Structure of cells

A. Comparison of prokaryotes and eukaryotes ●

Present-day living organisms can be divided into two large groups—the prokaryotes and eukaryotes. The **prokaryotes** are represented by bacteria *(eubacteria* and *archaebacteria).* These are almost all small unicellular organisms only a few microns (10^{-6} m) in size. The **eukaryotes** include *fungi*, *plants*, and *animals* and comprise both unicellular and multicellular organisms. Multicellular eukaryotes are made up of a wide variety of cell types that are specialized for different tasks. Eukaryotic cells are much larger than prokaryotic ones (volume ratio approximately 2000 : 1). The most important distinguishing feature of these cells in comparison with the prokaryotes is the fact that they have a **nucleus** (*karyon* in Greek—hence the term).

In comparison with the prokaryotes, eukaryotic cells have greater specialization and complexity in their structure and functioning. Eukaryotic cells are structured into *compartments* (see below). The metabolism and synthesis of macromolecules are distributed through these reaction spaces and are separately regulated. In prokaryotes, these functions are organized in a simpler fashion and are spatially closely related.

Although the storage and transfer of genetic information function according to the same principle in the prokaryotes and eukaryotes, there are also differences. Eukaryotic DNA consists of very long, linear molecules with a total of 10^7 to more than 10^{10} base pairs (bp), only a small fraction of which are used for genetic information. In eukaryotes, the genes (20000–50000 per genome) are usually interrupted by non-coding regions (*introns*). Eukaryotic DNA is located in the nucleus, where together with histones and other proteins it forms the chromatin (see p. 238).

In prokaryotes, by contrast, DNA is ring-shaped, much shorter (up to 5 10^6 bp), and located in the cytoplasm. Almost all of it is used for information storage, and it does not contain any introns.

B. Structure of an animal cell ●

In the human body alone, there are at least 200 different cell types. The illustration outlines the basic structures of an animal cell in an extremely simplified way. The details given regarding the proportion of the compartments relative to cell volume (highlighted in yellow) and their numbers per cell frequency (blue) refer to mammalian hepatocytes (liver cells). The figures can vary widely from cell type to cell type.

The eukaryotic cell is subdivided by membranes. On the outside, it is enclosed by a **plasma membrane.** Inside the cell, there is a large space containing numerous components in solution—the **cytoplasm**. Additional membranes divide the internal space into *compartments* (confined reaction spaces). Welldefined compartments of this type are known as **organelles**.

The largest organelle is the **nucleus** (see p. 208). It is easily recognized using the light microscope. The **endoplasmic reticulum** (ER), a closed network of shallow sacs and tubules (see pp. 226ff.), is linked with the outer membrane of the nucleus. Another membrane-bound organelle is the **Golgi apparatus** (see p. 228), which resembles a bundle of layered slices. The **endosomes** and **exosomes** are bubble-shaped compartments *(* vesicles*)* that are involved in the exchange of substances between the cell and its surroundings. Probably the most important organelles in the cell's metabolism are the **mitochondria,** which are around the same size as bacteria (see pp. 210ff.). The **lysosomes** and **peroxisomes** are small, globular organelles that carry out specific tasks. The whole cell is traversed by a framework of proteins known as the **cytoskeleton** (see pp. 204ff.).

In addition to these organelles, plant cells (see p. 43) also have plastids—eg., **chloroplasts**, in which photosynthesis takes place (see p. 128). In their interior, there is a large, fluid-filled **vacuole**. Like bacteria and fungi, plant cells have a rigid cell wall consisting of polysaccharides and proteins.

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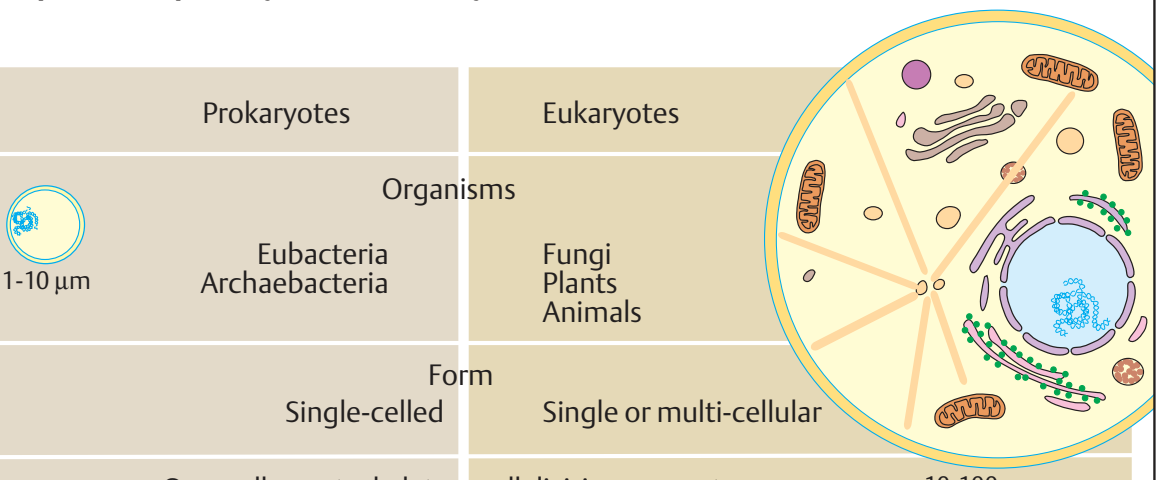
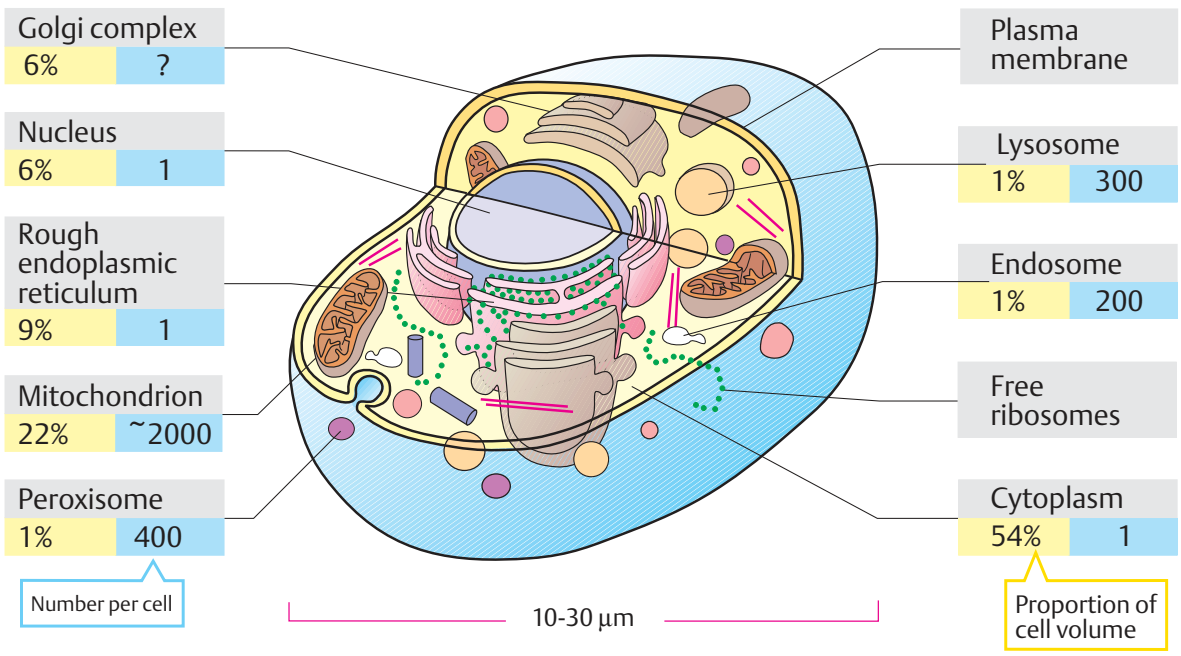
A. Comparison of prokaryotes and eukaryotes



Prokaryotes	Eukaryotes
Organisms	
Eubacteria Archaebacteria	Fungi Plants Animals
Form	
Single-celled	Single or multi-cellular
Organelles, cytoskeleton, cell division apparatus	
Missing	Present, complicated, specialized
DNA	
Small, circular, no introns, plasmids	Large, in nucleus, many introns
RNA: Synthesis and maturation	
Simple, in cytoplasm	Complicated, in nucleus
Protein: Synthesis and maturation	
Simple, coupled with RNA synthesis	Complicated, in the cytoplasm and the rough endoplasmic reticulum
Metabolism	
Anaerobic or aerobic very flexible	Mostly aerobic, compartmented
Endocytosis and Exocytosis	
no	yes

B. Structure of an animal cell



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Cell fractionation

A. Isolation of cell organelles ○

To investigate the individual compartments of the cell (see p. 196), various procedures have been developed to enrich and isolate cell organelles. These are mainly based on the size and density of the various organelles.

The isolation of cell components starts with **disruption** of the tissue being examined and subsequent **homogenization** of it (breaking down the cells) in a suitable buffer (see below). Homogenization using the "Potter" (the Potter–Elvehjem homogenizer, a rotating Teflon pestle in a glass cylinder) is particularly suitable for animal tissue. This method is very gentle and is therefore used to isolate fragile structures and molecules. Other cell disruption procedures include **enzymatic lysis** with the help of enzymes that break down the cell wall, **mechanical disruption** by grinding frozen tissue, cutting or smashing with rotating knives, large pressure changes, osmotic shock, and repeated freezing and thawing.

To isolate intact organelles, it is important for the homogenization solution to be *isotonic*—i. e., the osmotic value of the buffer has to be the same as that of the interior of the cell. If hypotonic solutions were used, the organelles would take up water and burst, while in hypertonic solutions they would shrink.

Homogenization is followed by coarse **filtration** through gauze to remove intact cells and connective-tissue fragments. The actual fractionation of cellular components is then carried out by **centrifugation steps**, in which the gravitational force (given as multiples of the earth's gravity, $g = 9.81\ m\ s^{-2}$) is gradually increased (*differential centrifugation*; see p. 200). Due to the different shapes and densities of the organelles, this leads to successive sedimentation of each type out of the suspension.

Nuclei already sediment at low accelerations that can be achieved with bench-top centrifuges. Decanting the residue (the "supernatant") and carefully suspending the sediment (or "pellet") in an isotonic medium yields a fraction that is enriched with nuclei. However, this fraction may still contain other cellular components as contaminants—e. g., fragments of the cytoskeleton.

Particles that are smaller and less dense than the nuclei can be obtained by step-by-step acceleration of the gravity on the supernatant left over from the first centrifugation. However, this requires very powerful centrifuges (high-speed centrifuges and ultracentrifuges). The sequence in which the fractions are obtained is: **mitochondria, membrane vesicles**, and **ribosomes**. Finally, the supernatant from the last centrifugation contains the **cytosol** with the cell's soluble components, in addition to the buffer.

The isolation steps are carried out at low temperatures on principle (usually 0–5 °C), to slow down degradation reactions—e. g., due to released enzymes and other influencing factors. The addition of thiols and chelating agents protects functional SH groups from oxidation. Isolated cell organelles quickly lose their biological activity despite these precautions. Nevertheless, it is possible by working carefully to isolate mitochondria that will still take up substrates for a few hours in the test tube and produce ATP via oxidative phosphorylation.

B. Marker molecules ○

During cell fractionation, it is very important to analyze the purity of the fractions obtained. Whether or not the intended organelle is present in a particular fraction, and whether or not the fraction contains other components, can be determined by analyzing characteristic **marker molecules.** These are molecules that occur exclusively or predominantly in one type of organelle. For example, the activity of organelle-specific enzymes **(marker enzymes)** is often assessed. The distribution of marker enzymes in the cell reflects the compartmentation of the processes they catalyze. These reactions are discussed in greater detail here under the specific organelles.

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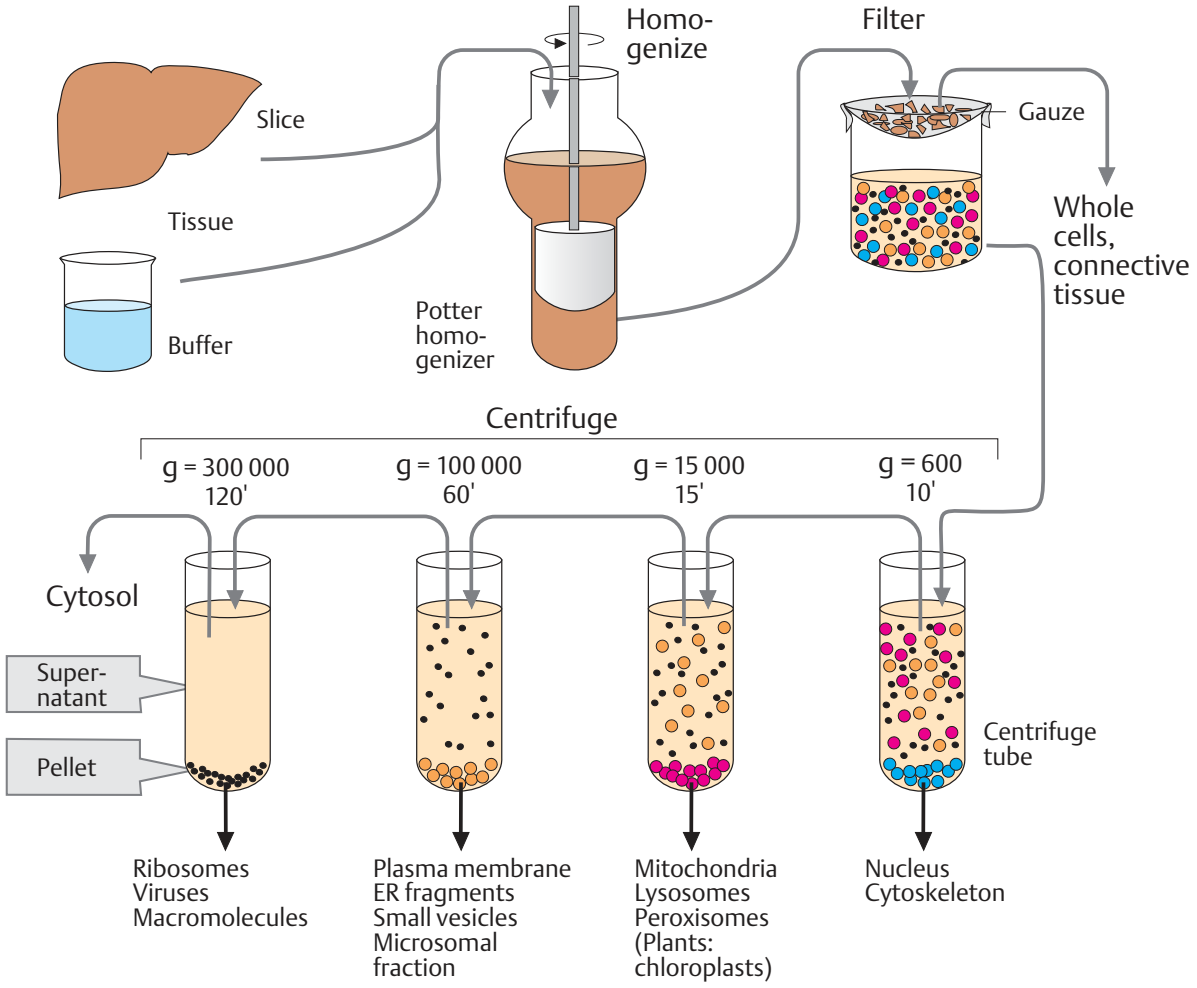
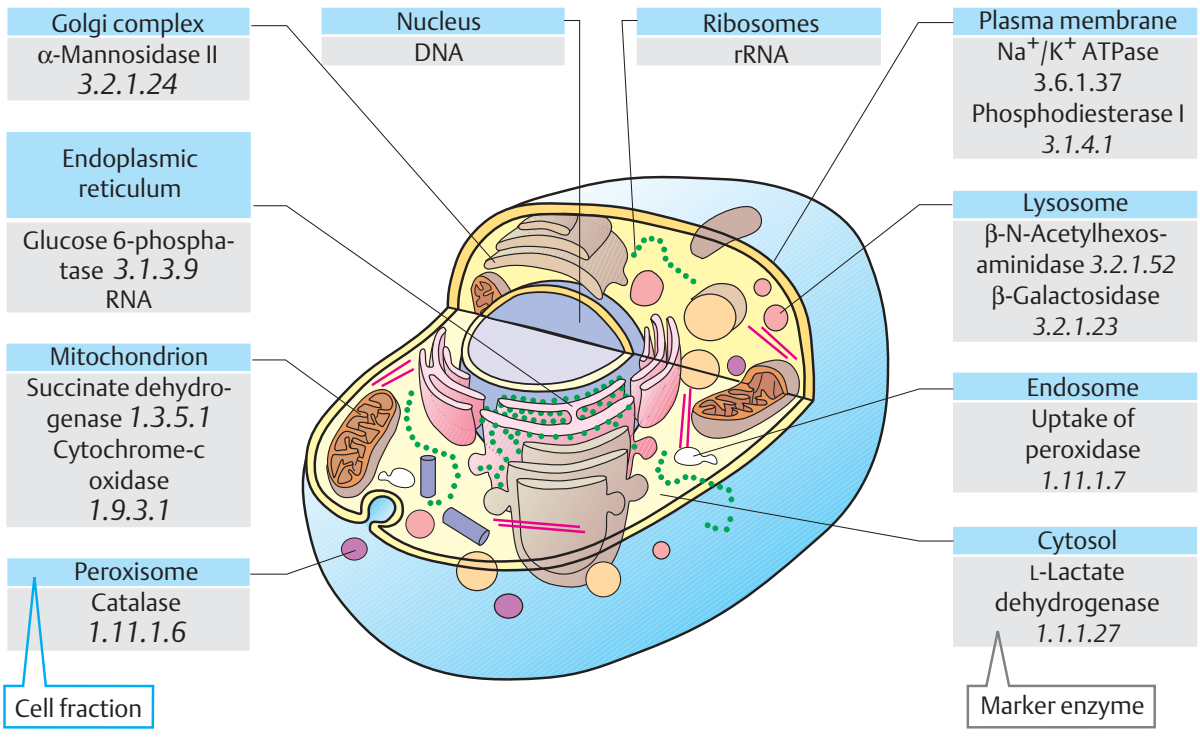
A. Isolation of cell organelles



B. Marker molecules



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Centrifugation

A. Principles of centrifugation ○

In a solution, particles whose density is higher than that of the solvent sink (*sediment*), and particles that are lighter than it *float* to the top. The greater the difference in density, the faster they move. If there is no difference in density (isopyknic conditions), the particles *hover*. To take advantage of even tiny differences in density to separate various particles in a solution, gravity can be replaced with the much more powerful "centrifugal force" provided by a centrifuge.

Equipment. The acceleration achieved by centrifugation is expressed as a multiple of the earth's gravitational force (g = 9.81 m s^{-2}). Bench-top centrifuges can reach acceleration values of up to 15000 g, while highspeed refrigerated centrifuges can reach 50000 g and ultracentrifuges, which operate with refrigeration and in a vacuum, can reach 500000 g. Two types of rotor are available in high-powered centrifuges: *fixed angle rotors* and *swingout rotors* that have movable bucket containers. The tubes or buckets used for centrifugation are made of plastic and have to be very precisely adjusted to avoid any imbalances that could lead to accidents.

Theory. The velocity (v) of particle sedimentation during centrifugation depends on the angular velocity ω of the rotor, its effective radius (r_{eff}, the distance from the axis of rotation), and the particle's sedimentation properties. These properties are expressed as the **sedimentation coef•cient** S (1 Svedberg, = 10^{-13} s). The sedimentation coef cient depends on the mass M of the particle, its shape (expressed as the coef cient of friction, f), and its density (expressed as the reciprocal density $\bar{v}$, "partial specific volume").

At the top right, the diagram shows the densities and sedimentation coef cients for biomolecules, cell organelles, and viruses. Proteins and protein-rich structures have densities of around 1.3 g cm^{-3}, while nucleic acids show densities of up to 2 g cm^{-3}. Equilibrium sedimentation of nucleic acids therefore requires high-density media—e.g., concentrated solutions of cesium chloride (CsCl). To allow comparison of S values measured in different media, they are usually corrected to values for water at 20 °C ("S_{20w}").

B. Density gradient centrifugation ○

Density gradient centrifugation is used to separate macromolecules that differ only slightly in size or density. Two techniques are commonly used.

In **zonal centrifugation,** the sample being separated (e.g., a cell extract or cells) is placed on top of the centrifugation solution as a thin layer. During centrifugation, the particles move through the solution due to their greater density. The rate of movement basically depends on their molecular mass (see **A**, formulae). Centrifugation stops before the particles reach the bottom of the tube. Drilling a hole into the centrifugation tube and allowing the contents to drip out makes it possible to collect the different particles in separate fractions. During centrifugation, the solution tube is stabilized in the tube by a **density gradient**. This consists of solutions of carbohydrates or colloidal silica gel, the concentration of which increases from the surface of the tube to the bottom. Density gradients prevent the formation of convection currents, which would impair the separation of the particles.

Isopyknic centrifugation, which takes much longer, starts with a CsCl solution in which the sample material (e.g., DNA, RNA, or viruses) is homogeneously distributed. A density gradient only forms *during* centrifugation, as a result of sedimentation and diffusion processes. Each particle moves to the region corresponding to its own *buoyant density*. Centrifugation stops once equilibrium has been reached. The samples are obtained by fractionation, and their concentration is measured using the appropriate methods.

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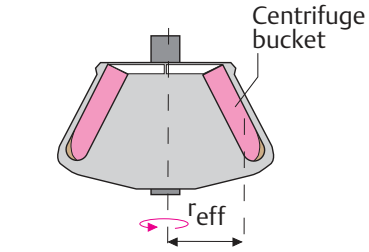
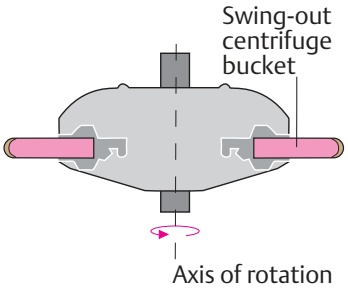
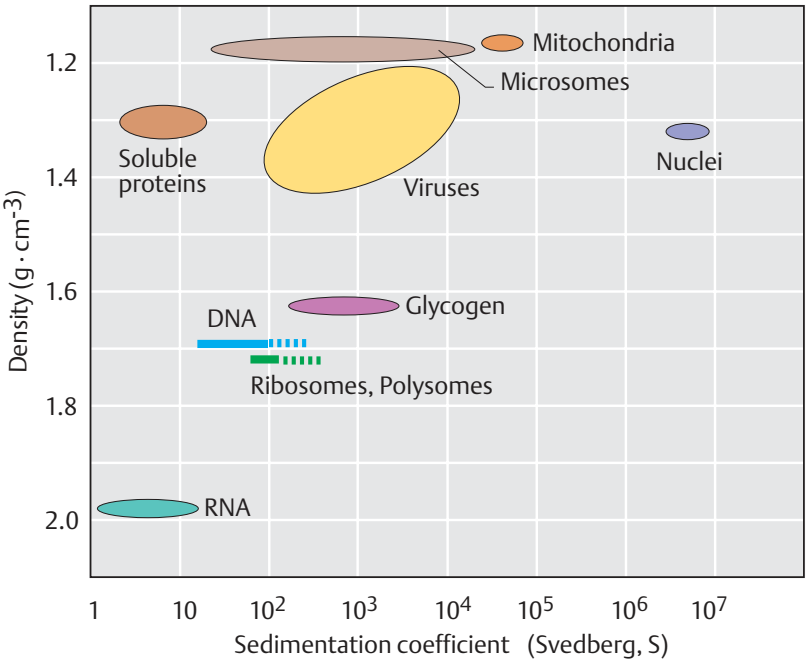
A. Principles of centrifugation



Fixed angle rotor



Swing-out bucket rotor



g: Gravitational acceleration

v: Sedimentation velocity (cm · s^{-1})

ω: Angular velocity (rad · s^{-1})

r_{eff}: Effective radius (cm)

$$g = \omega^2 \cdot r_{eff}$$

$$v = \omega^2 \cdot r_{eff} \cdot s$$

$$s = \frac{M \cdot (1 - \bar{v} \cdot r)}{f}$$

s: Sedimentation coefficient ($S = 10^{-13}$ s)

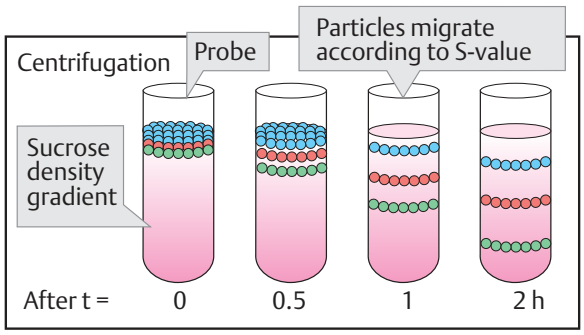
M: Molecular mass

$\bar{v}$: Partial specific particle volume ($cm^3 \cdot g^{-1}$)

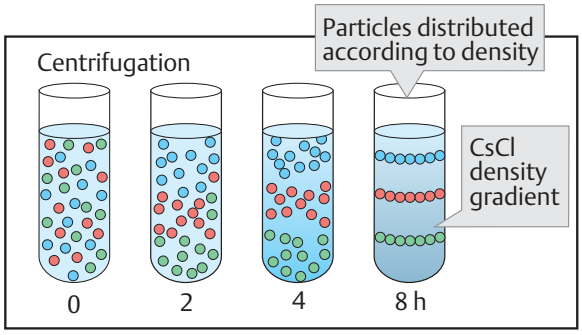
r: Density of the solution ($g \cdot cm^3$)

f: Coefficient of friction

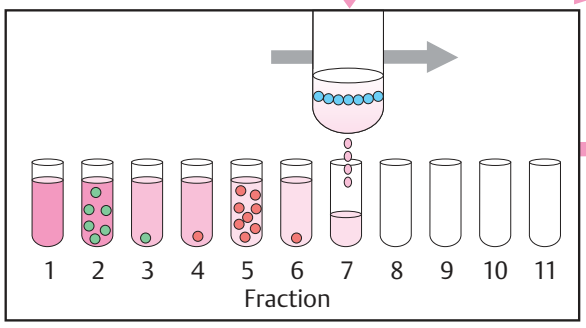
B. Density gradient centrifugation



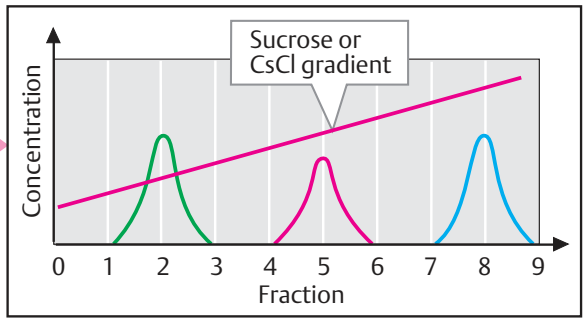
Zonal centrifugation



Isopyknic centrifugation



Fractionation



Detection

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Cell components and cytoplasm

The Gram-negative bacterium *Escherichia coli (E. coli)* is a usually harmless symbiont in the intestine of mammals. The structure and characteristics of this organism have been particularly well characterized. *E. coli* is also frequently used in genetic engineering (see p. 258).

A. Components of a bacterial cell ◑

A single *E. coli* cell has a **volume** of about 0.88 μm^3. One-sixth of this consists of membranes and one-sixth is DNA (known as the "nucleoid"). The rest of the internal space of the cell is known as **cytoplasm** (not "cytosol"; see p. 198).

The main component of *E. coli*—as in all cells—is **water** (70%). The other components are **macromolecules** (proteins, nucleic acids, polysaccharides), **small organic molecules**, and **inorganic ions**. The majority of the macromolecules are proteins, which represent ca. 55% of the dry mass of the cell. When a number of assumptions are made about the distribution and size (average mass 40 kDa) of proteins, it can be estimated that there are approximately 250000 protein molecules in the cytoplasm of an *E. coli* cell. In eukaryotic cells, which are about a thousand times larger, it is estimated that the number of protein molecules is in the order of several billion.

B. Looking inside a bacterial cell ○

The illustration shows a schematic view inside the **cytoplasm** of *E. coli*, magnified approximately one million times. At this magnification, a single carbon atom would be the size of a grain of salt, and an ATP molecule would be as large as a grain of rice. The detail shown is 100 nm long, corresponding to about 1/600th of the volume of a cell in *E. coli*. To make the macromolecules clearer, small molecules such as water, cofactors, and metabolites have all been omitted from the illustration. The section of the cytoplasm shown contains:

- Several hundred **macromolecules**, which are needed for protein biosynthesis—i. e., 30 ribosomes, more than 100 protein factors, 30 aminoacyl–tRNA synthases, 340 tRNA molecules, 2–3 mRNAs (each of which is 10 times the length of the section shown), and six molecules of RNA polymerase.
- About 330 other enzyme molecules, including 130 glycolytic enzymes and 100 enzymes from the tricarboxylic acid cycle.
- 30000 **small organic molecules** with masses of 100–1000 Da—e. g., metabolites of the intermediary metabolism and coenzymes. These are shown at a magnification 10 times higher in the bottom right corner.
- And finally, 50000 **inorganic ions.** The rest consists of water.

The illustration shows that the cytoplasm of cells is a compartment densely packed with macromolecules and smaller organic molecules. The distances between organic molecules are small. They are only separated by a few water molecules.

All of the molecules are in motion. Due to constant collisions, however, they do not advance in a straight path but move in zigzags. Due to their large mass, proteins are particularly slow. However, they do cover an average of 5 nm in 1 ms—a distance approximately equal to their own length. Statistically, a protein is capable of reaching any point in a bacterial cell in less than a second.

C. Biochemical functions of the cytoplasm ◑

In eukaryotes, the cytoplasm, representing slightly more than 50% of the cell volume, is the most important cellular compartment. It is the *central reaction space of the cell.* This is where many important pathways of the intermediary metabolism take place—e. g., glycolysis, the pentose phosphate pathway, the majority of gluconeogenesis, and fatty acid synthesis. Protein biosynthesis (translation; see p. 250) also takes place in the cytoplasm. By contrast, fatty acid degradation, the tricarboxylic acid cycle, and oxidative phosphorylation are located in the mitochondria (see p. 210).

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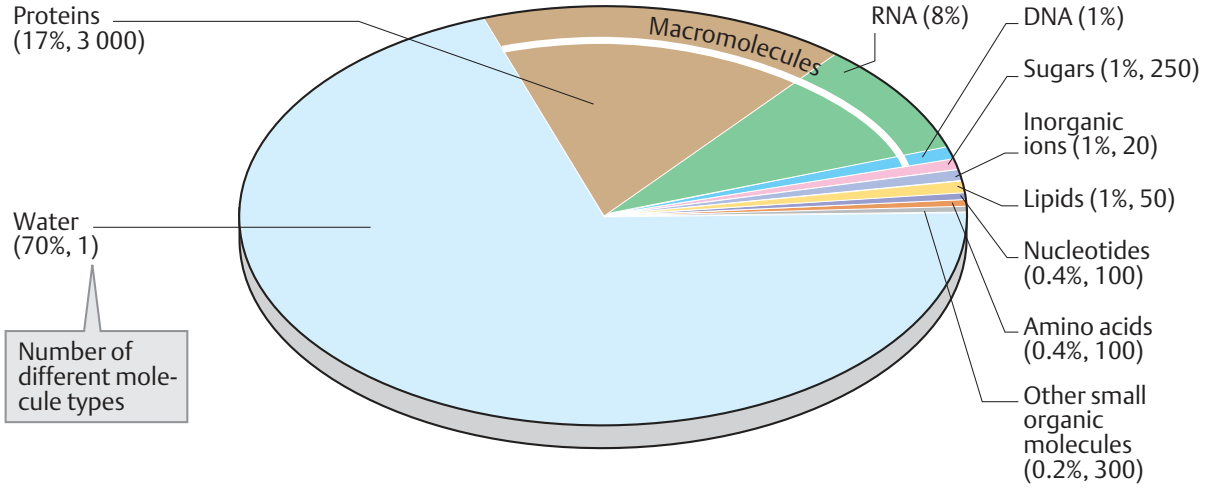
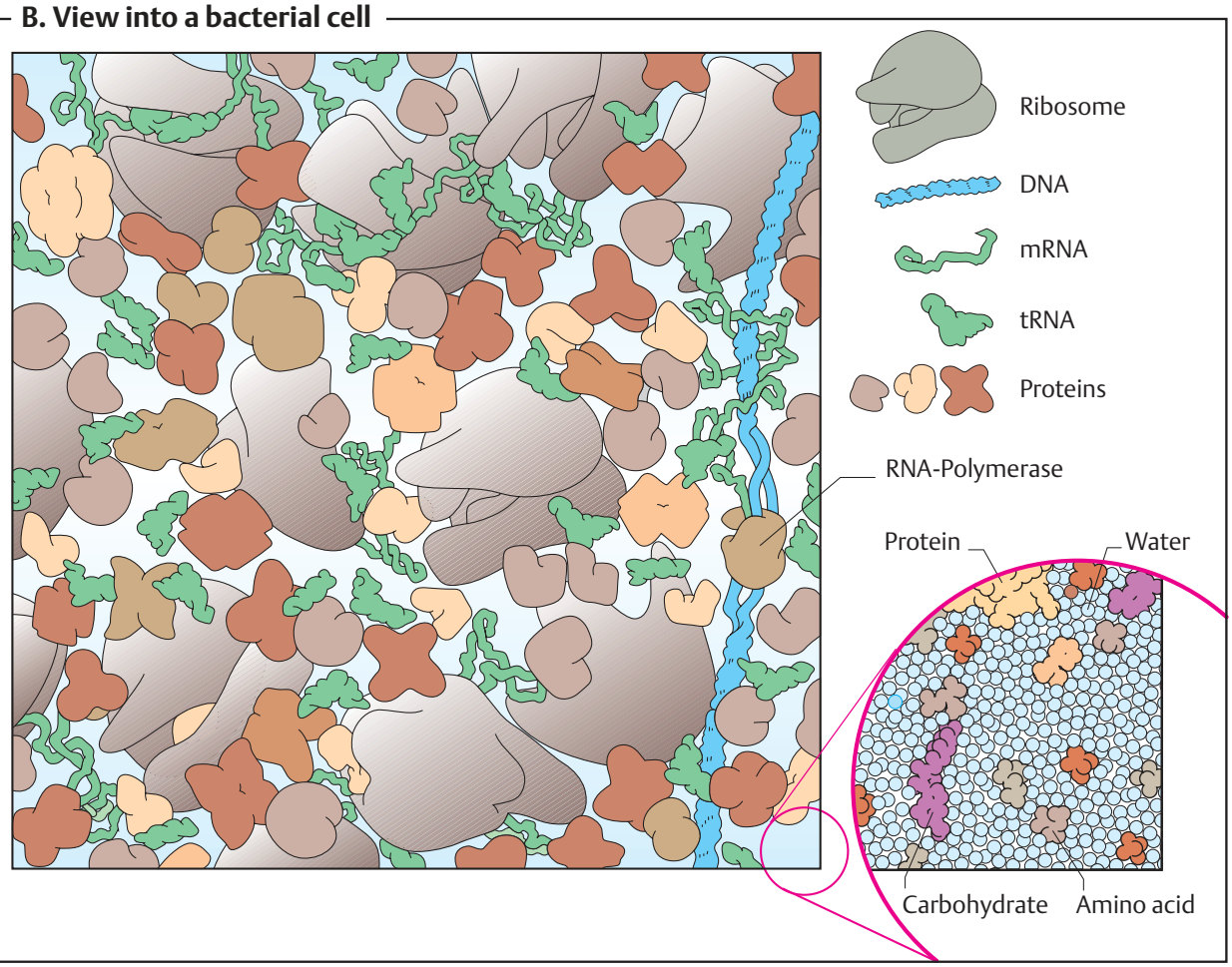
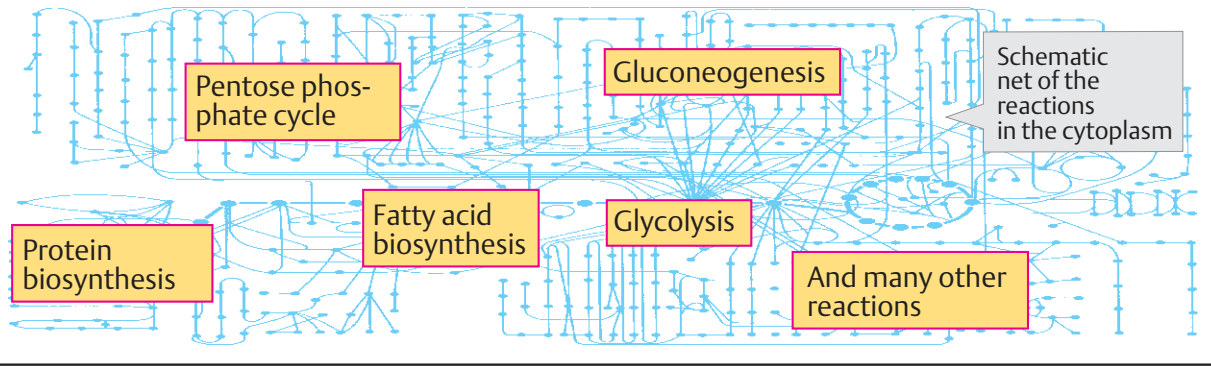
A. Components of a bacterial cell



B. View into a bacterial cell



C. Biochemical functions of the cytoplasm



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Cytoskeleton: components

The cytoplasm of eukaryotic cells is traversed by three–dimensional scaffolding structures consisting of filaments (long protein fibers), which together form the **cytoskeleton**. These filaments are divided into three groups, based on their *diameters*: **microfilaments** (6–8 nm), **intermediate filaments** (ca. 10 nm), and **microtubules** (ca. 25 nm). All of these filaments are polymers assembled from protein components.

A. Actin ◑

Actin, the most abundant protein in eukaryotic cells, is the protein component of the **microfilaments** (actin filaments). Actin occurs in two forms—a monomolecular form (**G actin**, globular actin) and a polymer (**F actin**, filamentous actin). G actin is an asymmetrical molecule with a mass of 42 kDa, consisting of two domains. As the ionic strength increases, G actin aggregates reversibly to form F actin, a helical homopolymer. G actin carries a firmly bound ATP molecule that is slowly hydrolyzed in F actin to form ADP. Actin therefore also has enzyme properties (*ATPase* activity).

As individual G actin molecules are always oriented in the same direction relative to one another, F actin consequently has *polarity*. It has two different ends, at which polymerization takes place at different rates. If the ends are not stabilized by special proteins (as in muscle cells), then at a critical concentration of G actin the (+) end of F actin will constantly grow, while the (–) end simultaneously decays. These partial processes can be blocked by fungal toxins experimentally. **Phalloidin**, a toxin contained in the *Amanita phalloides* mushroom, inhibits decay by binding to the (–) end. By contrast, **cytochalasins**, mold toxins with cytostatic effects, block polymerization by binding to the (+) end.

Actin–associated proteins. The cytoplasm contains more than 50 different proteins that bind specifically to G actin and F actin. Their actin uptake has various different functions. This type of bonding can serve to regulate the G actin pool (example: *profilin*), influence the polymerization rate of G actin (*villin*), stabilize the chain ends of F actin (*fragin, γ–actinin*), attach filaments to one another or to other cell components (*villin, α–actinin, spectrin),* or disrupt the helical structure of F actin (*gelsolin*). The activity of these proteins is regulated by protein kinases via Ca^{2+} and other second messengers (see p. 386).

B. Intermediate filaments ◑

The components of the intermediate filaments belong to five related protein families. They are specific for particular cell types. Typical representatives include the *cytokeratins, desmin, vimentin, glial fibrillary acidic protein* (GFAP), and *neurofilament*. These proteins all have a rod–shaped basic structure in the center, which is known as a *superhelix* ("coiled coil"; see keratin, p. 70). The dimers are arranged in an antiparallel fashion to form tetramers. A staggered head-to–head arrangement produces **protofilaments**. Eight protofilaments ultimately form an intermediary filament.

Free protein monomers of intermediate filaments rarely occur in the cytoplasm, in contrast to microfilaments and microtubules. Their polymerization leads to stable polymers that have no polarity.

C. Tubulins ◑

The basic components of the tube-shaped **microtubules** are α– and β–**tubulin** (53 and 55 kDa). These form α,β-heterodimers, which in turn polymerize to form linear protofilaments. Thirteen protofilaments form a ring-shaped complex, which then grows into a long tube as a result of further polymerization.

Like microfilaments, microtubules are dynamic structures with (+) and (–) ends. The (–) end is usually stabilized by bonding to the centrosome. The (+) end shows *dynamic instability*. It can either grow slowly or shorten rapidly. GTP, which is bound by the microtubules and gradually hydrolyzed into GDP, plays a role in this. Various proteins can also be associated with microtubules.

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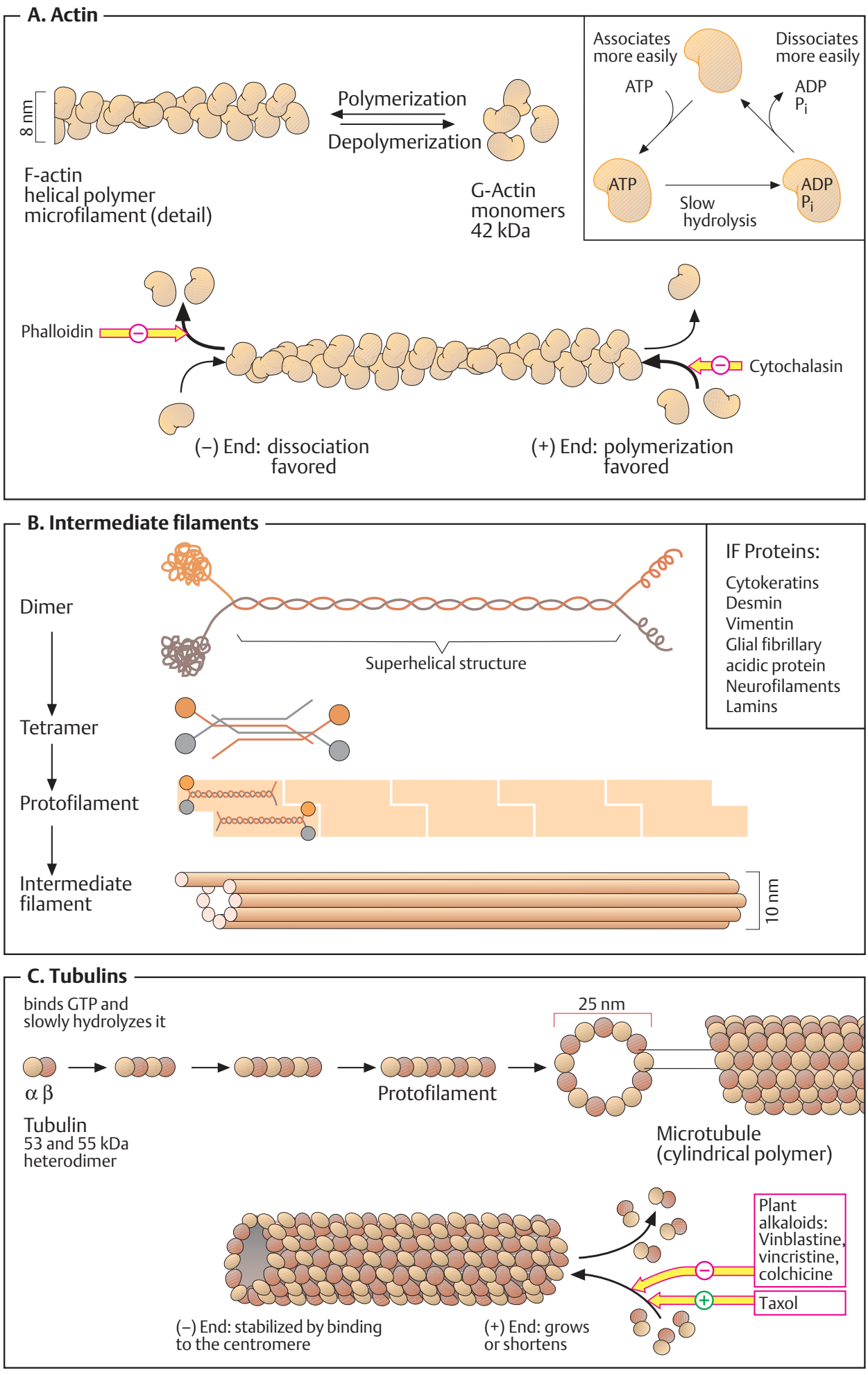

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Structure and functions

The cytoskeleton carries out three major tasks:

- It represents the cell's **mechanical scaffolding**, which gives it its typical shape and connects membranes and organelles to each other. This scaffolding has dynamic properties; it is constantly being synthesized and broken down to meet the cell's requirements and changing conditions.
- It acts as the **motor for movement** of animal cells. Not only muscle cells (see p. 332), but also cells of noncontractile tissues contain many different *motor proteins,* which they use to achieve coordinated and directed movement. Cell movement, shape changes during growth, cytoplasmic streaming, and cell division are all made possible by components of the cytoskeleton.
- It serves as a **transport track** within the cell. Organelles and other large protein complexes can move along the filaments with the help of the motor proteins.

A. Microfilaments and intermediate filaments ○

The illustration schematically shows a detail of the **microvilli** of an intestinal epithelial cell as an example of the structure and function of the components of the cytoskeleton (see also **C1**).

Microfilaments of *F actin* traverse the microvilli in ordered bundles. The microfilaments are attached to each other by actin–associated proteins, particularly *fimbrin* and *villin. Calmodulin* and a myosin–like *ATPase* connect the microfilaments laterally to the plasma membrane. *Fodrin,* another microfilament–associated protein, anchors the actin fibers to each other at the base, as well as attaching them to the cytoplasmic membrane and to a network of **intermediate filaments.** In this example, the microfilaments have a mainly static function. In other cases, actin is also involved in dynamic processes. These include muscle contraction (see p. 332), cell movement, phagocytosis by immune cells, the formation of microspikes and lamellipodia (cellular extensions), and the acrosomal process during the fusion of sperm with the egg cell.

B. Microtubules ○

Only the cell's **microtubules** are shown here. They radiate out in all directions from a center near the nucleus, the **centrosome**. The tube-shaped microtubules are constantly being synthesized and broken down at their (+) ends. In the centriole, the (–) end is blocked by associated proteins (see p. 204). The (+) end can also be stabilized by associated proteins—e.g., when the microtubules have reached the cytoplasmic membrane.

The microtubules are involved in defining the shape of the cell and also serve as guiding tracks for the transport of organelles. Together with associated proteins (*dynein, kinesin*), microtubules are able to carry out mechanical work—e.g., during the transport of mitochondria, the movement of cilia (hair-like cell protrusions in the lungs, intestinal epithelium, and oviduct) and the beating of the flagella of sperm. Microtubules also play a special role in the mitotic period of cell division (see p. 394).

C. Architecture ○

The complex structure and net-like density of the cytoskeleton is illustrated here using three examples in which the cytoskeletal components are visualized with the help of antibodies.

1. The border of an *intestinal epithelial cell* is seen here (see also **B**). There are **microfilaments** (**a**) passing from the interior of the cell out into the microvilli. The filaments are firmly held together by **spectrin** (**b**), an associated protein, and they are anchored to **intermediate filaments** (**c**).

2. Only **microtubules** are seen in this *fibroblast cell.* They originate from the microtubule organizing center (centrosome) and radiate out as far as the plasma membrane.

3. **Keratin filaments** are visible here in an *epithelial cell.* Keratin fibers belong to the group of **intermediate filaments** (see pp. 70, 204; **d** = nucleus).

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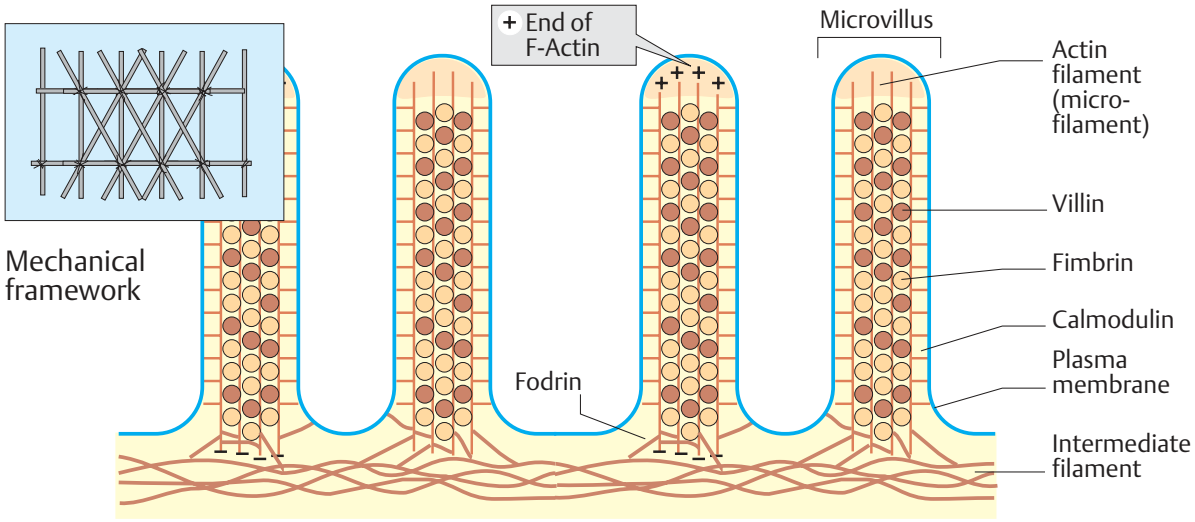
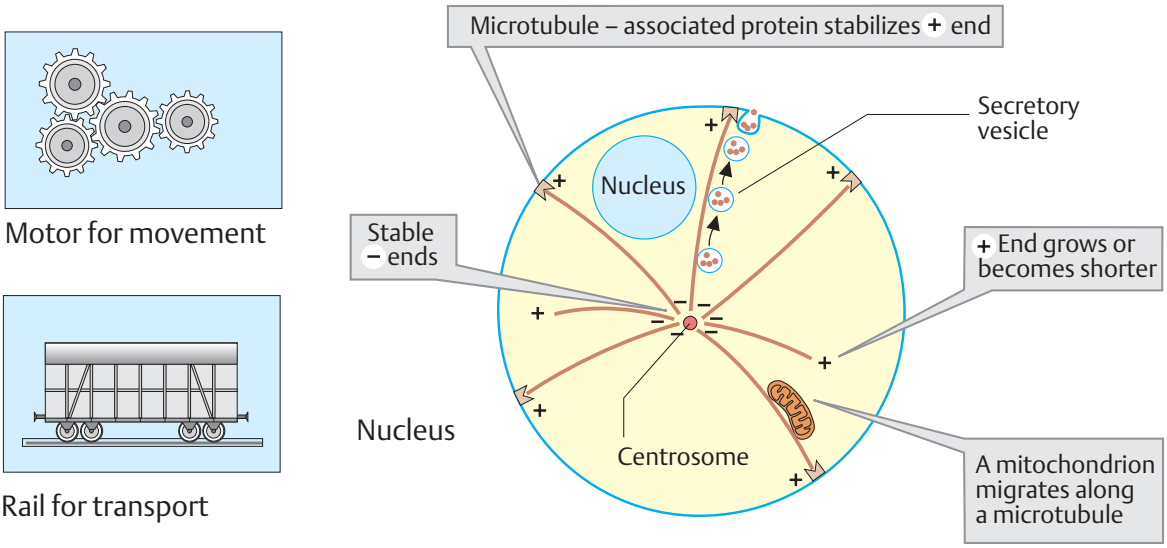
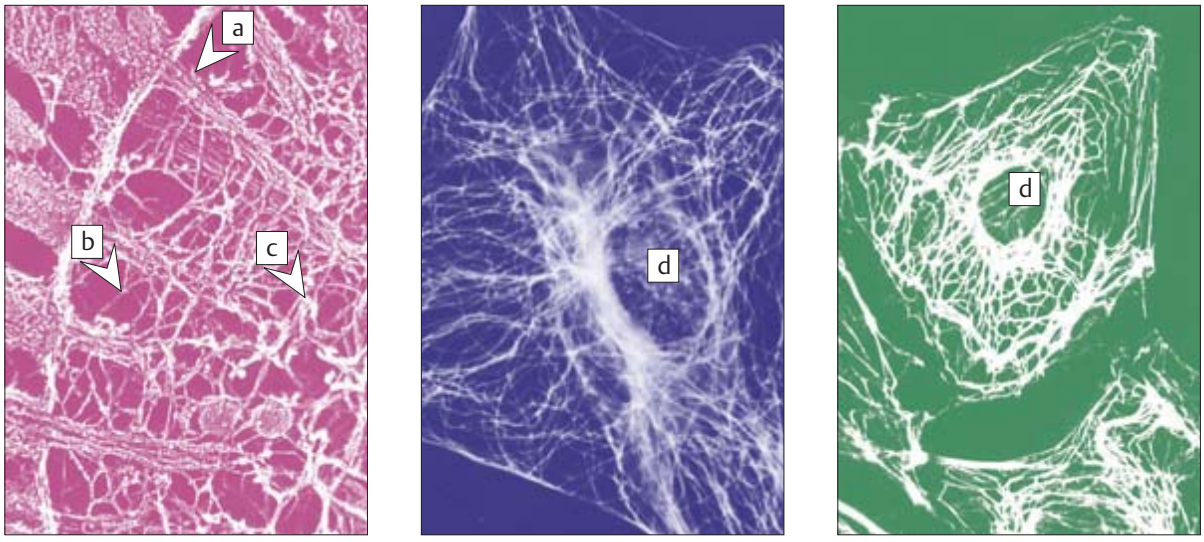
A. Microfilaments and intermediate filaments



B. Microtubules



C. Architecture



1. Microfilaments **2.** Microtubules **3.** Intermediate filaments

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Nucleus

A. Nucleus ●

The nucleus is the largest organelle in the eukaryotic cell. With a diameter of about 10 μm, it is easily recognizable with the light microscope. This is the location for *storage, replication,* and *expression* of genetic information.

The nucleus is separated from the cytoplasm by the **nuclear envelope**, which consists of the **outer** and **inner nuclear membranes**. Each of the two nuclear membranes has two layers, and the membranes are separated from each other by the **perinuclear space**. The outer nuclear membrane is continuous with the rough endoplasmic reticulum and is covered with ribosomes. The inner side of the membrane is covered with a protein layer (the nuclear lamina), in which the nuclear structures are anchored.

The nucleus contains almost all of the cell's **DNA** (around 1% of which is mitochondrial DNA). Together with histones and structural proteins, the nuclear DNA forms the **chromatin** (see p. 238). It is only during cell division that chromatin condenses into *chromosomes,* which are also visible with the light microscope. During this phase, the nuclear membrane temporarily disintegrates.

During the phase between cell divisions, the *interphase,* it is possible to distinguish between the more densely packed **heterochromatin** and loose **euchromatin** using an electron microscope. Active *transcription* of DNA into mRNA takes place in the region of the euchromatin. A particularly electron-dense region is noticeable in many nuclei—the **nucleolus** (several nucleoli are sometimes present). The DNA in the nucleolus contains numerous copies of the genes for rRNAs (see p. 242). They are constantly undergoing transcription, leading to a high local concentration of RNA.

B. Nuclear pores ◑

The exchange of substances between the nucleus and the cytoplasm is mediated by **pore complexes** with complicated structures, which traverse the nuclear membrane. The nuclear pores consist of numerous proteins that form several connected rings of varying diameter. Low-molecular structures and small proteins can enter the nucleus without difficulty. By contrast, larger proteins (over 40 kDa) can only pass through the nuclear pores if they carry a **nuclear localization sequence** consisting of four successive basic amino acids inside their peptide chains (see p. 228). mRNAs and rRNAs formed in the nucleus cross the pores into the cytoplasm as complexes with proteins (see below).

C. Relationships between the nucleus and cytoplasm ◑

Almost all of the RNA in the cell is synthesized in the nucleus. In this process, known as **transcription**, the information stored in DNA is transcribed into RNA (see p. 242). As mentioned above, *ribosomal RNA* (rRNA) is mainly produced in the nucleolus, while *messenger* and *transfer RNA* (mRNA and tRNA) are formed in the region of the euchromatin. Enzymatic duplication of DNA—**replication**—also only takes place in the nucleus (see p. 240).

The nucleotide components required for transcription and replication have to be imported into the nucleus from the cytoplasm. Incorporation of these components into RNA leads to primary products, which are then altered by cleavage, excision of introns, and the addition of extra nucleotides (**RNA maturation**; see p. 242). It is only once these process have been completed that the RNA molecules formed in the nucleus can be exported into the cytoplasm for protein synthesis (**translation**; see p. 250).

The nucleus is not capable of synthesizing proteins. All of the nuclear proteins therefore have to be imported—the *histones* with which DNA is associated in chromatin, and also the so–called *non–histone proteins* (DNA polymerases and RNA polymerases, auxiliary and structural proteins, transcription factors, and ribosomal proteins). Ribosomal RNA (rRNA) already associates with proteins in the nucleolus to form ribosome precursors.

A special metabolic task carried out by the nucleus is **biosynthesis of NAD^+**. The immediate precursor of this coenzyme, *nicotinamide mononucleotide* (NMN^+), arises in the cytoplasm and is then transported into the nucleolus, where it is enzymatically converted into the dinucleotide NAD^+. Finally, NAD^+ then returns to the cytoplasm.

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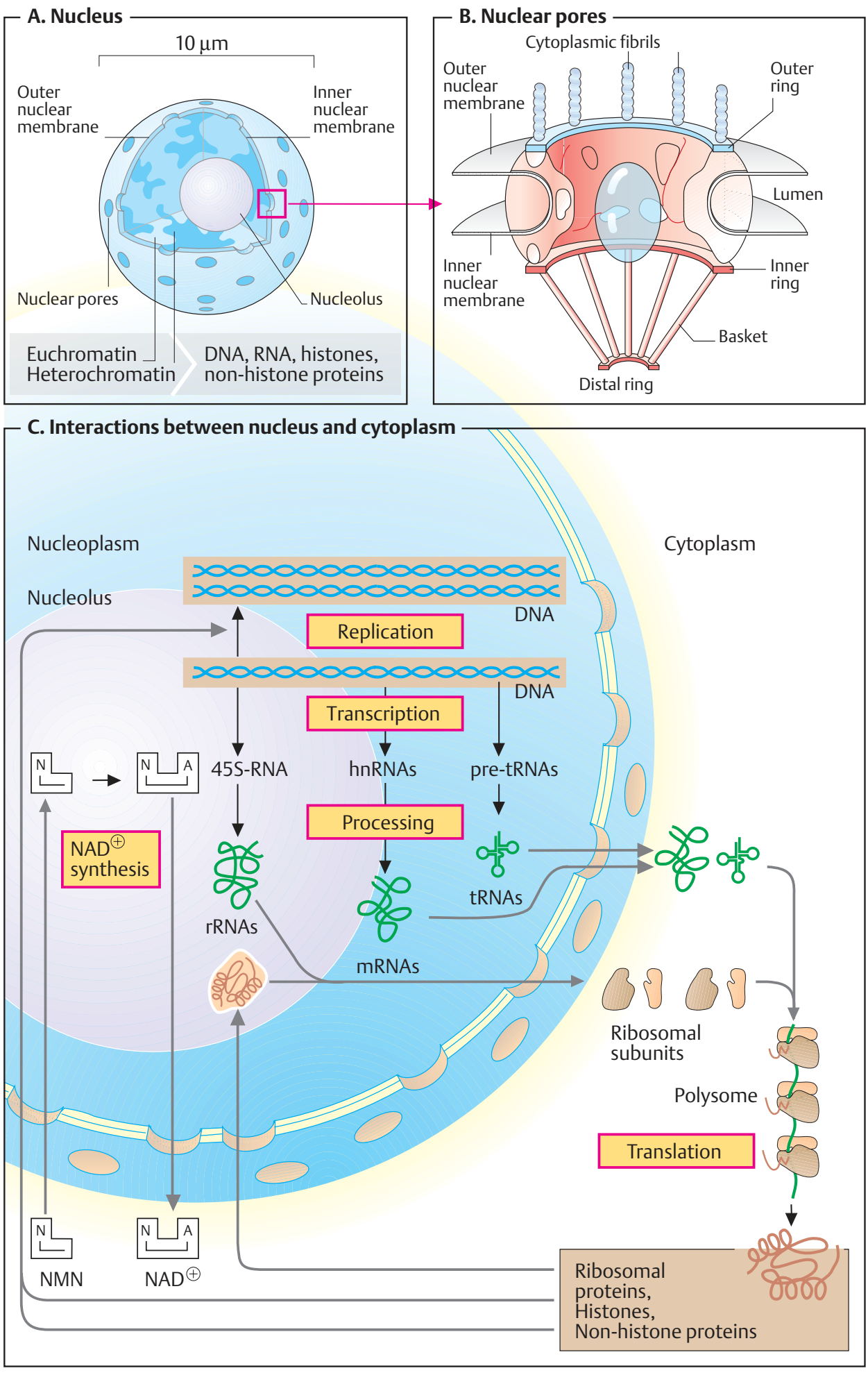

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Structure and functions

A. Mitochondrial structure ◑

Mitochondria are bacteria-sized organelles (about 1 × 2 μm in size), which are found in large numbers in almost all eukaryotic cells. Typically, there are about 2000 mitochondria per cell, representing around 25% of the cell volume. Mitochondria are enclosed by two membranes—a smooth **outer** membrane and a markedly folded or tubular **inner mitochondrial membrane**, which has a large surface and encloses the **matrix space**. The folds of the inner membrane are known as **cristae**, and tube-like protrusions are called **tubules**. The **intermembrane space** is located between the inner and the outer membranes.

The number and shape of the mitochondria, as well as the numbers of cristae they have, can differ widely from cell type to cell type. Tissues with intensive oxidative metabolism—e.g., heart muscle—have mitochondria with particularly large numbers of cristae. Even within one type of tissue, the shape of the mitochondria can vary depending on their functional status. Mitochondria are mobile, plastic organelles.

Mitochondria probably developed during an early phase of evolution from aerobic bacteria that entered into symbiosis with primeval anaerobic eukaryotes. This **endosymbiont theory** is supported by many findings. For example, mitochondria have a ring-shaped DNA (four molecules per mitochondrion) and have their own ribosomes. The mitochondrial genome became smaller and smaller during the course of evolution. In humans, it still contains 16 569 base pairs, which code for two rRNAs, 22 tRNAs, and 13 proteins. Only these 13 proteins (mostly subunits of respiratory chain complexes) are produced in the mitochondrion. All of the other mitochondrial proteins are coded by the nuclear genome and have to be imported into the mitochondria after translation in the cytoplasm (see p. 228). The mitochondrial envelope consisting of two membranes also supports the endosymbiont theory. The inner membrane, derived from the former symbiont, has a structure reminiscent of prokaryotes. It contains the unusual lipid cardiolipin (see p. 50), but hardly any cholesterol (see p. 216).

Both mitochondrial membranes are very rich in proteins. **Porins** (see p. 214) in the outer membrane allow small molecules (< 10 kDa) to be exchanged between the cytoplasm and the intermembrane space. By contrast, the inner mitochondrial membrane is completely impermeable even to small molecules (with the exception of O_2, CO_2, and H_2O). Numerous **transporters** in the inner membrane ensure the import and export of important metabolites (see p. 212). The inner membrane also transports **respiratory chain** complexes, **ATP synthase**, and other enzymes. The matrix is also rich in enzymes (see **B**).

B. Metabolic functions ◑

Mitochondria are also described as being the cell's *biochemical powerhouse,* since—through **oxidative phosphorylation** (see p. 112)—they produce the majority of cellular ATP. **Pyruvate dehydrogenase** (PDH), the **tricarboxylic acid cycle**, β-**oxidation** of fatty acids, and parts of the **urea cycle** are located in the matrix. The **respiratory chain**, **ATP synthesis**, and enzymes involved in **heme biosynthesis** (see p. 192) are associated with the inner membrane.

The inner membrane itself plays an important part in oxidative phosphorylation. As it is impermeable to protons, the respiratory chain—which pumps protons from the matrix into the intermembrane space via complexes I, III, and IV—establishes a **proton gradient** across the inner membrane, in which the chemical energy released during NADH oxidation is conserved (see p. 126). ATP synthase then uses the energy stored in the gradient to form ATP from ADP and inorganic phosphate. Several of the transport systems are also dependent on the H^+ gradient.

In addition to the endoplasmic reticulum, the mitochondria also function as an intracellular **calcium reservoir**. The mitochondria also play an important role in "programmed cell death"—**apoptosis** (see p. 396).

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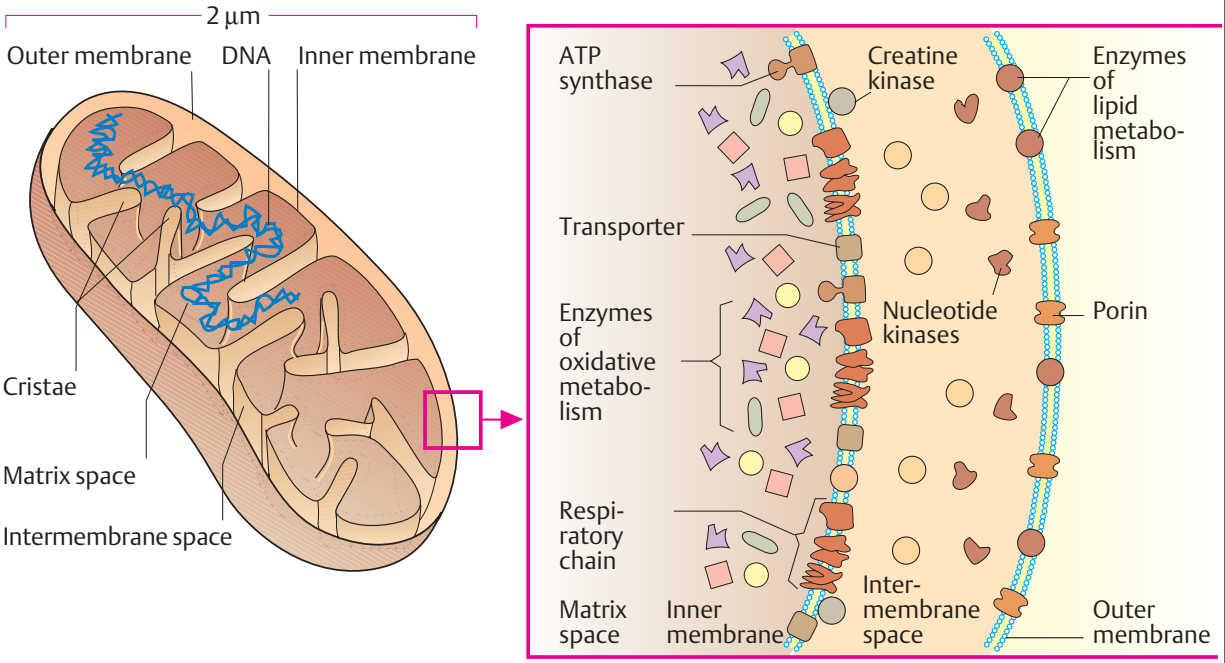
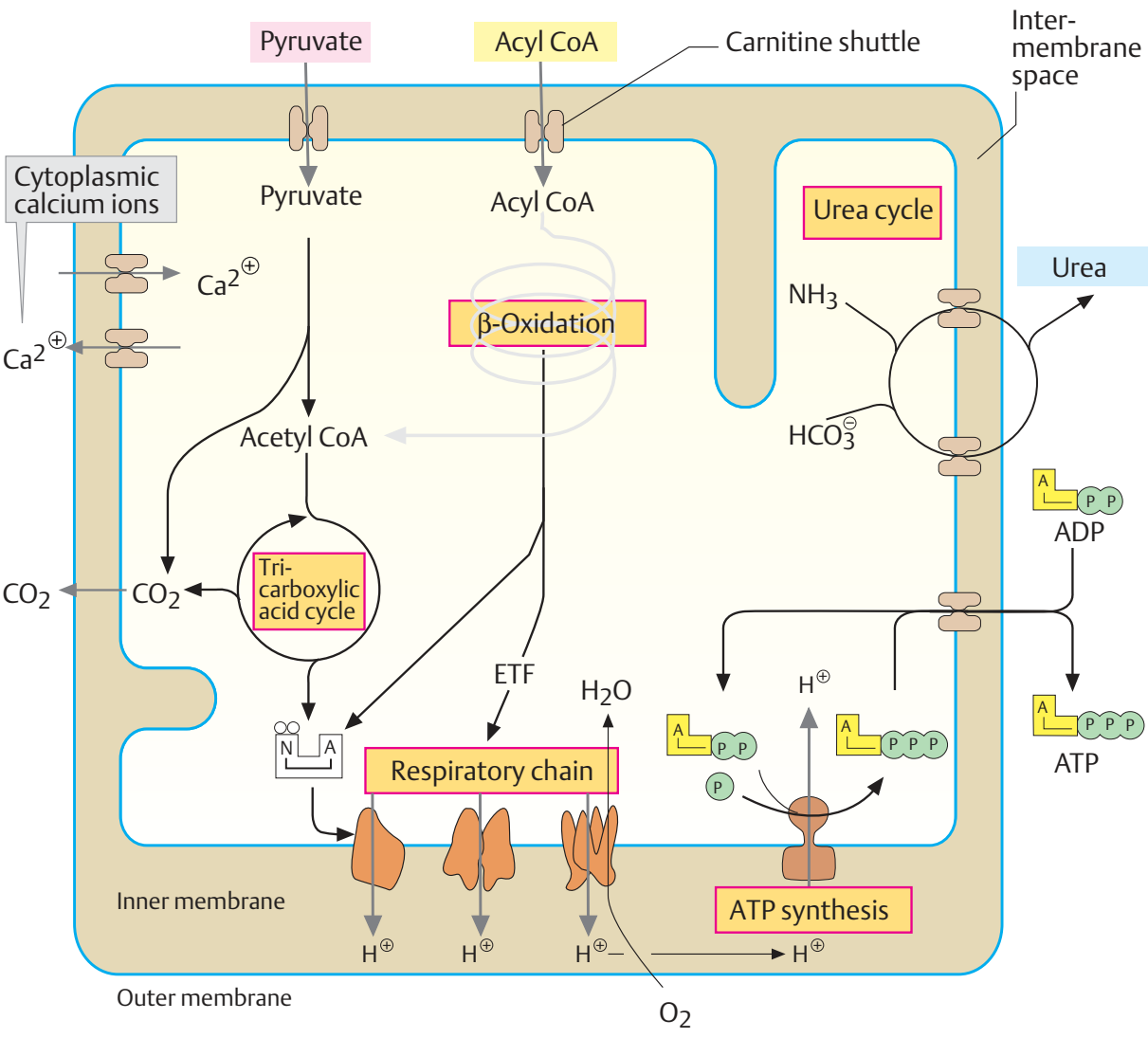
A. Mitochondrial structure



B. Metabolic functions



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Transport systems

Mitochondria are surrounded by an inner and an outer membrane (see p. 210). The **outer membrane** contains porins, which allow smaller molecules up to 10 kDa in size to pass. By contrast, the **inner membrane** is also impermeable to small molecules (with the exception of water and the gases O_2, CO_2, and NH_3). All of the other substrates of mitochondrial metabolism, as well as its products, therefore have to be moved through the inner membrane with the help of special **transporters**.

A. Transport systems ◑

The transport systems of the inner mitochondrial membrane use various mechanisms. Metabolites or ions can be transported alone (uniport, **U**), together with a second substance (symport, **S**), or in exchange for another molecule (antiport, **A**). Active transport—i. e., transport coupled to ATP hydrolysis—does not play an important role in mitochondria. The driving force is usually the **proton gradient** across the inner membrane (blue star) or the general membrane potential (red star; see p. 126).

The **pyruvate** (left) formed by glycolysis in the cytoplasm is imported into the matrix in antiport with OH^-. The OH^- ions react in the intermembrane space with the H^+ ions abundantly present there to form H_2O. This maintains a concentration gradient of OH^-. The import of **phosphate** ($H_2PO_4^-$) is driven in a similar way. The exchange of the **ATP** formed in the mitochondrion for **ADP** via an *adenine nucleotide translocase* (center) is also dependent on the H^+ gradient. ATP with a quadruple negative charge is exchanged for ADP with a triple negative charge, so that overall one negative charge is transported into the H^+-rich intermembrane space. The import of malate by the *tricarboxylate transporter*, which is important for the malate shuttle (see **B**) is coupled to the export of citrate, with a net export of one negative charge to the exterior again. In the opposite direction, malate can leave the matrix in antiport for phosphate. When Ca^{2+} is imported (right), the metal cation follows the membrane potential. An electroneutral antiport for two H^+ or two Na^+ serves for Ca^{2+} export.

B. Malate and glycerophosphate shuttles ◑

Two systems known as "shuttles" are available to allow the **import of reducing equivalents** that arise from glycolysis in the cytoplasm in the form of $NADH+H^+$. There is no transporter in the inner membrane for $NADH+H^+$ itself.

In the **malate shuttle** (left)—which operates in the heart, liver, and kidneys, for example—oxaloacetic acid is reduced to malate by malate dehydrogenase (MDH, [2a]) with the help of $NADH+H^+$. In antiport for 2-oxoglutarate, malate is transferred to the matrix, where the mitochondrial isoenzyme for MDH [2b] regenerates oxaloacetic acid and $NADH+H^+$. The latter is reoxidized by complex I of the respiratory chain, while oxaloacetic acid, for which a transporter is not available in the inner membrane, is first transaminated to aspartate by aspartate aminotransferase (AST, [3a]). Aspartate leaves the matrix again, and in the cytoplasm once again supplies oxaloacetate for step [2a] and glutamate for return transport into the matrix [3b]. On balance, only $NADH+H^+$ is moved from the cytoplasm into the matrix; ATP is not needed for this.

The **glycerophosphate shuttle** (right) was discovered in insect muscle, but is also active in the skeletal musculature and brain in higher animals. In this shuttle, $NADH+H^+$ formed in the cytoplasm is used to reduce glycerone 3-phosphate, an intermediate of glycolysis (see p. 150) to glycerol 3-phosphate. Via porins, this enters the intermembrane space and is oxidized again there on the exterior side of the inner membrane by the flavin enzyme *glycerol 3-phosphate dehydrogenase* back into glycerone 3-phosphate. The reducing equivalents are passed on to the respiratory chain via **ubiquinone (coenzyme Q)**.

The **carnitine shuttle** for transporting acyl residues into the mitochondrial matrix is discussed on p. 164.

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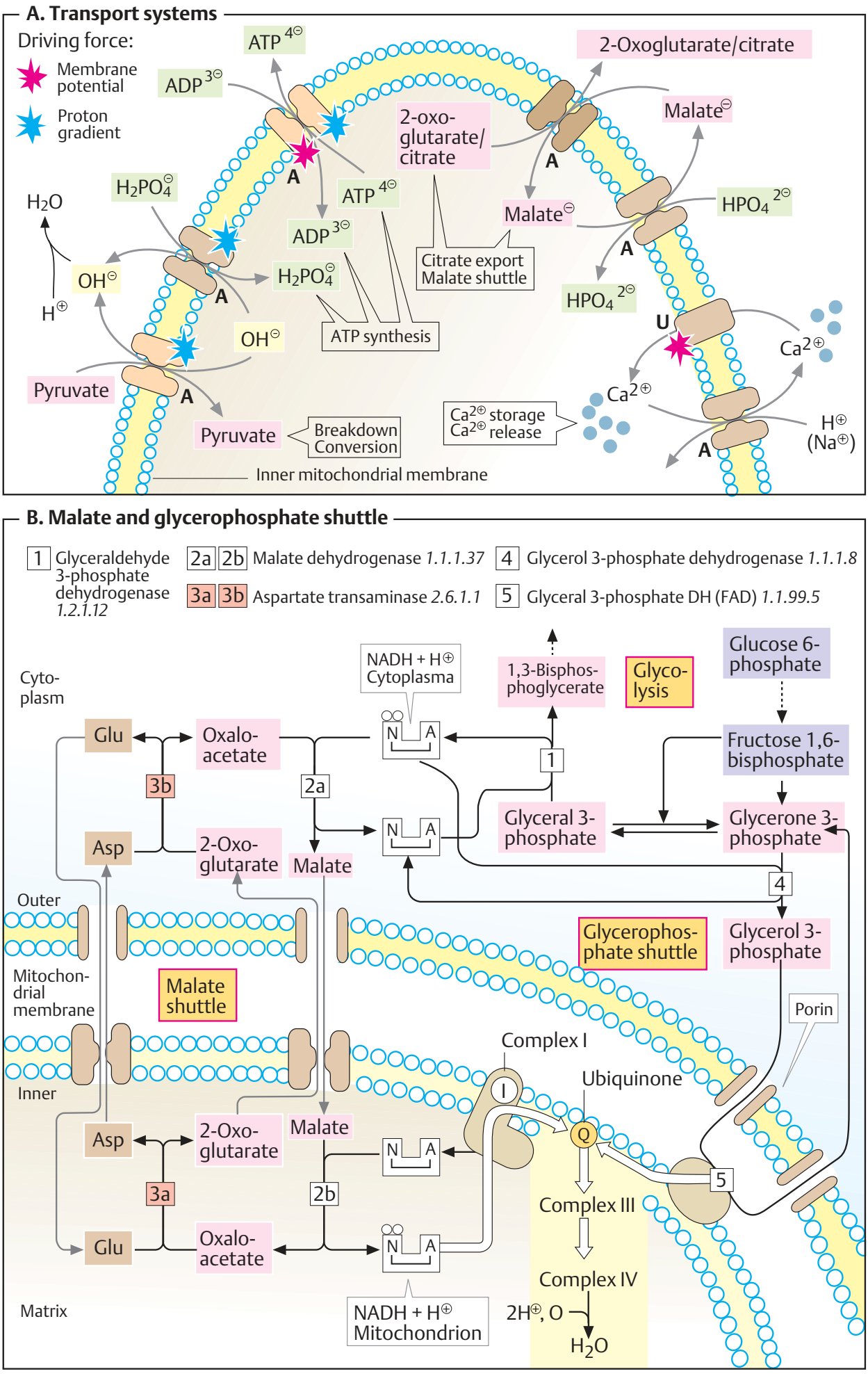

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Structure and components

A. Structure of the plasma membrane ◑

All biological membranes are constructed according to a standard pattern. They consist of a continuous **bilayer of amphipathic lipids** approximately 5 nm thick, into which **proteins** are embedded. In addition, some membranes also carry **carbohydrates** (mono- and oligosaccharides) on their exterior, which are bound to lipids and proteins. The proportions of lipids, proteins, and carbohydrates differ markedly depending on the type of cell and membrane (see p. 216).

Membrane lipids are strongly *amphipathic molecules* with a polar hydrophilic "head group" and an apolar hydrophobic "tail." In membranes, they are primarily held together by the hydrophobic effect (see p. 28) and weak Van der Waals forces, and are therefore mobile relative to each other. This gives membranes a more or less fluid quality.

The **fluidity** of membranes primarily depends on their lipid composition and on temperature. At a specific **transition temperature**, membranes pass from a semicrystalline state to a more fluid state. The double bonds in the alkyl chains of unsaturated acyl residues in the membrane lipids disturb the semicrystalline state. The *higher* the proportion of unsaturated lipids present, therefore, the *lower* the transition temperature. The cholesterol content also influences membrane fluidity. While cholesterol increases the fluidity of semicrystalline, closely-packed membranes, it *stabilizes* fluid membranes that contain a high proportion of unsaturated lipids.

Like lipids, proteins are also mobile within the membrane. If they are not fixed in place by special mechanisms, they float within the lipid layer as if in a two-dimensional liquid; biological membranes are therefore also described as being a "fluid mosaic."

Lipids and proteins can shift easily *within* one layer of a membrane, but switching between the two layers (*"flip/flop"*) is not possible for proteins and is only possible with difficulty for lipids (with the exception of cholesterol). To move to the other side, phospholipids require special auxiliary proteins (translocators, "flipases").

B. Membrane lipids ◑

The illustration shows a model of a small section of a membrane. The **phospholipids** are the most important group of membrane lipids. They include *phosphatidylcholine* (lecithin), *phosphatidylethanolamine*, *phosphatidylserine, phosphatidylinositol,* and *sphingomyelin* (for their structures, see p. 50). In addition, membranes in animal cells also contain **cholesterol** (with the exception of inner mitochondrial membranes). **Glycolipids** (a *ganglioside* is shown here) are mainly found on the outside of the plasma membrane. Together with the *glycoproteins,* they form the exterior coating of the cell (the *glycocalyx*).

C. Membrane proteins ◑

Proteins can be anchored in or on membranes in various ways. **Integral membrane proteins** cross right through the lipid bilayer. The sections of the peptide chains that lie within the bilayer usually consist of 20 to 25 mainly hydrophobic amino acid residues that form a right-handed α-helix.

Type I and II membrane proteins only contain *one* **transmembrane helix** of this type, while type III proteins contain several. Rarely, type I and II polypeptides can aggregate to form a type IV transmembrane protein. Several groups of integral membrane proteins—e.g., the porins (see p. 212)—penetrate the membrane with antiparallel β-sheet structures. Due to its shape, this tertiary structure is known as a "β-barrel."

Type V and VI proteins carry **lipid anchors.** These are fatty acids (palmitic acid, myristic acid), isoprenoids (e.g., farnesol), or glycolipids such as glycosyl phosphatidylinositol (GPI) that are covalently bound to the peptide chain.

Peripheral membrane proteins are associated with the head groups of phospholipids or with another integral membrane protein (not shown).

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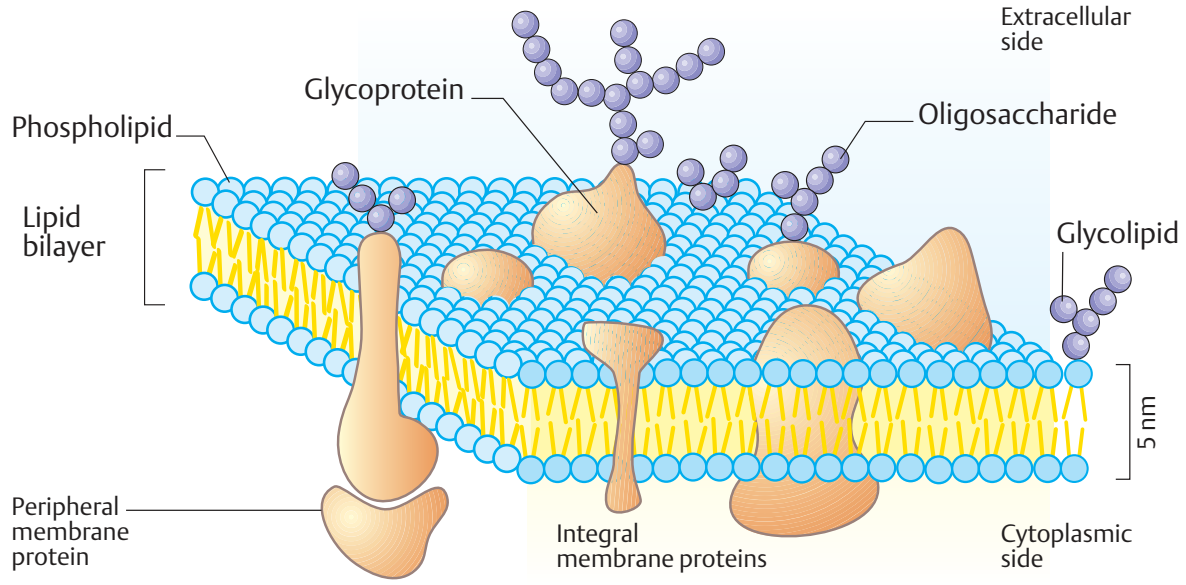
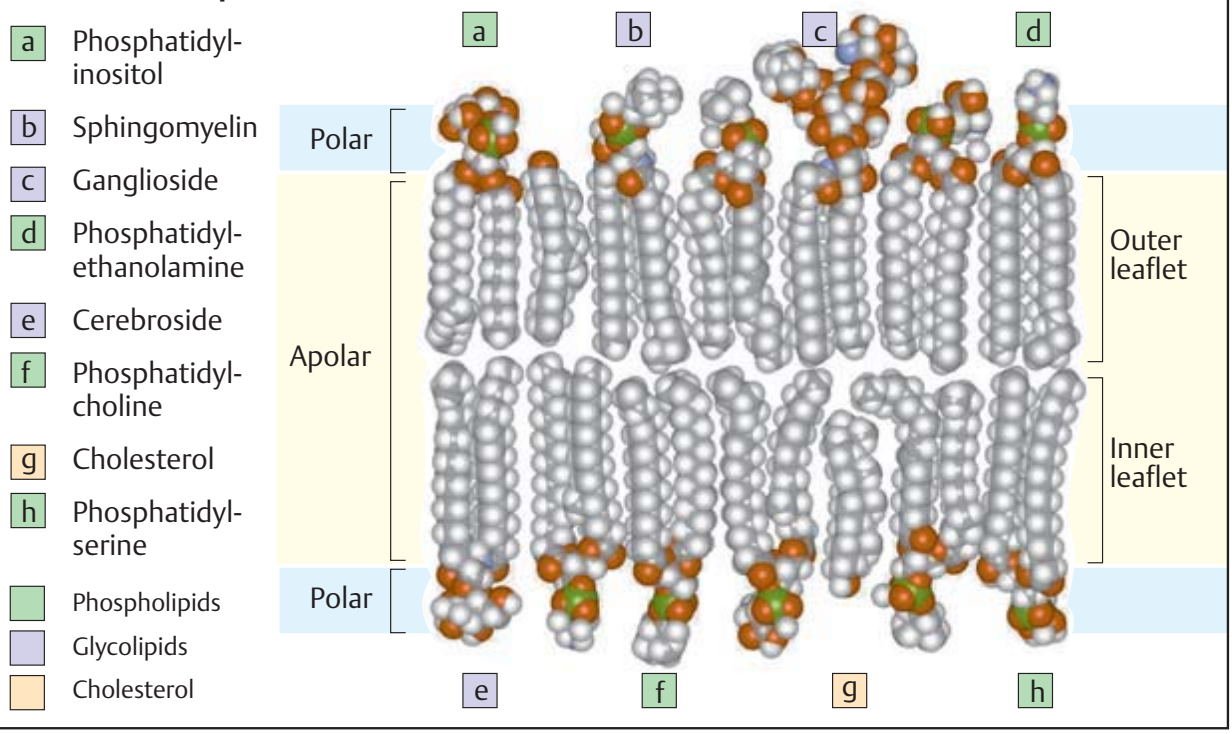
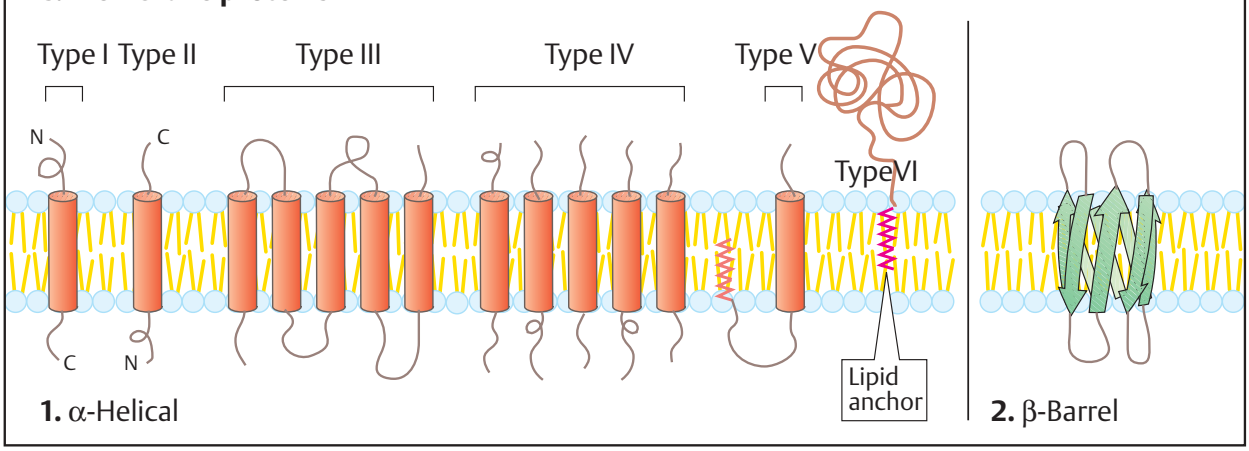
A. Structure of the plasma membrane



B. Membrane lipids



C. Membrane proteins



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Functions and composition

The most important membranes in animal cells are the *plasma membrane,* the inner and outer *nuclear membranes,* the membranes of the *endoplasmic reticulum* (ER) and the *Golgi apparatus,* and the inner and outer *mitochondrial membranes*. *Lysosomes, peroxisomes,* and various *vesicles* are also separated from the cytoplasm by membranes. In plants, additional membranes are seen in the plastids and vacuoles. All membranes show *polarity*—i. e., there is a difference in the composition of the inner layer (facing toward the cytoplasm) and the outer layer (facing away from it).

A. Functions of membranes ●

Membranes and their components have the following functions:

1. **Enclosure and insulation** of cells and organelles. The *enclosure* provided by the plasma membrane protects cells from their environment both mechanically and chemically. The plasma membrane is essential for maintaining differences in the concentration of many substances between the intracellular and extracellular compartments.

2. **Regulated transport of substances**, which determines the *internal milieu* and is a precondition for *homeostasis*—i. e., the maintenance of constant concentrations of substances and physiological parameters. Regulated and selective transport of substances through pores, channels, and transporters (see p. 218) is necessary because the cells and organelles are enclosed by membrane systems.

3. **Reception of extracellular signals** and transfer of these signals to the inside of the cell (see pp. 384ff.), as well as the production of signals.

4. **Enzymatic catalysis** of reactions. Important enzymes are located in membranes at the interface between the lipid and aqueous phases. This is where reactions with apolar substrates occur. Examples include *lipid biosynthesis* (see p. 170) and the *metabolism of apolar xenobiotics* (see p. 316). The most important reactions in energy conversion—i. e., *oxidative phosphorylation* (see p. 140) and *photosynthesis* (see p. 128)—also occur in membranes.

5. **Interactions with other cells** for the purposes of cell fusion and tissue formation, as well as communication with the extracellular matrix.

6. **Anchoring of the cytoskeleton** (see p. 204) to maintain the shape of cells and organelles and to provide the basis for movement processes.

B. Composition of membranes ◑

Biological membranes consist of **lipids**, **proteins**, and **carbohydrates** (see p. 214). These components occur in varying proportions (left). Proteins usually account for the largest proportion, at around half. By contrast, carbohydrates, which are only found on the side facing away from the cytoplasm, make up only a few percent. An extreme composition is seen in *myelin,* the insulating material in nerve cells, three-quarters of which consists of lipids. By contrast, the inner *mitochondrial membrane* is characterized by a very low proportion of lipids and a particularly high proportion of proteins.

When the individual proportions of **lipids** in membranes are examined more closely (right part of the illustration), typical patterns for particular cells and tissues are also found. The illustration shows the diversity of the membrane lipids and their approximate quantitative composition. *Phospholipids* are predominant in membrane lipids in comparison with *glycolipids* and *cholesterol*. Triacylglycerols (neutral fats) are not found in membranes.

Cholesterol is found almost exclusively in eukaryotic cells. Animal membranes contain substantially more cholesterol than plant membranes, in which cholesterol is usually replaced by other sterols. There is no cholesterol at all in prokaryotes (with a few exceptions). The inner mitochondrial membrane of eukaryotes is also low in cholesterol, while it is the only membrane that contains large amounts of cardiolipin. These facts both support the endosymbiotic theory of the development of mitochondria (see p. 210).

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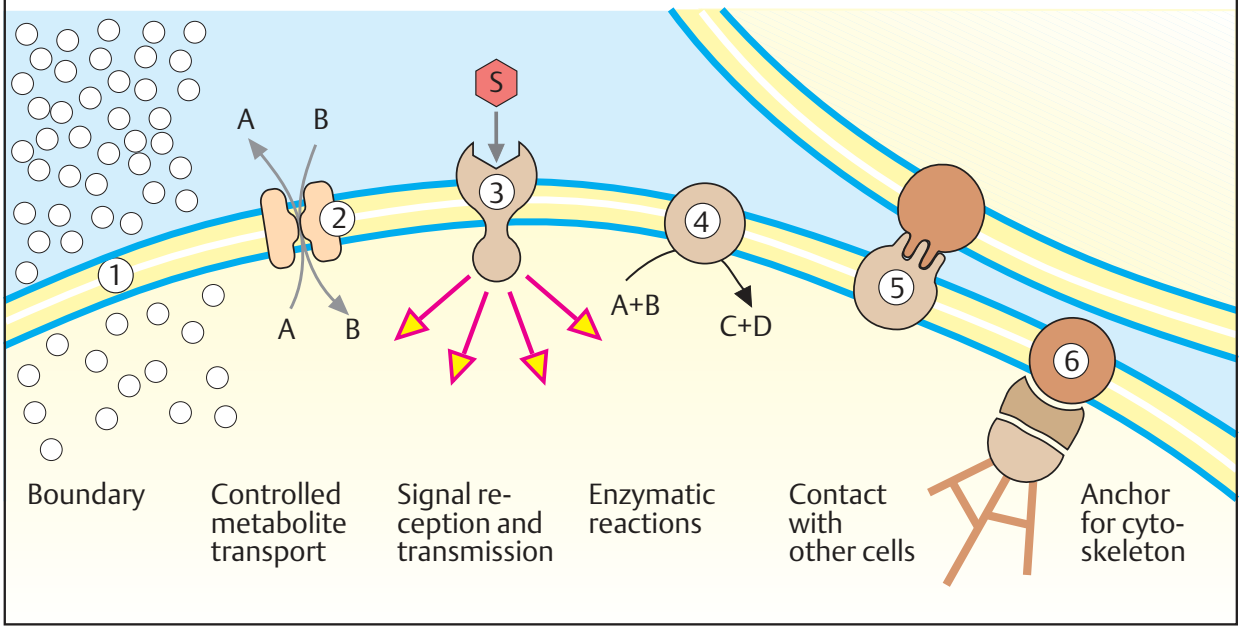
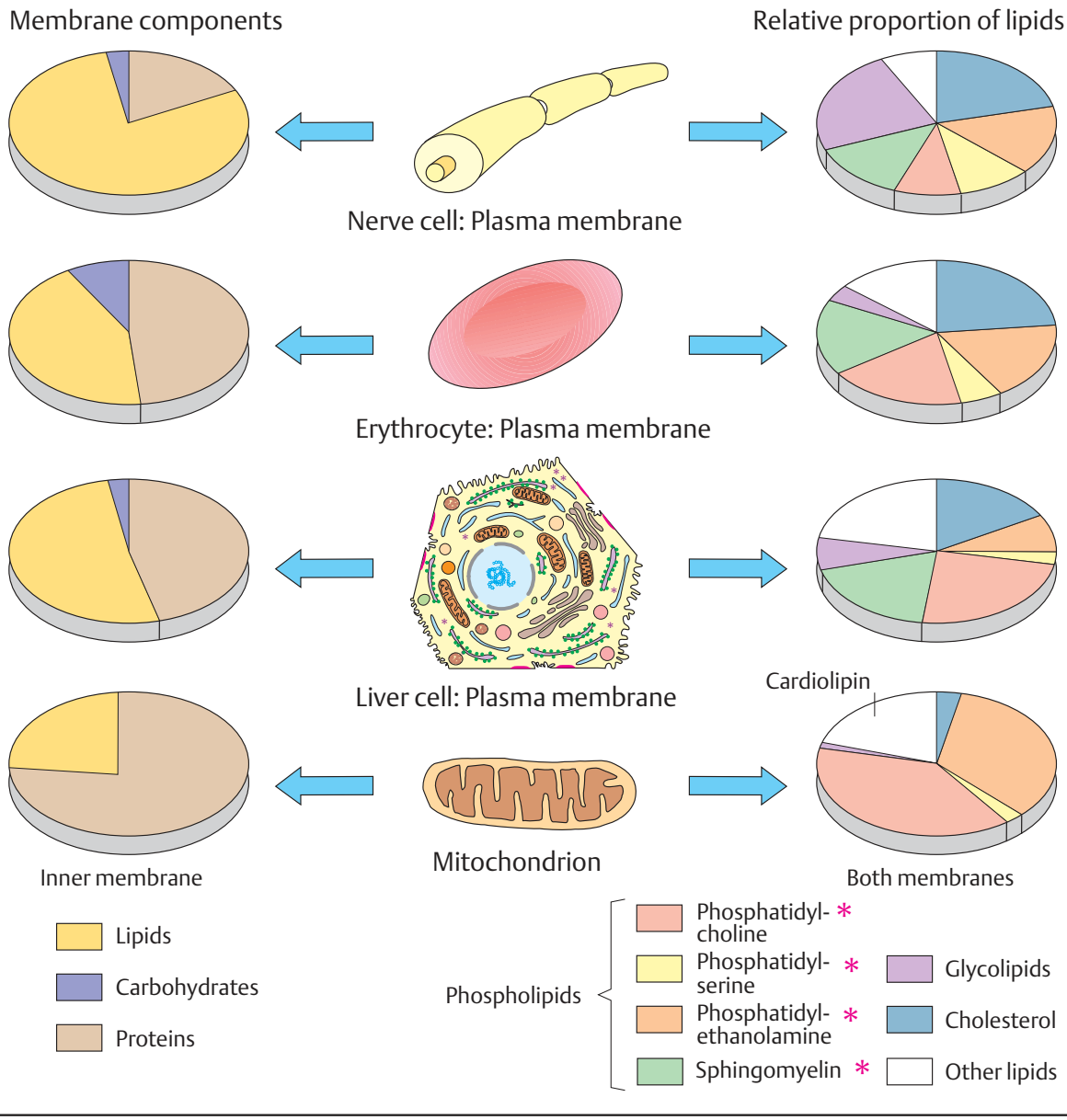
A. Functions of membranes



B. Composition of membranes



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Transport processes

A. Permeability ●

Only small, uncharged molecules such as gases, water, ammonia, glycerol, or urea are able to pass through biological membranes by *free diffusion*. With increasing **size**, even compounds of this type are no longer able to pass through. Membranes are impermeable to glucose and other sugars, for example.

The **polarity** of a molecule is also important. Apolar substances, such as benzene, ethanol, diethyl ether, and many narcotic agents are able to enter biological membranes easily. By contrast, membranes are impermeable to strongly polar compounds, particularly those that are electrically charged. To be able to take up or release molecules of this type, cells have specialized *channels* and *transporters* in their membranes (see below).

B. Passive and active transport ●

Free diffusion is the simplest form of membrane transport. When it is supported by integral membrane proteins, it is known as **facilitated diffusion** (or facilitated transport).

1. **Channel proteins** have a polar pore through which ions and other hydrophilic compounds can pass. For example, there are channels that allow selected ions to pass (**ion channels**; see p. 222) and **porins** that allow molecules below a specific size to pass in a more or less nonspecific fashion (see p. 212).
2. **Transporters** recognize and bind the molecules to be transported and help them to pass through the membrane as a result of a conformational change. These proteins (permeases) are thus comparable with enzymes—although with the difference that they "catalyze" vectorial transport rather than an enzymatic reaction. Like enzymes, they show a certain *affinity* for each molecule transported (expressed as the dissociation constant, K_d in mol L^{-1}) and a *maximum transport capacity* (V).

Free diffusion and transport processes facilitated by ion channels and transport proteins always follow a *concentration gradient*—i.e., the direction of transport is from the site of higher concentration to the site of lower concentration. In ions, the *membrane potential* also plays a role; the processes are summed up by the term *"electrochemical gradient"* (see p. 126). These processes therefore involve **passive transport**, which runs "downhill" on the slope of a gradient.

By contrast, **active transport** can also run "uphill"—i.e., against a concentration or charge gradient. It therefore requires an input of *energy,* which is usually supplied by the hydrolysis of ATP (see p. 124). The transporter first binds its "cargo" on one side of the membrane. ATP-dependent phosphorylation then causes a conformation change that releases the cargo on the other side of the membrane (see p. 220). A non-spontaneous transport process can also take place through coupling to another active transport process (known as *secondary active transport;* see p. 220).

Using the transport systems in the membranes, cells regulate their volume, internal pH value, and ionic environment. They concentrate metabolites that are important for energy metabolism and biosynthesis, and exclude toxic substances. Transport systems also serve to establish *ion gradients,* which are required for oxidative phosphorylation and stimulation of muscle and nerve cells, for example (see p. 350).

C. Transport processes ◑

Another classification of transport processes is based on the number of particles transported and the direction in which they move. When a *single* molecule or ion passes through the membrane with the help of a channel or transporter, the process is described as a **uniport** (example: the transport of glucose into liver cells). Simultaneous transport of *two different* particles can take place either as a **symport** (example: the transport of amino acids or glucose together with Na^+ ions into intestinal epithelial cells) or as an **antiport**. Ions are often transported in an antiport in exchange for another similarly charged ion. This process is **electroneutral** and therefore more energetically favorable (example: the exchange of HCO_3^- for Cl^- at the erythrocyte membrane).

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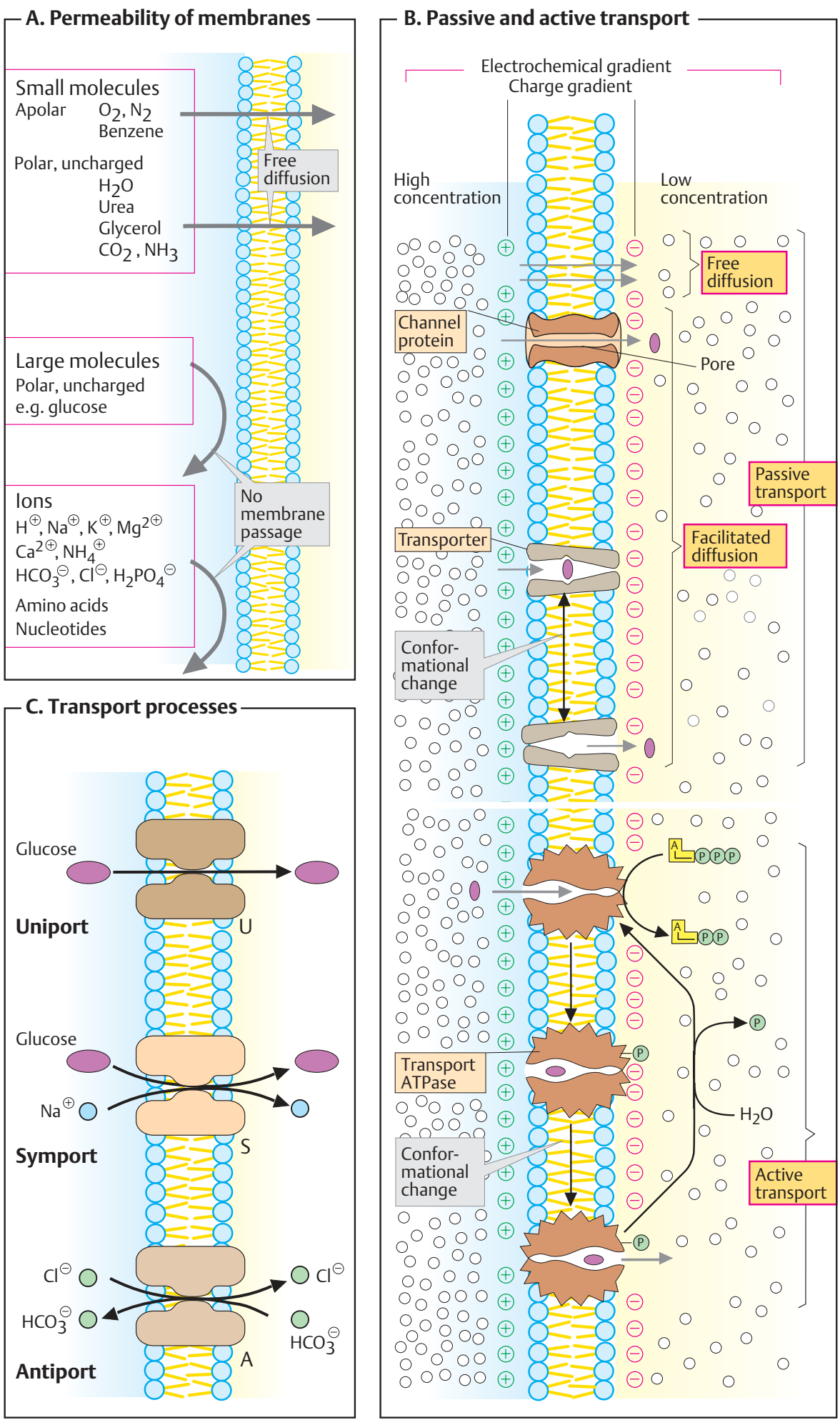

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Transport proteins

Illustrations **B–D** show transporters whose structure has been determined experimentally or established on analogy with other known structures. They all belong to group III of the α-helical transmembrane proteins (see p. 214).

A. Transport mechanisms ◑

Some cells couple the "pure" transport forms discussed on p. 218—i. e., passive transport (**1**) and active transport (**2**)—and use this mechanism to take up metabolites. In **secondary active transport** (**3**), which is used for example by epithelial cells in the small intestine and kidney to take up glucose and amino acids, there is a **symport** (S) located on the luminal side of the membrane, which takes up the metabolite M together with an Na^+ ion. An ATP-dependent Na^+ transporter (Na^+/K^+ ATPase; see p. 350) on the other side keeps the intracellular Na+ concentration low and thus indirectly drives the uptake of M. Finally, a uniport (U) releases M into the blood.

B. Glucose transporter Glut-1 ○

The glucose transporters (Glut) are a family of related membrane proteins with varying distribution in the organs. Glut-1 and Glut-3 have a relatively high af nity for glucose (K_d = 1 mM). They occur in nearly all cells, and ensure continuous glucose uptake. Glut-2 is found in the liver and pancreas. This form has a lower af nity (K_d = 15–20 mM). The rate of glucose uptake by Glut-2 is therefore strongly dependent on the blood glucose level (normally 4–8 mM). Transport by Glut-4 (K_d = 5 mM), which is mainly expressed in muscle and fat cells, is controlled by insulin, which increases the number of transporters on the cell surface (see p. 388). Glut-5 mediates secondary active resorption of glucose in the intestines and kidney (see **A**).

Glut-1 consists of a single peptide chain that spans the membrane with 12 α-helices of different lengths. The glucose is bound by the peptide loops that project on each side of the membrane.

C. Aquaporin-1 ○

Aquaporins help water to pass through biological membranes. They form hydrophilic pores that allow H_2O molecules, but not hydrated ions or larger molecules, to pass through. Aquaporins are particularly important in the kidney, where they promote the reuptake of water (see p. 328). Aquaporin-2 in the renal collecting ducts is regulated by **antidiuretic hormone** (ADH, vasopressin), which via cAMP leads to shifting of the channels from the ER into the plasma membrane.

Aquaporin-1, shown here, occurs in the proximal tubule and in Henle's loop. It contains eight transmembrane helices with different lengths and orientations. The yellow-colored residues form a narrowing that only H_2O molecules can overcome.

D. Sarcoplasmic Ca^{2+} pump ○

Transport ATPases transport cations—they are "ion pumps." ATPases of the **F type**—e. g., mitochondrial ATP synthase (see p. 142)—use H^+ transport for *ATP synthesis.* Enzymes of the **V type**, using up ATP, "pump" protons into lysosomes and other acidic cell compartments (see p. 234). **P type** transport ATPases are particularly numerous. These are ATP-driven cation transporters that undergo covalent phosphorylation during the transport cycle.

The **Ca^{2+} ATPase** shown also belongs to the P type. In muscle, its task is to pump the Ca^{2+} released into the cytoplasm to trigger muscle contraction back into the sarcoplasmic reticulum (SR; see p. 334). The molecule (**1**) consists of a single peptide chain that is folded into various domains. In the transmembrane part, which is formed by numerous α-helices, there are binding sites for two Ca^{2+} ions (blue) ATP is bound to the cytoplasmic N domain (green).

Four different stages can be distinguished in the enzyme's catalytic cycle (**2**). First, binding of ATP to the N domain leads to the uptake of two Ca^{2+} into the transmembrane part (**a**). Phosphorylation of an aspartate residue in the P domain (**b**) and dissociation of ADP then causes a conformation change that releases the Ca^{2+} ions into the SR (**c**). Finally, dephosphorylation of the aspartate residue restores the initial conditions (**d**).

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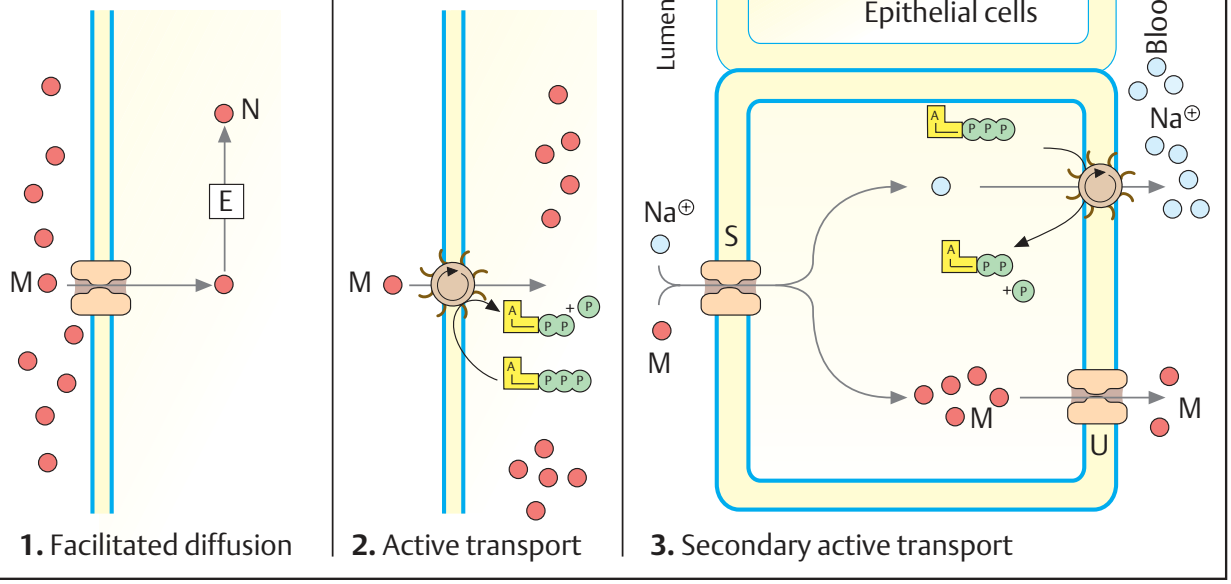
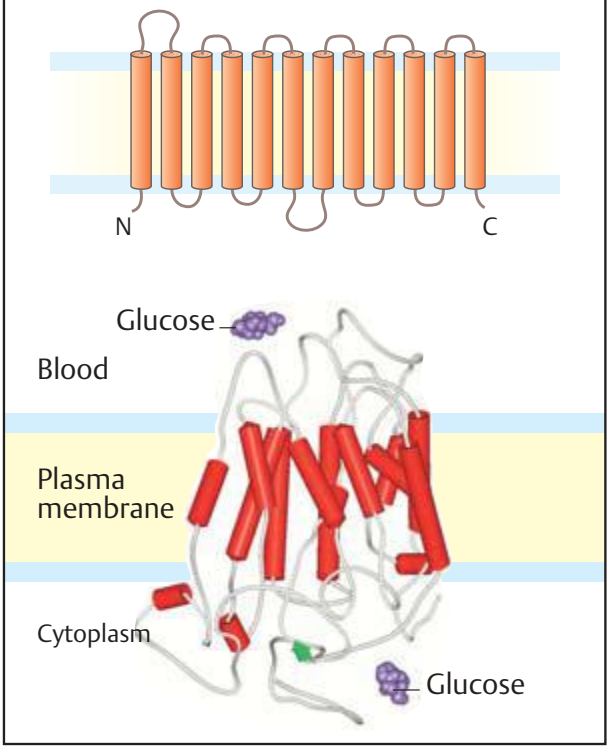
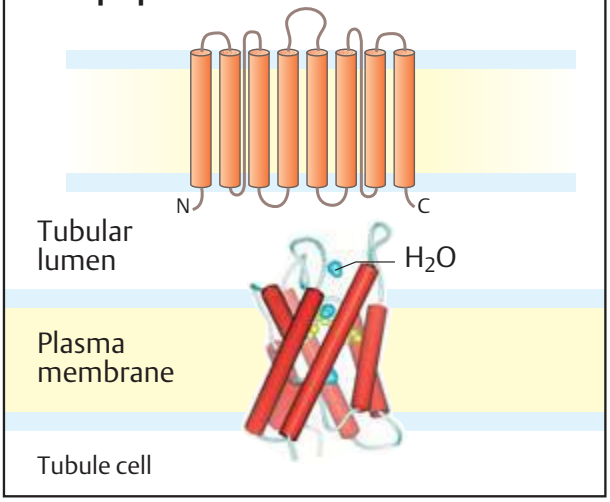
A. Transport mechanisms



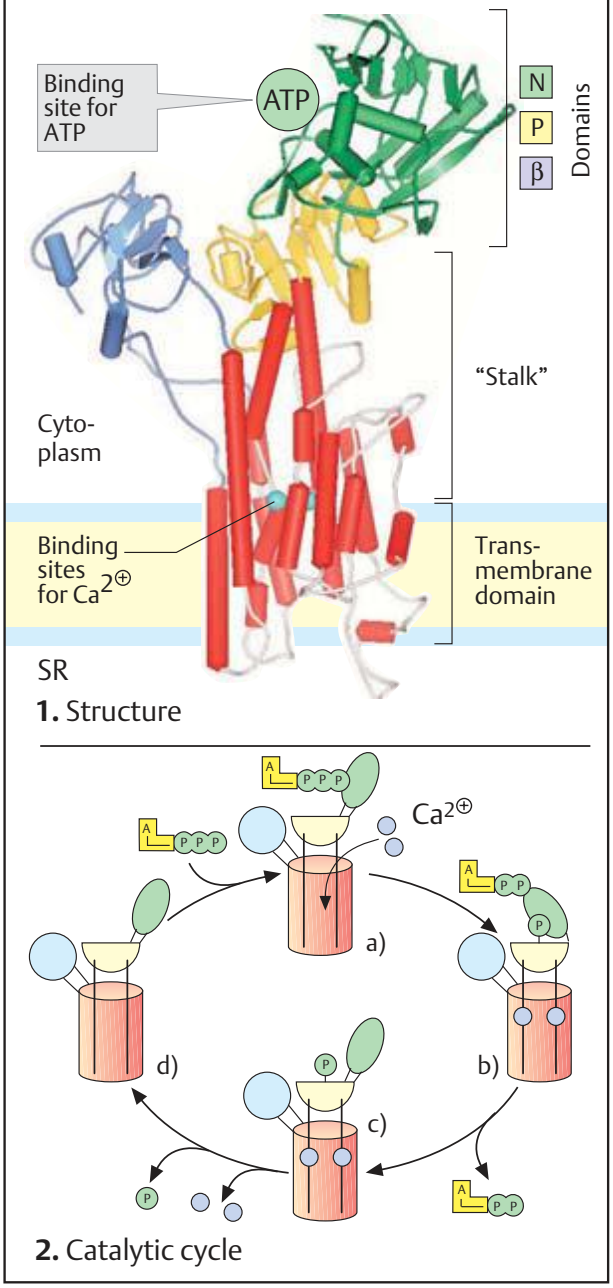
B. Glucose transporter Glut-1



C. Aquaporin-1



D. Sarcoplasmic $Ca^{2\oplus}$ pump



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Ion channels

Ion channels facilitate the diffusion of ions through biological membranes. Some ion channels open and close depending on the membrane potential (**voltage-gated channels, A**) or in response to specific ligands (**ligand-gated channels, B**). Other channels operate passively. In these cases, transport depends only on the concentration gradient (**C**).

A. Voltage-gated Na^+ channel ○

Voltage-gated Na^+ channels play a decisive part in the conduction of electrical impulses in the nervous system (see p. 350). These channels open when the membrane potential in their environment reverses. Due to the high equilibrium potential for Na^+ (see p. 126), an inflow of Na^+ ions takes place, resulting in local **depolarization** of the membrane, which propagates by activation of neighboring voltage-dependent Na^+ channels. A spreading depolarization wave of this type is known as an **action potential** (see p. 350). Externally directed K^+ channels are involved in the repolarization of the membrane. In their functioning, these resemble the much more simply structured K^+ channels shown in **C**. The Ca^{2+} channels that trigger exocytosis of vesicles (see p. 228) are also controlled by the action potential.

The voltage-gated Na^+ channels in higher animals are large complexes made up of several subunits. The α-subunit shown here mediates Na^+ transport. It consists of a very long peptide chain (around 2000 amino acid residues), which is folded into four domains, each with six transmembrane helices (left). The S6 helices of all the domains (blue) together form a centrally located hydrophilic pore which can be made narrow or wide depending on the channel's functional status. The six S4 helices (green) function as voltage sensors.

The current conception of the way in which the opening and closing mechanism functions is shown in a highly simplified form on the right. For the sake of clarity, only one of the four domains (domain IV) is shown. The S4 helices contain several positively charged residues. When the membrane is polarized (**a**), the surplus negative charges on the inner side keep the helix in the membrane. If this attraction is removed as a result of local depolarization, the S4 helices are thought to snap upwards like springs and thus open the central pore (**b**).

B. Nicotinic acetylcholine receptor ○

Many receptors for neurotransmitters function as ligand-gated channels for Na^+, K^+ and/or Ca^{2+} ions (see p. 354). The ones that have been studied in the greatest detail are the nicotinic receptors for **acetylcholine** (see p. 352). These consist of five separate but structurally closely related subunits. Each forms four transmembrane helices, the second of which is involved in the central pore in each case. The type of monomer and its arrangement in the complex is not identical in all receptors of this type. In the neuromuscular junction (see p. 334), the arrangement $\alpha\beta\gamma\alpha\delta$ is found (**1**).

In the interior of the structure, acetylcholine binds to the two α-subunits and thus opens the pore for a short time (1–2 ms). Negatively charged residues are arranged in three groups in a ring shape inside it. They are responsible for the receptor's ion specificity. It is thought that binding of the neurotransmitter changes the position of the subunits in such a way that the pore expands (**3**). The bound acetylcholine dissociates again and is hydrolytically inactivated (see p. 356). The receptor is thus able to function again.

C. K^+ channel in *Streptomyces lividans* ○

The only detailed structures of ion channels established so far are those of potassium channels like that of an outwardly directed K^+ channel in the bacterium *Streptomyces lividans*. It consists of four identical subunits (blue, yellow, green, and red), each of which contains two long α-helices and one shorter one. In the interior of the cell (bottom), the K^+ ions (violet) enter the structure's central channel. Before they are released to the outside, they have to pass through what is known as a "selectivity filter." In this part of the channel, several C=O groups in the peptide chain form a precisely defined opening that is only permeable to non-hydrated K^+ ions.

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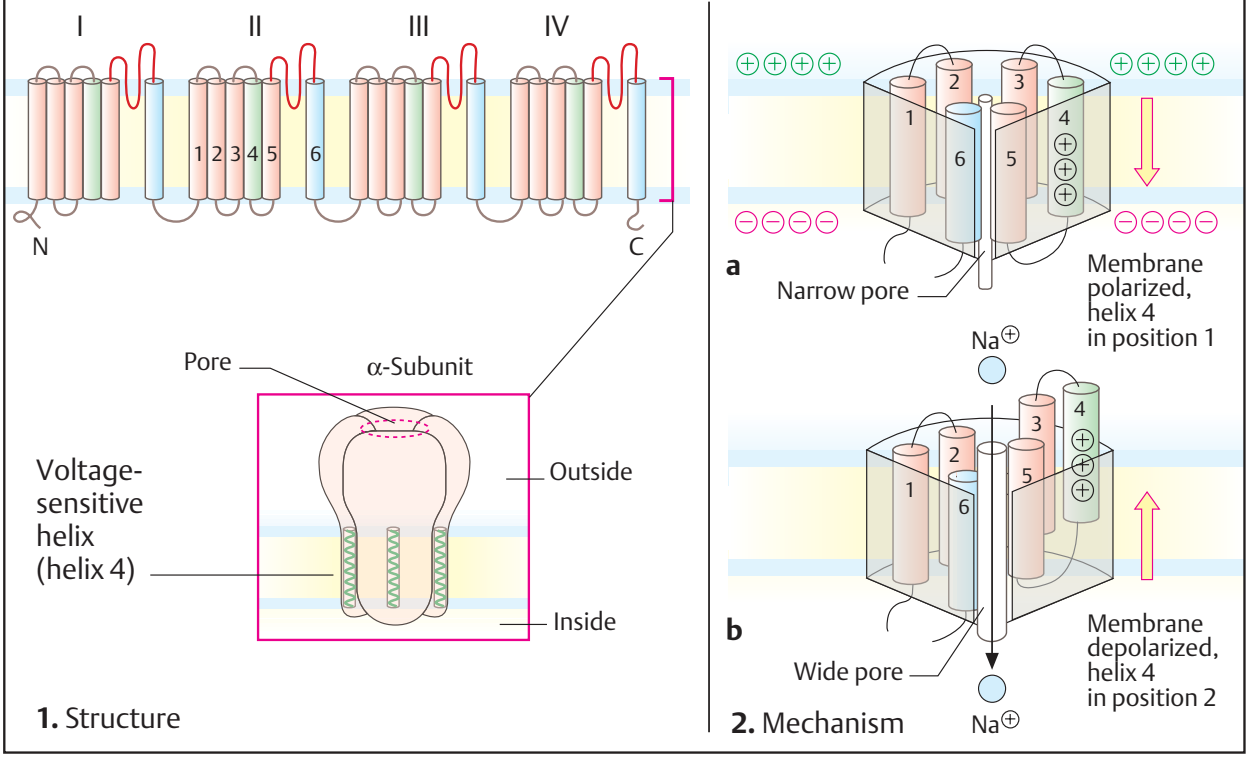
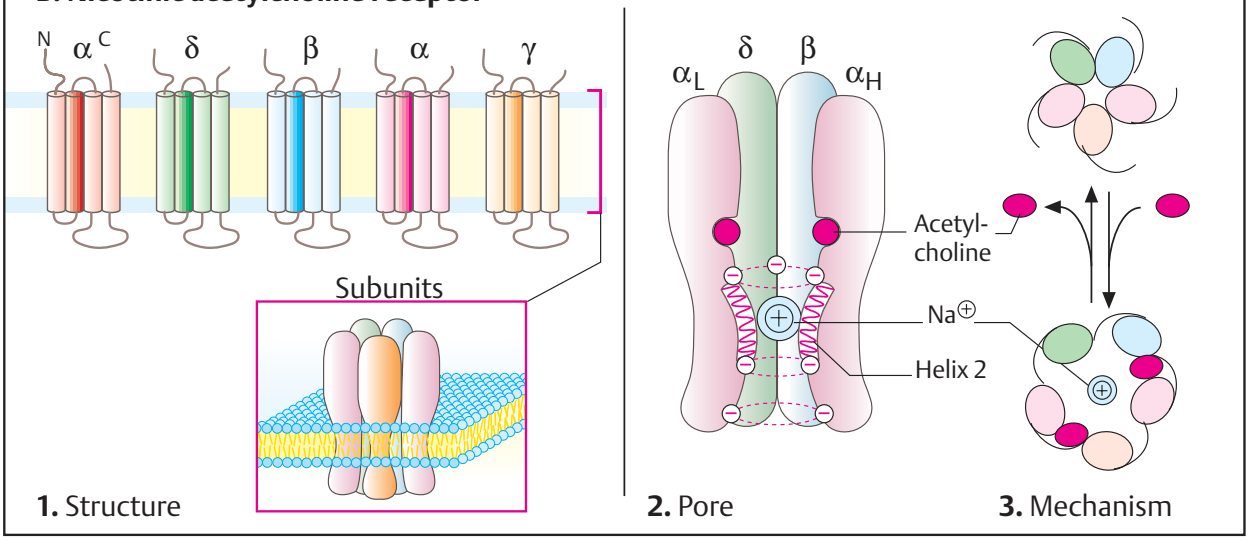
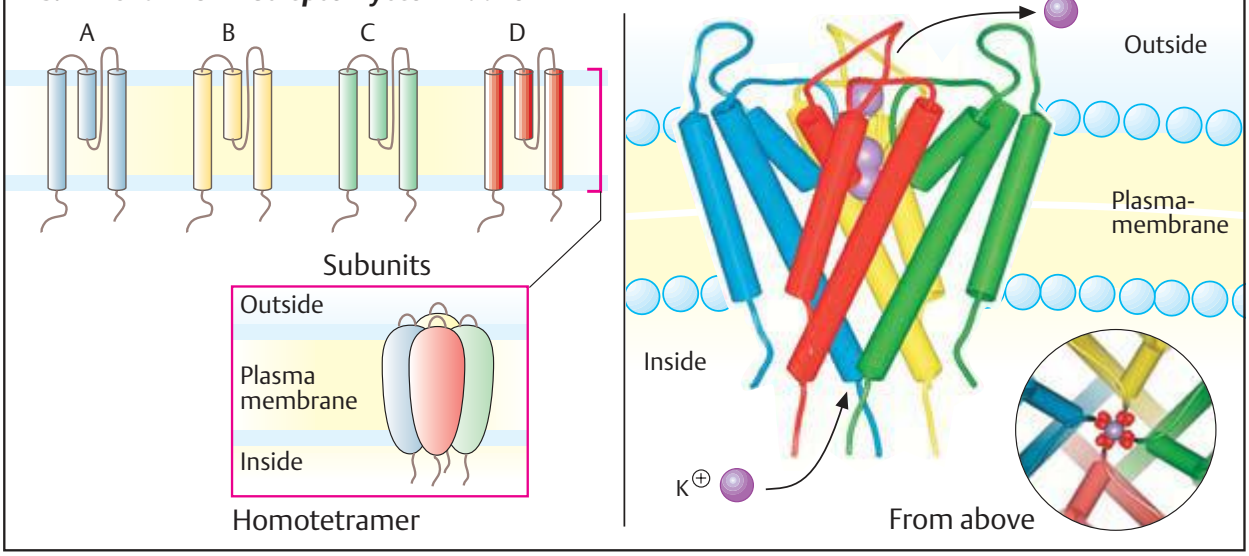
A. Voltage-gated $Na^{\oplus}$ channel



B. Nicotinic acetylcholine receptor



C. $K^{\oplus}$ channel in *Streptomyces lividans*



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Membrane receptors

To receive and pass on chemical or physical signals, cells are equipped with **receptor proteins**. Many of these are integral membrane proteins in the plasma membrane, where they receive signals from their surroundings. Other receptor proteins are located in intercellular membranes. The receptors for lipophilic hormones are among the few that function in a soluble form. They regulate gene transcription in the nucleus (see p. 378).

A. Principle of receptor action ●

Membrane-located receptors can be divided into three parts, which have different tasks. The **receptor domain** reacts specifically to a given signal. Signals of this type can be of a purely physical nature. For example, many organisms react to light. In this way, plants adapt growth and photosynthesis to light conditions, while animals need light receptors for visual processing (**C**; see p. 358). Mechanoreceptors are involved in hearing and in pressure regulation, among other things. Channels that react to action potentials (see p. 350) can be regarded as receptors for electrical impulses.

However, most receptors do not react to physical stimuli, but rather to signal molecules. Receptors for these chemical signals contain binding sites in the receptor domain that are complementary to each ligand. In this respect, they resemble enzymes (see p. 94). As the **effector domain** of the receptor is usually separated by a membrane, a mechanism for **signal transfer** between the domains is needed. Little is yet known regarding this. It is thought that conformation changes in the receptor protein play a decisive part. Some receptors dimerize after binding of the ligand, thereby bringing the effector domains of two molecules into contact (see p. 392).

The way in which the effector works differs from case to case. By binding or interconversion, many receptors activate special **mediator proteins**, which then trigger a signal cascade (signal transduction; see p. 384). Other receptors function as **ion channels**. This is particularly widespread in receptors for neurotransmitters (see p. 354).

B. Insulin receptor ◑

The receptor for the hormone insulin (see p. 76) belongs to the family of **1-helix receptors**.

These molecules span the membrane with only one α-helix. The subunits of the dimeric receptor (red and blue) each consist of two polypeptides (α and β) bound by disulfide bonds. The α-chains together bind the insulin, while the β-chains contain the transmembrane helix and, at the C-terminus, domains with **tyrosine kinase** activity. In the activated state, the kinase domains phosphorylate themselves and also mediator proteins (receptor substrates) that set in motion cascades of further phosphorylations (see pp. 120 and 388).

C. 7-helix receptors ◑

A large group of receptors span the membrane with α-helices seven times. These are known as **7-helix receptors**. Via their effector domains, they bind and activate trimeric proteins, which in turn bind and hydrolyze GTP and are therefore called G proteins. Most G proteins, in turn, activate or inhibit enzymes that create secondary signaling molecules (**second messengers**; see p. 386). Other G proteins regulate ion channels. The illustration shows the complex of the light receptor **rhodopsin**, with the associated G protein **transducin** (see p. 358). The GTP-binding α-subunit (green) and the γ-subunit (violet) of transducin are anchored in the membrane via lipids (see p. 214). The β-subunit is shown in detail on p. 72.

D. T-cell receptor ◑

The cells of the immune system communicate with each other particularly intensively. The **T-cell receptor** plays a central role in the activation of T lymphocytes (see p. 296). The cell at the top has been infected with a virus, and it indicates this by presenting a viral peptide (violet) with the help of a class I **MHC protein** (yellow and green). The combination of the two molecules is recognized by the dimeric T-cell receptor (blue) and converted into a signal that activates the T cell (bottom) and thereby enhances the immune response to the virus.

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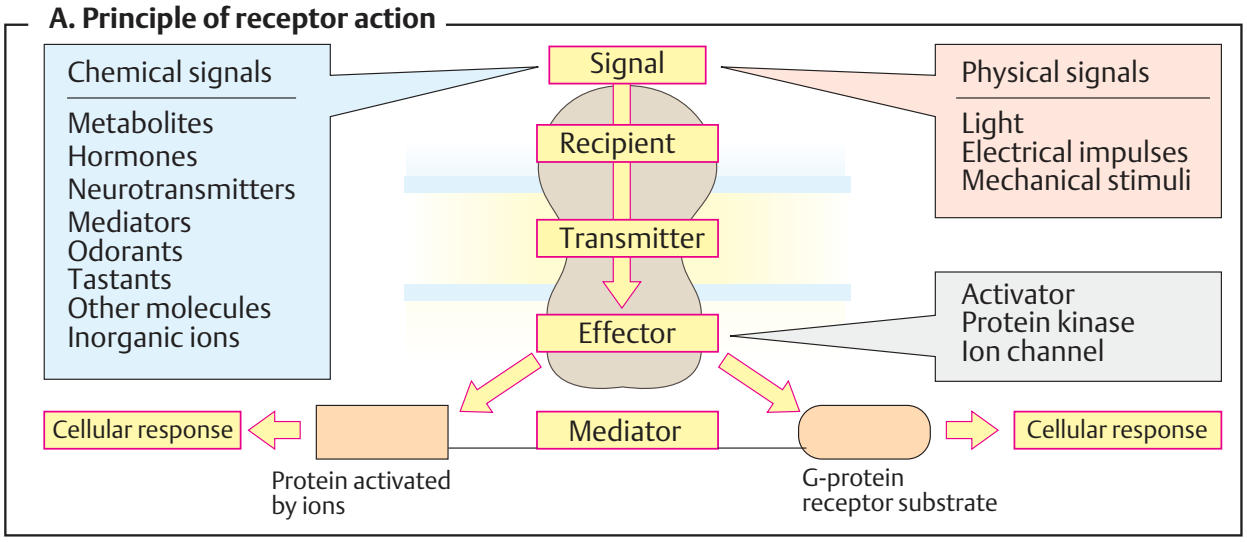

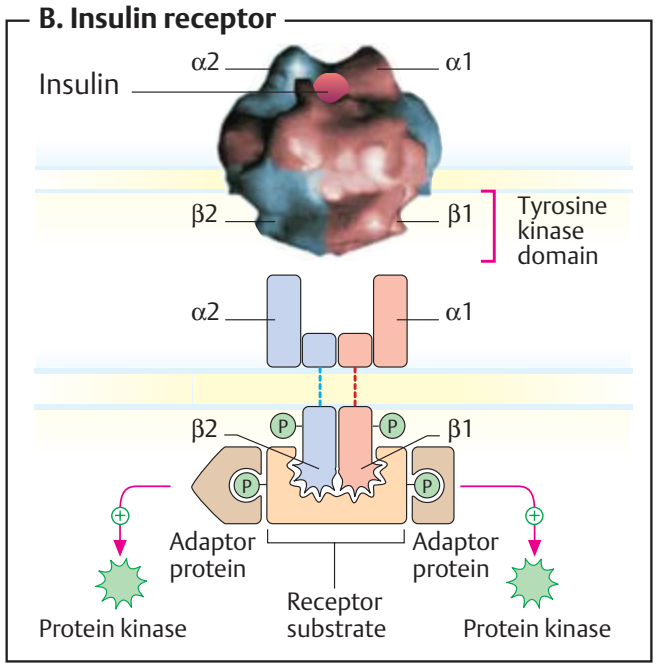

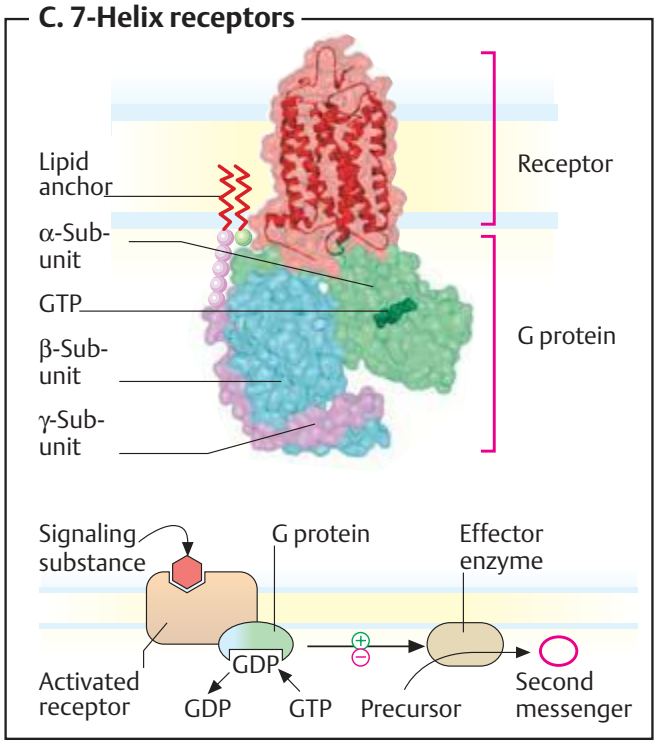

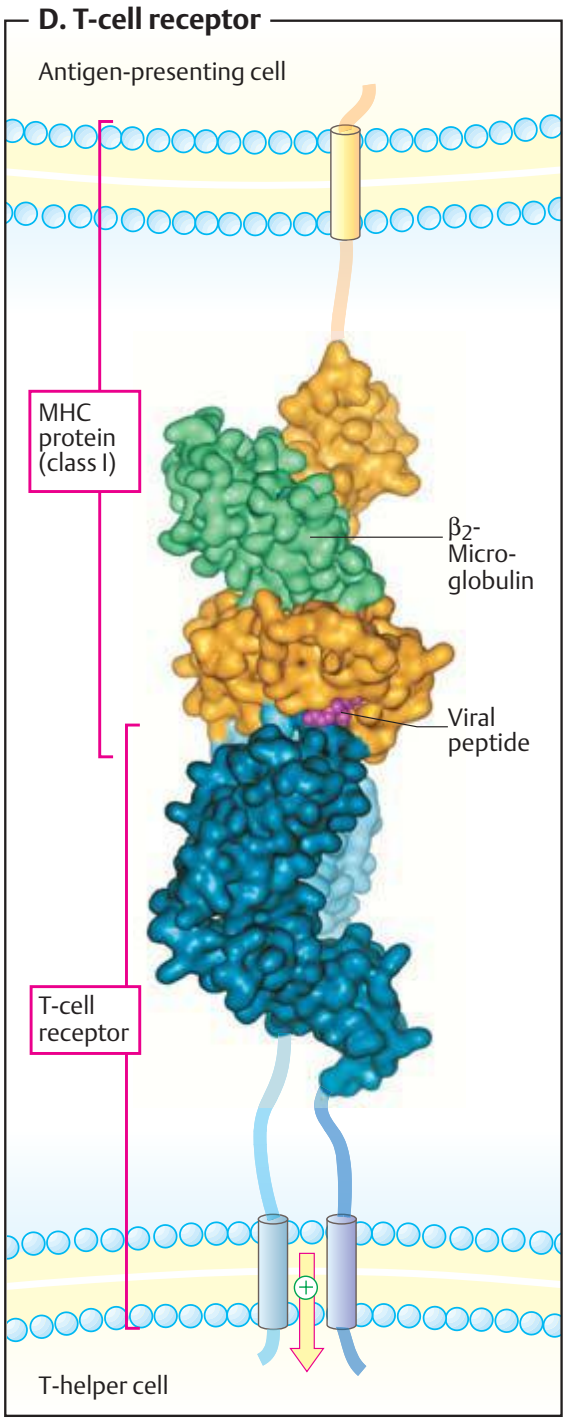

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ER: structure and function

The endoplasmic reticulum (ER) is an extensive closed membrane system consisting of tubular and saccular structures. In the area of the nucleus, the ER turns into the external nuclear membrane. Morphologically, a distinction is made between the **rough ER** (rER) and the **smooth ER** (sER). Large numbers of ribosomes are found on the membranes of the rER, which are lacking on the sER. On the other hand, the sER is rich in membrane-bound **enzymes**, which catalyze partial reactions in the lipid metabolism as well as biotransformations.

A. Rough endoplasmic reticulum and the Golgi apparatus ◑

The **rER** (**1**) is a site of active *protein biosynthesis.* This is where proteins destined for membranes, lysosomes, and export from the cell are synthesized. The remaining proteins are produced in the cytoplasm on ribosomes that are not bound to membranes.

Proteins synthesized at the rER (**1**) are folded and modified after translation (protein maturation; see p. 230). They remain either in the rER as membrane proteins, or pass with the help of transport vesicles (**2**) to the Golgi apparatus (**3**). Transport vesicles are formed by budding from existing membranes, and they disappear again by fusing with them (see p. 228).

The **Golgi apparatus** (**3**) is a complex network, also enclosed, consisting of flattened membrane saccules ("cisterns"), which are stacked on top of each other in layers. Proteins mature here and are sorted and packed. A distinction is made between the *cis, medial,* and *trans* Golgi regions, as well as a *trans* Golgi network (tGN). The *post–translational modification of proteins,* which starts in the ER, continues in these sections.

From the Golgi apparatus, the proteins are transported by vesicles to various targets in the cells—e.g., to lysosomes (**4**), the plasma membrane (**6**), and secretory vesicles (**5**) that release their contents into the extracellular space by fusion with the plasma membrane (**exocytosis**; see p. 228). Protein transport can either proceed continuously (*constitutive*), or it can be *regulated* by chemical signals. The decision regarding which pathway a protein will take and whether its transport will be constitutive or regulated depends on the signal sequences or signal structures that proteins carry with them like address labels (see p. 228). In addition to proteins, the Golgi apparatus also transports membrane lipids to their targets.

B. Smooth endoplasmic reticulum ◑

Regions of the ER that have no bound ribosomes are known as the **smooth endoplasmic reticulum** (sER). In most cells, the proportion represented by the sER is small. A marked sER is seen in cells that have an active lipid metabolism, such as hepatocytes and Leydig cells. The sER is usually made up of branching, closed tubules.

Membrane-located enzymes in the sER catalyze **lipid synthesis**. Phospholipid synthesis (see p. 170) is located in the sER, for example, and several steps in cholesterol biosynthesis (see p. 172) also take place there. In endocrine cells that form *steroid hormones,* a large proportion of the reaction steps involved also take place in the sER (see p. 376).

In the liver's hepatocytes, the proportion represented by the sER is particularly high. It contains enzymes that catalyze so-called **biotransformations**. These are reactions in which apolar foreign substances, as well as endogenous substances—e.g., steroid hormones—are chemically altered in order to inactivate them and/or prepare them for conjugation with polar substances (phase I reactions; see p. 316). Numerous *cytochrome P450 enzymes* are involved in these conversions (see p. 318) and can therefore be regarded as the major molecules of the sER.

The sER also functions as an intracellular **calcium store**, which normally keeps the Ca^{2+} level in the cytoplasm low. This function is particularly marked in the *sarcoplasmic reticulum*, a specialized form of the sER in muscle cells (see p. 334). For release and uptake of Ca^{2+}, the membranes of the sER contain signal-controlled Ca^{2+} channels and energy-dependent Ca^{2+} ATPases (see p. 220). In the lumen of the sER, the high Ca^{2+} concentration is buffered by Ca^{2+}-binding proteins.

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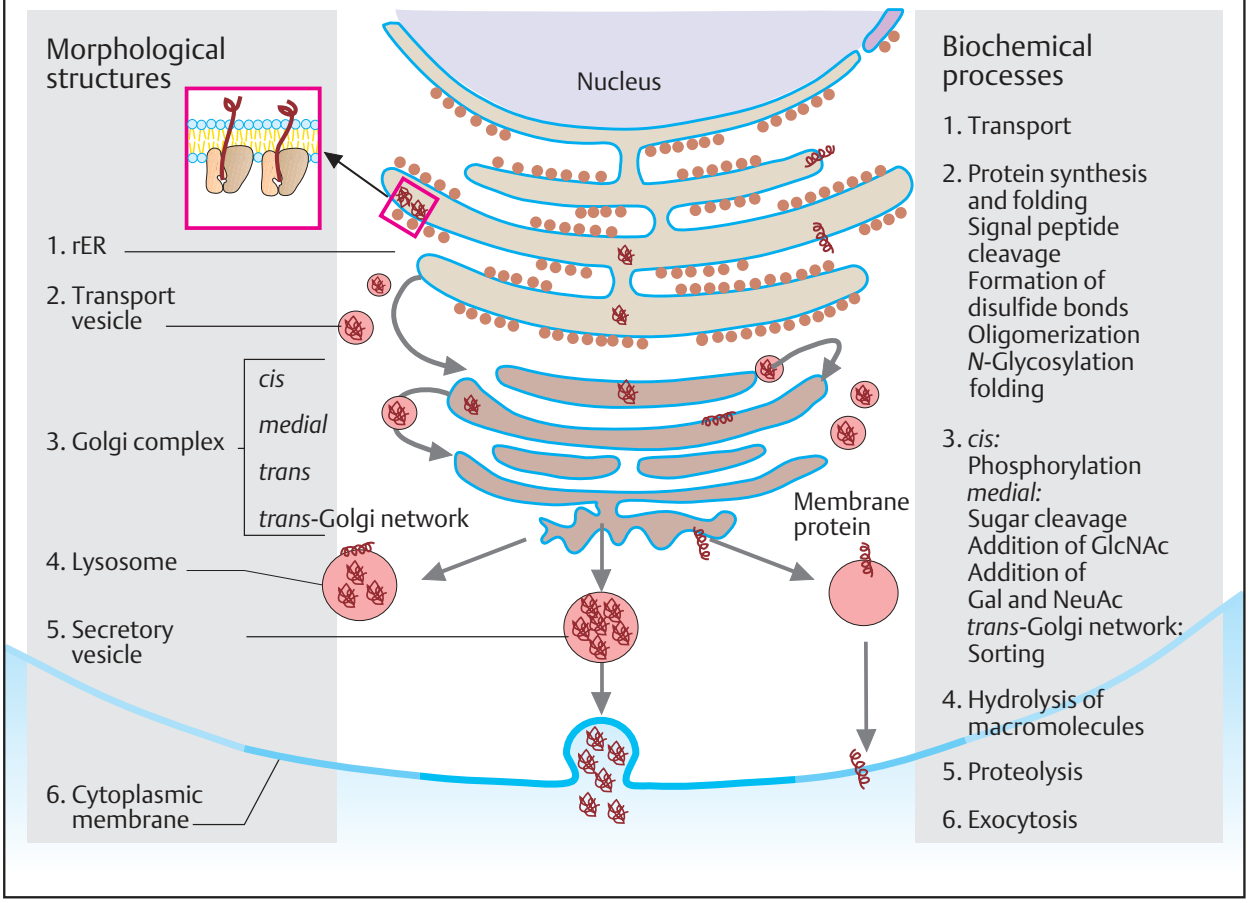
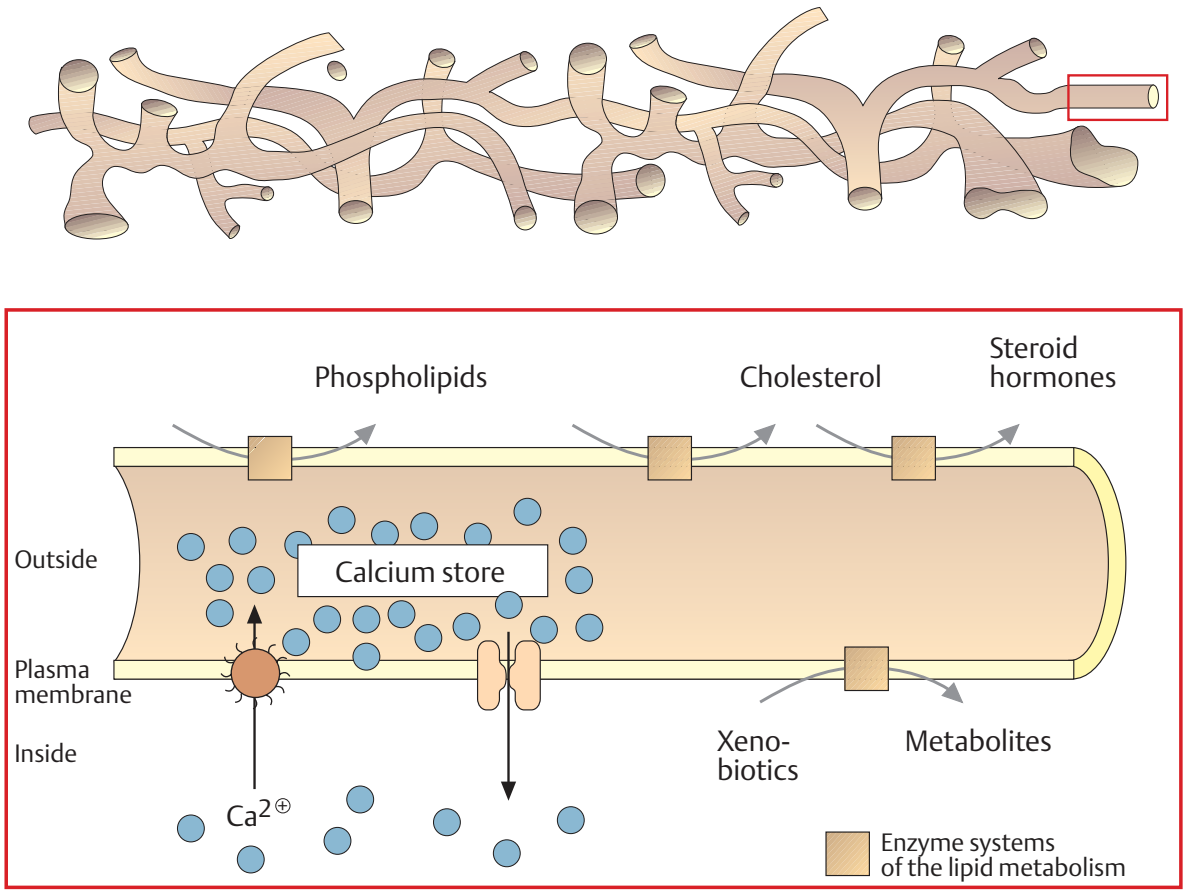
A. Rough endoplasmic reticulum and Golgi apparatus



B. Smooth endoplasmic reticulum



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Protein sorting

A. Protein sorting ◑

The biosynthesis of all proteins starts on free ribosomes (top). However, the paths that the proteins follow soon diverge, depending on which target they are destined for. Proteins that carry a *signal peptide for the ER* (**1**) follow the *secretory pathway* (right). Proteins that do not have this signal follow the *cytoplasmic pathway* (left).

Secretory pathway. Ribosomes that synthesize a protein with a signal peptide for the ER settle on the ER (see p. 228). The peptide chain is transferred into the lumen of the rER. The presence or absence of other signal sequences and signal regions determines the subsequent transport pathway.

Proteins that have *stop-transfer sequences* (**4**) remain as integral membrane proteins in the ER membrane. They then pass into other membranes via vesicular transport (see p. 226). From the rER, their pathway then leads to the Golgi apparatus and then on to the plasma membrane. Proteins destined to remain in the rER—e. g., enzymes—find their way back from the Golgi apparatus to the rER with the help of a *retention signal* (**2**). Other proteins move from the Golgi apparatus to the lysosomes (**3**; see p. 234), to the cell membrane (integral membrane proteins or constitutive exocytosis), or are transported out of the cell (**9;** signal-regulated exocytosis) by secretory vesicles (**8**).

Cytoplasmic pathway. Proteins that do not have a signal peptide for the ER are synthesized in the cytoplasm on free ribosomes, and remain in that compartment. Special signals mediate further transport into the mitochondria (**5**; see p. 232), the nucleus (**6**; see p. 208) or peroxisomes (**7**).

B. Translocation signals ○

Signal peptides are short sections at the N or C terminus, or within the peptide chain. Areas on the protein surface that are formed by various sections of the chain or by various chains are known as **signal regions**. Signal peptides and signal regions are *structural signals* that are usually recognized by *receptors* on organelles (see **A**). They move the proteins, with the help of additional proteins, into the organelles (*selective protein transfer*). Structural signals can also activate *enzymes* that modify the proteins and thereby determine their subsequent fate. Examples include lysosomal proteins (see p. 234) and membrane proteins with lipid anchors (see p. 214).

After they have been used, signal peptides at the N terminus are cleaved off by specific hydrolases (symbol: scissors). In proteins that contain several successive signal sequences, this process can expose the subsequent signals. By contrast, signal peptides that have to be read several times are not cleaved.

C. Exocytosis ○

Exocytosis is a term referring to processes that allow cells to expel substances (e. g., hormones or neurotransmitters) quickly and in large quantities. Using a complex protein machinery, secretory vesicles fuse completely or partially with the plasma membrane and release their contents. Exocytosis is usually *regulated* by chemical or electrical signals. As an example, the mechanism by which neurotransmitters are released from synapses (see p. 348) is shown here, although only the most important proteins are indicated.

The decisive element in exocytosis is the interaction between proteins known as SNAREs that are located on the vesicular membrane (v-SNAREs) and on the plasma membrane (t-SNAREs). In the resting state (**1**), the v-SNARE *synaptobrevin* is blocked by the vesicular protein *synaptotagmin.* When an action potential reaches the presynaptic membrane, voltage-gated Ca^{2+} channels open (see p. 348). Ca^{2+} flows in and triggers the machinery by conformational changes in proteins. Contact takes place between synaptobrevin and the t-SNARE *synaptotaxin* (**2**). Additional proteins known as SNAPs bind to the SNARE complex and allow fusion between the vesicle and the plasma membrane (**3**). The process is supported by the hydrolysis of GTP by the auxiliary protein *Rab.*

The toxin of the bacterium *Clostridium botulinum,* one of the most poisonous substances there is, destroys components of the exocytosis machinery in synapses through enzymatic hydrolysis, and in this way blocks neurotransmission.

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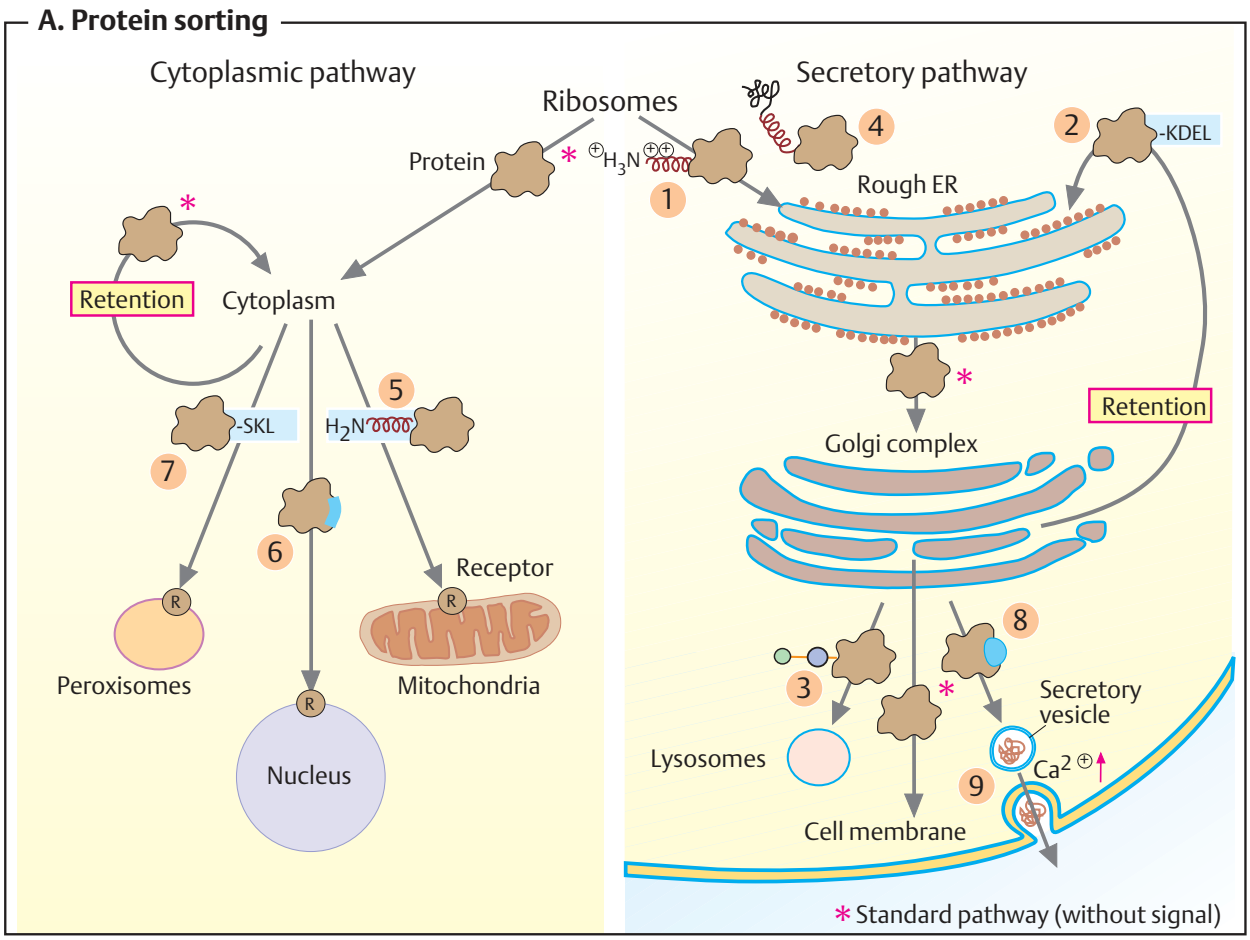

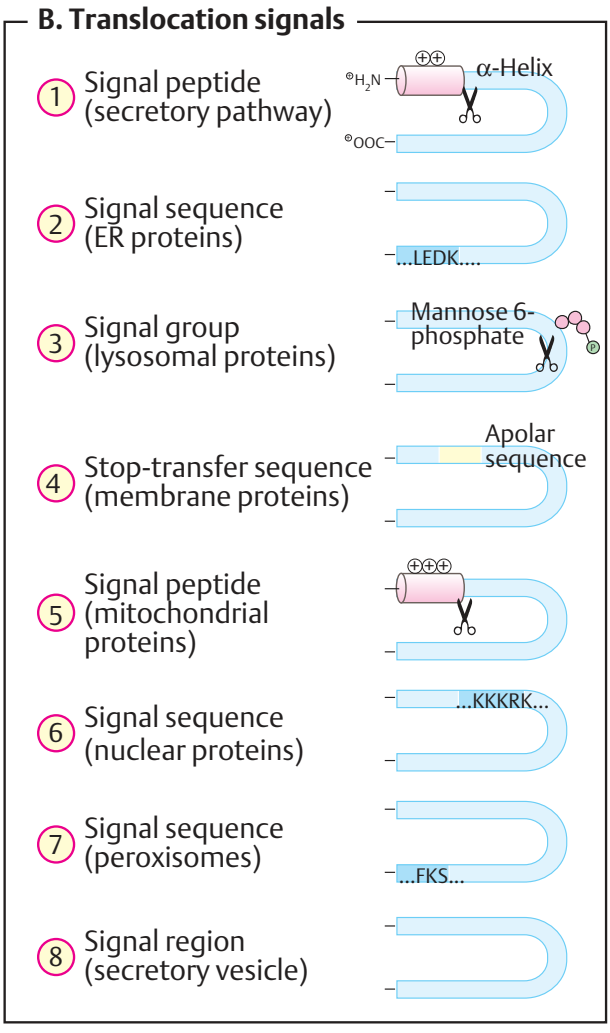

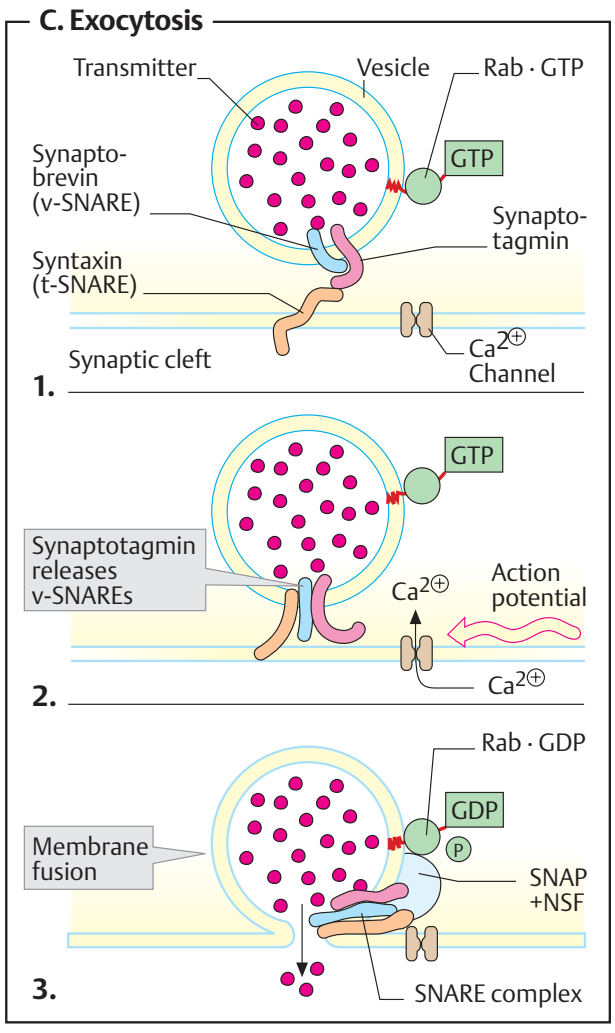

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Protein synthesis and maturation

A. Protein synthesis in the rER ◑

With all proteins, protein biosynthesis (**Translation**; for details, see p. 250) starts on free ribosomes in the cytoplasm (**1**). Proteins that are exported out of the cell or into lysosomes, and membrane proteins of the ER and the plasma membrane, carry a **signal peptide for the ER** at their N-terminus. This is a section of 15–60 amino acids in which one or two strongly basic residues (Lys, Arg) near the N-terminus are followed by a strongly hydrophobic sequence of 10–15 residues (see p. 228).

As soon as the signal peptide (red) appears on the surface of the ribosome (**2**), an RNA-containing *signal recognition particle* (**SRP**, green) binds to the sequence and initially interrupts translation (**3**). The SRP then binds to an **SRP receptor** in the rER membrane, and in this way attaches the ribosome to the ER (**4**). After this, the SRP dissociates from the signal peptide and from the SRP receptor and is available again for step 3. This endergonic process is driven by GTP hydrolysis (**5**). Translation now resumes. The remainder of the protein, still unfolded, is gradually introduced into a channel (the **translocon**) in the lumen of the rER (**6**), where a *signal peptidase* located in the inner ER membrane cleaves the signal peptide while translation is still taking place (**7**). This converts the **preprotein** into a **proprotein**, from which the mature protein finally arises after additional post-translational modifications (**8**) in the ER and in the Golgi apparatus.

If the growing polypeptide contains a **stop-transfer signal** (see p. 228), then this hydrophobic section of the chain remains stuck in the membrane outside the translocon, and an *integral membrane protein* arises. In the course of translation, an additional signal sequence can re-start the transfer of the chain through the translocon. Several repetitions of this process produce integral membrane proteins with several transmembrane helices (see p. 214).

B. Protein glycosylation ○

Most extracellular proteins contain covalently bound oligosaccharide residues. For example, all plasma proteins with the exception of albumin are glycosylated. Together with glycolipids, numerous **glycoproteins** on the cell surface form the **glycocalyx**. Inside the ER, the carbohydrate parts of the glycoproteins are cotranslationally transferred to the growing chain, and are then converted into their final form while passing through the ER and Golgi apparatus.

N-bound oligosaccharides (see p. 44) are always bound to the acid-amide group of asparagine residues. If a **glycosylation sequence** (–Asn–X–Ser(Thr)–, where X can be any amino acid) appears in the growing peptide chain, then a *transglycosylase* in the ER membrane [1] transfers a previously produced **core oligosaccharide** consisting of 14 hexose residues *en-bloc* from the carrier molecule **dolichol diphosphate** to the peptide.

Dolichol is a long-chain isoprenoid (see p. 52) consisting of 10–20 isoprene units, which is embedded in the ER membrane. A hydroxyl group at the end of the molecule is bound to diphosphate, on which the nuclear oligosaccharide is built up in an extended reaction sequence (not shown here in detail). The core structure consists of two residues of N-acetylglucosamine (GlcNAc), a branched group of nine mannose residues (Man) and three terminal glucose resides (Glc).

As the proprotein passes through the ER, *glycosidases* [2] remove the glucose residues completely and the mannoses partially ("trimming"), thereby producing the **mannose-rich type** of oligosaccharide residues. Subsequently, various *glycosyltransferases* [3] transfer additional monosaccharides (e.g., GlcNAc, galactose, fucose, and N-acetylneuraminic acid; see p. 38) to the mannose-rich intermediate and thereby produce the **complex type** of oligosaccharide. The structure of the final oligosaccharide depends on the type and activity of the glycosyltransferases present in the ER of the cell concerned, and is therefore genetically determined (although indirectly).

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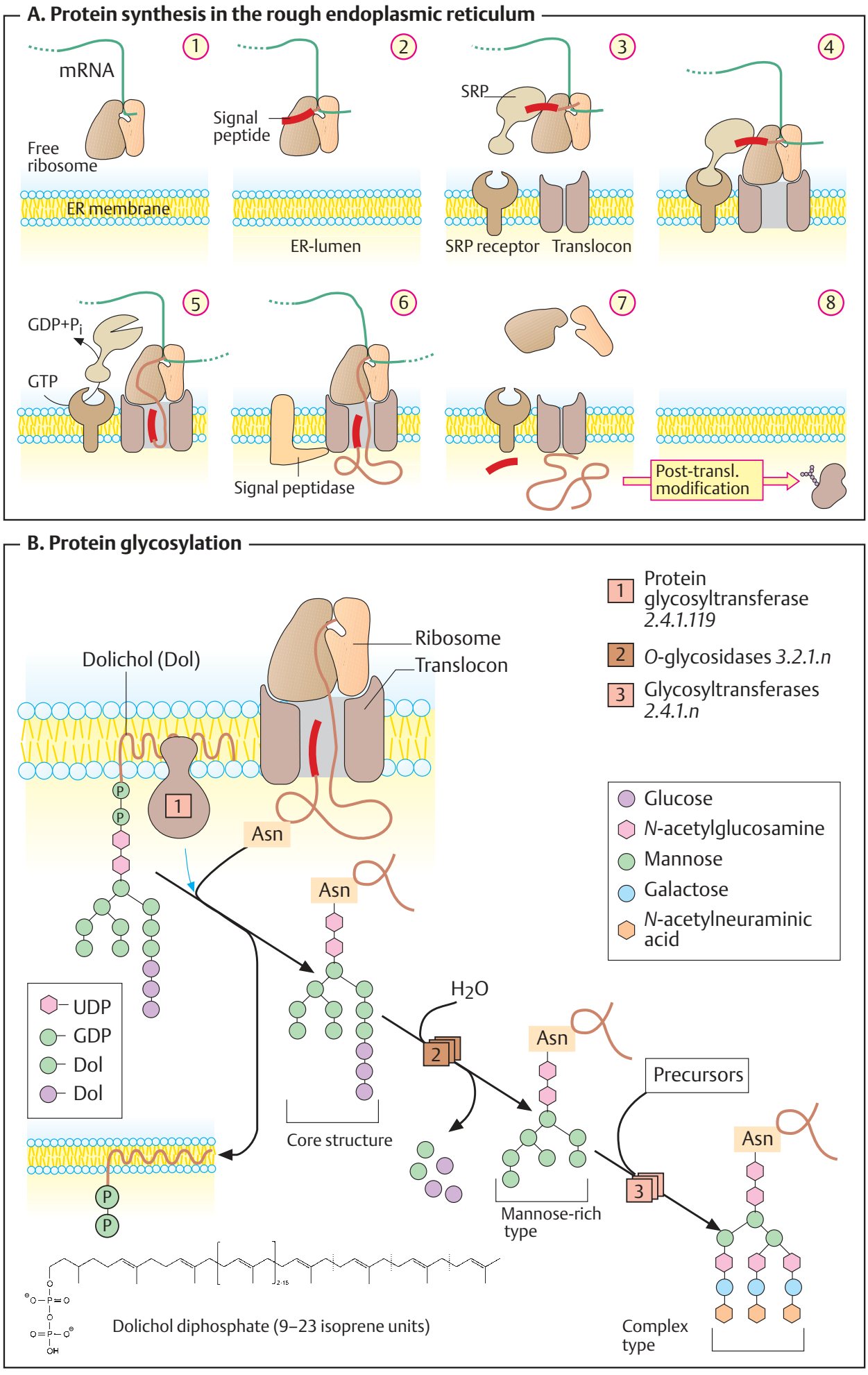

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Protein maturation

After translation, proteins destined for the secretory pathway (see p. 228) first have to fold into their native conformation within the rER (see p. 230). During this process they are supported by various *auxiliary proteins.*

A. Protein folding in the rER ●

To prevent incorrect folding of the growing protein during protein biosynthesis, **chaperones** (see **B**) in the lumen of the rER bind to the peptide chain and stabilize it until translation has been completed. Binding protein (**BiP**) is an important chaperone in the ER.

Many secretory proteins—e. g., pancreatic ribonuclease (RNAse; see p. 74)—contain several disulfide bonds that are only formed oxidatively from SH groups after translation. The eight cysteine residues of the RNAse can in principle form 105 different pairings, but only the combination of the four disulfide bonds shown on p. 75 provides active enzyme. Incorrect pairings can block further folding or lead to unstable or insoluble conformations. The enzyme *protein disulfide isomerase* [1] accelerates the equilibration between paired and unpaired cysteine residues, so that incorrect pairs can be quickly split before the protein finds its final conformation.

Most peptide bonds in proteins take on the *trans* conformation (see p. 66). Only bonds with proline residues (–X–Pro–) can be present in both *cis* and *trans* forms.

In the protein's native conformation, every X–Pro bond has to have the correct conformation (*cis* or *trans*). As the uncatalyzed transition between the two forms is very slow, there is a *proline* cis–trans *isomerase* [2] in the ER that accelerates the conversion.

B. Chaperones and chaperonins ●

Most proteins fold spontaneously into their native conformation, even in the test tube. In the cell, where there are very high concentrations of proteins (around 350 g L^{-1}), this is more dif cult. In the unfolded state, the apolar regions of the peptide chain (yellow) tend to aggregate—due to the hydrophobic effect (see p. 28)—with other proteins or with each other to form insoluble products (2). In addition, unfolded proteins are susceptible to proteinases. To protect partly folded proteins, there are auxiliary proteins called **chaperones** because they guard immature proteins against damaging contacts. Chaperones are formed increasingly during temperature stress and are therefore also known as **heat-shock proteins** (hsp). Several classes of hsp are distinguished. Chaperones of the hsp70 type (Dna K in bacteria) are common, as are type hsp60 **chaperonins** (GroEL/ES in bacteria). Class hsp90 chaperones have special tasks (see p. 378).

While small proteins can often reach their native conformation without any help (1), larger molecules require hsp70 proteins for protection against aggregation which bind as monomers and can dissociate again, dependent on ATP (3). By contrast, type hsp60 chaperonins form large, barrel-shaped complexes with 14 subunits in which proteins can fold independently while shielded from their environment (4). The function of hsp60 has been investigated in detail in the bacterial chaperonin **GroEL** (right). The barrel has two chambers, which are closed with a lid (**GroES**) during folding of the guest protein. Driven by ATP hydrolysis, the chambers open and close alternately—i. e., the release of the fully folded protein from one chamber is coupled to the uptake of an unfolded peptide in the second chamber.

C. Protein import in mitochondria ●

Class hsp70 chaperones are also needed for translocation of nuclear-coded proteins from the cytoplasm into the mitochondria (see p. 228). As two membranes have to be crossed to reach the matrix, there are two translocator complexes: **TOM (**"transport outer membrane") and **TIM** ("transport inner membrane"). For transport, proteins are unfolded in the cytoplasm and protected by hsp70. TOM recognizes the positively charged signal sequence at the protein's N terminus (see p. 228) and with the help of the membrane potential threads the chains through the central pores of the two complexes. Inside TIM, further hsp70 molecules bind and pull the chain completely into the matrix. As with import into the ER, the signal peptide is proteolytically removed by a signal peptidase during translocation.

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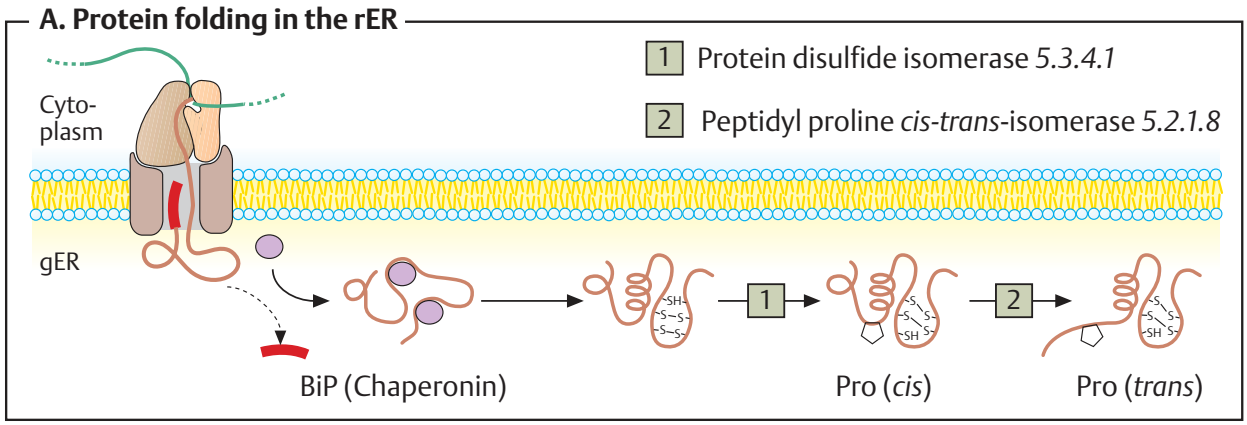

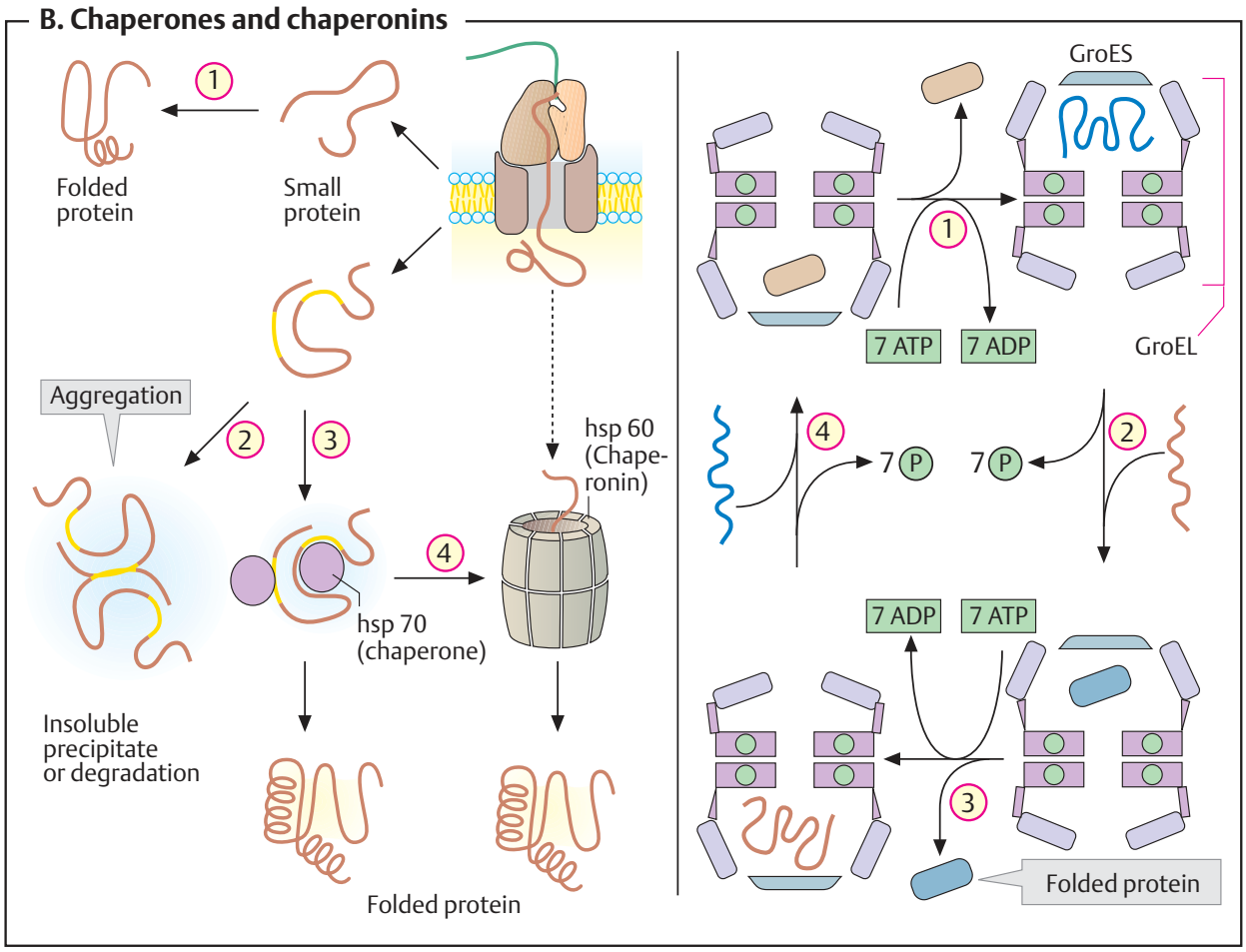

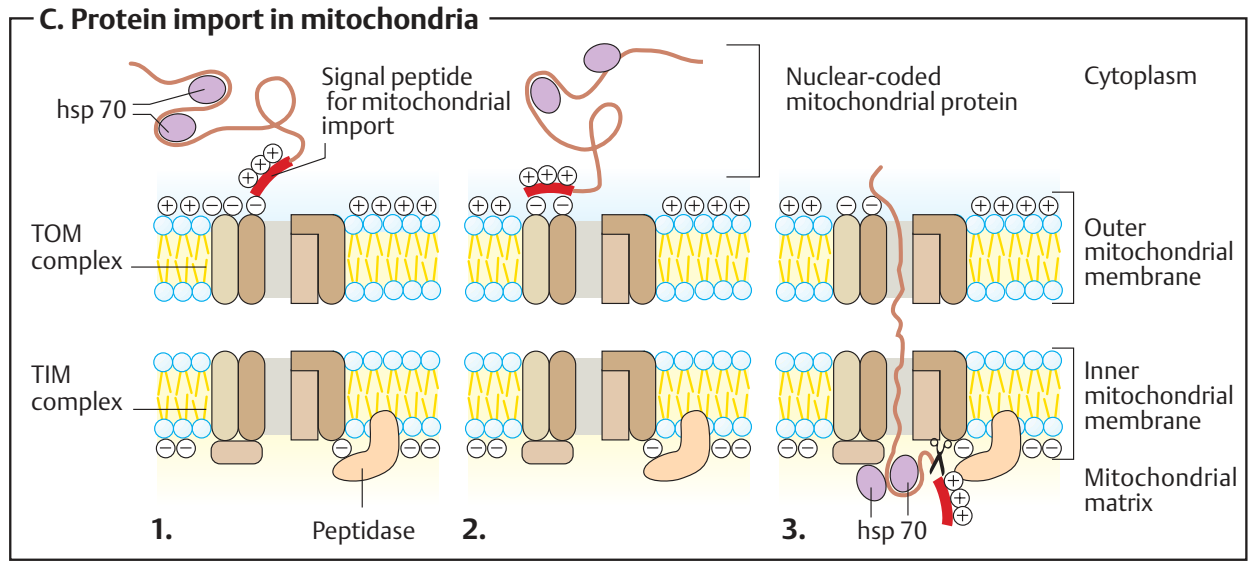

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Lysosomes

A. Structure and contents ◑

Animal lysosomes are organelles with a diameter of 0.2–2.0 μm with various shapes that are surrounded by a single membrane. There are usually several hundred lysosomes per cell. ATP-driven V-type proton pumps are active in their membranes (see p. 220). As these accumulate H^+ in the lysosomes, the content of lysosomes with pH values of 4.5–5 is much more acidic than the cytoplasm (pH 7–7.3).

The lysosomes are the cell's "stomach," serving to break down various cell components. For this purpose, they contain some 40 different types of **hydrolases**, which are capable of breaking down every type of macromolecule. The marker enzyme of lysosomes is *acid phosphatase*. The pH optimum of lysosomal enzymes is adjusted to the acid pH value and is also in the range of pH 5. At neutral pH, as in the cytoplasm, lysosomal enzymes only have low levels of activity. This appears to be a mechanism for protecting the cells from digesting themselves in case lysosomal enzymes enter the cytoplasm at any time. In plants and fungi, the **cell vacuoles** (see p. 43) have the function of lysosomes.

B. Functions ◑

Lysosomes serve for enzymatic degradation of macromolecules and cell organelles, which are supplied in various ways. The example shows the degradation of an overaged mitochondrion by *autophagy*. To accomplish this, the lysosome encloses the organelle (**1**). During this process, the **primary lysosome** converts into a **secondary lysosome**, in which the hydrolytic degradation takes place (**2**). Finally, **residual bodies** contain the indigestible residues of the lysosomal degradation process. Lysosomes are also responsible for the degradation of macromolecules and particles taken up by cells via *endocytosis* and *phagocytosis*—e. g., lipoproteins, proteohormones, and bacteria (*heterophagy*). In the process, lysosomes fuse with the **endosomes** (**3**) in which the endocytosed substances are supplied.

C. Synthesis and transport of lysosomal proteins ◑

Primary lysosomes arise in the region of the Golgi apparatus. **Lysosomal proteins** are synthesized in the rER and are glycosylated there as usual (**1**; see p. 228). The next steps are specific for lysosomal proteins (right part of the illustration). In a two-step reaction, terminal mannose residues (Man) are phosphorylated at the C–6 position of the mannose. First, *N*-acetylglucosamine 1-phosphate is transferred to the OH group at C-6 in a terminal mannose residue, and *N*-acetylglucosamine is then cleaved again. Lysosomal proteins therefore carry a terminal **mannose 6–phosphate** (Man6–P; **2**).

The membranes of the Golgi apparatus contain receptor molecules that bind Man 6–P. They recognize lysosomal proproteins by this residue and bind them (**3**). With the help of *clathrin*, the receptors are concentrated locally. This allows the appropriate membrane sections to be pinched off and transported to the endolysosomes with the help of transport vesicles (**4**), from which primary lysosomes arise through maturation (**5**). Finally, the phosphate groups are removed from Man 6–P (**6**).

The *Man 6–P receptors* are reused. The fall in the pH value in the endolysosomes releases the receptors from the bound proteins (**7**) which are then transported back to the Golgi apparatus with the help of transport vesicles.

Further information

Many hereditary diseases are due to genetic defects in lysosomal enzymes. The metabolism of glycogen (→ *glycogenoses*), lipids (→ *lipidoses*), and proteoglycans (→ *mucopolysaccharidoses*) is particularly affected. As the lysosomal enzymes are indispensable for the intracellular breakdown of macromolecules, unmetabolized macromolecules or degradation products accumulate in the lysosomes in these diseases and lead to irreversible cell damage over time. In the longer term, enlargement takes place, and in severe cases there may be failure of the organ affected—e. g., the liver.

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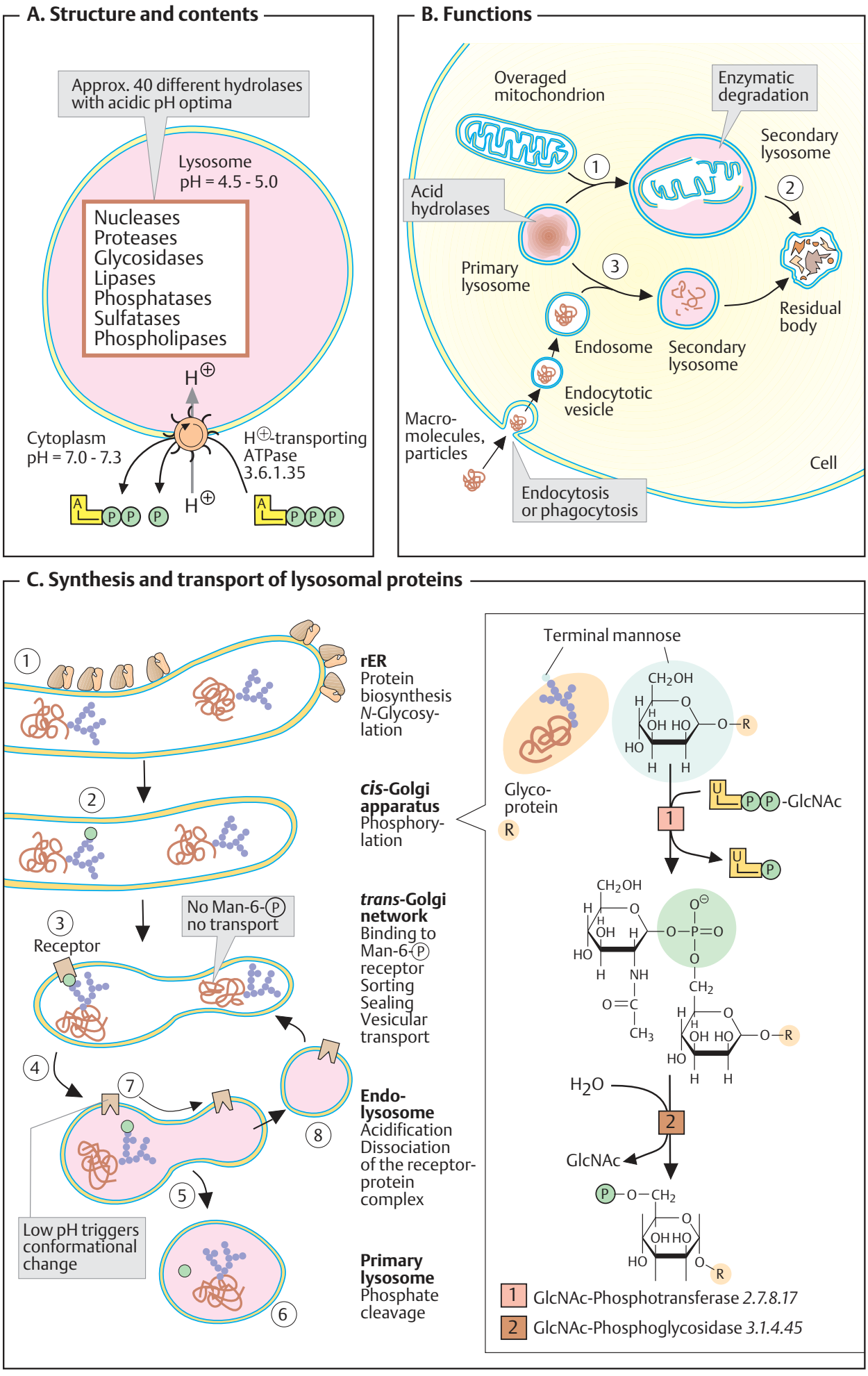

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