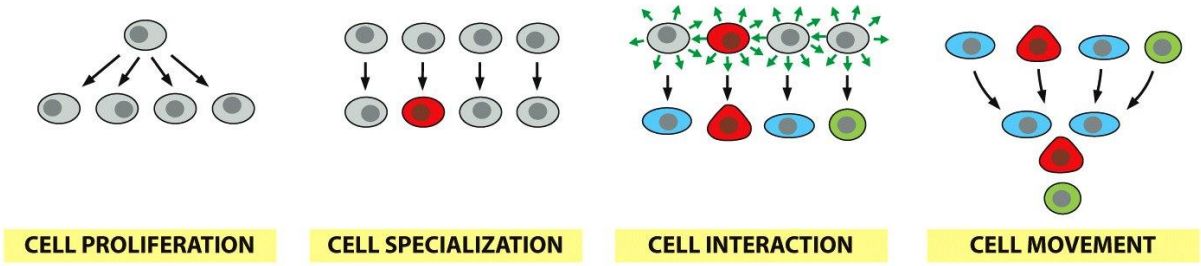
  Different types: hyalkronan, chondroitin sulphate/dermatan sulphate, eparan sulphate, keratin sulphate

- **Hyaluronan: a simple GAG**
  - 25 000 disacharide units
  - Not linked to a core protein

    - Resists compressive forces in tissues and joints, important space filler in embryos
- **Proteoglycans**
    - GAG chains linked to a core protein
    - Molecular and selective (size and charge) sieve (gel)
    - Signaling: binding of signal molecules (growth factors) that regulates the localization, activation and lifetime of the signal.
- **Collagens**
    - Fibrous proteins
    - In all multicellular animals
    - Secreted by many cells
    - 25% of the total proteins mass of the body
    - Long, stiff, triple stranded helical structure = superhelix
- **Elastic fibers**
    - Elastic fibers: skin, blood vessels, lungs
    - 5x more elastic than rubberband
    - Made of: elastin + microfibrils

Topic 4

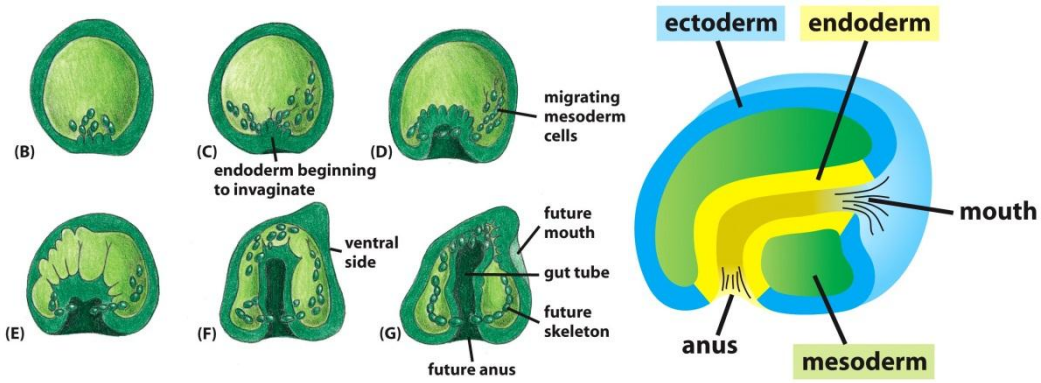
- **Processes that are driving the multicellularity – 4**
  - *Cell proliferation*: Producing many cells from one
  - *Cell specialization*: creating cells with different characteristics at different positions
  - *Cell interactions*: coordinating the behavior of one cell with that of its neighbors
  - *Cell movement*: rearranging the cells to form structured tissues and organs



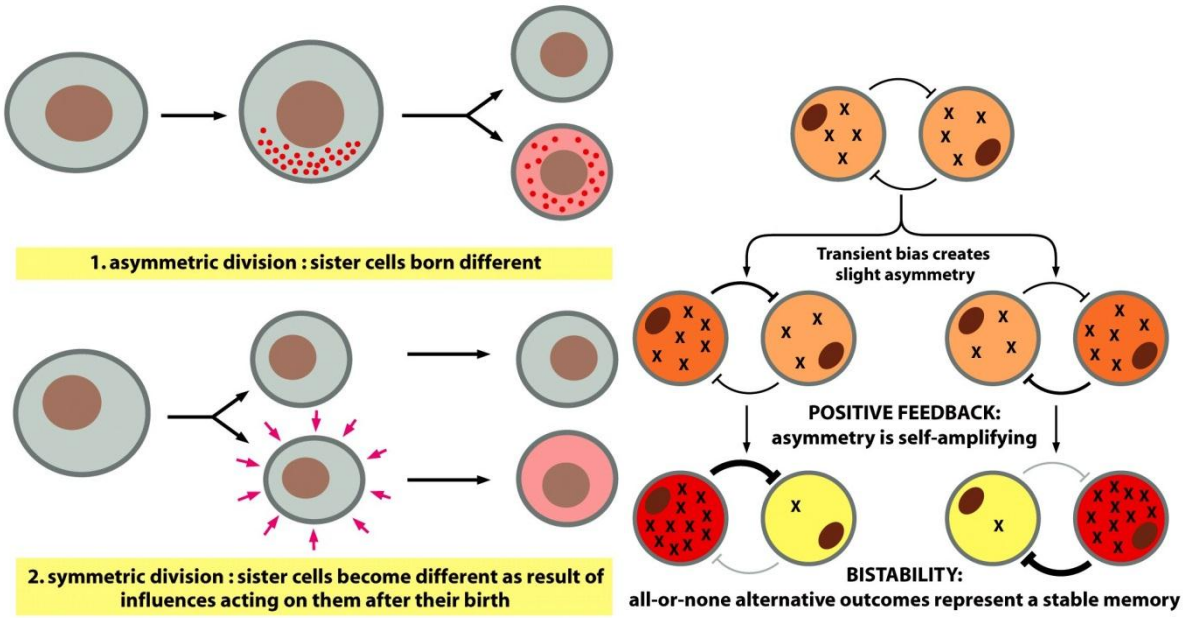
- **How are we (all living cells) similar – at what level**
  - Same method to make all
  - Not only principles are conserved but entire pathways and molecules
    - Homologous proteins are interchangeable between species
      - the protein (Engrailed-1) from the fly can develop cerebellum in mice
      - the protein (Pax6) from a squid or mouse can develop an eye in the fly

  - **Gastrulation**
    - The common ancestor had a set of genes that are preserved: involved in structures, epidermal cells, gut cells, muscle cells, neurons
    - Common to all animals: outer layer of skin, a feeding tube, muscle and neuron in between
    - Gastrulation: universal feature of animal development:
      - *Ectoderm*: epidermis and nervous system
      - *Endoderm*: gut and appendages (liver, lungs etc)
      - *Mesoderm*: muscles, connective tissues
- **How are we (all living cells) different – at what level**
  - Sequencing of genomes
    - *Caenorhabditis elegans, Drosophila melanogaster, Homo sapiens*
  - Vertebrates' tree is 600 million years distant
    - *Worm*: 20 000 genes
    - *Fly*: 14 000 genes
    - *Human*: 25 000 genes
  - A kit can build many different models
    - Genes=proteins=similar
    - Noncoding DNA, regulatory sequences = instructions for kit, more specific sequences
- **What is gastrulation and what are 3 germinative layers**

- *Gastrulation*: the transformations of a simple ball or hollow into a structure with a gut
- *3 germinative layers*
    - **Ectoderm:** the precursor of the epidermis and of the nervous system
    - **Endoderm**: the precursor of the gut and its appendages, such as lung and liver
    - **Mesoderm**: the precursor of muscles, connective tissues, and various other components

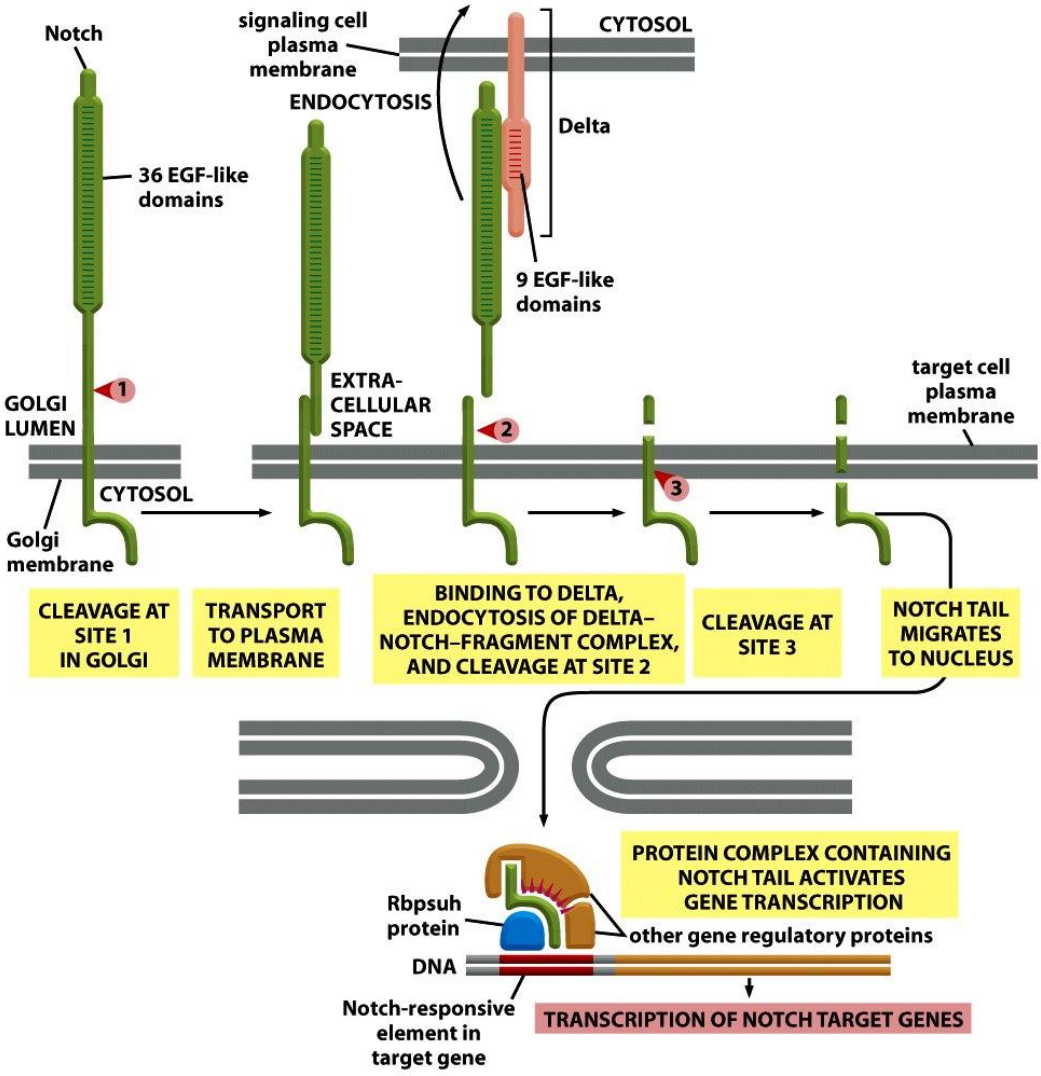


- **What is asymmetry in biological development, what are causes of it and what are the consequences**
    - To create initial states and cells that are not identical
    - Positive feedback can accentuate the slight differences that are originally due to external bias or inherent fluctuations of the system (noise)
    - Some significant set of molecules is divided unequally between two cells at the time of division.
    - Positive feedback can create asymmetry where there was none

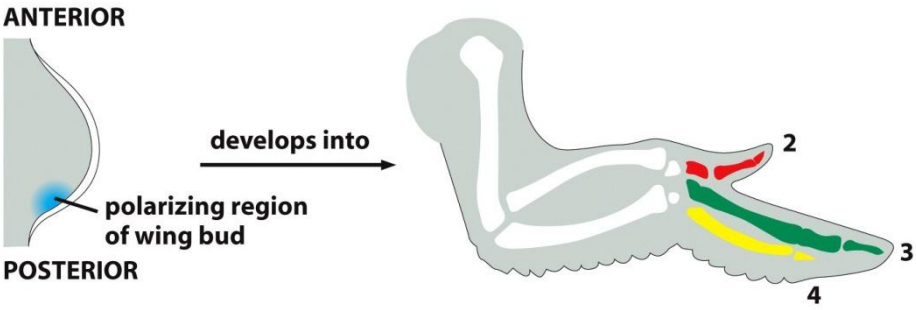


- A general principle of how diversification is produced in animal tissues
- Mediated by Notch signaling

- **What is Notch signaling**
  - Has a general role in controlling the cell fate choices and regulating patterns formations during the development of most tissues, as well as continual renewal of tissues such as the lining of the gut.
  - When a precursor cell commits to become becoming a nerve cell, it signals to its immediate neighbors not to do the same. This process is called *lateral inhibition*, and is a contact-dependent signaling mechanism that is activated by a signal protein called **Delta**, displayed on the surface of the future neural cell.



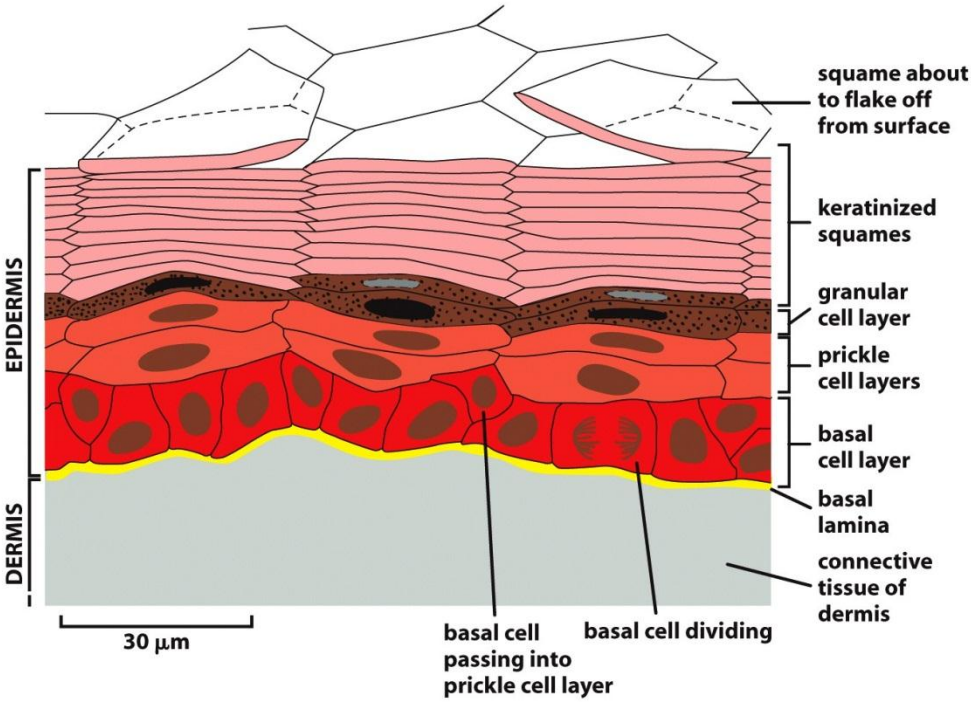
- **What are morphogens and what do they do**
  - Signal molecules often govern a simple yes-no choice depending on if the concentration of the signal molecule is high or low. In many cases responses are more finely graded: a high concentration may direct target cells into one developmental pathway, an intermediate concentration into another, and a low concentration into yet another. An important case is that in which the signal molecule diffuses out from a localized signaling center, creating a signal concentration gradient. Cells at different distances from the source are driven to develop in different way according to the concentration that they experience. A signal molecule that imposes a pattern on a whole field of cells in this way is called a **morphogen**. Vertebrates limbs is one example.



- **Worm (know the name) as a model, why and how it is a model, examples from worm regulations**
    - *Caenorhabditis elegans*
    - Benefits: Ceap, easy, transparent, small, rapid cycle
    - Drawbacks: Lack of more complex organs (heart, eye, limb etc)
- **Fly (know the name) as a model, why and how it is a model, examples from fly regulations**
    - *Drosophila melanogaster*
    - 100x more cells than the worm
    - less genes than the worm(14 000 vs 20 000)
    - Almost 2x more DNA/gene than the worm (in average, genes of 10 000 nt vs 5 000 nt)
    - The kit is almost the same, the instructions are bigger
- **Frog (know the name) as a model, why and how it is a model, examples from frog regulations**
    - *Xenopus laevis*
    - Vertebrate
    - Big egg cell (over 1 mm)
- **Mouse (know the name) as a model, why and how it is a model, examples from mouse regulations**
    - *Mus musculus*
    - Model mammal
    - Distant from human ca 100 million years
    - Similar genome size
    - 80-90% homology (protein)
    - Large similarities with human regulatory sequences

Topic 5

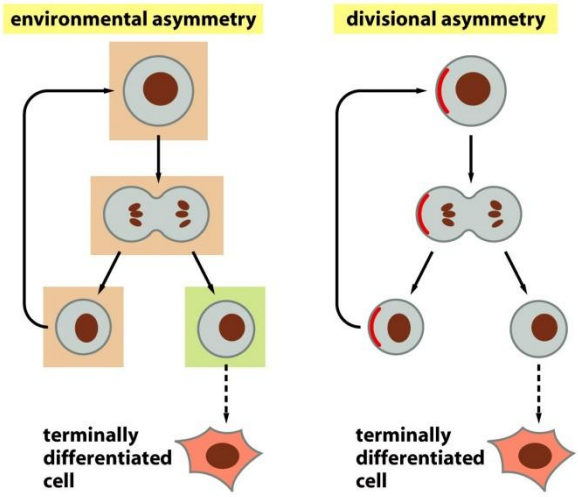
- **What are tissues, what do they derive from**
  - Non-free living cells specialized for multicellularity, 200 cell types in the human body.
  - Derived from:
    - Ectoderm: **epidermis, sensory epithelia**
    - Endoderm: gut and its appendages (airways, glands → **liver**)
    - Mesoderm: endothelia (lymphatic and vascular system), **blood cells**
- **How is epidermis made and maintained**
  - The interfollicular epidermis is a multilayered (stratified) epithelium composed of keratinocytes (so named because their characteristic differentiated activity is the synthesis of keratin intermediate filament proteins, which give the epidermis its toughness). Down at the bottom closest to the basal lamina is the *basal cell* layer which contains the stem cells that are necessary for maintaining and renewing the epidermis. Above the basal cells there are several layers of *prickle cells* – each a site of anchorage for thick tufts of keratin filaments. Beyond the prickle cells lies the thin, darkly staining *granular cell* layer. It is at this lever that the cells are sealed together to form a waterproof barrier. The granular layer with its barrier to the movement of water and solutes, marks the boundary between the inner, metabolically active strata and the outermost layer of the epidermis, consisting of dead cells whose intracellular organelles have disappeared. These outermost cells are reduced to flattened scales, or *squames*, filled with densely packed keratin.



In the basal layer, there always have to be cells that can remain undifferentiated and carry on dividing, these are called **stem cells**. The defining properties of a stem cell are as follows:

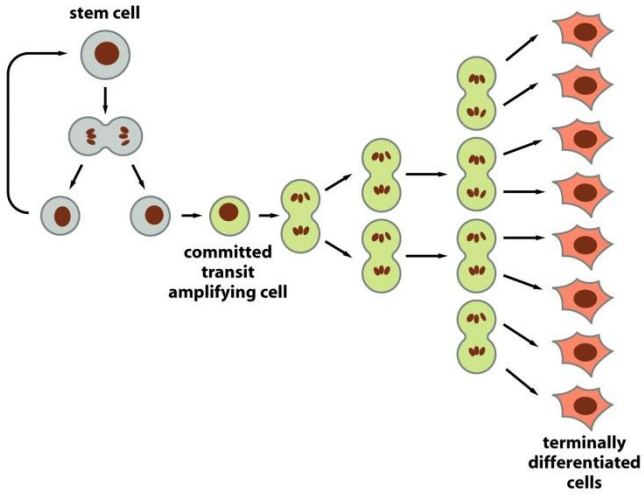
1. It is not itself terminally differentiated

2. It can divide without limit
3. When it divides, each daughter has a choice: it can either remain a stem cell, or it can embark on a course that commits it to terminal differentiation.



If a patch of epidermis is destroyed, the surrounding epidermal cells repair the damage by migrating in and proliferating to cover the denuded area. In this process, a new self-renewing patch of epidermis is established, implying that additional stem cells have been generated to make of for the loss. These must have been produced by symmetric divisions in which one stem cell gives rise to two.

Stem cells in many tissues divide only rarely but give rise to **transit amplifying cells** – daughters committed to differentiation that go through a limited series of more rapid divisions before completing the process.

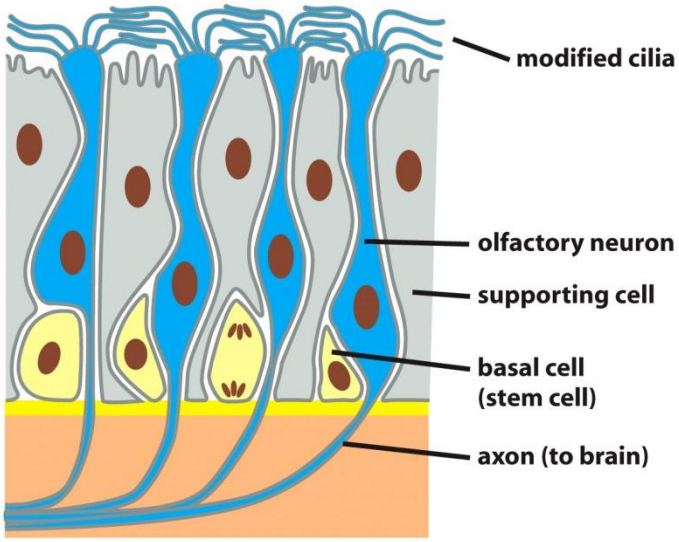


- **What are 3 sensory epithelia, what are the cells, proteins, components- 3**
  - Sensory tissues of nose, ears and eyes
  - Detection of smell (olfactory sensory neurons), sound (auditory hair cells) and light (photoreceptors)

Within each sensory epithelium lie sensory cells that act as transducers, converting signals from the outside world into an electrical form that the nervous system can interpret. All of these cell types are either neurons or neuron-like. Each carries at its

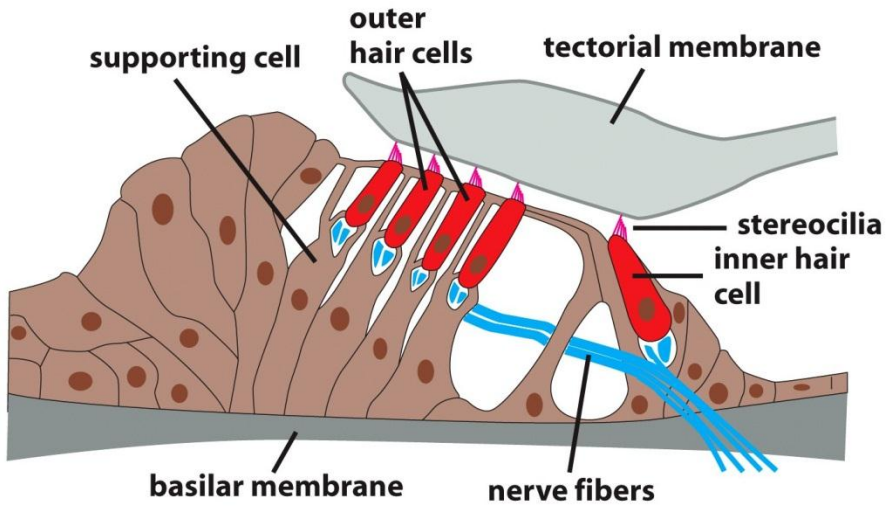
apical end a specialized structure that detects the external stimulus and converts it to a change in the membrane potential. At its basal end, each makes synapses with neurons that relay the sensory information to specific sites in the brain.

- **Olfactory system – what is the basic functional unit, how does it work**
  - In the olfactory epithelium of the nose, a subset of epitherial cells differentiate as **olfactory sensory neurons**. These cells have modified, immotile cilia on their free surfaces, containing odorant *odorant receptor proteins,* and a single axon extending from their basal end toward the brain. *Supportive cells* that span the thickened epithelium and have properties similar to those of glial cells in the central nervous system hold the neurons in place and separate them from one another. The sensory surfaces are kept moist and protected by a layer of fluid secreted bya cells sequestered in glands glands that communicate with the exposed surface. Even with this protection, however, each olfactory neuron survives only for a month or two, and a third class of cells – *basal cells* – is present in the epithelium to generate replacemants for the olfactory neurons that are lost.

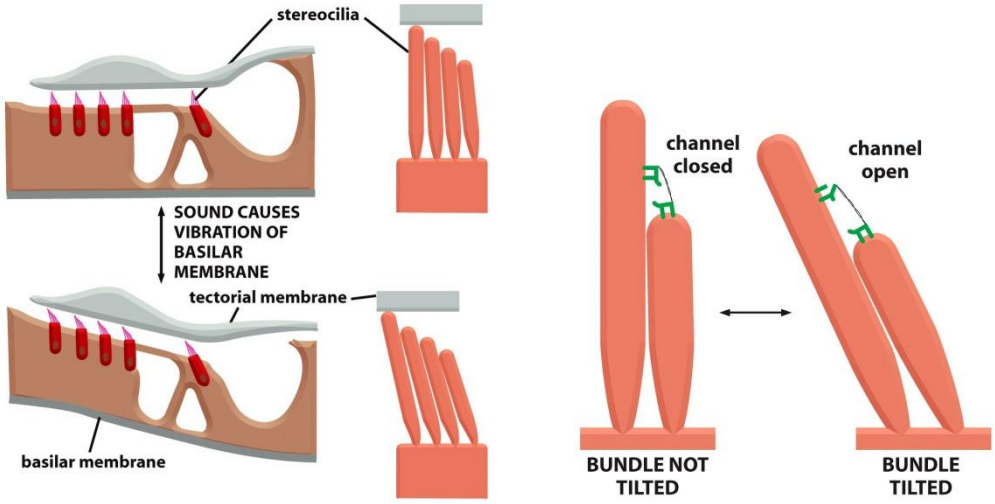


An olfactory neuron most probably only responds to one particular class of odorants, sharing some structural feature that the odorant receptor protein recognizes. Regardless of the odor, every olfactory neuron responds in the same way and sends a train of action potential back along its axon to the brain, the discriminating sensibility of an individual olfactory neuron is therefor useful only if its axon delivers its message to the specific relay station in the brain that is dedicated to the particular range of odors that the neuron senses. These relay stations are called *glomeruli*. They are located in structures called the *olfactory bulbs* (one on each side of the brain). As new olfactory neurons are generated, replacing those that die, they must in turn send their axons to the correct glomerulus. The odorant receptor protein thus have a second function, guiding the growing tips of the new axon along specific paths to the appropriate target glomeruli in the olfactory bulbs. If it were hot for the continual guiding system, a rose might smell in one month like a lemon, in the next like a rotten fish.

- **Auditory system - what is the basic functional unit, how does it work**
  - the sensory epithelium responsible for hearing is the most precisely and minutely engineered of all the tissues in the body. Its sensory cells, the **auditory hair cells**, are held in a rigid framework of supporting cells and overlaid by a mass of extracellular matrix (the tectorial membrane), in a structure called the *organ of corti*. The hair cells convert mechanical stimuli into electrical signals. Each has a characteristic organ-pipe array of giant microvilli (called **stererocilia**) protruding from its surface as rigid rods, filled with crosslinked actin filaments, and arrange in ranks of graded height.



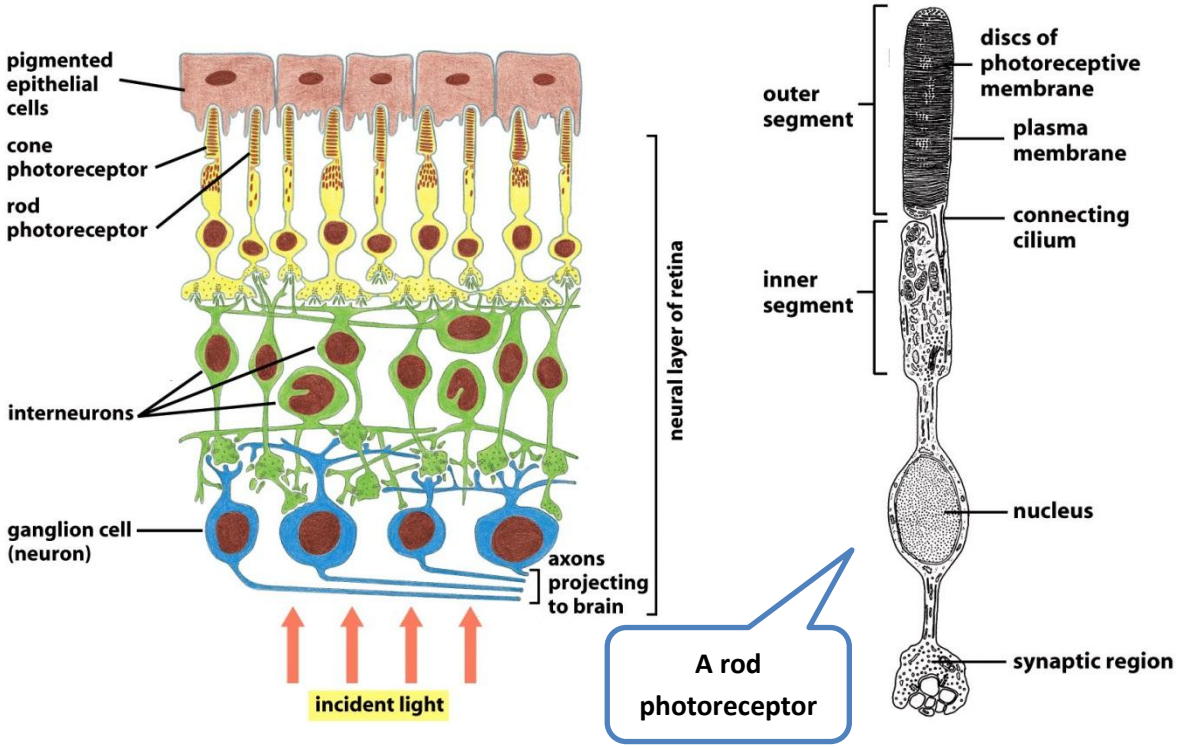
  - Sound vibrations rock the organ of Corti, causing the bundles of stereocilia to tilt and mechanically gated ion channels in the membranes of the stereocilia to open os close. The flow of electric charge carried into the cell by the ions alter the membrane potential and thereby controls the release of neurotransmitter at the cell's basal end, where the cell synapses with a nerve ending.



The cell functions as a transducer, generating an electrical signal in response to sound vibrations that rock the organ of Corti and so cause the stereocilia to tilt. A fine fine filament runs more or less vertically upward from the tip of each shorter stereocilium to attach at a higher point on its adjacent taller neighbor. Tilting the bundles puts tension on the filaments, which pull on mechanically gated ion channels in the membrane of the stereocilia. Opening of these channels allows an influx of positive

charge, depolarizing the the hair cell. Each filament consists, in part at least, of members if the cadherin superfamily of cell-cell adhesion molecules. Mutant individuals lacking these specific cadherins lack the filaments and are deaf. In humans and other mammals the auditory hair cells, unlike olfactory neurons have to last a lifetime, if they are destroyed they are not regenerated and the resulting hearing loss is permanent. But in other vertebrates, destruction of auditory hair cells triggers the supporting cells to divide and behave as stem cells, generating progeny that can differentiate as replacements for the hair cells that are lost.

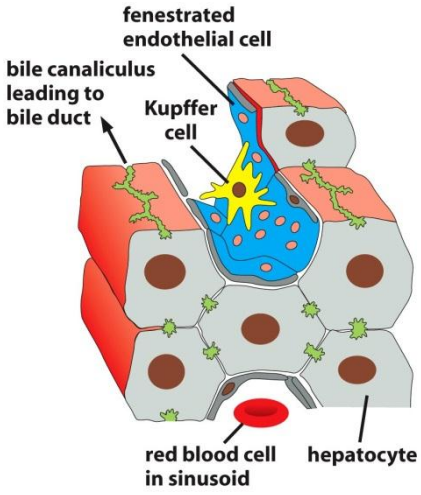
- **Visual system – what is the basic functional unit, how does it work**
  - The neurons that transmits the signals from the eye to the brain (called *retinal ganglion cells*) lie closest to the external world, so that the light, focused by the lens, must pass through them to reach the photoreceptor cells. The **photoreceptors**, which are classified as *rods* or *cones*, according to their shape, lie with their photoreceptive ends, or outer segments, partly buried in the *pigment epithelium*. Rods and cones contain different *visual pigments* – photosensitive complexes of *opsin* protein with the light-absorbing small molecule *retinal*. Rods, whose visual pigments is called rhodopsin, are especially sensitive at low light levels, while cones (of which there are three types in humans, each with a different opsin, giving a different spectral response) detect color and fine detail. When light stimulates the photoreceptors, the resulting electrical signal is relayed via interneurons to the ganglion cells, which then convey the signal to the brain.



The outer segment of a photoreceptor appears to be a modified cilium with a characteristic ciliumlike arrangement of microtubules in the region connecting the outer segment to the rest of the cell. The remainder if the outer sgment os almost entirely filled fint a dense stack of membranes in which the photosensitive complexes are embedded; light absorbed here produces an electrical response.
photoreceptors in humans, like human auditory hair cells, are permanent cells that do

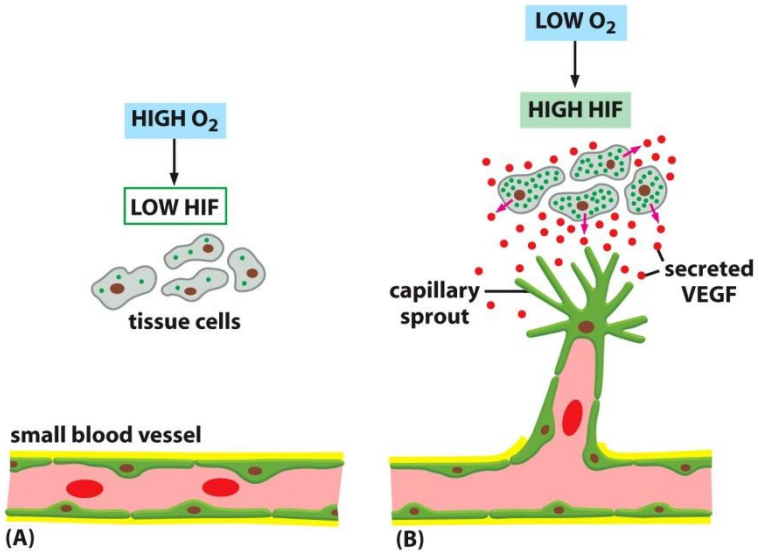
not divide and are nor replaced if destroyed by disease or a misdirected laser beam. The photosensitive molecules of visual pigment, however, are not permanent but are continually degraded and replaced.

- **What are the gut appendages**
  - Airways system
  - Digestive system
  - Glands associated with DS
  - Originates from endoderm
- **What is liver, what does it do, what is it made of, why is it special**
  - The liver is a gland that develops at a site where a major vein runs close to the wall of the primitive gut tube. Cells in the liver that derive from the primitive gut epithelium - the **hepatocytes** – are arranged in interconnected sheets and cords, with blood-filled spaces called **sinusoids** running between them. The blood is separated from the surface of the hepatocytes by a single layer of flattened epithelial cells. The liver is the main site at which nutrient that have been absorbed from the gut and then transferred to the blood are processed for use by other cells of the body. It receives a major part of its blood supply directly from the intestinal tract (via the **portal vein**). The hepatocytes play a central part in the carbohydrate and lipid metabolism in the body as a whole, and they secrete most of the protein found in the blood plasma. They remain connected with the lumen of the gut via a system of minute channels (or **canaliculi**) and larger ducts and secrete into the gut by this route both waste productsof their metabolism and an emulsifying agent, **bile**, which helps in the absorption of fats. Hepatocytes are big cells, and about 50% of them are polyploidy, with two, four, eight or even more times the normal diploid quantity of DNA per cell.



  - *Interface of digestive system and blood, gland at the interface of a vein and gut tube*
  - *Hepatocytes (gut epithelium derived) – big polyploidy cells*
  - *All cells do all (metabolism, division)*
  - *Sheets of cell with sinus for blood*
  - *Metabolic organ*
  - *Input from the portal vein: synthesis, storage, degradation*
  - *Produce bile (bile duct)*
  - *Caniculi: pipes to the gut*

- **How does HIF regulation work**
    - A shortage of oxygen, in practically any type of cell, causes an increase in the intracellular concentration of a gene regulatory protein called **hypoxia-inducible factor 1α (HIF1 α)**. HIF1α stimulates transcription of **VEGF** (and other genes whose products are needed when oxygen is in short supply). The VEGF protein is secreted, diffuses through the tissue, and acts on nearby endothelial cells, stimulating them to proliferate, to produce proteases to help them digest their way through the basal lamina of the parent capillary or venule, and to form sprouts. The tip cells of the sprouts detect the VEGS gradient and moves towards its source. As the new vessels form, bringing blood to the tissue, the oxygen concentration rises, HIF1α activity declines, VEGS production is shut off, and angiogenesis comes to a halt.



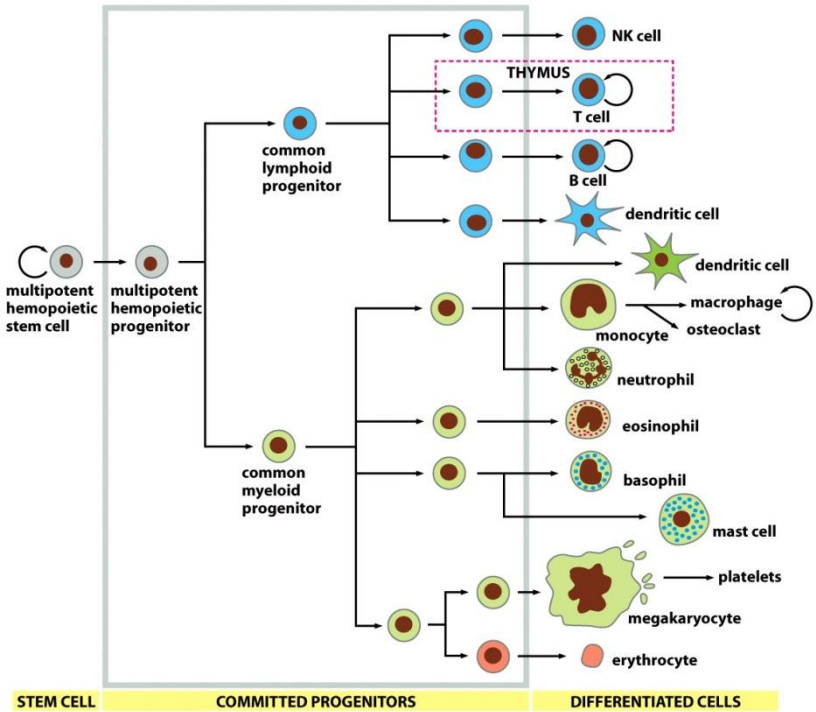
- **What is blood made of**
    - It is composes of blood cells suspended in a liquid called blood plasma. The blood plasma is mostly water and contains dissipated proteins, glucose, mineral ions, hormones, and so on. Albumin is the main protein in plasma, and it functions to regulate the colloidal osmotic pressure of blood.
- **What are the blood cells, where do they come from, how are they made**
    - Originate from the mesoderm and produced all the time from the multipotent hematopoietic stem cells in the bone marrow.

Table 23–1 Blood Cells

TYPE OF CELL	MAIN FUNCTIONS	TYPICAL CONCENTRATION IN HUMAN BLOOD (CELLS/LITER)
Red blood cells (erythrocytes)	transport O_2 and CO_2	5×10^{12}
White blood cells (leucocytes)		
Granulocytes		
Neutrophils (polymorphonuclear leucocytes)	phagocytose and destroy invading bacteria	5×10^9
Eosinophils	destroy larger parasites and modulate allergic inflammatory responses	2×10^8
Basophils	release histamine (and in some species serotonin) in certain immune reactions	4×10^7
Monocytes	become tissue macrophages, which phagocytose and digest invading microorganisms and foreign bodies as well as damaged senescent cells	4×10^8
Lymphocytes		
B cells	make antibodies	2×10^9
T cells	kill virus-infected cells and regulate activities of other leucocytes	1×10^9
Natural killer (NK) cells	kill virus-infected cells and some tumor cells	1×10^8
Platelets (cell fragments arising from *megakaryocytes* in bone marrow)	initiate blood clotting	3×10^{11}

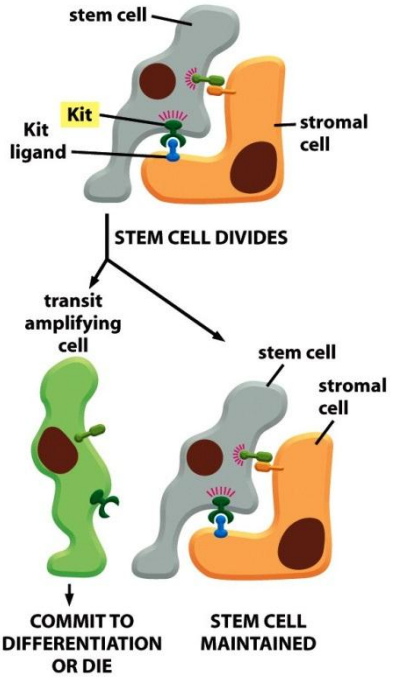
Humans contain about 5 liters of blood, accounting for 7% of body weight. Red blood cells constitute about 45% of this volume and white blood cells about 1%, the rest being the liquid blood plasma.

- All the blood cells are generated ultimately from a common stem cell in the bone marrow. This *hemopoietic* (blood-forming) *stem cell* is thus multipotent, giving rise to all the types of terminally differentiated blood cells as well as some other types of cells, such as osteoblasts in bone.



- **What is erythropoietin's role**
  - **Erythropoietin** is a hormone that controls erythropoiesis (the formation of red blood cells).
  - A lack of oxygen or a shortage of erythrocytes stimulates specialized cells in the kidney to synthesize and secrete increased amounts of erythropoietin into the bloodstream. The erythropoietin, in turn, stimulates the production of more erythrocytes. Since a change in a rate of release of new erythrocytes into the bloodstream is observed as early as 1-2 days after an increase in erythropoietin levels in the bloodstream, the hormone must act on cells that are very close precursors of the mature erythrocytes.
- **What is the role of Kit**
  - Stem cells depend on contact signal from stromal cells. Hematopoietic cells can survive, proliferate and differentiate in culture if, and only if, they are provided with specific signal proteins or are accompanied by cells that produce these proteins. In the bone marrow where they normally live, the hematopoietic stem cells are mostly located in close contact with the *osteoblasts* that line the bony surfaces of the marrow cavity – the cells that produce the bone matrix.

    Kit is a gene that codes for receptor tyrosine kinase on the hematopoietic stem cells. The Kit receptor protein together with its ligand (expressed by stromal cells) form a contact dependent signaling mechanism involved in hematopoietic stem cell maintenance.



Topic 6

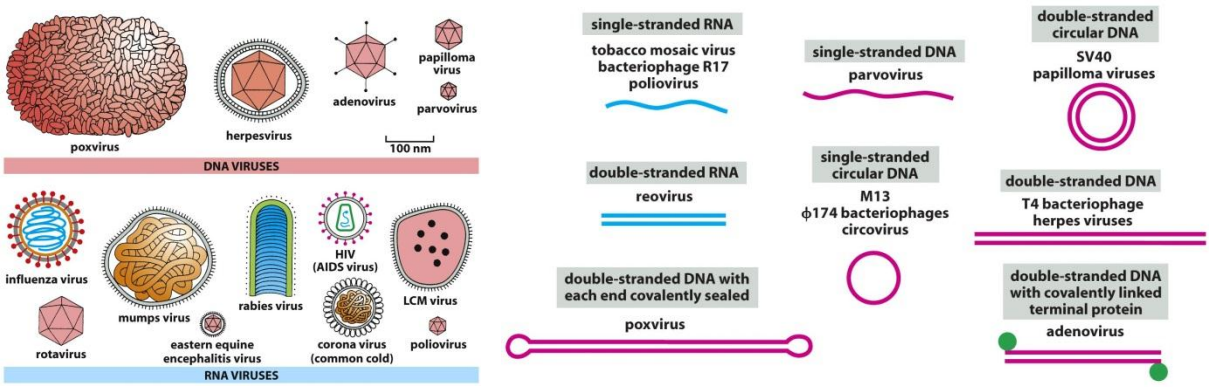
- **What are pathogens, what kind of type can they be, what makes a successful pathogen**
  - Pathogens are agents that cause infectious diseases. They can either be commensal microbes called the **normal flora**, which usually are confined to certain areas of the body but can affect our health if they enter sterile areas of the body, or they can be **primary pathogens**, which are able to breach barriers and survive in host locations where other microorganisms cannot.
  - In order to be a successful pathogen it must be able to:
    1. Colonize the host
    2. Find a nutritionally compatible niche in the host's body
    3. Avoid , subvert, or circumvent the host's innate and adaptive immune responses
    4. Replicate, using the host resources
    5. Exit and spread to a new host

- **What kind of response we can have to pathogens**
  - **Innate immune response**: spring into action immediately after an infection begins and do not depend on the host's previous exposure to the pathogen
  - **Adaptive immune response**: operate later in an infections and are highly specific for the pathogen that induced them

- **What are prions and how they work**
  - Prions are infectious proteins that replicate in the host by copying an aberrant protein structure. The most well-known infections caused be prions is *bovine spongiform encephalopathy* (BSE, or mad cow disease), which occasionally spreads to humans who eat infected parts of the cow. The host makes the infectious protein, and the prion's amino acid sequence is identical to that of a normal host protein. The only difference is between them appears to be in their three-dimensional structure.

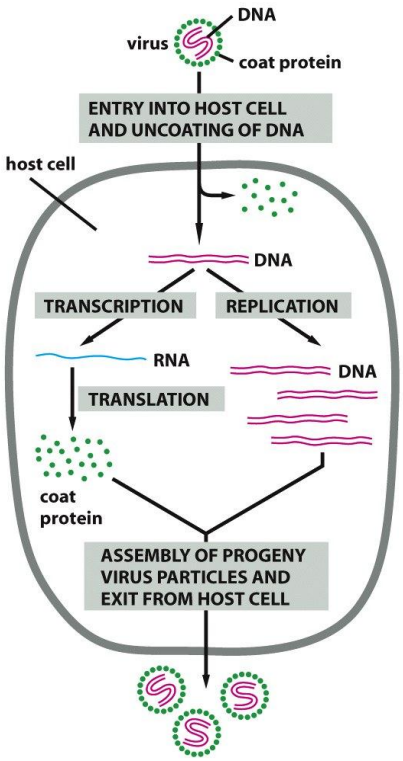
    The misfolded prion protein tends to aggregate to form helical fibers called *amyloid*. The amyloid fibers grow at the end, much like the cytoskeletal protein filaments, except that the protein subunits undergo a structural conversion from the normal folded form of the protein to the misfolded form as they become part of the amyloid polymer. In other words, the misfolded prion form has the remarkable capacity ti cause the normal protein to adopt its misfolded prion conformation and thereby become infectious. When one of the amyloid fibrils is broken into smaller pieces, each one can seed the conversion process in a new cell.

- **What are viruses and their different features**
  - Viruses carry little more than information in the form of nucleic acid. The information is largely replicated, packaged and preserved by the host cells. Viruses have a small genome, made up by a single nucleic acid type – either DNA or RNA – which, in either case, may be single-stranded or double-stranded. The genome is packaged in a protein coat, which in some viruses is further enclosed by a lipid envelope.



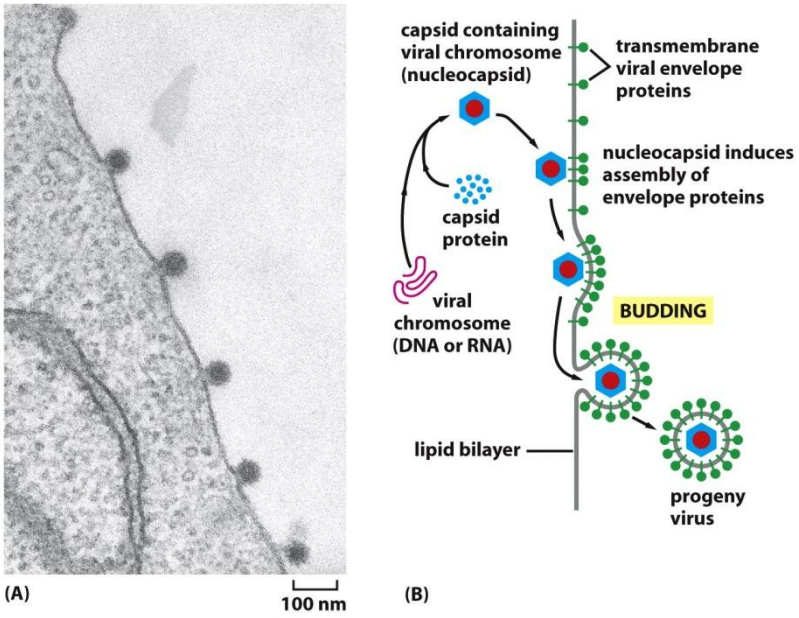
- Viruses replicate in various ways. In general, replication involves:
  1. Disassembly of the infectious virus particle
  2. Replication of the viral genome
  3. Synthesis of viral proteins by the host cell translation machinery
  4. Reassembly of these components into progeny virus particles

  A single virus particle (a *virion*) that infects a single host cell can produce thousands of progeny in the infected cell. Such prodigious multiplication often kills the host cell: the infected cell breaks open (lyses) and thereby allows the progeny virions access to nearby host cells.



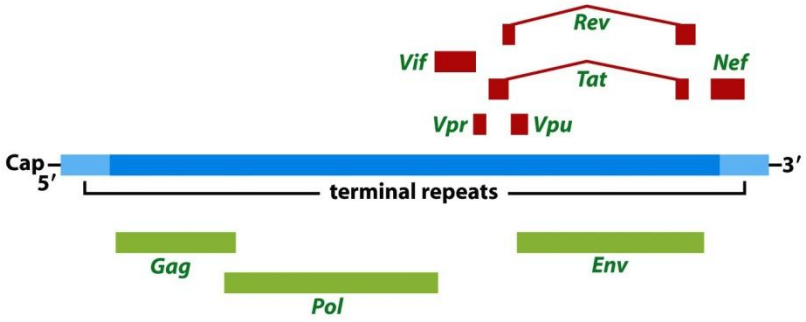
- The **capsid** that encloses the viral genom is made of one or several proteins, arranged in regularly repeating layers and patterns; the viral genome together with the capsid is called a **nuclecapsid**. In *enveloped viruses*, the nucleocapsid is enclosed by a lipid bilayer membrane that the virus acquires in the process of budding from the host cell plasma membrane. Whereas *nonenveloped viruses* usually leave an infected cell by lysing it, an enveloped virus can leave the cell without disrupting the plasma membrane and, therefore, without killing the cell. Enveloped viruses can

cause persistent infections that may last for years, often without noticeable deleterious effects on the host.



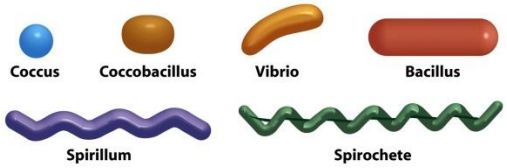
- All viruses encode three types of proteins:
  1. Proteins for replicating the genome
  2. Proteins for packaging the genome and delivering it to more host cells
  3. Proteins that modify the structure or function of the host cell to enhance the replication of the virions

Example of viral genome: HIV

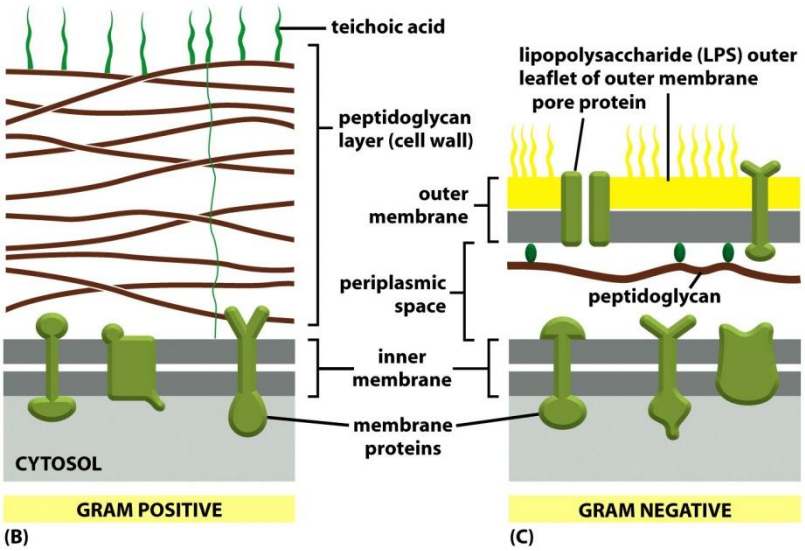


Gag encodes capsid proteins, *Env* encodes envelope proteins, and *Pol* encodes both the reverse transcriptase (which copies RNA into DNA) and the integrase (which inserts the DNA copy into the host cell genome).

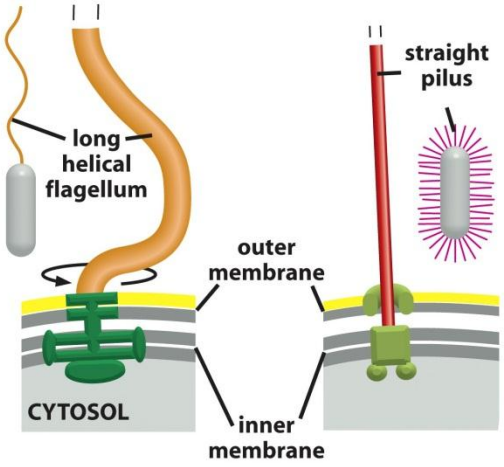
- **What are bacteria and their different features, what does it mean to be G+ or G-**
  - Bacteria are small and appear structurally simple. Most can be classified broadly by their shape as rods, spheres, or spirals and by their so-called **Gram-staining** properties.



- **Gram-positive** bacteria have a single membrane and a thick cell wall made of cross-linked *peptidoglycan*. They retain the violet dye used in the Gram staining procedure and are thus called Gram-positive
- **Gram-negative** bacteria have two membranes, separated by a periplasmic space. The peptidoglycan layer in the cell wall of these organisms is located in the periplasmic space and is thinner than in Gram-positive bacteria; they therefor fail to retain the dye in the Gram-staining procedure. The inner membrane if Gram-negative bacteria is a phospholipid bilayer, and the inner leaflet of the outer membrane is also med primarily of phospholipids; the outer leaflet of the outer membrane, however, is composed of a unique glycosylated lipid called *lipopolysaccharide* (**LPS**).



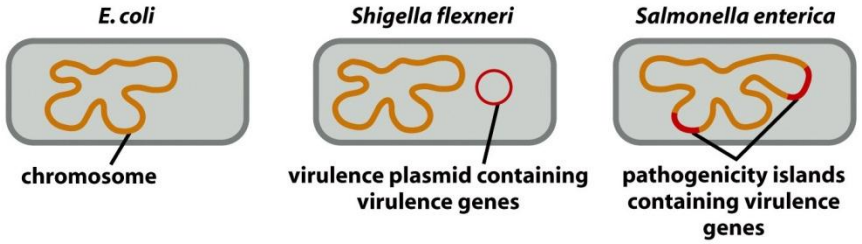
- Cell-surface appendages are important for bacterial behavior. Many bacteria swim using the rotation of helical *flagella*. Straight *pili* (also called *fimbriae*) are used to edhere to various surfaces in the host, as well to facilitate genetic exchange between bacteria. Some kinds if pili can retract to generate force and thereby help bacteria move across surfaces. Both flagella and pili are anchored to the cell surface by large multiprotein complexes.



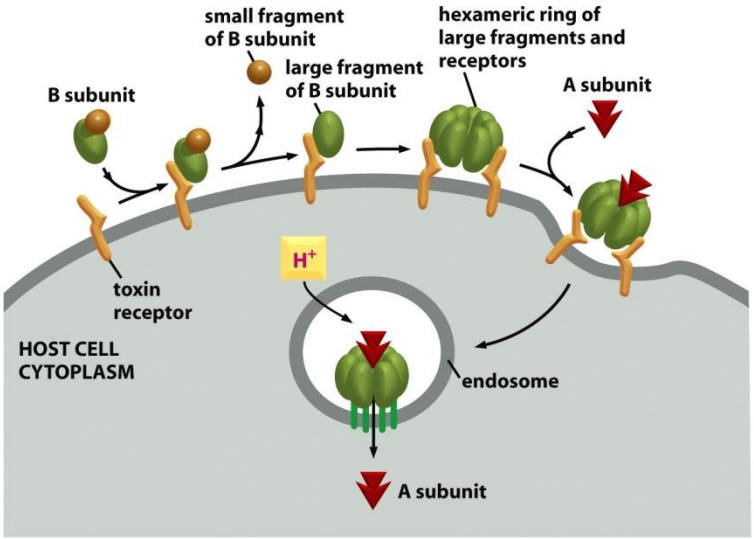
- Only a minority of bacterial species have the ability to cause disease in humans. Some of those that do cause disease can only replicate inside the body of their host and are called **obligate pathogens**. Others replicate in an environmental reservoir such as water or soil and only cause disease if they happen to encounter a

susceptible host; these are called **facultative pathogens**. Many bacteria are normally harmless but have a latent ability to cause disease in an injured or immunocompromised host; these are called **opportunistic pathogens.** Some bacterial pathogens are fastidious in their choice if host and will infect only a single species or a group of related species, whereas others are generalists.

- A relatively small number of genes cause the significant differences between a virulent pathogenic bacterium and its closest nonpathogenic relative. Genes that contribute to the ability of an organism to cause disease are called **virulence genes**, and the proteins they encode are called **virulence factors**. Virulence genes are frequently clustered together, either in groups on the bacterial chromosome called **pathogenicity islands** or on extrachromosomal **virulence plasmids**.
  These genes may also be carried on mobile **bacteriophages** (bacterial viruses). Large chunks of DNA can be exchanged betwenn bacteria driving the evolution forward.



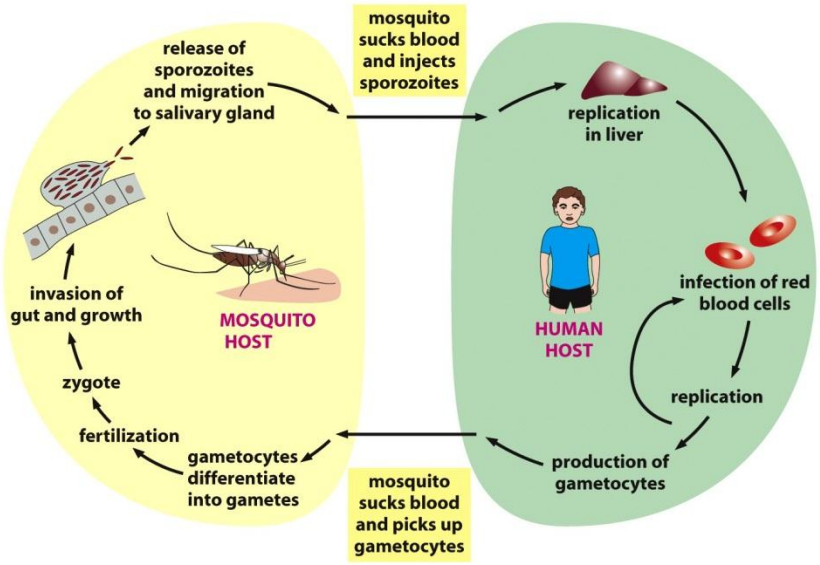
- **How does anthrax toxin get into the cell**
  - Anthrax does not spread directly from person to person. Dormant spores can survive in soil for long periods and are highly resistant to adverse environmental conditions, including heat, ultraviolet and ionizing radiation, pressure and chemical agents. After the spores are inhaled, ingested, or rubbed into breaks in the skin, the spores germinate and the bacteria begin to replicate. The bacteria secrete two toxins, called **lethal toxin** and **edema toxin** either of which is sufficient to cause signs of infection. Like cholera toxin, both anthrax toxins are made of two subunits. The B subunit is identical in the two anthrax toxins, and it binds to a host cell-surface receptor protein to transfer the different A subunits into host cells.



- The A subunit if edema toxin is and adenylyl cyclase that directly converts host-cell ATP into cyclic AMP, leading to an ion imbalance that can cause an accumulation of extracellular fluid (*edema*) in the infected skin or lung. The A subunit of lethal toxin is a protease that cleaves several members of the MAP kinase family. Injections of lethal toxin into the bloodstream in an animal causes shock (a fall in blood pressure) and death. The molecular mechanisms leading to death in anthrax remain uncertain.

- **How pathogens (and which) influence cancer development (which cancers)**
  - *Human papillomavirus*, which causes genital warts, is also responsible for more than 90% of cervical cancers. Worldwide, cervical cancer is the second most common cancer in women and has a mortality rate of ~40%.
  - The *Epstein-Barr virus* (*EBV*) is so common that nearly 90% of adults in the United States over the age of 40 have detectable levels of anti-EBV antibodies in their blood. EBV prefers to invade B cells of the adaptive immune system especially long-lived memory B cells. It is the cause of *mononucleosis* (also called *glandular fever*). After symptoms subside, EBV can reman dormant in the B cells for life, with its genome maintained as an extrachromosomal plasmid in the B cell nucleus.
  - Some of the gene products encoded by the EBV virus and Human papillomavirus inhibit apoptosis and thereby presumably help to prevent the virus from being cleared from the body. Thus, when an infected cell acquires cancer-promoting mutations, the usual mechanism for eliminating precancerous cells by apoptosis is inhibited, and for either cervical cancer or a form a B cells caner called *Burkitt's lymphoma*.

- **How does Plasmodium live and why is it good to have sickle cell anemia (heterozygote) if you live in areas of malaria, what is Hbs**
  - *Plasmodium* is a **Protozoan parasite**, which are single-celled eukaryote that frequently require the services of more than one host. Malaria is the most commin protozoal disease and it is caused by four species of plasmodium, which are transmitted to humans by the bite of the female of any of 60 species of *Anopheles* mosquito. Gametocytes are formed in the bloodstream of infected humans, but they can only differentiate and fuse to form a zygote on the gut of the mosquito. Three of the *Plasmodium* forms are highly specialized to invade and replicate in specific tissues – the insect gut lining, the human liver, and the human bred blood cell.
  - Because malaria is so widespread and devastating, it has acted as a strong selective pressure on human populations in areas of the world that harbor the *Anopheles* mosquito. **Sickle-cell anemia**, for example, is a recessive genetic disorder caused by a point mutation in the gene that codes for the hemoglobin β chain. The malarial parasites grow poorly in the sickle cells because plasmodium development takes more time than the lifetime of the sickle REB – therefore the population of plasmodia is diluted if there are more sickle cells than normal RBC.



- **How can parasitic infection change the behavior of the individual organism and influence the populations of species**
    - *Trypanosoma brucel*, which causes sleeping sickness, makes the tsetse flies that carries it bite much more frequently and ingest more blood than do uninfected flies. The presence of trypanosomes impairs the function of the insect mechanoreceptors that measure blood flow through the gullet to assess the fullness of the stomach, effectively fooling the tsetse fly into thinking it is still hungry.
    - *Yerstina pestis*, which causes bubonic plague, uses a dirrefent mechanism to ensure that a flea carrying it bites more repeatedly: it multiplies in the flea's foregut to form aggregated masses that eventually enlarge and physically block the digestive tract. The insect is then unable to feed normally and begins to starve. During repeated attempts to alleviate its hunger by feeding, some of the bacteria in the foregut are flushed into the bite site, thus transmitting plague to a new host.
    - *Rabies* replicates in neurons and causes infected people or animals to become "rabid": they are unusually aggressive and develop a strong desire to bite, the virus is shed in the saliva and transmitted through the bite wound into the bloodstream if the victim.
    - *Wolbachia* manipulate the sexual behavior of their host to maximize their dissemination. In some species of *Drosophila, Wolbachia* modify the sperm of their host so that they can fertilize eggs only of infected females. In other host species, a *Wolbachia* infections kills males but spares females, increasing the number of individuals that can produce eggs to oass on the infection. In a few wasps, *Wolbachia* infections enable the females to produce eggs that develop parthenogenetically, without the need for fertilization by sperm; in this species, males have been completely eliminated. For some of its hosts, *Wolbachia* has become an indispensable symbiont, and curing the infection causes death of the host. In one case, human are making use of this dependence: the filarial nematode that causes African river blindness is difficult to kill with antiparasitic medications, but when people with river blindness are treated with antibiotics that cure the nematode's *Wolbachia* infection, the nematode infection is also arrested.

- **Why is Neisseria successful in evolutionary adaption**

  G+ coccus

  - Genetic recombination (pilin genes – many variations in one expression site)
  - Slippage mechanisms in transcription and translation of surface components
  - Natural competence (extremely adept at taking up foreign DNA)
  - Lack of several DNA repair mechanisms

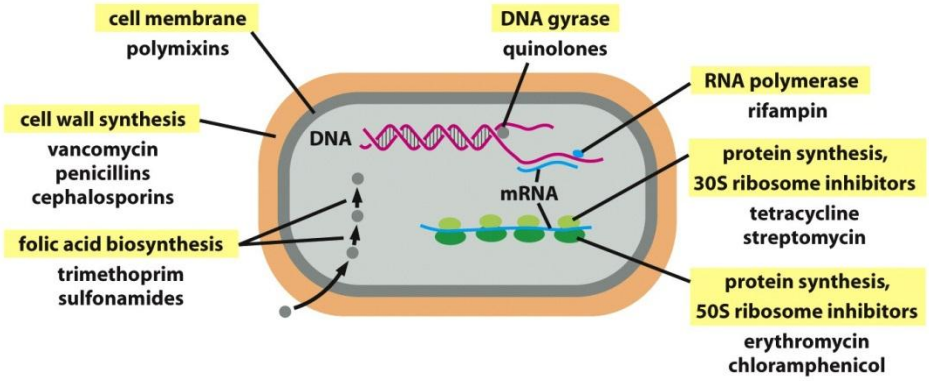
  Horizontal gene transfer, rather than point mutations, often causes rapid evolution in bacteria. The acquisition of plasmids and bacteriophages mediates most of this horizontal gene transfer. Bacteria readily pick up pathogenicity island and virulence plasmids from other bacteria.

- **Why did the flue of 1918 kill more people than WWI and how does the flu virus evolve**

  - Influenza viruses are unusual in that their genome consists of several (usually eight) strands of RNA. When two strains of influenza infect the same host, the strands of the two strains can recombine to form a novel type of influenza virus.

  - A particularly virulent of avian influenza crossed the species barrier to infect humans in 1918, triggering the Spanish flu. Subsequent influenza pandemics have been triggered by recombination, in which a new DNA segment from an avian form of the virus replaced one or more of the viral DNA segments governing human immune response to the virus.

- **How antibiotics work and how is the resistance to antibiotics conferred**
  - The vast majority of antibiotics inhibit either protein synthesis or bacterial cell wall synthesis. A complete summary can be seen in the picture.



  - There are three general strategies by which a pathogen can develop drug resistance
    1. It can alter the molecular target of the drug so that it is no longer sensitive to the drug
    2. It can produce an enzyme than destroys the drug
    3. It can prevent access to the target by, for example, actively pumping the drug out of the pathogen

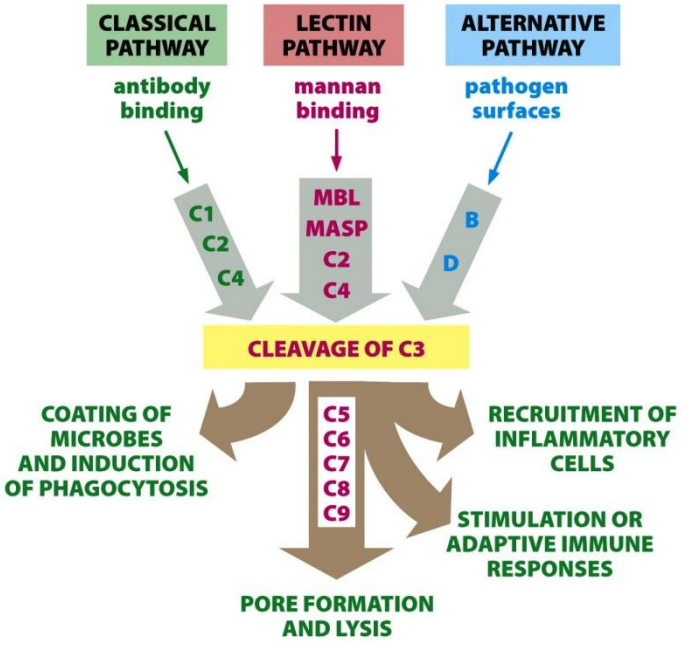
- *Horizontal gene transfer* is the most powerful tool for the pathogens to gain resistance

- **What two responses to infection make up the immune system**
  - *Innate immune response*
  - *Adaptive immune response*

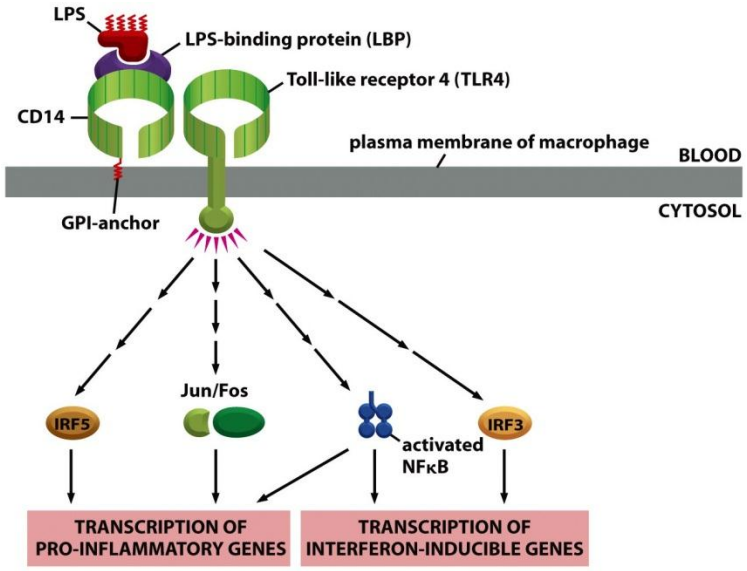
- **What is each response made of (components, cells, proteins, tissues, organs) and what are their roles**
  - **Innate immune response:**
    - Physical and chemical barriers (skin, tight junctions, acidic pH, mucus with defensin peptides, normal flora)
    - Cell-intrinsic responses (phagocytosis, lysosome, degradation of dsRNA)
    - Specific cells and proteins: phagocytic cells (neutrophils, macrophages, NK cell) + complement system

    Defensins: small peptides (12-50 AA), non specific, broad spectrum of antimicrobial activites, present in neutrophils, cations, amphipathic or hydrophobic domains

- **What is the role of the complement system, what is it made of, how does it work**
  - Consists of about 20 soluble proteins, made by the liver, circulating in the plasma and extracellular fluid.
    - Amplifies and "complements" the action of antibodies
    - 3 pathways that result in activation of C3 (proteolytic cascade)
    - Recognized by specific receptors on phagocytic cells and so and enhance the ability of these cells to phagocytose the cells.



- **What are TLR and NOD**
  - Many of the mammalian pattern recognition receptors responsible for triggering innate immune responses to pathogens are members of the **Toll-like receptor** (**TLR**) family. They are transmembrane leucine-rich motifs.
    - At least 10 TLRs in humans
      - TLR4: LPS of G-
      - TLR5: Flagellum DNA
      - TLR9: CpG DNA
    - In plants and animals
  - A second family of pattern recognition receptors is exclusively intracellular. They are called **NOD proteins** and also have leucine-rich motifs. Functionally similar to TLRs but recognize a distinct set of ligands, including bacterial cell wall components.

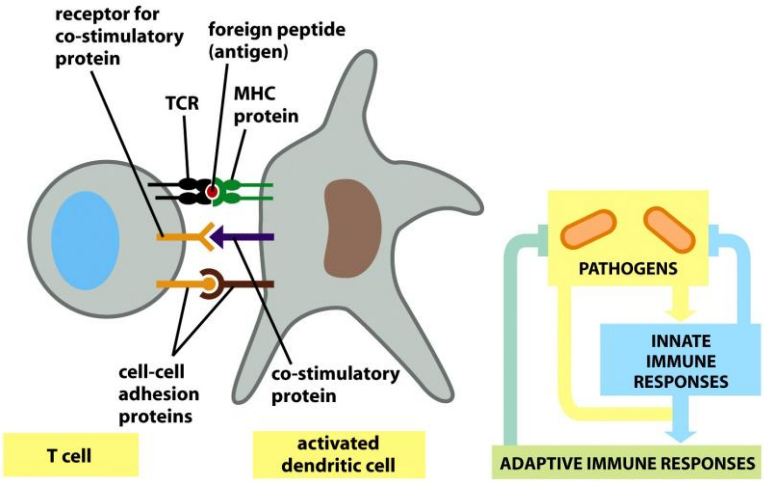


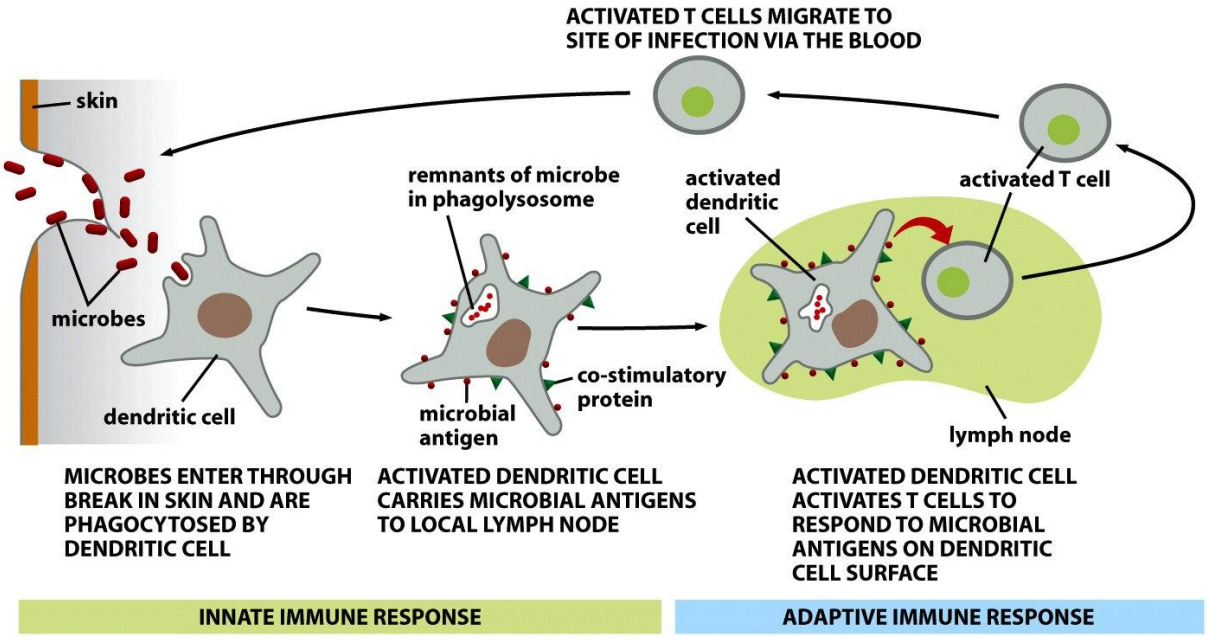
- **What is phagocytosis, role, who is doing it, why and how**
  - Phagocytosis is the engulfment and destruction of pathogens by phagocytic cells. This innate immune response is present in all animals, invertebrates as well as vertebrates, but plants lack this ability to defend themselves.
    - **Macrophages** are professional phagocytes that residue in tissues throughout the body, abundant in areas where infections are likely to start. They are also present in large numbers in connective tissues, in the liver and spleen. They are long-lived.
    - **Neutrophils** are the second major type of professional phagocytic cells in vertebrates. In contrast to macrophages they are short-lived, abundant in blood but not present in normal, healthy tissues. They are rapidly recruited to sites of infection by activated macrophages and other molecules that indicate infection.
  - Macrophages and neutrophils display a variety of cell-surface receptors, these include pattern recognition receptors such as TLRs, receptors for antibodies produced by the adaptive immune system, and receptors for the C3b component of *complement*.
    Binding to any of these receptors induces actin polymerization at the site of

pathogen attachment, causing the phagocyte's plasma membrane to surround and engulf it in a large membrane-enclosed phagosome.

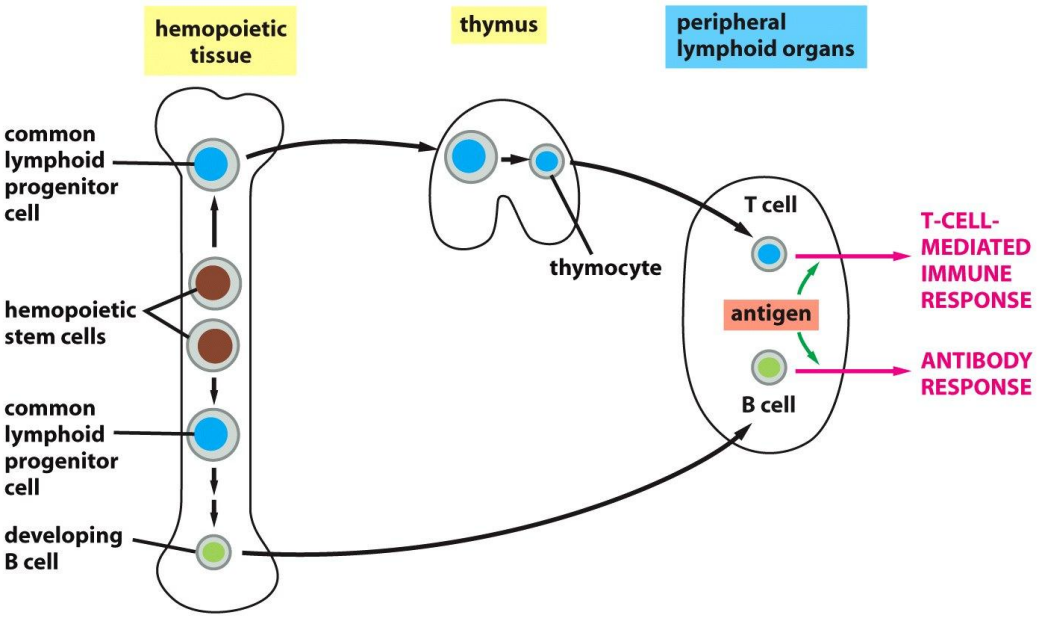
- Chemical weapons released by macrophages and neutrophils:
  - *Granules* containing enzymes
  - Defensins
  - ROS (respiratory burst), contains oxygen-derived toxins
  - Basic pH

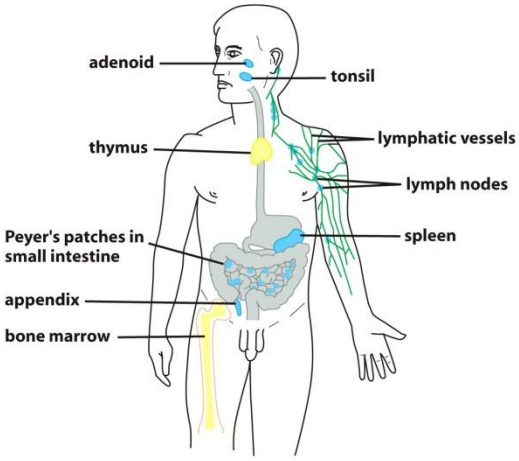
- **How is the interaction between the two types of immune responses mediated, via what cells**
  - **Dendritic cells** are crucially important cells of the innate immune system that are widely distributed in the tissues and organs of vertebrates. The display a variety of pattern recognition receptors, including **TLRs** and **NOD** proteins.
  - The dendritic cells cleave the proteins of the pathogens into peptide fragments, which then bind to MHC proteins that carry the fragments to the cell surface. The activated dendritic cells now carry the pathogen-derived peptides, as complexes with MHC proteins, to a nearby lymphoid organ such as a lymph node, where they activate T cells of the adaptive immune system.
  - Activated dendritic cells display three types of protein molecules on their surface that have a role in activating a T cell to become an effector cell or a memory cell.
    1. *MHC proteins* – present foreign antigen to the TCR
    2. *Co-stimulatory proteins* – bind to complementary receptors on the T cell surface
    3. *Cell-cell adhesion molecules* – enable a T cell to bind to the antigen-presenting cell for long enough to become activated, which usually takes hours.



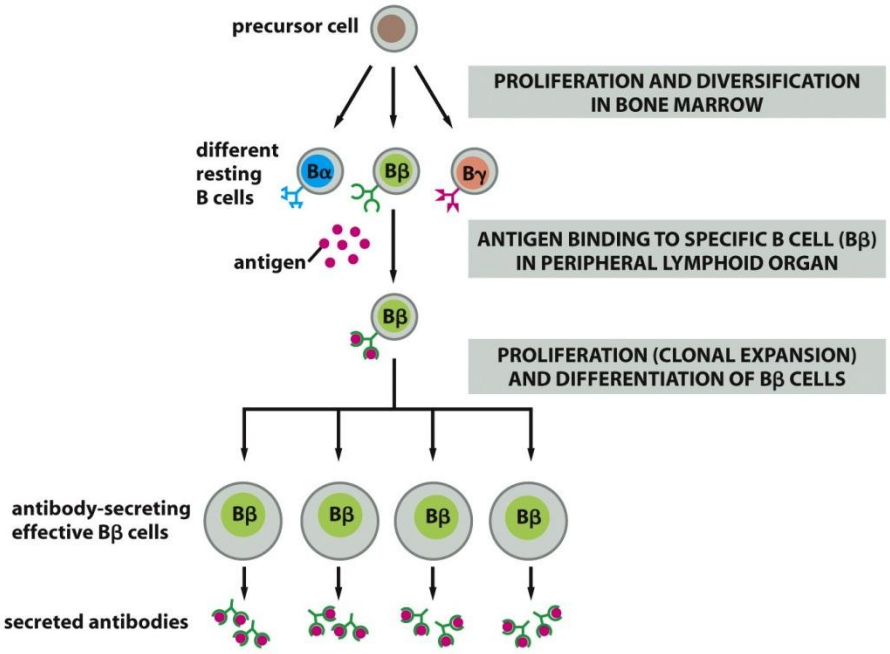


- **What are the B (1) and T (3) cells, roles, different places of maturation**
  - **T and B cells** derive their names from the organs in which they develop. T cells develop in the *thymus*, and B cells, in mammals develop in the *bone marrow* in adults or the liver in fetuses. The thymus and bone marrow is referred to as **central (primary) lymphoid organs.** When mature they migrate via the blood to the **peripheral (secondary) lymphoid organs**.
  - Three main classes of T cells:
    - ***Cytotoxic T cells*** – directly kill infected host cells
    - ***Helper T cells*** – help activate macrophages, dendritic cells, B cells, and cytotoxic T cells by secreting a variety of cytokines and displaying a variety of co-stimulatory proteins on their surface.
    - ***Regulatory T cells*** – are thought to use similar strategies to inhibit the functions of helper T cells, cytotoxic T cells, and dendritic cells. Thus, whereas B cells can act over long distances by secreting antibodies, T cells can migrate to distant sites, but, once there, they can only act locally on neighboring cells.
  - ***B cells*** – Produce and secrete antibodies, which are proteins called **immunoglobulins.**

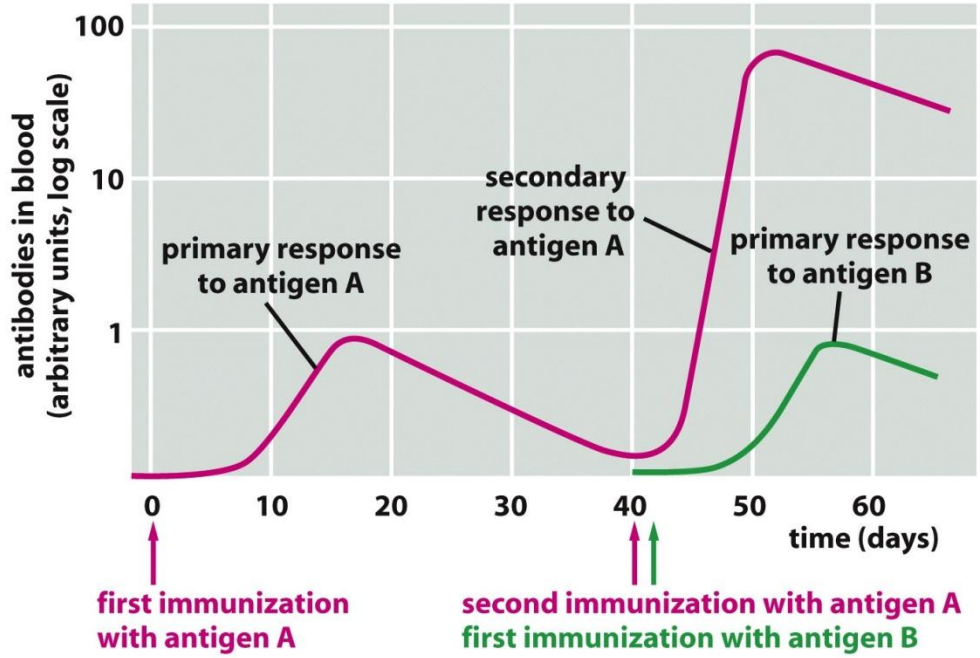




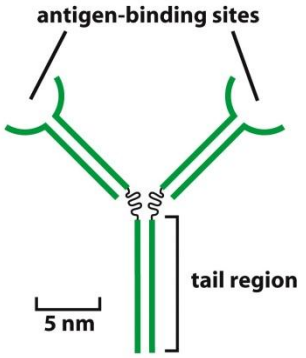
- **What is clonal selection and expansion, why is it necessary**
  - As each lymphocyte develops in a central lymphoid organ, it becomes committed to react with a particular antigen before ever being exposed to the antigen. It expresses this commitment in the form of cell-surface receptor proteins that specifically bind to the antigen. When a lymphocyte encounters its antigen in a peripheral lymphoid organ, the binding of the antigen to the receptors activates the lymphocyte, causing it to proliferate, a process called **clonal expansion**. The encounter with antigen also causes the cells to differentiate into **effector cells**.

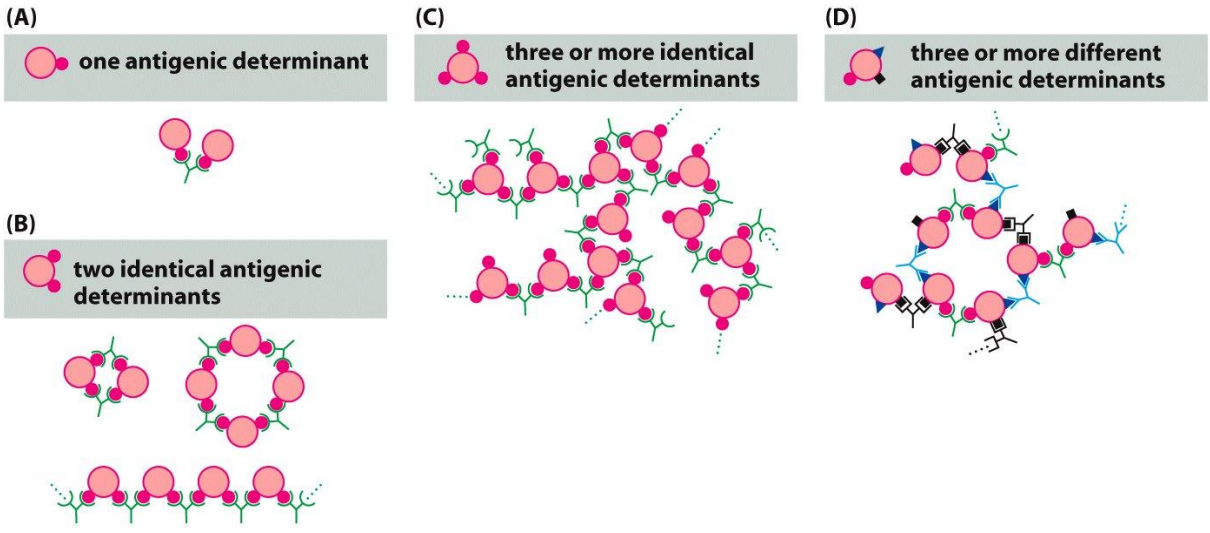


- **How is the memory of the immune system created and why is it necessary, how do we use that phenomenon**
    - In an adult animal, the peripheral lymphoid organs contain a mixture of lymphocytes in at least three stages of maturation: *naïve cells, effector cells,* and *memory cells.* When **naïve cells** encounter their antigen for the first time, the antigen stimulates some of them to proliferate and differentiate into **effector cells**, which then carry out an immune response (effector B cells secrete antibody, while effector T cells either kill infected cells or influence the response of other cells).
    - Some of the antigen-stimulated naïve cells multiply and differentiate into **memory cells**, which do not themselves carry out immune responses but are more easily and more quickly induced to become effector cells by a later encounter with the same antigen.
    - Memory cells can persist for the lifetime of the animal, even in the absence of their specific antigen, thereby providing lifelong immunological memory.
    - Memory B cells produce antibodies of different classes and much higher affinity for antigen than those produced by naïve B cells. This is the main reason that secondary antibody responses are much more effective at eliminating pathogens than are primary antibody responses



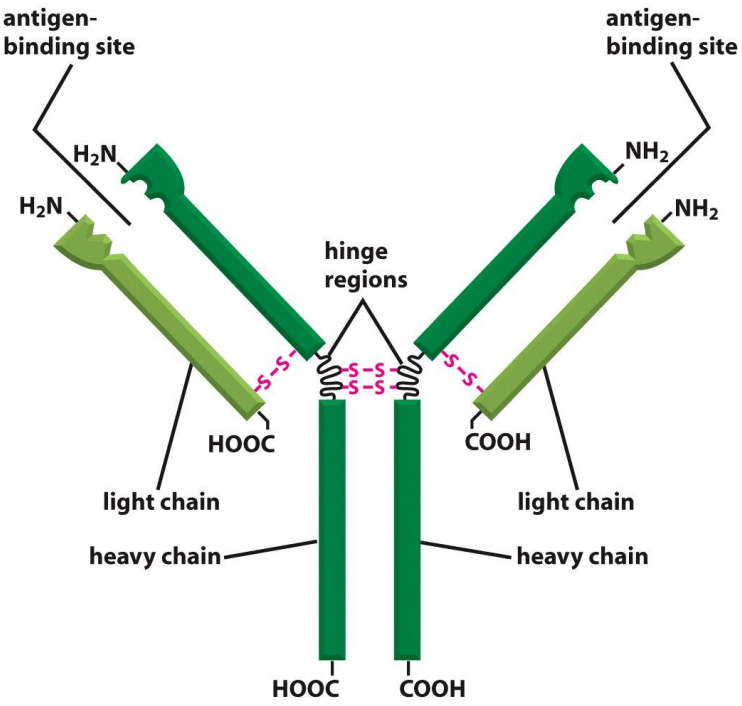
- **Structure and function of antibodies, how many types (names)**
  - The simplest antibodies are Y-shaped molecules with two identical antigen-binding sites, one at the tip of each arm of the Y. Because of their two antigen-binding sites, they are described as *bivalent*. As long as an antigen has three or more antigenic determinants, bivalent antibody molecules can cross-link it into a larger lattice that macrophages can readily phagocytose and degrade.





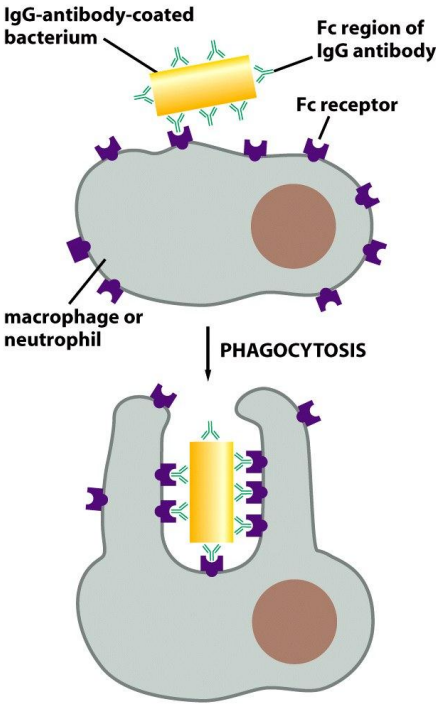
- The protective effect of antibodies is not due simply to their ability to bind and cross-link antigen. The tail of the Y-shaped molecule mediates many other activities of antibodies. Each type of tail region gives the antibody different functional properties, such as the ability to activate the complement system, to bind to phagocytic cells, or to cross the placenta from mother to fetus.
- In mammals there of five classes of antibodies, each with its own class of heavy chain
  - **IgA** - α
  - **IgD -** δ
  - **IgE -** ε
  - **IgG -** γ
  - **IgM -** μ
- In addition to the five classes of heavy chains, higher vertebrates have two types of light chains, κ and λ, which seem to be functionally indistinguishable. Either type of light chain may be associated with any of the heavy chains. An individual antibody molecule, however, always contain identical light chains and identical heavy chains.

- **Detailed structure of antibodies (light, heavy, variable, constant, Fab, Fc, types of bonds that make the structures, Ig domains)**
  - The structural unit of an antibody consists of four polypeptide chains, two identical **light (L) chains** (each containing about 220 amino acids) and two identical **heavy (H) chains** (each usually containing about 440 amino acids). A combination of noncovalent and covalent (disulfide) bonds holds the four chains together. The molecule is composed of two identical halves, each with the same antigen-binding site.



  - The antibody tails are called **Fc regions**, besides activating complement the tail region of an IgG molecule binds to specific Fc receptors on macrophages and

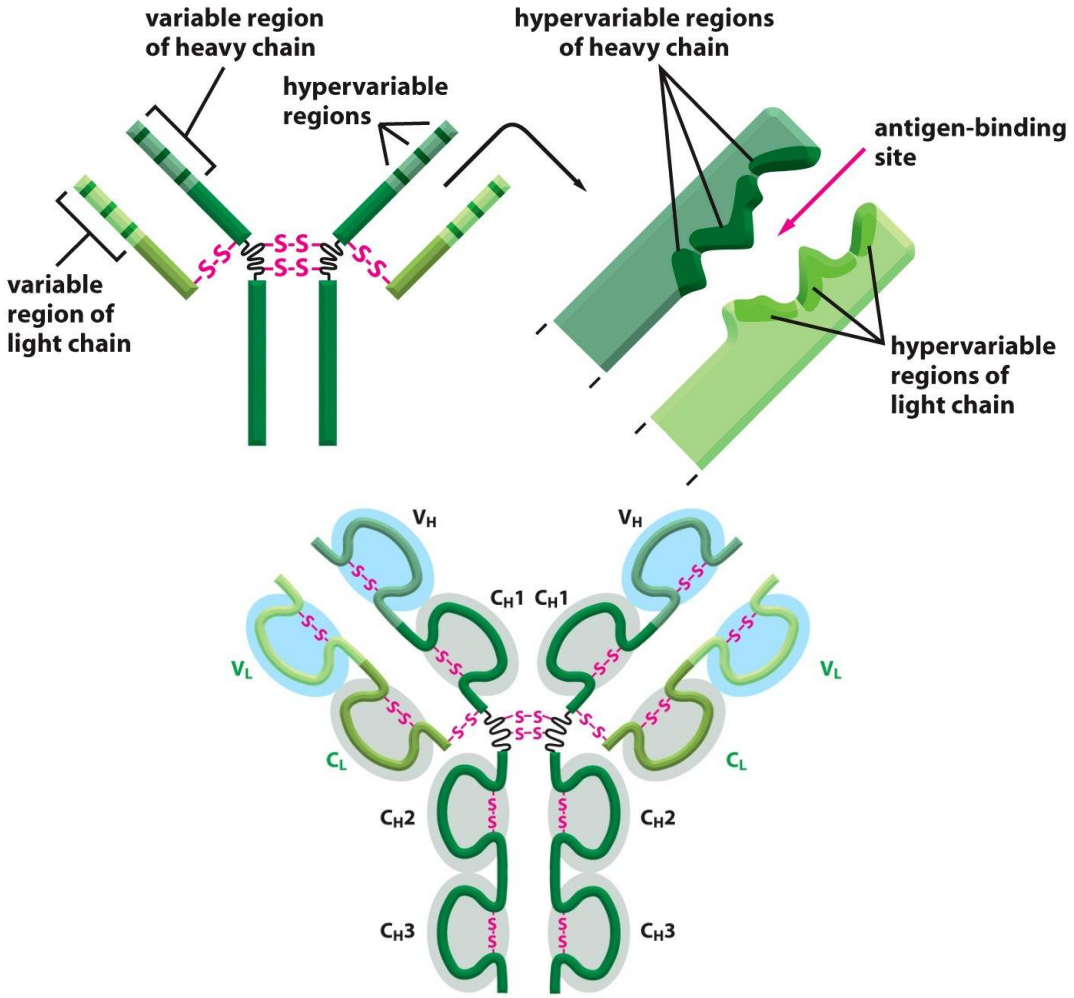
neutrophils. It is the region by which the antibody interacts with other molecules via their various types of Fc receptors.



- Both light and heavy chains have a variable sequence at their N-terminal ends but a constant sequence at their C-terminal ends. Consequently, when the amino acid sequences of many different κ chains are compared, the C-terminal halves are the same or show only minor differences, whereas the N-terminal halves all differ. Light chains have a **constant region** about 110 amino acids long and a **variable region** of the same size. The variable region of the heavy chains is also about 110 amino acids long, but the constant region is about three or four times longer.

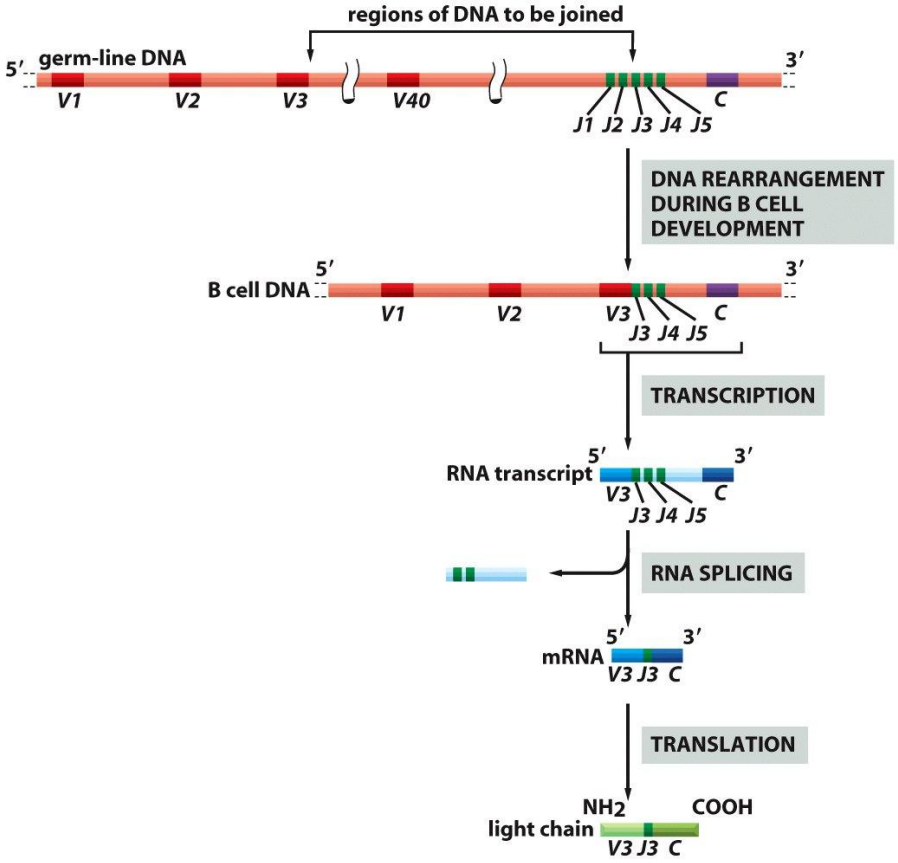
  It is the N-terminal ends of the light and heavy chains that come together to form the antigen-binding site, and the variability of their amino acid sequences provides the structural basis for the diversity of antigen binding sites. The greatest diversity occurs in three small **hypervariable regions** in the variable regions of both light and heavy chains; the remaining parts of the variable region, known as *framework regions*, are relatively constant.

- Both light and heavy chains are made up of repeating segments – β sheets about 110 amino acids long and each containing one intrachain disulfide bond. Each repeating segments folds independently to form a compact functional unit called an **immunoglobulin (Ig) domain**. The variable domains (shaded in blue) of light and heavy chains make up the antigen-binding sites, while the constant domains of the heavy chains (mainly C_H2 and C_H3) determine the other biological properties of the molecule. A light chain has one variable (V_L) and one constant (C_L) domain, while a heavy chain has one variable (V_H) and either three or four constant (C_H) domains.

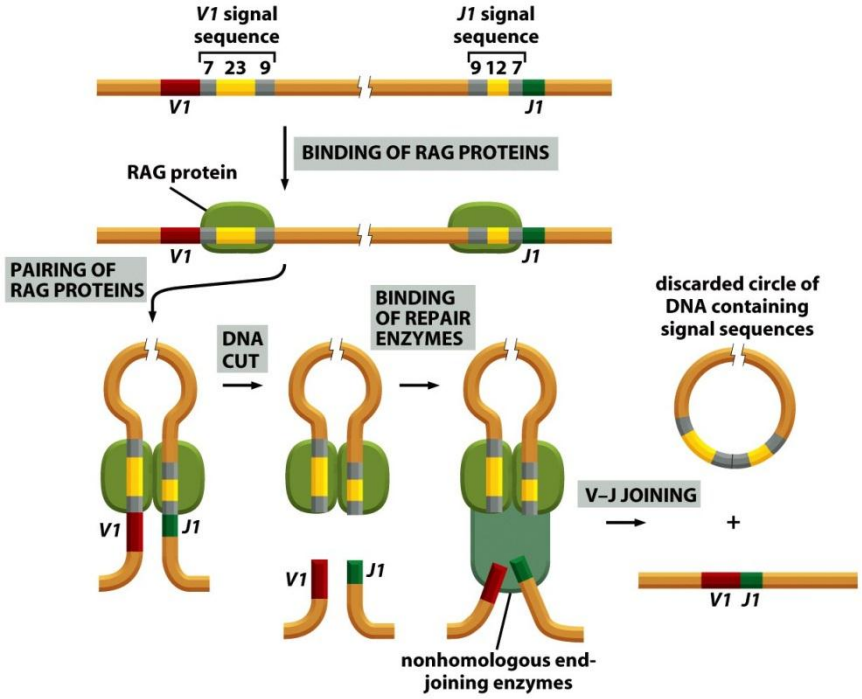


- **What is the mechanism for antibody variability**
    - Mice and humans produce their primary antibody repertoire by joining separate antibody **gene segments** together during B cell development. Each type of antibody chain (light chains, heavy chains) is encoded by a separate locus on a separate chromosome. Each locus contains a large number of gene segments encoding the V region, and one or more segments encoding the C region.
    - Each light-chain V region is encoded by a DNA sequence assembled from two gene segments – a long **V gene segment** and a short *joining*, or **J gene segment**. Each heavy-chain region is similarly constructed by combining gene segments, but here and additional *diversity segment*, or **D gene segment**, is also required.

      The large number of inherited *V, J* and *D* gene segments available for encoding antibody chains contributes substantially to antibody diversity, and the combinatorial joining of these segments (called *combinatorial diversification)* greatly increases this contribution. The mechanism is called *V(D)J recombination*.

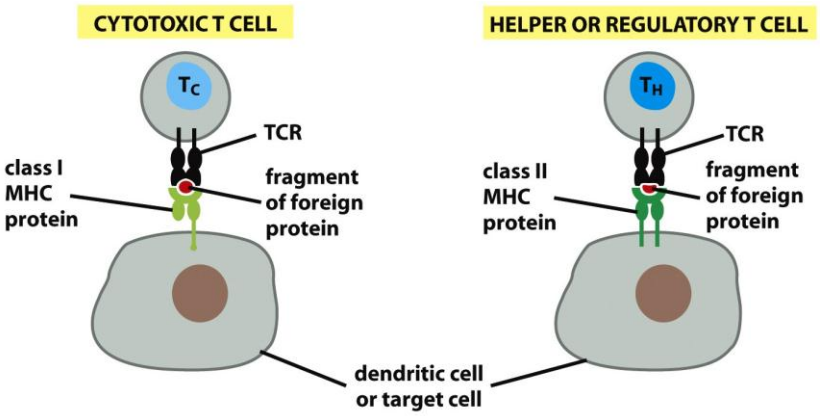


- In the process of **V(D)J recombination**, site-specific recombination joins separate antibody gene segments together to form a functional V_L- or V_H-region coding sequence.
  Two closely linked genes called *Rag1* and *Rag2* (*Rag* = *r*ecombination *a*ctivating *g*enes) encode the lymphocyte-specific proteins of the V(D)J recombinase, RAG1 and RAG2. To mediate V(D)J joining, the two proteins come together to form a complex (called **RAG**), which functions as a endonuclease, introducing double-stranded breaks precisely between gene segments to be joined and their flanking recombination signal sequences. RAG then initiates the rejoining process by recruiting enzymes involved in DNA double-strand repair in all cells.
  Mice or human deficient in either of the two *Rag* genes or in nonhomologous end joining are highly susceptible for infection because they are anable to carry out V(D)J recombination and consequently do not have functional B or T cells, a condition called *severe combined immunodeficiency (SCID)*.

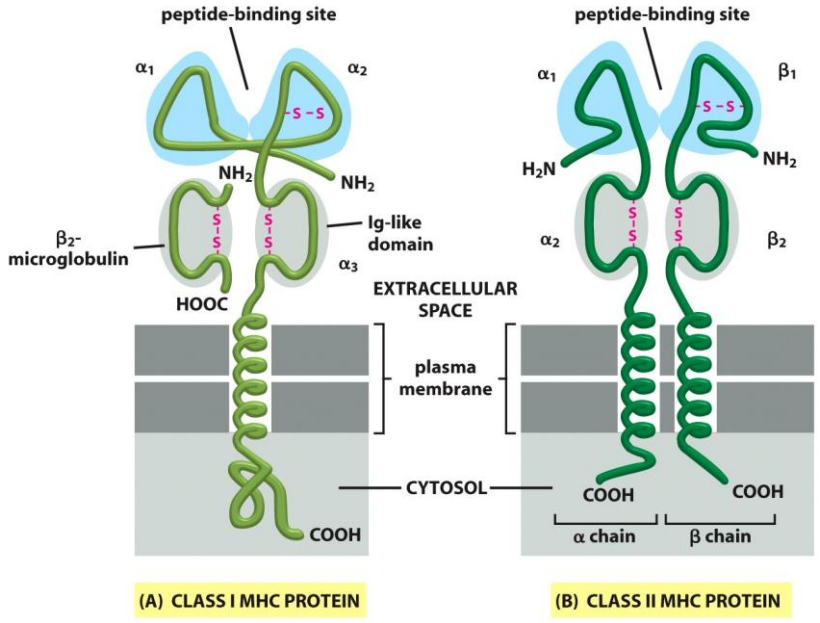


- During the joining of antibody (and T cell receptors) gene segments, as in nonhomologous end-joining, a variable number of nucleotides are often lost from ends of the recombining gene segments, and one or more randomly chosen nucleotides may also be inserted. This random loss and gain of nucleotides at joining sites is called **junctional diversification**, and it enormously increases the diversity if V-region coding sequences created by V(D)J recombination, specifically in the third hypervariable region. This increased diversification comes at a price, however. In many cases, it will shift the reading frame to produce a nonfunctional gene. Because roughly two in every three rearrangements are “nonproductive” in this way, many developing B cells never make a functional antibody molecule and consequently die in the bone marrow.

- **What is MHC system, what are the components and the roles**
  - T cells require *antigen-presenting cells* for activation because of the form of antigen they recognize are fragments of proteins antigens that have been partly degraded inside the antigen-presenting cell. Special proteins called **MHC proteins** bind to the peptide fragments and carry them to the surface of the antigen-presenting cell, where T cells can recognize them.
  - A large complex of genes called the **major histocompatibility complex** (**MHC**) encodes MCH proteins. There are two main classes of MHC proteins. *Class I MHC proteins* mainly present foreign peptides to cytotoxic T cells, and *class II MHC proteins* mainly present foreign peptides to helper and regulatory T cells.

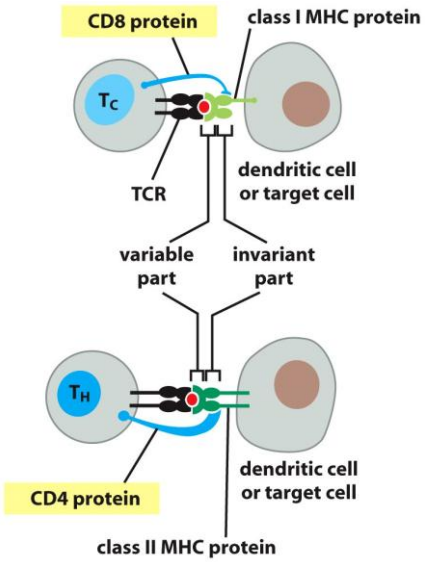


- Class I and class II MHC proteins have very similar overall structures. They are both transmembrane heterodimers with extracellular N-terminal domains that bind antigen for presentation to T cells. Any individual can only make a small number of different classic MHC proteins, which together must be able to present peptide fragments from almost any foreign proteins to T cells. Thus, unlike an antibody molecule, each MHC protein has to be able to bind a very large number of different peptides.



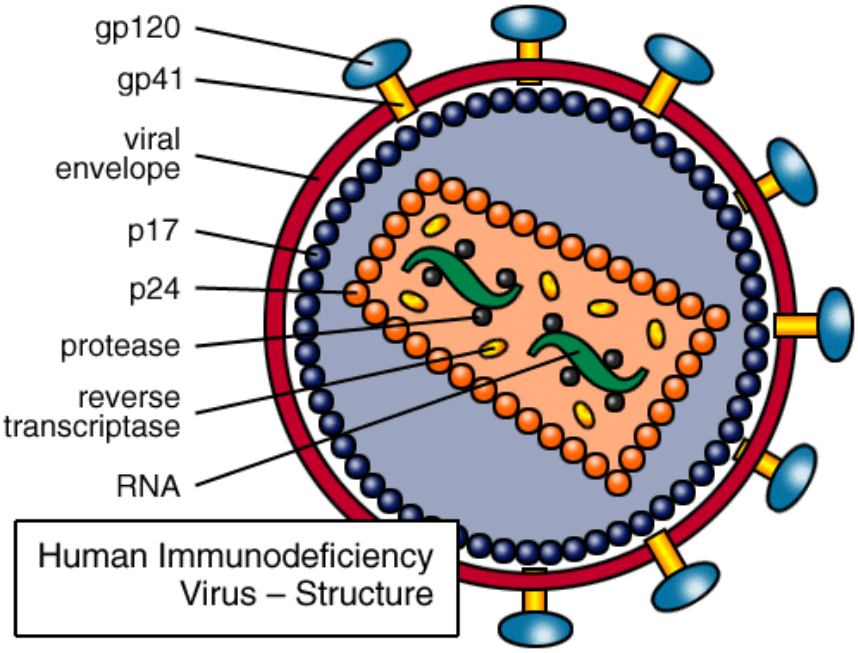
- The affinity if TCRs for peptide-MHC complexes on an antigen-presenting cell or target cell is usually too low by itself to mediate a functional interaction between the two cells. When accessory receptors have a direct role on activating the T cell by generating their own intracellular signals, they are called **co-receptors**. The most important and best understood of the co-receptors on T cells are the **CD4** and **CD8** proteins, both of which are single-pass transmembrane proteins with extracellular Ig-like domains. Like TCRs they recognize MHC proteins, but unlike TCRs, they bind to invariant parts of the protein, far away from the petide-binding groove.
    - **CD4** is expressed on both helper T cells and regulatory T cells and binds to class II MHC proteins

    - **CD8** is expressed on cytotoxic T cells and binds to class I MHC proteins.
- Thus, CD4 and CD8 contributes to T cell recognition by helping the T cell to focus of particular MHC proteins, and thereby on particular types of target cells: the recognition of class I MHC proteins allows cytotoxic T cells to focus on any host cell, while the recognition of class II MHC proteins allows helper T cells to focus on a small subset of cells – most notably dendritic cells, macrophages, and B cells.

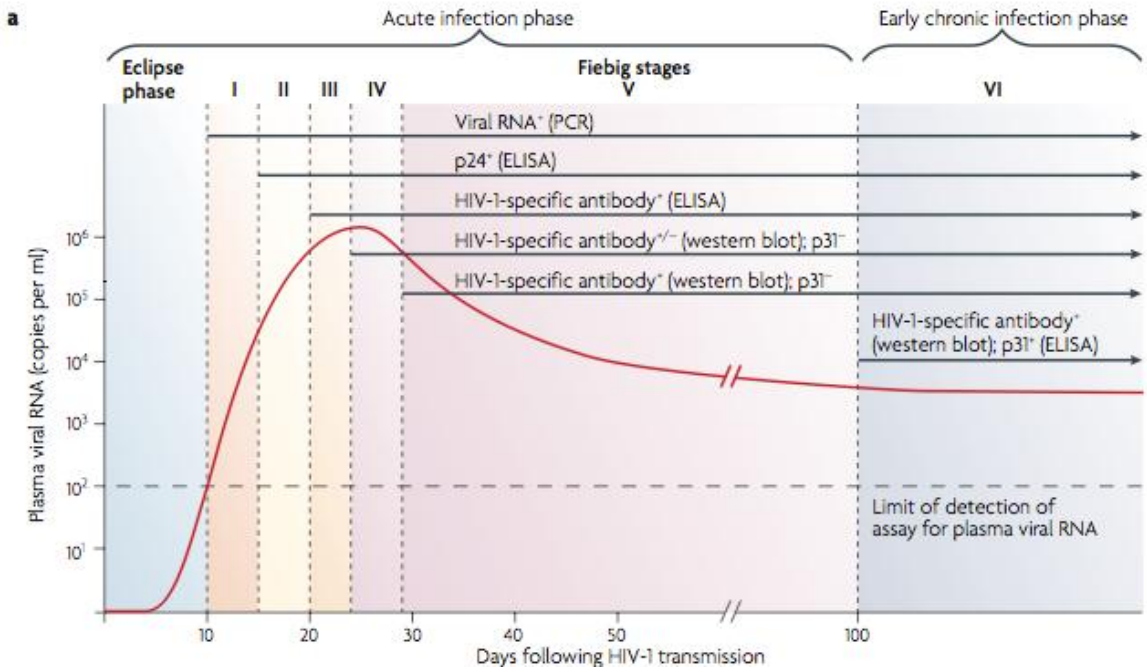


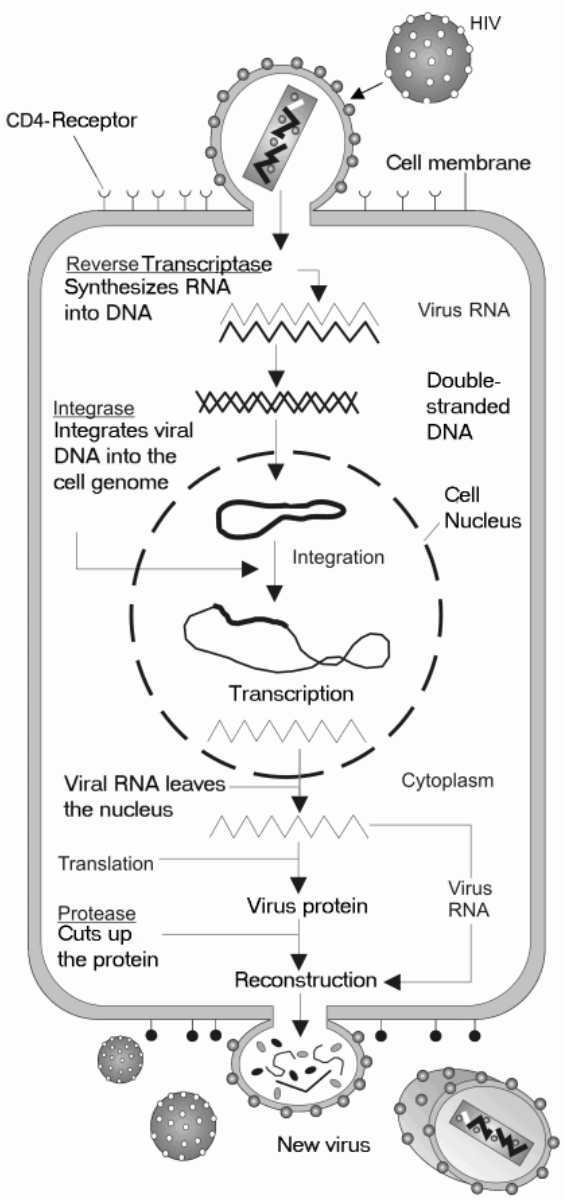
Topic A

- **Structure of the virus**



- **Mode and stages of infections**





- **Problems connected to vaccine design**
  - High genetic variability
  - Fast replication cycle
  - High mutation rate
  - Recombinogenic properties of reverse transcriptase

Topic B

- **What is a biofilm**
  - Colonies of microbial cells encased in a porous matrix and attached to a surface
    - Trap nutrients, help prevent detachment from surfaces in flowing system, favorable niche for Bacteria, increased chance of survival and ability for easy genetic exchange, but also for protection.

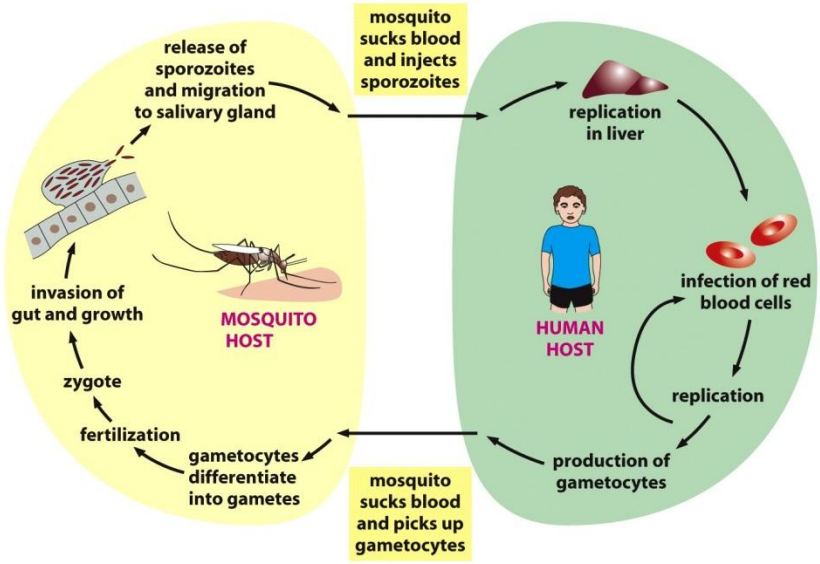
- **Terminology:**
  - **Public goods –** The production of pyoverdin is metabolically costly to the individual; and as these molecules can be utilized by other cells following release, they represent a potential public good
  - **Cheating bacteria –** Does not produce public goods
  - **Kin discrimination –** Recognition of your own kin. It can be achieved by cellular communication and recognition of genetically similar cells (quorum sensing) or limited dispersal.
  - **Direct fitness benefits –** Gain for the organism itself
  - **Indirect fitness benefits –** Gain for your own kin

- **Concept of quorum sensing**
  - Communication within a microbial population via secretion of autoinducers/pheromones
  - Coordination of gene expression
  - Accumulation of extracellular signal allows a cell to assess the number of bacteria in the same population, so that the whole population can coordinate action

- **Altruistic behavior in fruiting bodies (*dictyostelium discoideum)***
  - The cells form a fruiting body, containing spores, to be able to spread to new territories. The formation of this stalk requires sacrifices from the cells creating it that causes their death.

Topic C

- **The life cycle of *Plasmodium falciparum***



- **Genetic determinants of human resistance to malaria**
    - Sickle cell anemia, see Topic 6.

- **Antimalaria drugs**
    - **Chloroquine** – Inhibits hemozoin formation, thus killing the parasite with excess haematin,
    - **Artemmisinin** – Maybe activated by Fe-containing compounds, mechanisms not known
        - **Hypthesis**: ER, vacuole or mitochondrion

- **Vaccine development**
    - **Pre-erythrotic vaccines** – Target sporozoites or hepatic schizonts
    - **Blood-stage vaccines** – Will not stop the infection but prevents clinical illness and death.