Cell Biology

Todd H. Rider thor@riderinstitute.org 13 November 2019[1]

Any suggestions for improvements would be greatly appreciated.

The guinea pigs grew drowsier and drowsier. In two days they rolled over, kicked convulsively, and died. Full of dramatic expectation, the class reassembled for the necropsy. On the demonstrator's table was a wooden tray, scarred from the tacks which for years had pinned down the corpses. The guinea pigs were in a glass jar, rigid, their hair ruffled. The class tried to remember how nibbling and alive they had been. The assistant stretched out one of them with thumbtacks. Gottlieb swabbed its belly with a cotton wad soaked in lysol, slit it from belly to neck, and cauterized the heart with a red-hot spatula–the class quivered as they heard the searing of the flesh. Like a priest of diabolic mysteries, he drew out the blackened blood with a pipette. With the distended lungs, the spleen and kidneys and liver, the assistant made wavy smears on glass slides which were stained and given to the class for examination. The students who had learned to look through the microscope without having to close one eye were proud and professional, and all of them talked of the beauty of identifying the bacillus, as they twiddled the brass thumbscrews to the right focus and the cells rose from cloudiness to sharp distinctness on the slides before them. But they were uneasy, for Gottlieb remained with them that day, stalking behind them, saying nothing, watching them always, watching the disposal of the remains of the guinea pigs, and along the benches ran nervous rumors about a bygone student who had died from anthrax infection in the laboratory.

–Sinclair Lewis, *Arrowsmith* (1925)

"...it does look as though there is a method for making proteins just waiting to be used. Properly making them, synthesising them, I mean: it sounds fantastic, and the method's more fantastic than you can possibly believe. Not because it is complicated, but because it's easy."

"Where are the results?" I asked. "Can I see them?"

"Everything's at the lab," he said. "I've been living there for the last fortnight. Literally living there, and sleeping beside the apparatus." He laughed. "It hasn't given me much extra time, but it's kept people away." [...]

"The physicists won't like me because I'm a renegade from physics," said Constantine, with his smile of humorous humility. "And the chemists won't like me because I am a physicist. And the biologists won't like me because I do biology. And the mathematicians won't know about me because I don't do mathematics."

–C. P. Snow, *The Search* (1934)

Overview

A cell is a relatively simple, self-replicating biological system that may exist by itself or as part of a larger multicellular organism. Cell biology may be divided into three areas:

(1) The internal structures or organelles found in different cell types, including those in simpler prokyarotic (bacteria) cells and those in more complex eukaryotic (animal, plant, and fungus) cells.

(2) Metabolic and communication pathways that are collectively carried out by those cell structures working together, including nutrient metabolism, transcription and translation to produce proteins, stress survival pathways, microbial defense pathways, cell death pathways, and cell differentiation.

(3) Cell division in which a cell replicates itself to create more cells, including mitotic cell division, meiotic cell division, pathways controlling cell division, and cancers that occur when division occurs in an uncontrolled fashion.

Contents

1 Cell Structures and Functions

This section will begin by providing some context for cell biology, then discuss the major types of cells and the various structures within those cells.

1.1 Introduction to Cell Biology

The logical way to view all of biology is to envision, as shown in Fig. 1, the progression from smaller and simpler systems to larger and more complex systems:

- Chemistry is the science of various atoms, molecules composed of atoms, and reactions among those atoms and molecules. See the *Inorganic Chemistry* and *Organic Chemistry* summaries for more information on all of that stuff.
- Biochemistry (see the *Biochemistry* summary) concerns chemical molecules and reactions that are specifically relevant in biological systems.
- *Molecular Biology and Genetics* focuses on how detailed information is encoded in certain biomolecules, mainly deoxyribonucleic acid (DNA), ribonucleic acid (RNA), and proteins.
- Cell biology shows how individual biological cells can operate as fairly self-sufficient and self-replicating systems of organized biomolecules. For more information, stay awake!
- *Microbiology* is the study of cell-based microorganisms such as bacteria and protists, as well as smaller beasties like viruses and prions that at least need to find a cell to replicate.
- *Botany* concerns plants, which are mostly multicellular, and covers their evolution, classification, function, and ecological interrelationships.
- *Zoology* is likewise the study of multicellular animals, including their evolution, classification, function, and ecological interrelationships.
- Since humans are animals too, some more so than others, the various organ systems of animals are worthy of in-depth study. See *Cardiopulmonary and Renal Physiology*; *Gastrointestinal and Hepatic Physiology*; *Neural, Sensory, and Motor Physiology*; *Immunology*; *Reproductive and Developmental Biology*; and *Structural and Connective Tissues* for the gory details.

Unfortunately, studies have shown that explaining biology in that order and first teaching new students all the complex biochemical reactions that are the building blocks of biological systems causes too many of those students to give up and become lawyers. Therefore, for the sake of the students and society in general, we will follow the example of the *Star Wars* movies and begin this story in the middle. Cell biology is a good starting place, since cells are large enough to provide some helpful context for later studying the biochemical and molecular biology details, and small enough to later explain how they function in whole plants and animals.

As shown in Fig. 2, cell biology may be divided into three areas:

1. Individual cell structures and their functions, which will be explained in this section.
2. Metabolic and communication pathways that are collectively carried out by those cell structures working together, which will be explained in Section 2.
3. Cell division in which a cell replicates itself to create more cells, which will be explained in Section 3.

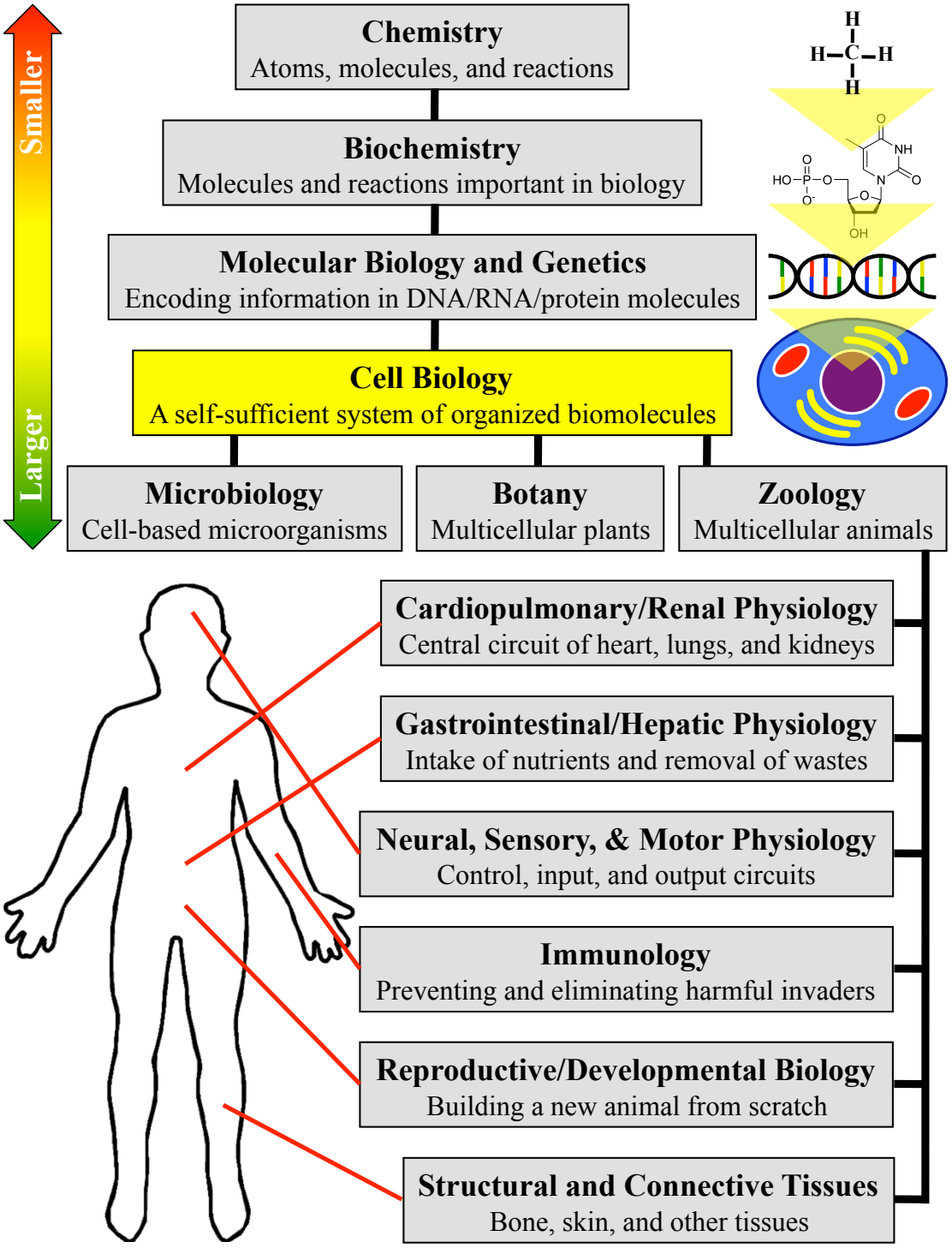
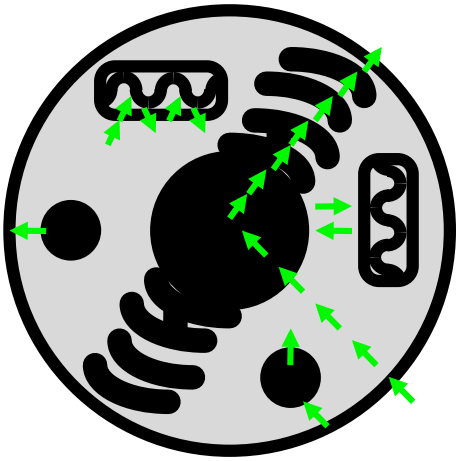
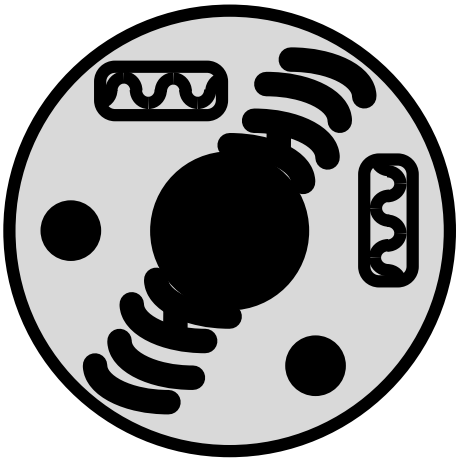


Fig. 1. Relationship between cell biology and other subjects. Cell biology gives context to smaller biological processes, and cells make up organisms and tissues, so cell biology is probably the best place to begin studying biology.

1. Cell structures:
- **Membranes**
- **Nucleus**
- **Endoplasmic reticulum**
- **Golgi apparatus**
- **Endosomes, lysosomes, etc.**
- **Mitochondria**
- **Chloroplasts**
- **Cytoskeleton**
- **Extracellular matrix**



2. Cell pathways:
- **Transcription and translation pathways**
- **Metabolic pathways**
- **Intercellular signaling methods**
- **Intracellular signaling methods**
- **Heat shock/unfolded protein responses**
- **Interferon/inflammatory pathways**
- **Cell death pathways**
- **Cell type differentiation pathways**



3. Cell division
- **Mitosis**
- **Control of cell division**
- **Cancer**
- **Meiosis**

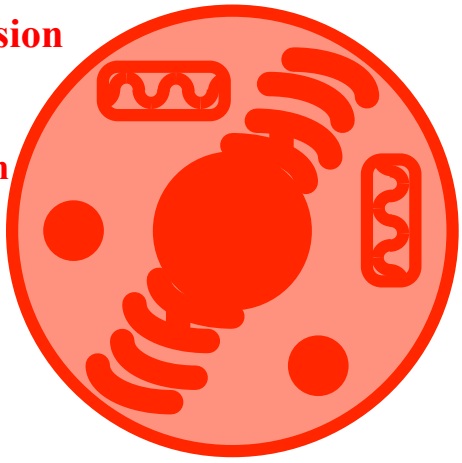


Fig. 2. Graphical overview of cell biology. Cell biology may be divided into **(1)** individual cell structures and their functions, **(2)** metabolic and communication pathways that are collectively carried out by the cell structures, and **(3)** division of the cell to create a new cell.

1.2 Major Types of Cells and Their Structures

Here we will discuss the major types of cells and the structures that they contain; subsequent subsections will go into each of those substructures in more detail.

But first we will begin with a word about our sponsors, the major molecular components of cells that make us all possible. Biological systems are mostly water (H_2O) with some ions (hydrogen or H^+, hydroxyl or HO^-, sodium or Na^+, potassium or K^+, calcium or Ca^{2+}, chlorine or Cl^-, etc.) floating around. However, that is the sort of stuff that you learned about in preschool, so we will concentrate on the stranger components of cells. To keep our PG rating, we will only describe them in general terms, and leave the really hard-core stuff for the later *Biochemistry* summary.

As shown in Fig. 3, there are five major components of cells:

1. Nucleic acids include DNA and RNA, and are used to store and transmit genetic information. They are composed of individual nucleotides strung together. Fig. 3 shows four nucleotides of DNA, containing adenine, cytosine, guanine, and thymine. RNA is extremely similar, except each blue hydrogen (H) in DNA is a hydroxyl (OH) in RNA, and the red methyl (CH_3) in thymine in DNA is just a hydrogen (H) in uracil in RNA. In addition to being strung together to make genes, two nucleotides (adenine- and guanine-containing nucleotides) play key roles individually. Adenosine triphosphate (ATP) and guanosine triphosphate (GTP) are very important sources of energy that power most things in cells. Cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP) are frequently used to send signals inside cells.

2. Proteins are commonly thought of as meat or muscle. As shown in Fig. 3, each protein is composed of different amino acids strung together. Depending on the specific amino acids, the red Rs in Fig. 3 could stand for anything from a simple hydrogen (H) to a whole ring of interconnected atoms. Individual proteins do most of the important jobs in cells, from serving as structural building blocks to acting as little nanomachines to carry out specialized jobs.

3. Lipids are the fatty greasy stuff that you think you aren't supposed to eat, but everyone needs at least some of them. They include fatty acids, triglycerides, cholesterol, and other molecules. They all contain a lot of carbons (C) and hydrogens (H) and not much else, so they don't have much electrical charge or electrical polarity, whereas water molecules (H_2O) are very polar (fairly negative oxygen and fairly positive hydrogens). As a result, lipids are hydrophobic–they don't like to be in water. Thus lipids will float on the top of water, form clumps in water, or do anything but dissolve in water. That's why you have to use soap (another lipid) to get greasy residue off dinner plates, instead of simply rinsing them with water.

4. Carbohydrates are mainly composed of carbon (C), hydrogen (H), and oxygen (O). The most familiar carbohydrates are sugars, including simple or blood sugar (glucose, shown in Fig. 3), fruit sugar (fructose), table sugar (sucrose), milk sugar (lactose), etc. Individual sugars can be strung together in various ways to make everything from starch to cell walls to that super coating that makes cockroaches so darned indestructible.

5. Porphyrins are flower-shaped molecules with a metal ion [usually iron (Fe) or magnesium (Mg)] at their center. They generally help to convert one form of energy into another, doing everything from transporting oxygen in the blood (hemoglobin) to absorbing light in plants (chlorophyll).

Most reactions involving biomolecules have many steps, each of which is facilitated by different enzymes, proteins that act as specialized catalysts to greatly speed up and control reactions.

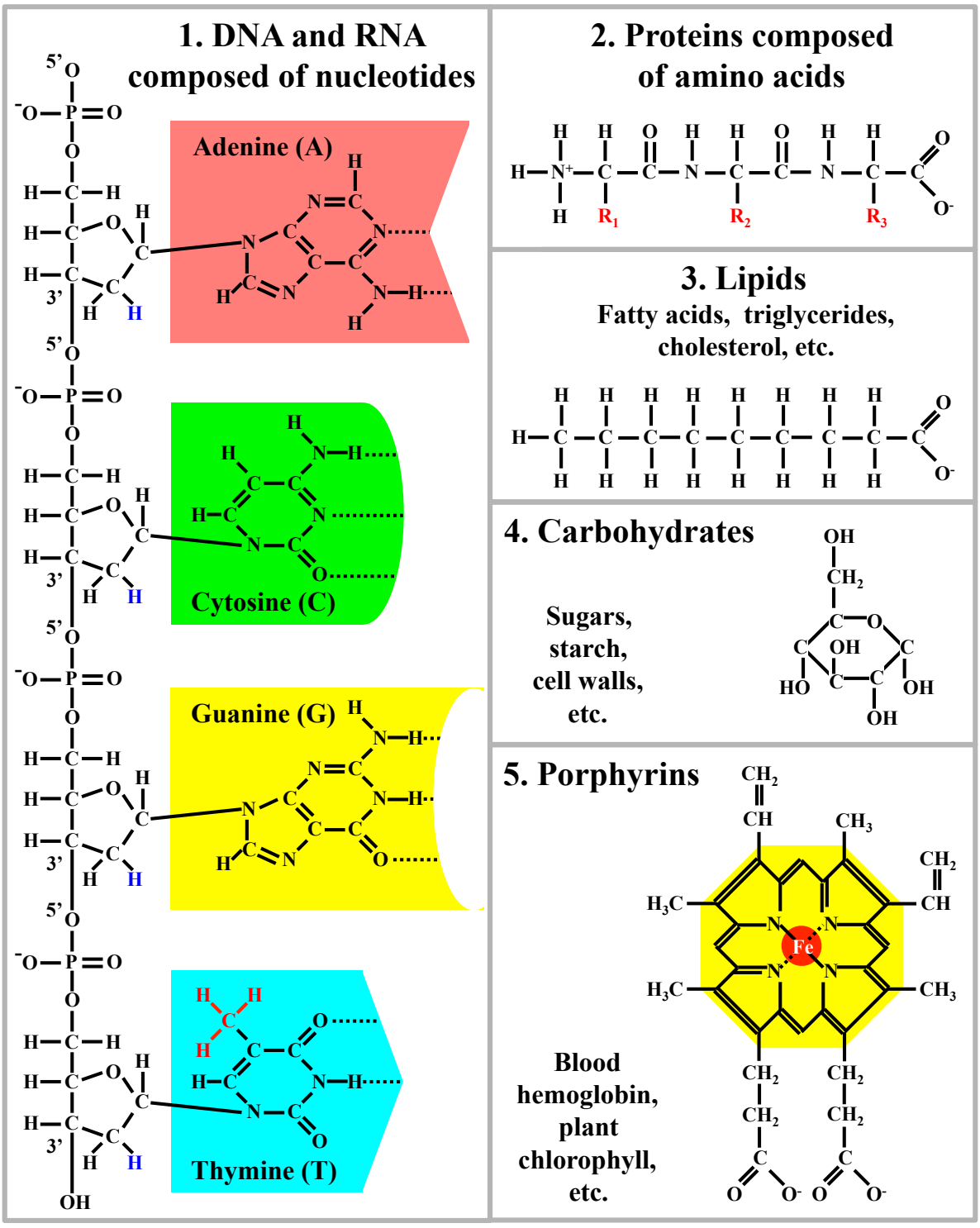


Fig. 3. Major components of cells. Most biological molecules fall into five categories: (1) nucleic acids such as deoxyribonucleic acid (DNA), ribonucleic acid (RNA), and their component nucleotides; (2) proteins and their component amino acids; (3) lipids such as fatty acids, triglycerides, and cholesterol; (4) carbohydrates such as simple sugars and various polymers composed of them; and (5) iron- or magnesium-containing porphyrins in hemoglobin, chlorophyll, etc.

Animal cells (Fig. 4) and plant and fungal cells (Fig. 5) have many similarities and are very complex; they are called **eukaryotic** ("true nucleus") cells just to sound impressive. Bacterial cells (Fig. 6) are much smaller and simpler than animal and plant cells; they get the fancy name of **prokaryotic** ("dreaming of having a nucleus someday") cells. Those of us who are not vegetables or bacterial slime monsters are rather biased toward animal cells, so we will think largely in terms of those (Fig. 4), with reference to differences in Figs. 5-6 as needed. Just as the body is composed of organs with different functions, cells are composed of **organelles** (little organs) with different functions. A helpful analogy is to think of a cell as a city:

- The **plasma membrane** (Section 1.3) surrounds the cell and carefully controls what molecules can enter or leave, just as ancient cities were surrounded by city walls to control who could enter or leave. Plant, fungal, and bacterial cells tend to live in harsher environments than animal cells, so they are also surrounded by thick cell walls made of various carbohydrates.
- The **nucleus** (Section 1.4) contains master blueprints (DNA) for everything in the cell, just like city hall. Since those blueprints are very large and valuable, for individual jobs the nucleus just copies the needed page (gene) as a temporary working copy (RNA) that is sent out of the nucleus. Just as city hall is guarded to control who enters and leaves, the nucleus is surrounded by its own membrane with pores that carefully regulate what enters and leaves.
- **Ribosomes**, often on the **endoplasmic reticulum** (Section 1.5), read the individual plans (RNA copies) coming out of the nucleus and train workers (assemble proteins) to carry out those plans. For all of you students out there, that is basically where you are stuck right now.
- The **Golgi apparatus** (Section 1.6) provides further training for some of the workers (further modifications of some of the proteins). Afterward, different proteins take up different specialized roles in the cell, like workers pursuing their careers in the city.
- **Mitochondria** (Section 1.7) consume carbohydrate fuels and convert that energy into ATP molecules, which are distributed throughout the cell to power everything else in the cell, just as power plants consume fuel to produce electricity that powers everything else in a city.
- **Chloroplasts** (Section 1.8) are only present in plant cells. They are solar power plants that absorb sunlight and convert that energy into carbohydrate fuels, which are stored in the cell for later use by the mitochondria. Thus plants can basically live on light, whereas animals must find external sources of carbohydrates to eat.
- Small membrane bubbles surround and transport stuff in cells (Section 1.9), just as large trucks can haul things in a city. Some haul in things from the outside (**endosomes**), some carry things around inside or take things out (**vesicles**), some store things (**vacuoles**), and some haul off things to be destroyed (**lysosomes** and **peroxisomes**).
- The **cytoskeleton** (Section 1.10) provides structural and transport connections throughout the inside of a cell, just as roads and bridges tie together a city.
- The **extracellular matrix** (Section 1.11) provides connections to other cells, just as cities have outside connections to other cities.
- The **cytosol** is all the intracellular fluid not in the organelles. Just to be confusing, the **cytoplasm** is all the intracellular fluid not in the nucleus. (Cytoplasm includes fluid in non-nuclear organelles, but cytosol does not.) Don't worry–even most biologists use those two terms interchangeably.

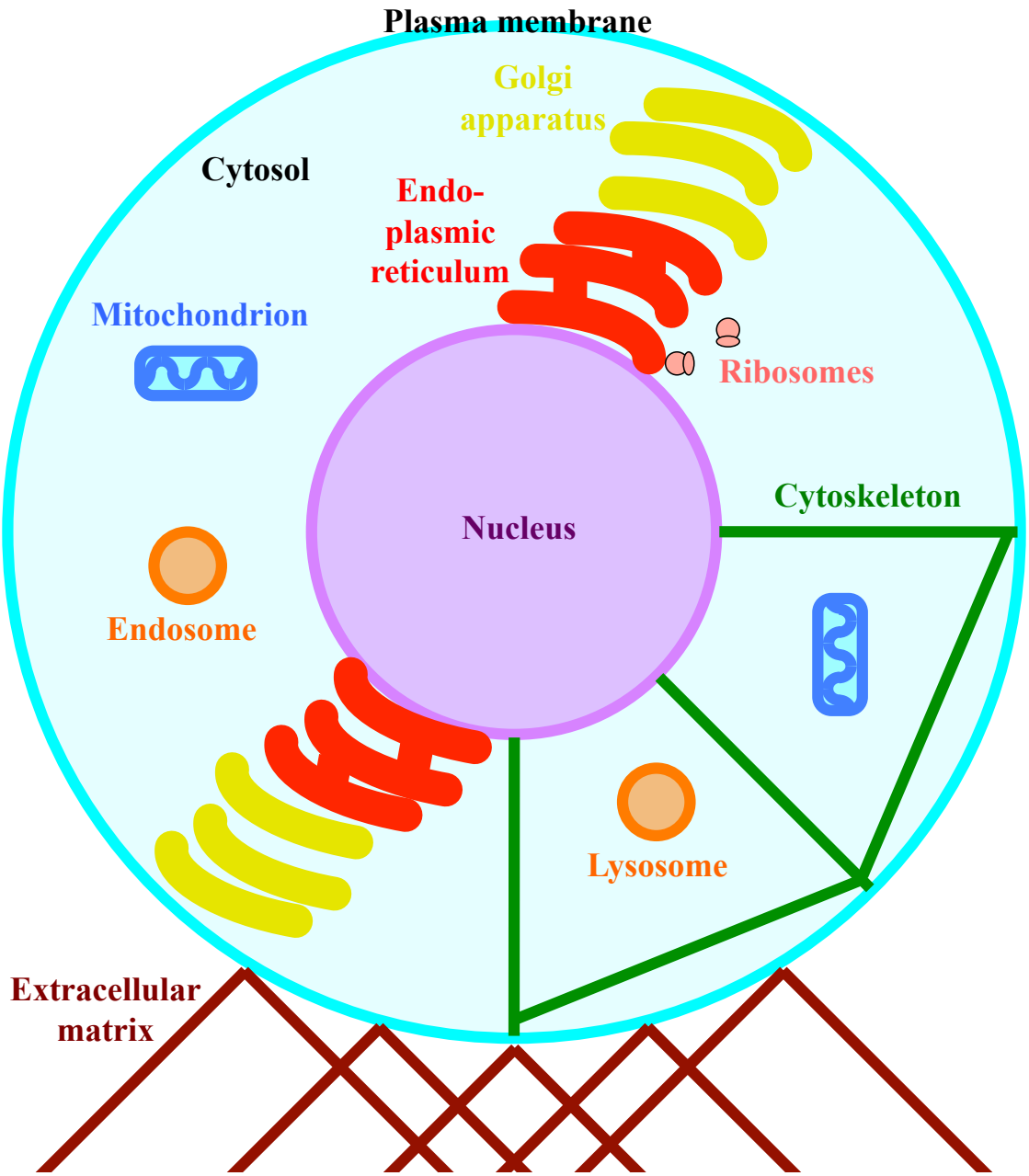


Fig. 4. Typical eukaryotic animal cell. Some major structures in cells include the membranes (which separate different compartments within the cell, and also separate the cell from the outside world), nucleus (where the cell's genes are stored), ribosomes and endoplasmic reticulum (where proteins are made), Golgi apparatus (where some proteins are processed), endosomes/lysosomes/etc. (which transport or destroy molecules in the cell), mitochondria (which produce energy for the rest of the cell), chloroplasts (which are only present in plant cells, where they also produce energy by absorbing sunlight), cytoskeleton (which provides internal connections and support within the cell), and extracellular matrix (which connects the cell to other cells).

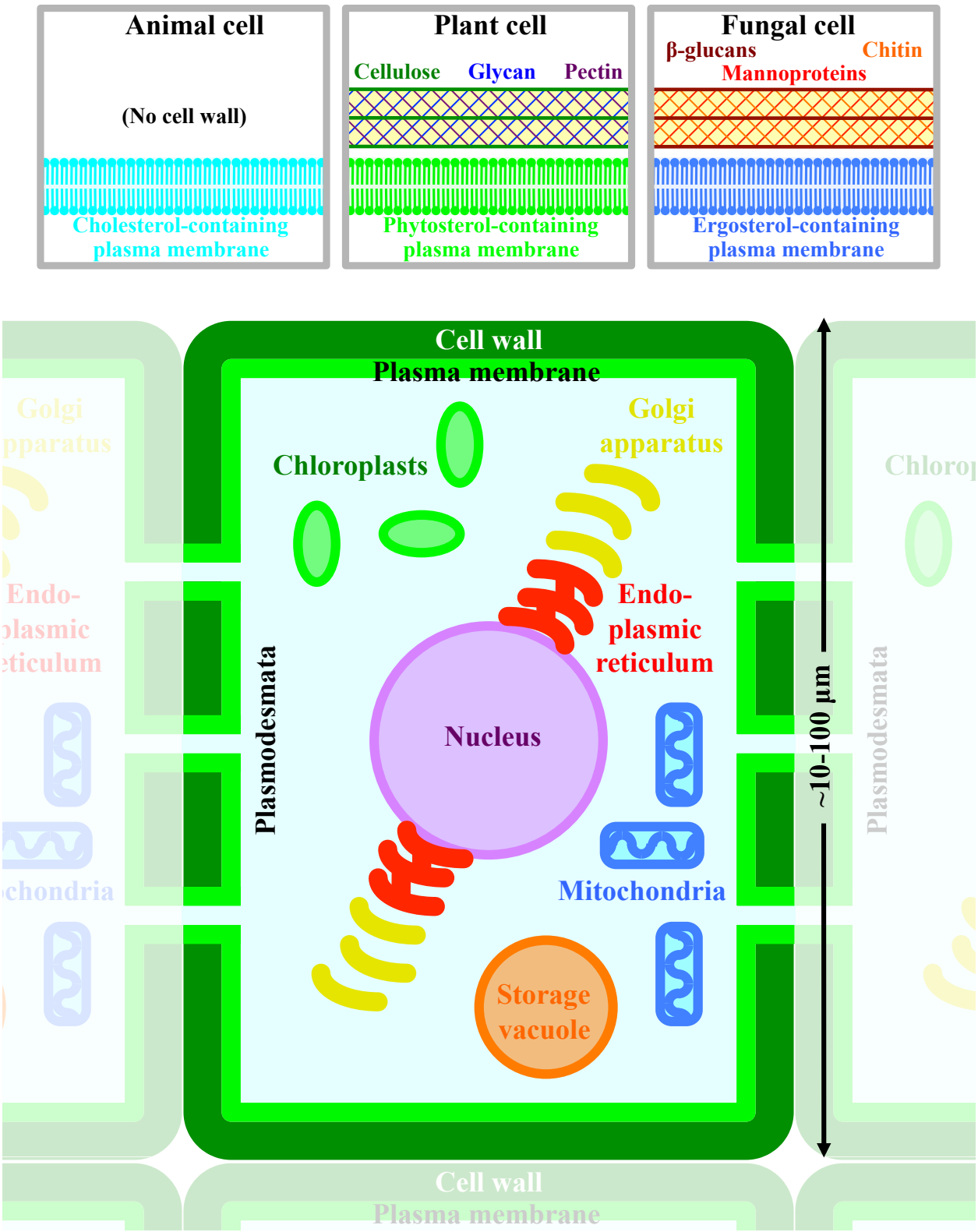


Fig. 5. Typical eukaryotic plant cell. Animal, plant, and fungal cell membranes contain different types of sterols. Plant and fungal cells both have cell walls, but of different composition. Otherwise fungal cells look very similar to plant cells, but smaller and without chloroplasts.

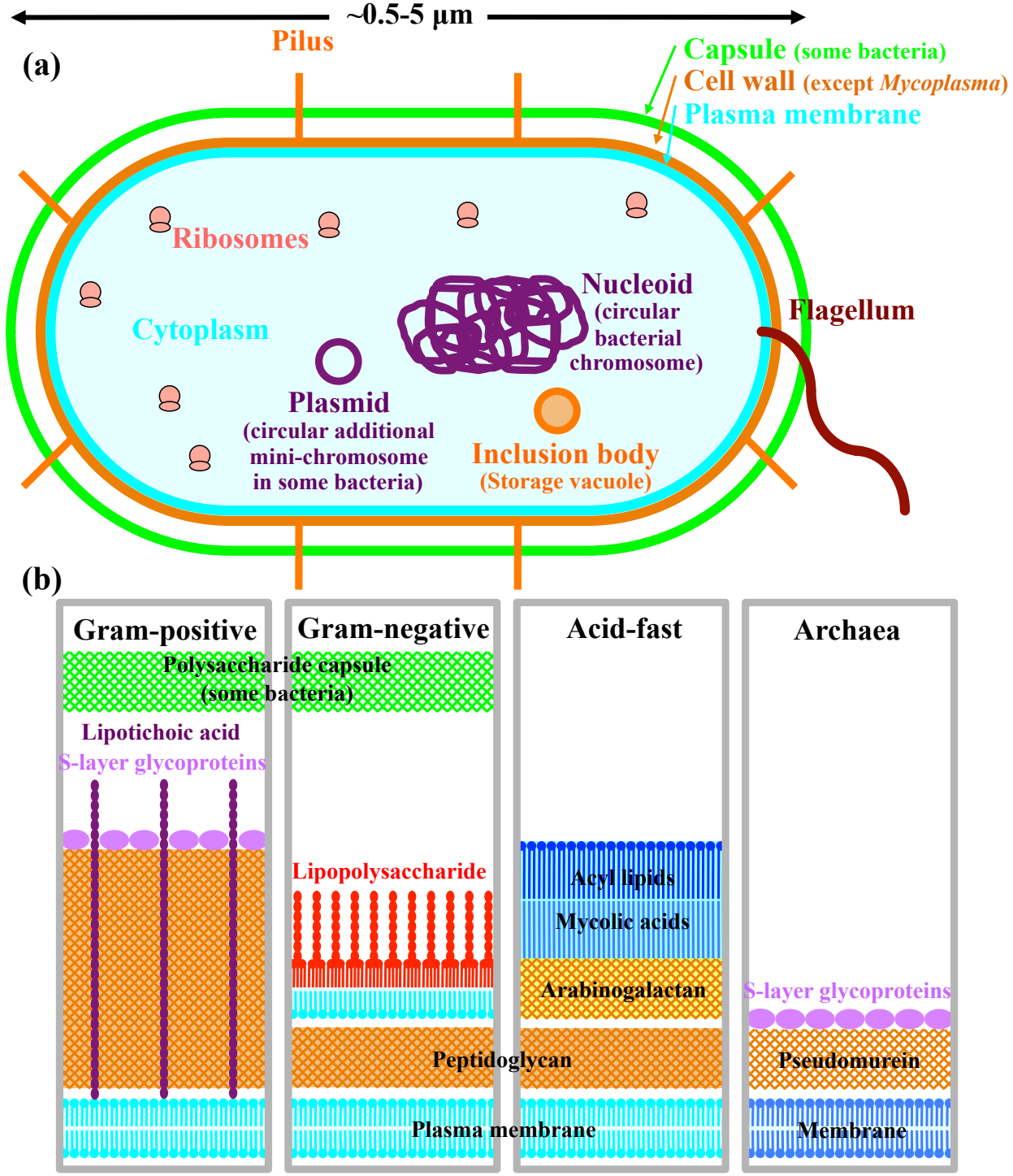


Fig. 6. Typical prokyarotic cell, showing (a) the overall structure, and (b) the layers of the cell wall for different families of bacteria. Prokaryotic cells are roughly ~ 10 times smaller than eukaryotic cells. Although they have specialized functions similar to those described for eukaryotic cells, they do not have membranes that divide those different functions into different compartments as in eukaryotic cells. While most prokaryotic cells have fairly similar structures, the major classes of prokaryotes (gram-positive bacteria, gram-negative bacteria, acid-fast bacteria, and archaea) have different types of cell walls. For more information on prokaryotes, see *Microbiology*.

1.3 Membranes

The **plasma membrane** surrounds the cell and carefully controls what molecules can enter or leave the cell. Many organelles within cells wanted their own little gated communities and thus are also surrounded by very similar membranes to control what enters and leaves those organelles.

As shown in Fig. 7(a), membranes are composed of phospholipid molecules. Each phospholipid molecule has a head that is hydrophilic (water-loving), due to its electrically charged and electrically polarized molecular components, and two tails that are hydrophobic or water-avoiding, because they are more neutral than Switzerland. Because of their dualistic nature, phospholipids form bilayer membranes that contain two layers of phospholipids, with the hydrophilic heads facing the water on each side and the hydrophobic tails hiding from the water in the middle of the membrane.

Just as ancient city walls contained gates, observation towers, defenses, drawbridges, and other structures, cell membranes contain various proteins that serve many different functions. To live happily in the membrane, these proteins are generally hydrophobic (with neutral amino acids) in their ticklish middle **transmembrane** regions and hydrophilic (with electrically charged or polar amino acids) in their water-exposed **extracellular** and **intracellular domains**. As shown in Fig. 7(b), most membrane proteins perform one or more of the following functions:

- Attach to extracellular and/or intracellular connections.
- Transport molecules through the membrane.
- Receive signals from outside the cell.
- Act as enzymes to catalyze certain reactions.

In addition to phosopholipids and proteins, membranes contain other components, including sterols. As shown in Fig. 8(a), sterols are fairly small lipids that are hydrophobic all the way around, and hence they like to hide somewhere in the middle in membranes. Cells from different critters contain slightly different types of sterols, which can come in handy if you want to kill one type of critters (e.g., a fungal infection) without killing other types of critters (e.g., the human who has the fungal infection). As shown in Fig. 8(b), animal cell membranes contain cholesterol, plant cell membranes contain any of several phytosterols (e.g., stigmasterol), fungal cell membranes contain ergosterol, and bacterial cell membranes contain any of several sterol-like hopanoids (e.g., diploptene).

Molecules floating around in a liquid solution are like people–wherever they are at any given time, they just want to be somewhere else. As a result, a herd of molecules in one location will rapidly **diffuse** or spread out to visit all the surrounding areas until ultimately they are all fairly evenly distributed [Fig. 9(a)]. If there is a high concentration of molecules of a given type on one side of a membrane and a low concentration on the other side, and if the molecules can pass through the membrane, they will diffuse through the membrane from the side of higher concentration to the side of lower concentration [Fig. 9(b)]. Eventually each side will have about the same concentration of molecules, and on average there will be as many molecules zipping one way across the membrane as zipping the other way.

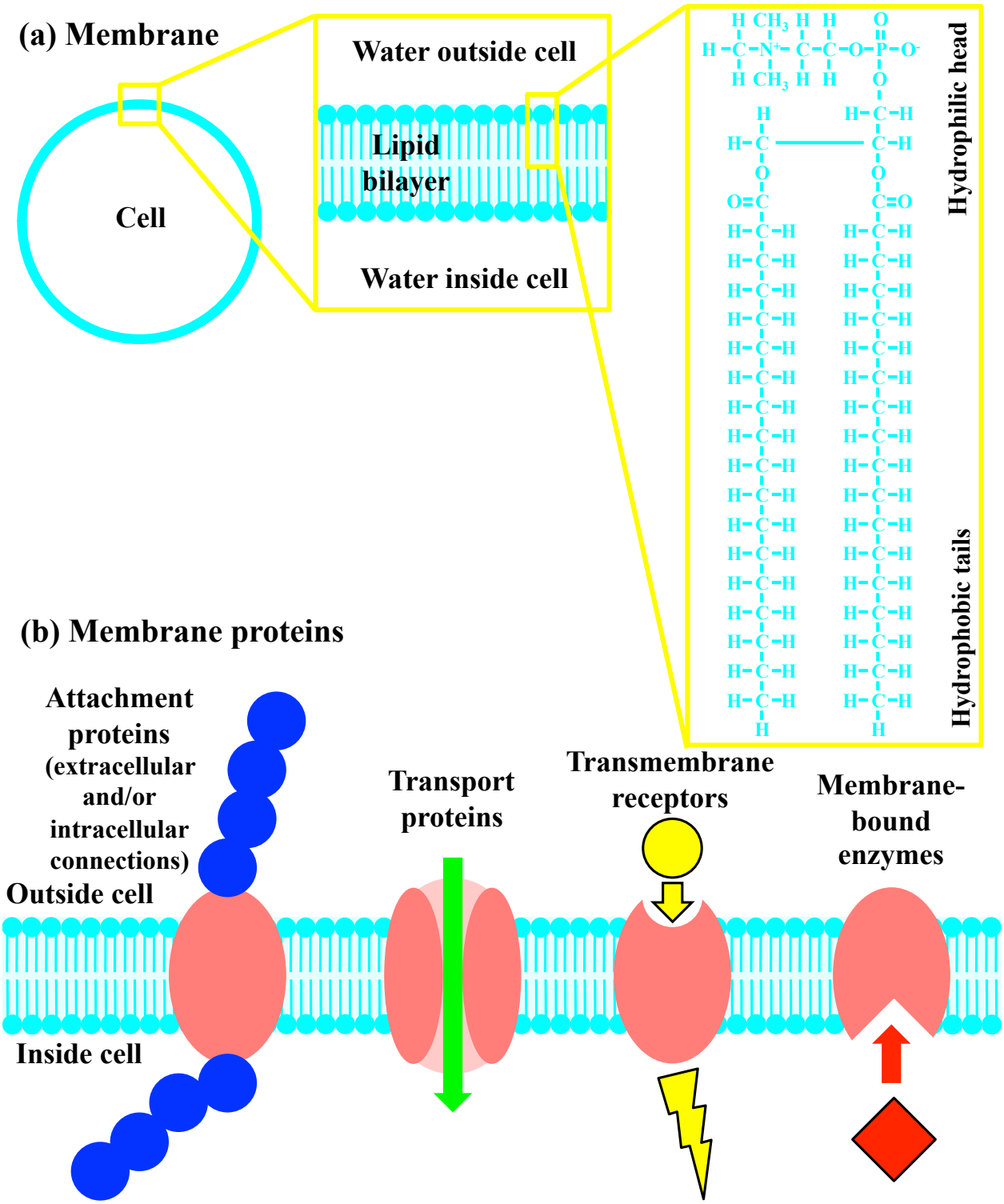


Fig. 7. Cell membrane structure. **(a)** Membranes are made of phospholipid molecules, which have a hydrophilic (water-loving) head and two hydrophobic (water-avoiding) tails, and form two layers, with the hydrophilic heads facing each side and the hydrophobic tails in the middle. **(b)** Membranes contain proteins that attach to extracellular or intracellular connections, transport molecules through the membrane, receive signals, and act as enzymes to catalyze certain reactions.

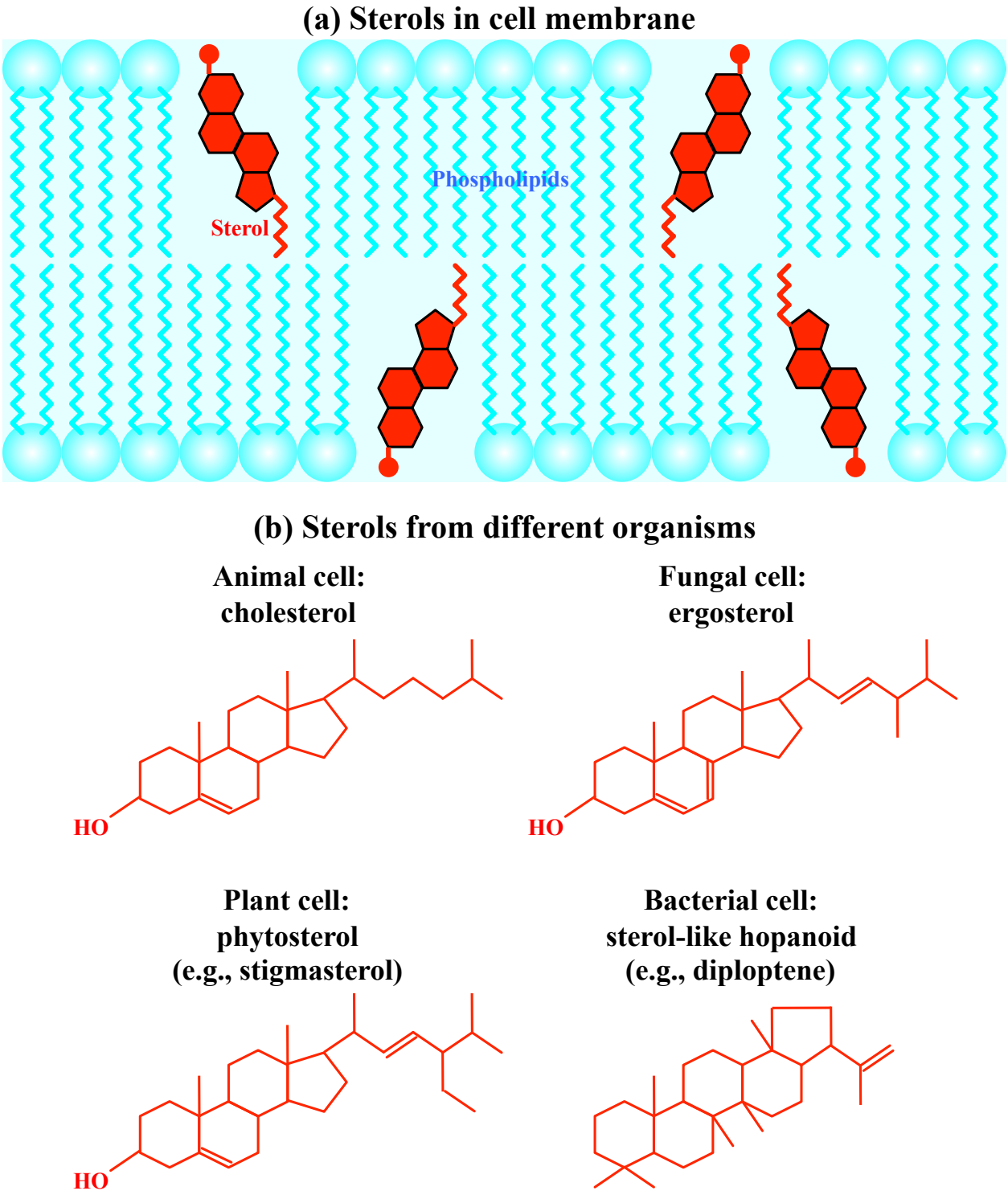


Fig. 8. Membrane sterols. **(a)** Location of sterols in cellular membranes. **(b)** Major types of sterols in membranes from different cell types. (In this compact and widely used notation, unless otherwise indicated, carbon atoms sit where lines end or change directions, and any of the four bonds of each carbon not otherwise used are occupied by hydrogens that are not shown).

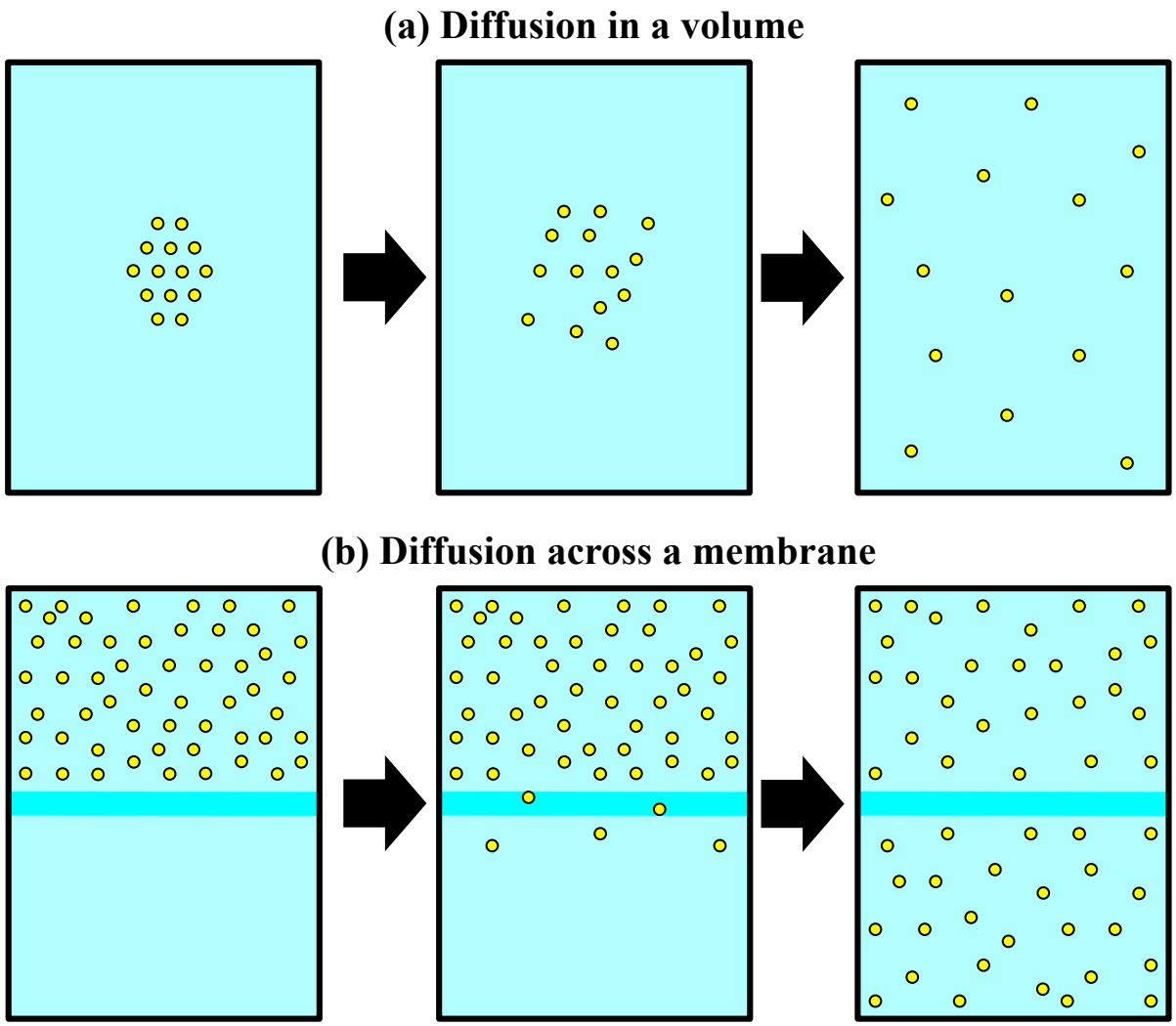


Fig. 9. Diffusion. (a) Diffusion of molecules within a volume of water. **(b)** Diffusion of molecules in water across a membrane that is permeable to those molecules.

We have been assuming that these diffusing molecules are dissolved in a sea of water molecules, but the water molecules themselves can diffuse, a process called **osmosis**. If side A of a membrane has a higher concentration of molecules (call them "X" molecules) dissolved in water than side B, by the scientific law of conservation of room to store all of your junk, that means that side A automatically has a lower concentration of water molecules than side B [Fig. 10(a)]. If water molecules can diffuse through the membrane but X molecules cannot, water molecules will head from the side where they have a higher concentration (B) to the side where they have a lower concentration (A). If a lot of water molecules make the trip, they will take up a lot of room, so the volume of side A will expand and the volume of side B will shrink. In order to keep their membranes from exploding or imploding [Fig. 10(b)], cells are very careful to keep the fluids on each side of their membranes osmotically balanced (same total concentration of non-water molecules, generally 290 mM for mammalian cells [cells in mammals, including humans], in units of mM or 10^{-3} moles/liter, where 1 mole $\approx 6.022 \times 10^{23}$ molecules).

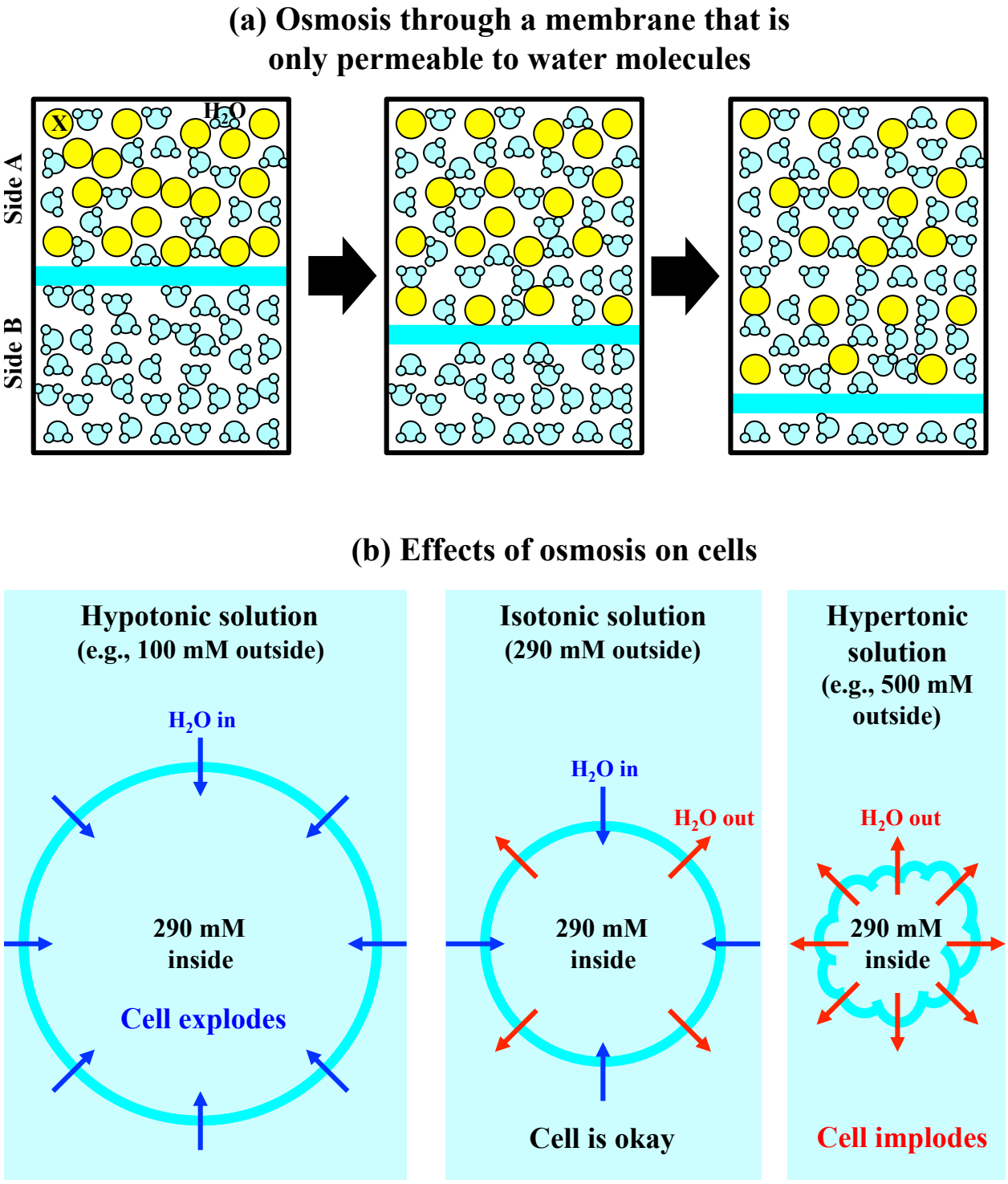


Fig. 10. Osmosis. **(a)** Osmosis, or diffusion of water molecules across a membrane that is permeable to water but not to X molecules, which have a higher concentration on one side. **(b)** Effects of osmosis on cells placed in **hypotonic** (lower concentration of dissolved molecules outside than inside the cell), **isotonic** (same concentration of dissolved molecules), and **hypertonic** (higher concentration of dissolved molecules outside than inside the cell) solutions.

As shown in Fig. 11, molecules may be transported across cell membranes by:

(a) Passive diffusion through the membrane. The hydrophobic, tightly packed interior dissuades most molecules from making the trip, but molecules that are both small and hydrophobic (for example, O_2, CO_2, and steroid hormones) can sneak across the border. Water molecules are very small and very plentiful but very polar and by definition not hydrophobic; thus water molecules can diffuse across lipid bilayers, but rather slowly.

(b) Facilitated diffusion through a pore in the membrane. For example, water molecules pass far more quickly through special water-carrying pores (aquaporins) in some membranes (such as those in some kidney cells) than through membranes without pores.

(c) Facilitated diffusion through a gated channel in the membrane. For example, there are various ion-specific channels for sodium, potassium, calcium, chloride, and other ions. These channels open or close in response to certain chemical, electrical, or other stimuli.

(d) Facilitated diffusion via a carrier protein that moves to give the molecules a little push in the right direction (e.g., the glucose transporter GLUT-1).

(e) Active transport via an ATP-powered pump (e.g., pumps for protons, sodium, potassium, calcium, chloride, etc.). ATP molecules are a widespread form of energy in cells and can provide enough energy for a pump to forcibly send molecules uphill against their concentration gradient, from the side of lower concentration to the side of higher concentration.

(f) Active cotransport via a symporter (e.g., Na^+-glucose) **or antiporter** (e.g., Na^+-Ca^+); letting one type of molecule flow down its concentration gradient (from the side of higher concentration to the side of lower concentration) powers a sort of revolving door that sweeps the other type of molecule opposite the way it would normally want to go (from lower to higher concentration). In a symporter, that happens to be the same direction as the first molecules, and in an antiporter, the two types of molecules go in opposite directions.

By these methods, mammalian cells generally maintain the extracellular and intracellular concentrations of molecules listed in Table 1. Note that although individual types of molecules can have very different concentrations outside vs. inside the cell, the total concentrations of everything come to a nicely osmotically balanced 290 mM on both sides of the cell membrane.

Solute	**Extracellular concentration**	**Intracellular concentration**
Sodium (Na^+)	145 mM	12 mM
Potassium (K^+)	4 mM	120 mM
Calcium (Ca^{2+})	2.5 mM	0.0001 mM
Magnesium (Mg^{2+})	1 mM	0.5 mM
Chloride (Cl^-)	110 mM	15 mM
Bicarbonate (HCO_3^-)	24 mM	12 mM
Phosphate (PO_4^{3-})	0.8 mM	0.7 mM
Glucose ($C_6H_{12}O_6$)	5 mM	< 1 mM
Protons (H^+)	4×10^{-5} mM (pH 7.4)	6×10^{-5} mM (pH 7.2)
Proteins	0.2 mM	4 mM
Osmolarity (total)	290 mM	290 mM

Table 1. Extracellular and intracellular concentrations of some important solutes for mammalian cells (in units of mM or 10^{-3} moles/liter, where 1 mole $\approx 6.022 \times 10^{23}$ molecules).

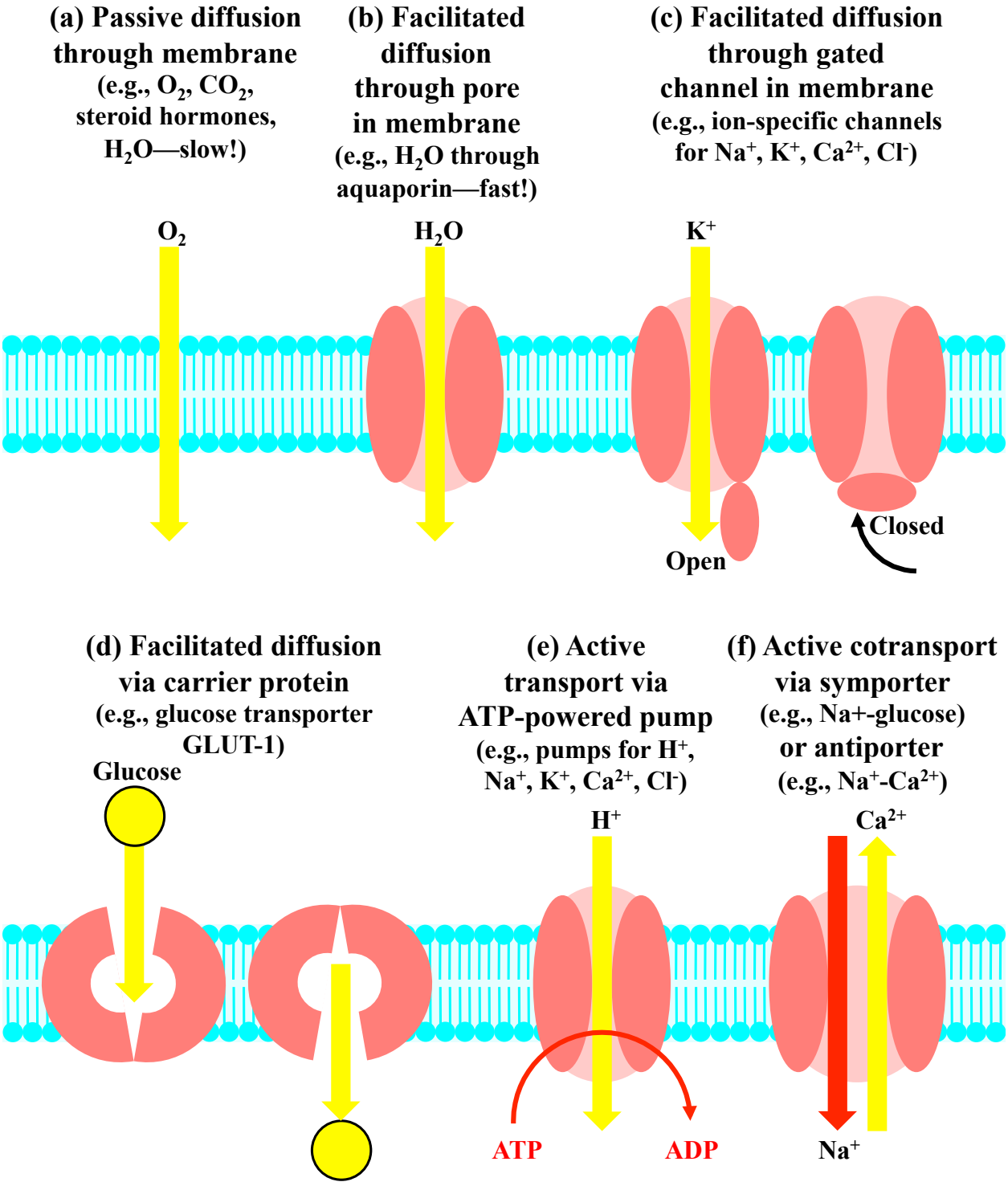


Fig. 11. Molecules may be transported across cell membranes by (a) passive diffusion through the membrane, (b) facilitated diffusion through a pore in the membrane, (c) facilitated diffusion through a gated channel in the membrane, (d) facilitated diffusion via a carrier protein, (e) active transport via an ATP-powered pump, or (f) active cotransport via a symporter or antiporter.

1.4 Nucleus

Figure 12(a) shows the structure of a eukaryotic cell nucleus. Key features include:

- The **nucleoplasm** occupies most of the volume of the nucleus and contains DNA, RNA, and accessory proteins. Human DNA is divided into 46 chromosomes. If they were stretched out into one continuous strand of DNA, that strand would be approximately 2 meters long, yet they are wadded up like a ball of yarn and stored in the nucleus, which is roughly 10 μm wide. To make matters even more challenging, various parts of that DNA must be continually accessed to create RNA copies of individual genes or to replicate the DNA when the cell decides to divide into two cells. As a result, the nucleoplasm is incredibly densely packed, incredibly chaotic, and yet somehow incredibly organized. Some people have rooms like that. If you want to learn more details, you will have to wait in suspense until Sections 2 and 3.

- The **nucleolus** is not separated from the rest of the nucleus by a membrane or any physical barrier, but it is an even more densely packed blob of ribosomes being assembled. Ribosomes are assembled from ribosomal RNAs, copied from certain sections of DNA, and ribosomal proteins, which are encoded by other sections of DNA. Mature ribosomes are then shipped out of the nucleus to hang out on or near the endoplasmic reticulum, read messenger RNAs (mRNAs) coming out of the nucleus, and make the corresponding proteins encoded by those mRNAs. When a cell is very busy, it needs to make a lot of proteins, so it makes a lot of ribosomes, so its nucleolus gets visibly larger.

- A **nuclear envelope** composed of both **outer and inner membranes** surrounds the nucleus. The cell tries very hard to prevent irrelevant cellular molecules or invading pathogens from wandering into the nucleus and causing trouble, or essential components of the nucleus from escaping, so it erected not one Berlin wall but two.

- **Laminin** is a tightly woven net of proteins that support and shape the inner surface of the inner membrane. If that sounds boring, just bear in mind that mutations that impede laminin's proper functioning lead not only to a wobbly looking nuclear envelope, but to Hutchinson-Gilford progeria, a rapid-aging-like disease in which kids die by age $\sim$12-14 with almost all the symptoms of old age–wrinkles, hair loss, heart disease, failing eyesight, and atrophy of muscles and bones.

- **Nuclear pores** carefully control what molecules enter or leave the nucleus through the nuclear envelope, as will be explained next.

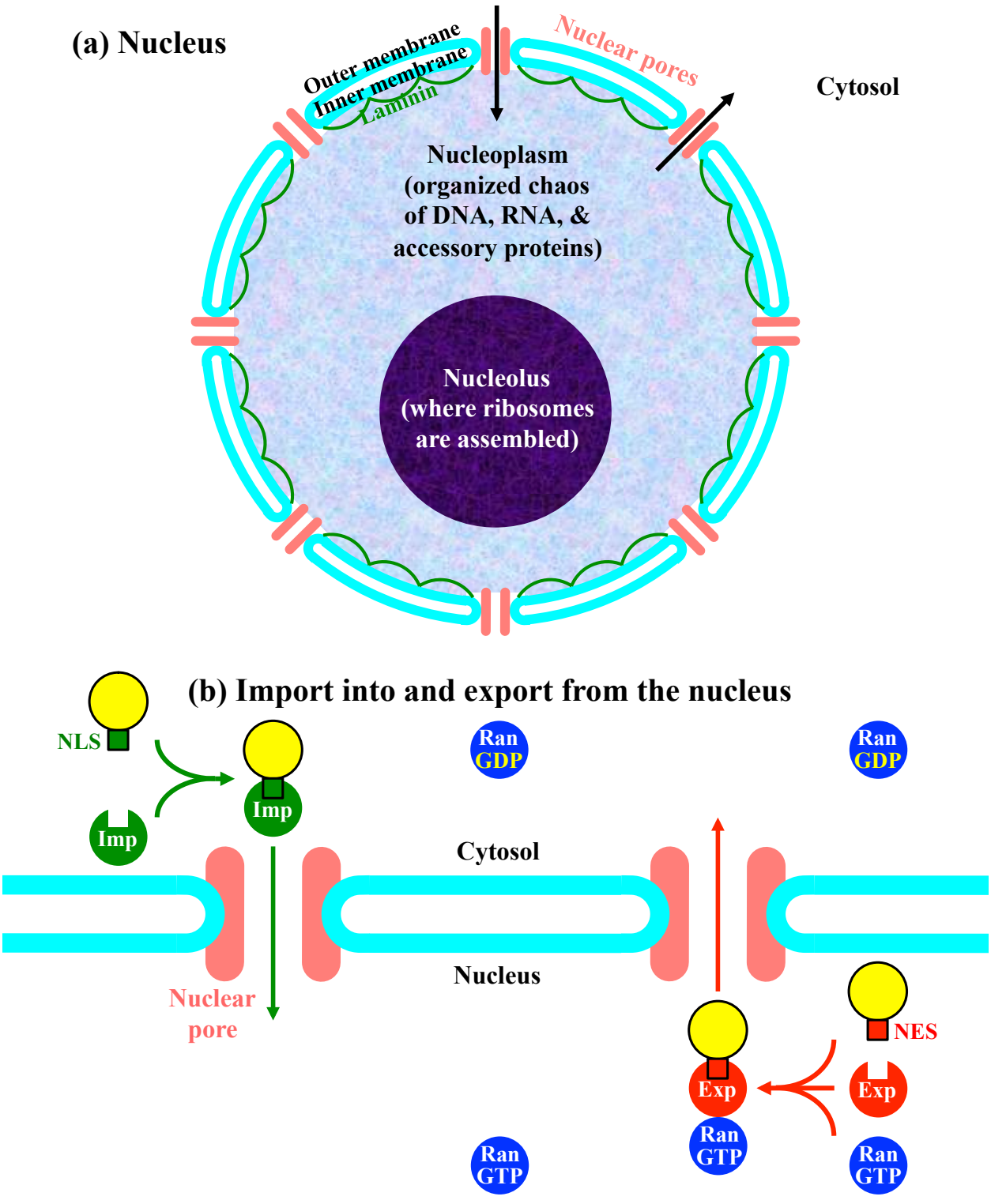


Fig. 12. Structure and function of the cell nucleus. **(a)** The nucleus includes the nucleoplasm and nucleolus and is surrounded by a double membrane with pores for transport. **(b)** Using nuclear pores, importins carry molecules bearing a nuclear localization signal (NLS) into the nucleus, and exportins carry molecules bearing a nuclear export signal (NES) out of the nucleus.

As shown in Fig. 12(b), using nuclear pores, importins carry molecules bearing a nuclear localization signal (NLS) into the nucleus, and exportins carry molecules bearing a nuclear export signal (NES) out of the nucleus. There are a wide variety of NLS and NES tags, as well as various corresponding importins and exportins that recognize them. mRNAs recently copied from genes in the nucleus are carried out of the nucleus by specific types of exportins, so they can be used to produce proteins in ribosomes outside the nucleus. Newly made proteins that are intended to perform roles in the nucleus contain an NLS tag that shows they need to be delivered to the nucleus. Proteins that want to come and go, like a pet that cannot make up its mind, may have both NLS and NES tags, and temporarily hide one or the other depending on which way they want to go.

A protein called Ran helps move cargo-carrying exportins (as well as empty importans that have finished bringing in their cargo) out of the nucleus. Ran also lets everybody know which side of the nuclear envelope they are on. When Ran is inside the nucleus, it is bound to GTP (guanosine triphosphate), an energy-carrying molecule similar to ATP. When Ran leaves the nucleus, its GTP gets converted to GDP (guanosine diphosphate), which has less energy. Thus if you see lots of Ran-GTPs floating around, you know you are inside the nucleus, and if you see lots of Ran-GDPs, you are outside the nucleus.

Whereas eukaryotic cells have a compartmentalized nucleus with all the bells and whistles outlined above, their poor cousins the prokaryotic cells have a simple nucleoid (Fig. 6) that is not separated from the rest of the cell by any membranes. Most eukaryotic cells have their DNA divided among several chromosomes, but prokaryotic cells have only one actual chromosome, a large circular piece of DNA that is covered with accessory proteins and wadded up.

Some prokaryotic cells have miniature additional chromosomes, small circular DNAs called plasmids. These plasmids encode a fairly small number of genes, often genes that make bacteria produce protein toxins or become resistant to antibiotics, and thus they are important components of many pathogenic (disease-causing) bacteria. Plasmids can be gained, lost, replicated, and spread from one prokaryotic cell to surrounding prokaryotic cells like an infection.

1.5 Ribosomes, Endoplasmic Reticulum, and Proteasomes

Messenger RNAs (mRNAs) copied from genes in the nucleus are exported from the nucleus and used by ribosomes to make the corresponding proteins. Many ribosomes are free-floating in the cytosol outside the nucleus, but some are anchored to the membrane-enclosed **endoplasmic reticulum**, which aids in preparing some proteins. Also floating around in the cytosol are **proteasomes**, "anti-ribosomes" that are ready to destroy any old or incorrectly made proteins.

Figure 13 shows the structure and function of ribosomes. The S numbers in the various names are a convention referring to sedimentation rates when the components are centifuged (smaller components have smaller S numbers); just take them as part of the names. Prokaryotic ribosomes are composed of a large subunit, which contains two ribosomal RNAs or rRNAs and 31 proteins, and a small subunit, which contains one rRNA and 21 proteins [Fig. 13(a)]. Eukaryotic ribosomes similar but larger; their large subunit contains three rRNAs and 50 proteins, and their small subunit contains one rRNA and 33 proteins [Fig. 13(b)]. Despite their differences in size, prokyarotic and eukaryotic ribosomes work in a similar fashion to create proteins by translating an mRNA sequence into the amino acid sequence of the corresponding protein [Fig. 13(c)]. Transfer RNAs (tRNAs) bring each new amino acid to the ribosome.

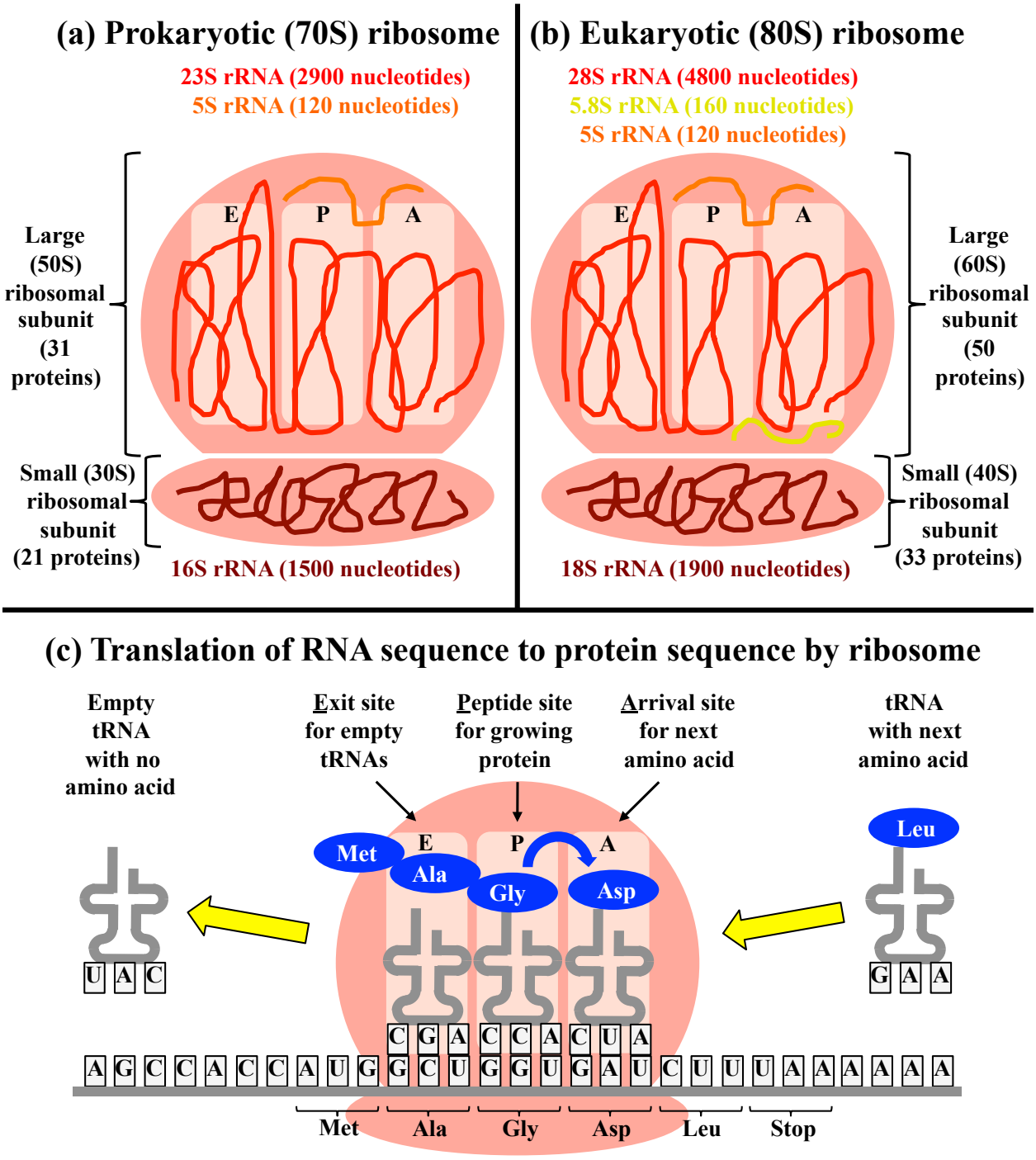


Fig. 13. Ribosomes. **(a)** Prokaryotic ribosomes are composed of a large subunit (which contains two ribosomal RNAs or rRNAs and 31 proteins) and a small subunit (which contains one rRNA and 21 proteins). **(b)** Eukaryotic ribosomes are composed of a large subunit (which contains three rRNAs and 50 proteins) and a small subunit (which contains one rRNA and 33 proteins). **(c)** Despite their differences in size, prokyarotic and eukaryotic ribosomes work in a similar fashion to create proteins by translating a messenger RNA (mRNA) sequence into the amino acid sequence of the corresponding protein. Transfer RNAs (tRNAs) bring each new amino acid to the ribosome.

As shown in Fig. 14(a), the endoplasmic reticulum is a membrane-enclosed, labyrinth-shaped structure that surrounds the nucleus. Free ribosomes floating around outside the nucleus make proteins that are destined for the cytosol, nucleus, peroxisomes, mitochondria, and chloroplasts (in plant cells). Ribosomes bound to the ER (in regions called rough ER, since the ribosomes look like bumps on the membrane of the ER) make proteins that are destined for the Golgi apparatus, lysosomes, plasma membrane, and outside the cell. As shown in Fig. 14(b), proteins that require the ER begin with a signal sequence. If a freely floating ribosome begins making a protein with a signal sequence, a signal recognition particle (SRP) protein spots the signal sequence and drags that ribosome to the surface of the ER. The ribosome docks with a pore called a tranlocon and spits the protein it is making into the inside of the ER. An internal membrane-bound signal peptidase whacks off the signal sequence, leaving the rest of the new protein. Inside the ER, new proteins are chemically processed in various ways that help them fold up properly to do their ultimate jobs. Proteins requiring further work are packaged into little bubbles called vesicles and transported to the Golgi apparatus.

In addition to aiding in protein synthesis, the ER performs at least two other important functions. Portions without attached ribosomes, thus called smooth ER, make lipids and other biomolecules needed by the cell. The interior of rough and smooth ER also stores calcium ions (Ca^{2+}), stockpiling them by pumping them from the rest of the cell into the ER, then suddenly opening channels to release a flood of calcium back into the cytosol when needed. These sudden bursts of calcium are especially important in muscle cells, where the calcium-storing endoplasmic reticulum is called the sarcoplasmic reticulum just to be confusing.

Proteasomes, shown in Fig. 15, are the opposite of ribosomes; ribosomes are large machines composed of lots of protein components (and some rRNA components) that make proteins, and proteasomes are large machines composed of lots of protein components that destroy proteins.

Ubiquitin enzymes E1-E3 identify proteins that are old, damaged, incorrectly made, or that otherwise need to be snuffed out [Fig. 15(a)]. E1 and E2 work together to prepare a small protein label called ubiquitin, while E3 grabs the protein to be destroyed. Together these enzymes attach first one and then several more ubiquitin labels to the ill-fated protein. attach ubiquitin labels to proteins to be destroyed.

A proteasome is basically a tube with caps at each end that can be opened and closed [Fig. 15(b)]. The cap on one end recognizes and only lets in ubiquitin-labelled proteins. As the proteins are on the way in, the cap removes the ubiquitins (so they can be used on some other protein) and unfolds the protein into a long string. The unfolded protein move into the core, where it is sliced and diced by proteases, protein-cutting enzymes. The other cap expels the pieces, peptides or small protein fragments with approximately 7 or 8 amino acids each. Subsequently cytoplasmic proteases whack those peptides into individual amino acids, which can be used by ribosomes as building blocks for new proteins. It's a regular Disney "Circle of Life."

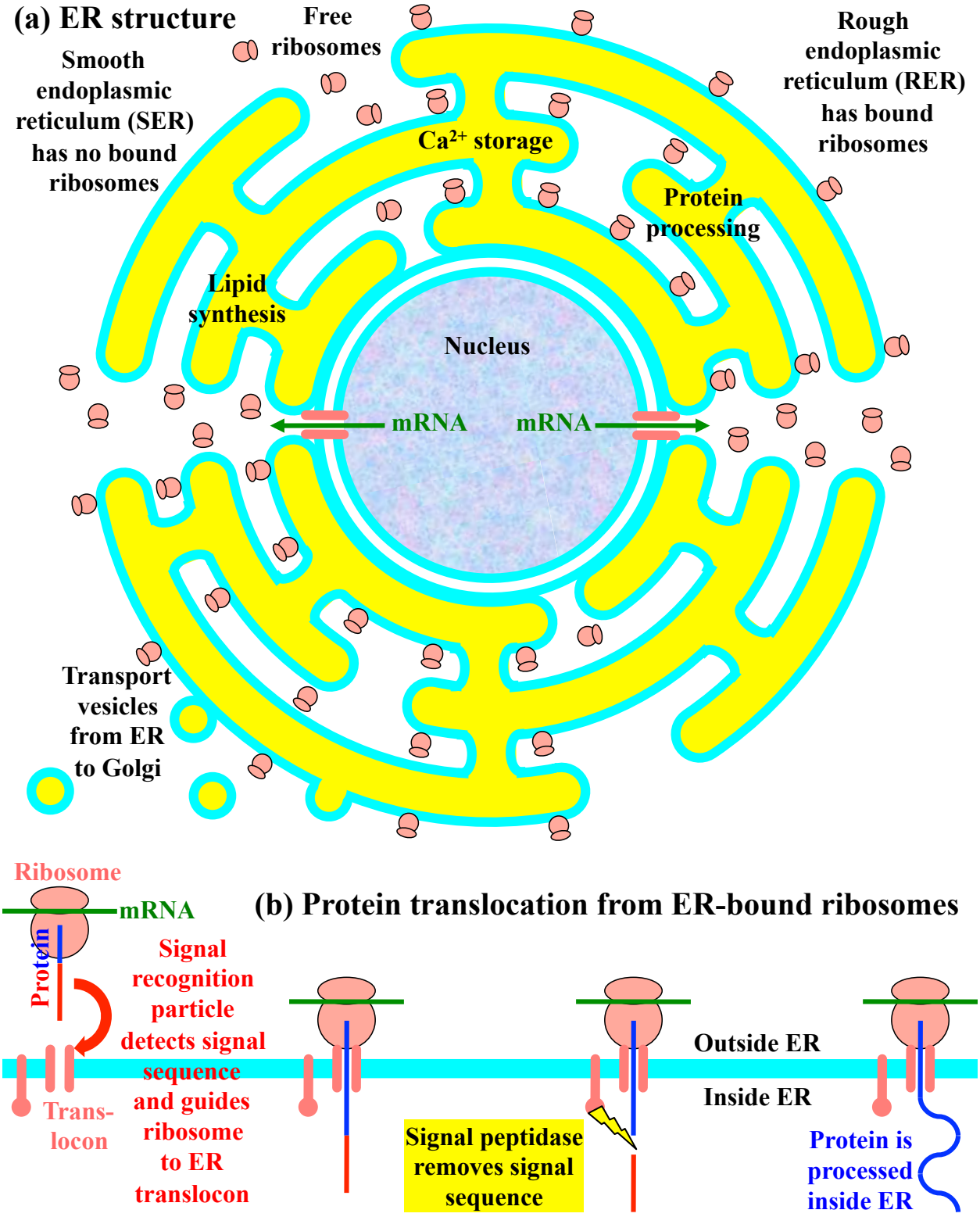


Fig. 14. Endoplasmic reticulum (ER). **(a)** Outside the nucleus, free ribosomes make many proteins, ribosomes bound to rough ER make membrane-bound/secreted proteins, and smooth ER makes lipids, etc. **(b)** Proteins with a signal sequence are translocated into the ER for processing.

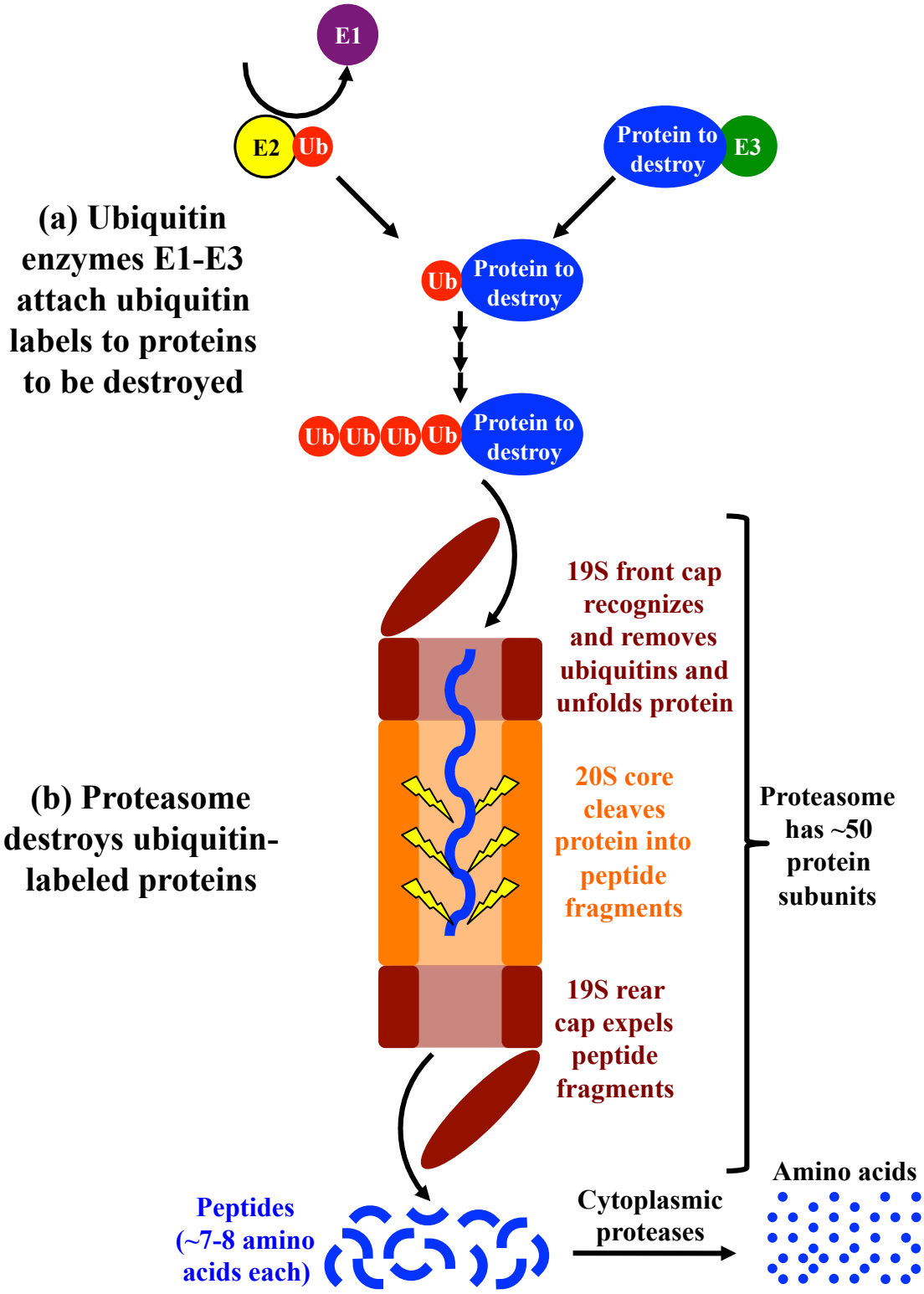


Fig. 15. Proteasome functioning. **(a)** Ubiquitin enzymes E1-E3 attach ubiquitin labels to proteins to be destroyed. **(b)** The proteasome destroys ubiquitin-labeled proteins.

1.6 Golgi Apparatus

Most proteins that are initially processed in the ER and then sent to the Golgi apparatus for further processing, sort of like graduating from high school and discovering that then you have to go to college for many years. Like the ER, the Golgi is a complex of membrane-enclosed compartments (each called a **cisterna**, or plural **cisternae**). Unlike the ER, the membrane-enclosed compartments of the Golgi do not connect directly to each other, as shown in Fig. 16.

Small membrane bubbles or vesicles transport proteins from the ER to the first (**cis**) Golgi compartment, next to later (**medial**) Golgi compartments, then to the final (**trans**) Golgi compartments, and finally on to their final destinations. Vesicles carrying proteins in this outward direction are said to be moving in the **anterograde** direction; vesicles carrying rejected or lost proteins back toward the ER are said to be moving in the **retrograde** direction. Entire individual Golgi compartments also appear to slowly move in the anterograde direction as the protein they contain mature, sort of like an entire class of students being promoted along to the next grade. As Golgi compartments move outward, new cis compartments form and old trans compartments break up into delivery vesicles.

Starting in the cis compartments, the Golgi apparatus modifies proteins in ways that will help them do their ultimate jobs, especially by adding and tweaking sugar or glycan groups on proteins, a process called glycosylation. Along the way, the Golgi also adds targeting signals that indicate the ultimate destinations of different proteins. In the trans Golgi compartments, proteins are sorted into vesicles for delivery to:

- Lysosomes (for some proteins to be destroyed and for digestive enzymes and other lysosomal components).
- The outside of the cell (for example, for secreted hormones).
- The plasma membrane (for membrane proteins like ion channels and receptors).
- Back in the retrograde direction (for incoming, defective, or lost proteins).

Vesicles intended for different destinations are coated with different proteins and delivery tags, as will be discussed next.

1.7 Endosomes, Lysosomes, and Peroxisomes, Oh My!

Cells use membrane bubbles to transport, store, or destroy molecules. Depending on their specific role, these little bubbles go by different names, as shown in Fig. 17:

- **Endosomes** import things into the cell from the outside, including many nutrients and (unintentionally) viruses. This process of hauling something into the cell is called **endocytosis**.
- **Vesicles** transport things within the cell (for example proteins going from the endoplasmic reticulum to the Golgi apparatus) or transport things to the outside of the cell (for example proteins that will become part of the cells' plasma membrane or proteins that will be sent out to other cells). The process of hauling something out of the cell is called **exocytosis**.

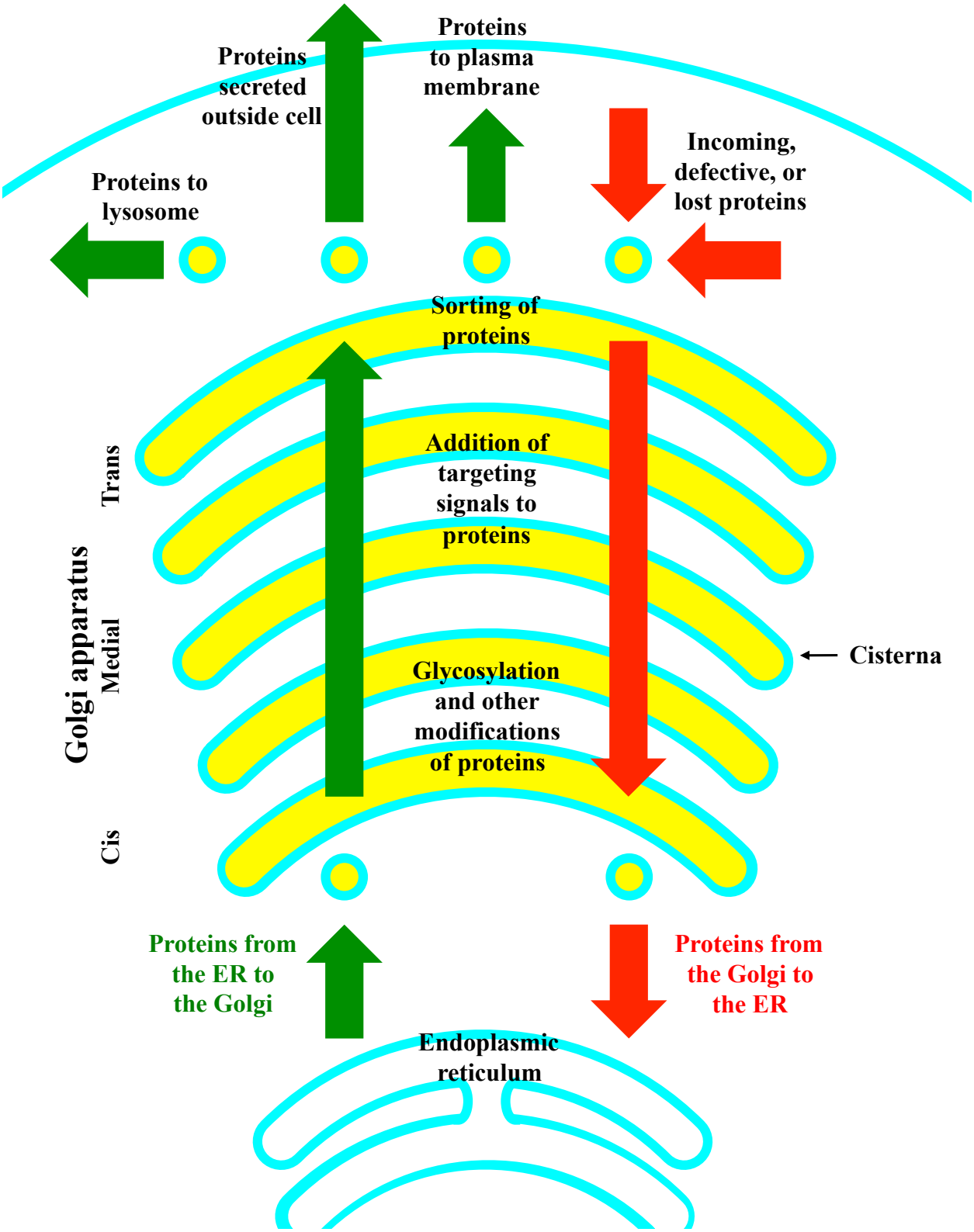


Fig. 16. Golgi apparatus.

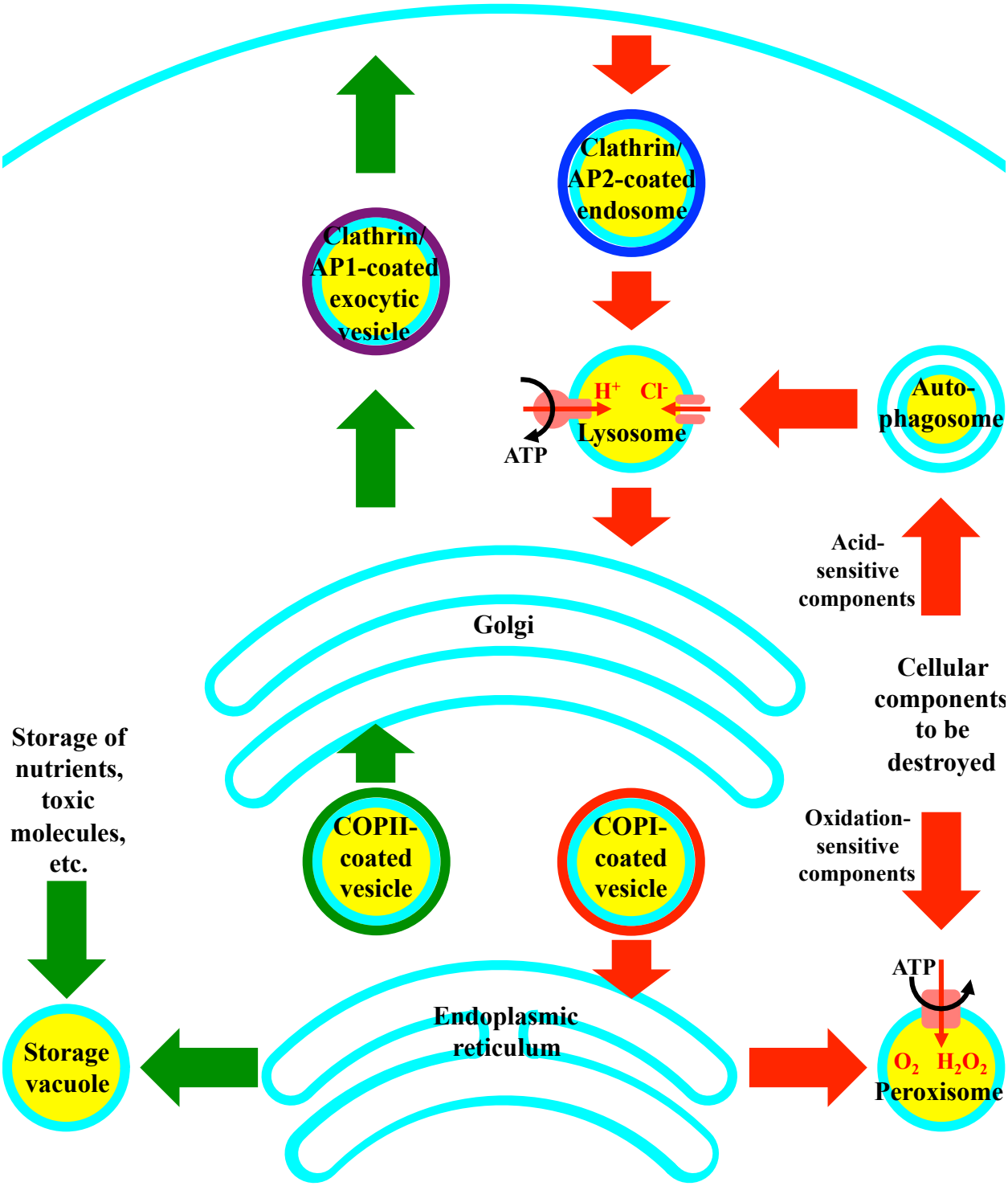


Fig. 17. Endosomes, Lysosomes, Peroxisomes, etc. Endosomes import things into the cell, vesicles transport things within or to the outside of the cell, vacuoles store things to get them out of the way, autophagosomes and lysosomes destroy things by acid and enzymatic digestion, and peroxisomes destroy things by oxidation and enzymatic digestion.

- **Vacuoles** store things to get them out of the way. Plant cells and some other cell types stockpile nutrients in vacuoles in case they get hungry later. If cells accidentally create or ingest toxic substances that they cannot otherwise get rid of, they may also store them in endosomes, sort of like storing drums of nuclear waste.

- **Autophagosomes** and **lysosomes** destroy things by acid and enzymatic digestion. Autophagosomes engulf molecules to be destroyed with a unique double membrane, then pass their contents along to lysosomes for destruction. Lysosomes have ATP-powered pumps in their membranes that yank loose protons (H^+) out of the surrounding cytosol and concentrate them into the interior of the endosome. Attracted by all of those positively charged protons, negatively charged chloride ions (Cl^-) rush through special chloride-selective ion channels in the lysosomal membrane, so lysosomes end up filled with hydrochloric acid (HCl) with a pH of 4.8. The Golgi apparatus also ships to the lysosomes a wide variety of digestive enzymes that work well under these acidic conditions and destroy different types of molecules. Between the acid and the digestive enzymes, lysosomes destroy most molecules they receive, spitting out the pieces to be reused by the cell to build other molecules.

- **Peroxisomes** destroy things by oxidation and enzymatic digestion. Whereas lysosomes pump in acid to destroy things, peroxisomes pump in oxygen and oxygen-rich molecules like hydrogen peroxide (H_2O_2), which basically bleach anything to death. Just as the Golgi apparatus send lysosomes digestive enzymes that work well at highly acidic conditions, the endoplasmic reticulum sends peroxisomes enzymes that work well at highly oxidizing conditions.

Note that cells have at least three different ways to destroy unwanted molecules: proteasomes as discussed previously, lysosomes, and peroxisomes. Presumably cells send molecules to be destroyed to the place best able to do the job for those particular molecules.

Figure 18 shows how vesicles deliver cargo molecules from inside a donor membrane to inside a target membrane. Coat and other proteins aid with vesicle budding from the donor membrane, by drawing out, pinching off, and surrounding part of the membrane, trapping cargo molecules inside. Vesicles traveling from the ER to the Golgi are covered with COPII coat proteins, vesicles traveling from the Golgi to the ER are coated with COPI proteins, outgoing exocytic vesicles are coated with a combination of clathrin and AP1 proteins, and incoming endosomes are coated with a combination of clathrin and AP2 proteins (Fig. 17).

After a vesicle has been formed and sent on its way, the coat proteins come off, leaving the vesicle with just external Rab targeting proteins and vesicle SNARE (v-SNARE) tethering proteins (Fig. 18). Mammalian cells have at least 70 different Rab proteins, which function like zip codes to indicate which part of which cellular membrane a vesicle should be delivered to. At that target membrane, a highly specific Rab effector protein recognizes and grabs the particular Rab targeting proteins on the vesicle. The specific Rab binding pulls the vesicle in close enough that nonspecific target SNARE proteins (t-SNARE) get entangled with the vesicle v-SNAREs like Velcro, pulling the vesicle even closer to the membrane until it fuses and delivers its cargo molecules.

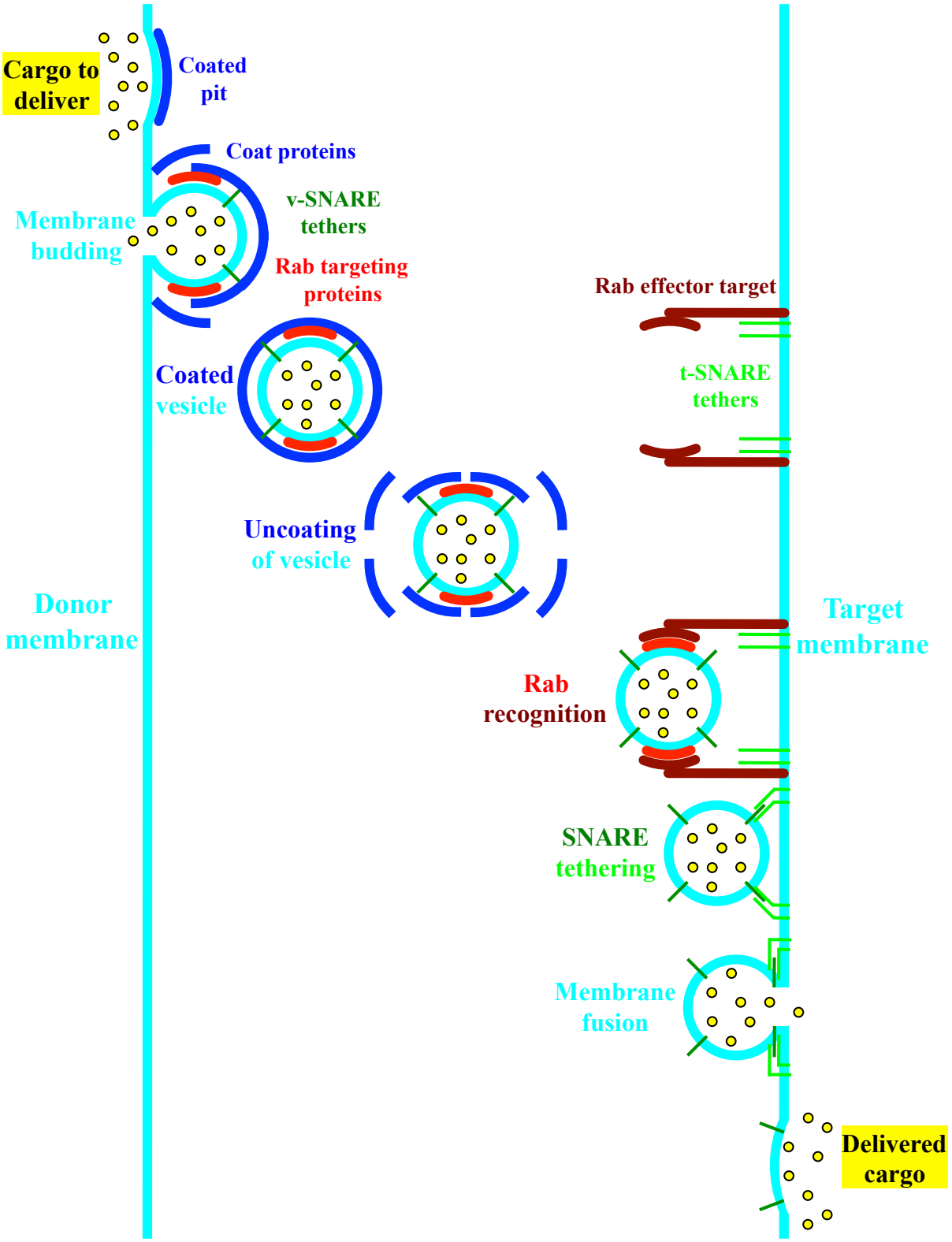


Fig. 18. Vesicles deliver cargo molecules from inside the donor membrane to inside the target membrane. Coat and other proteins aid with vesicle budding from the donor membrane. Rab, SNARE, and other proteins aid with vesicle fusion at the target membrane.

1.8 Mitochondria

Mitochondria are double-membraned organelles that serve as the power plants of the cell, consuming carbohydrate fuels and converting that energy into adenosine triphosphate (ATP) molecules, which are distributed throughout the cell to power everything else in the cell. A cell may contain hundreds or even thousands of mitochondria. Cells that need the most energy, like muscle cells, tend to have the most mitochondria.

Mitochondria appear to have been independent bacteria that invaded ancient cells and developed a symbiotic relationship, with the surrounding host cell providing free room and board for the mitochondria, and the mitochondria providing free energy in the form of ATP for the surround host cell. Over time mitochondria lost many of the genes and features that would allow them to be truly independent organisms, but they retain many signs of their origin.

Fig. 19(a) shows the typical structure of a mitochondrion. Mitochondria are rod-shaped like many bacteria, and have two membranes like Gram-negative bacteria (Fig. 6). They have lost any cell wall they may have originally had, presumably to facilitate transport of nutrients and ATP between the mitochondria and the surrounding host cell. Like bacteria, mitochondria have a nucleoid with their own genes, ribosomes to make their own proteins, and storage granules to store some nutrients they keep for themselves. Unlike most bacteria, the inner membrane of mitochondria zigs and zags wildly, which greatly increases its surface area. As will be discussed very shortly, that inner membrane is filled with proteins that convert energy from nutrients into ATP, so maximizing its surface area maximizes the energy that can be converted.

As in bacteria, the nucleoid of a mitochondrion is a circular piece of DNA that is wadded up and bound by various accessory proteins. As shown in Fig. 19 (b) the mitochondrial genome contains genes encoding ribosomal RNAs (rRNAs), transfer RNAs (tRNAs), and the membrane proteins involved in ATP production (ATP synthase, cytochromes, dehydrogenases, etc.). These genes are used to make those encoded RNAs and proteins inside the mitochondria, just as bacteria do. Over time, many other mitochondrial genes have gradually been transferred to the cell nucleus, so the surrounding cell makes those corresponding proteins and then delivers them to the mitochondria. Between the mitochondrial genes in the nucleus and those in the mitochondria themselves, a mitochondrion can reproduce itself by dividing into two new mitochondria, just as bacteria do.

Figure 20 shows the respiration pathway outside and inside a mitochondrion:

- In the cell cytosol outside the mitochondrion, saccharides are converted into glucose ($C_6H_{12}O_6$), which is then split into half-sugars (pyruvate, $C_3H_4O_3$). This process of tearing sugars in half is called **glycolysis** ["sugar splitting"].
- In the inner matrix of the mitochondrion, half-sugars are stripped of their hydrogen to make carbon dioxide (CO_2).
- In the inner membrane of the mitochondrion, that hydrogen is combined with oxygen (O_2) to produce water (H_2O) plus stored chemical energy (ATP). This process is called **oxidative phosphorylation**.

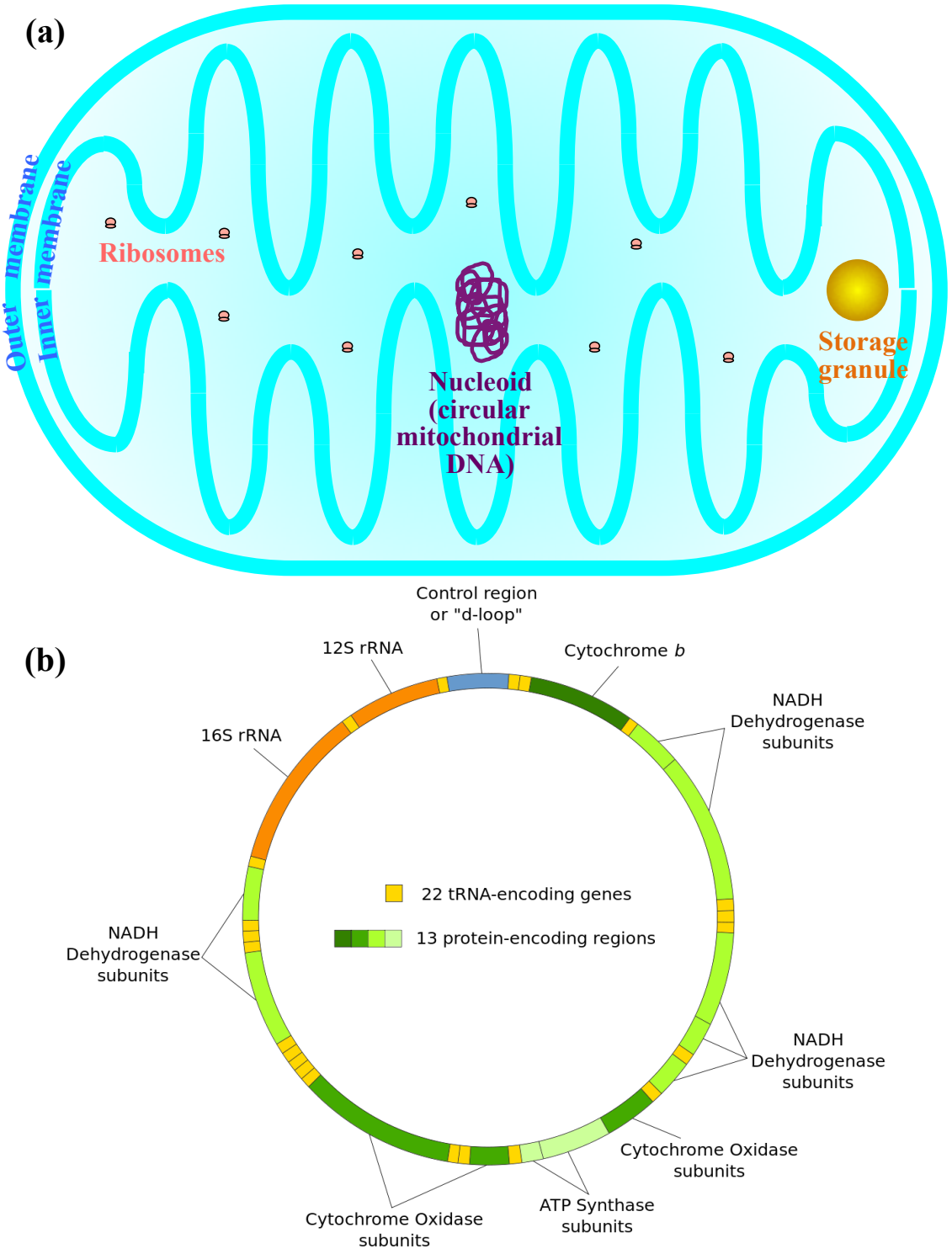


Fig. 19. Mitochondrion, showing (a) typical structure including double membranes and (b) the mitochondrial genome, a circular piece of DNA that forms a nucleoid within the mitochondrion. [Image in (b) from https://en.wikipedia.org/wiki/Mitochondrial_DNA.]

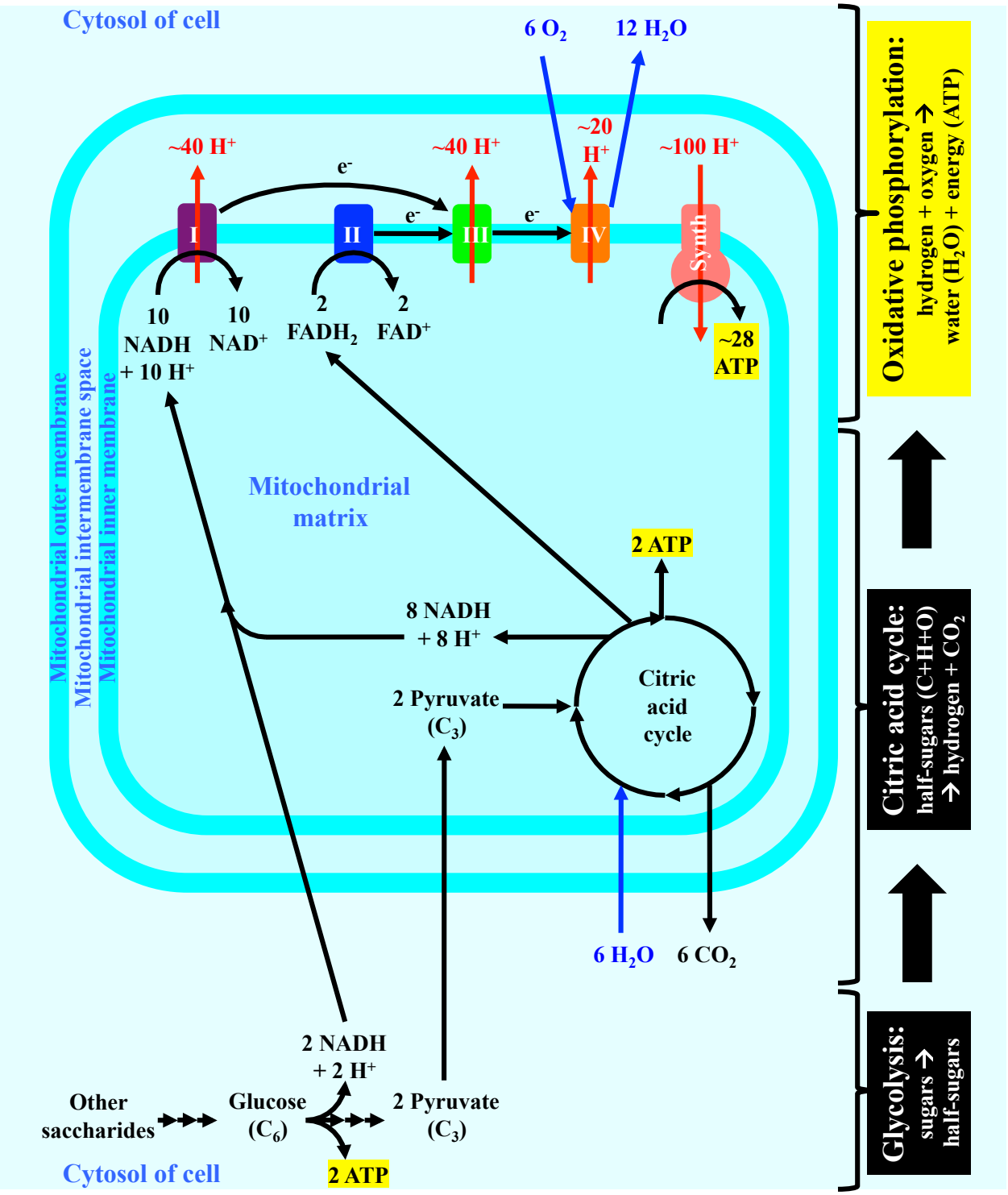


Fig. 20. Respiration pathway in a mitochondrion. In the cell cytosol outside the mitochondrion, saccharides are converted into glucose, which is then split into half-sugars (pyruvate, $C_3H_4O_3$). In the inner matrix of the mitochondrion, half-sugars are stripped of their hydrogen to make CO_2. In the inner membrane of the mitochondrion, that hydrogen is combined with oxygen to produce water (H_2O) plus stored chemical energy (ATP).

1.9 Chloroplasts

Chloroplasts are only present in plant cells. Like mitochondria (which are also present in plant cells), chloroplasts are double-membraned organelles that are former bacteria now turned into resident power plants inside cells. Whereas mitochondria are power plants that burn carbohydrate fuels to make energy, chloroplasts are solar-powered. They are greener energy, literally.

Figure 21(a) shows a typical chloroplast's structure. The chloroplast is enclosed by outer and inner membranes, but (unlike in mitochondria) the inner membrane is not distended, since nothing terribly important happens on its surface. Instead, most of the magic happens within a third, innermost membrane, in disc-shaped structures called **thylakoids**. Thylakoids contain light-absorbing chlorophyll molecules and do most of the hard work in converting sunlight into stored chemical energy, a process called **photosynthesis**. Thylakoids are arranged into stacks (each stack is called a **granum**) and connected by bridges (called a **lamella**). Like the bacteria from which they descended, chloroplasts have a nucleoid, ribosomes, and storage granules for nutrients (starch).

As shown in Fig. 21(b), the chloroplast's genome is a circular piece of DNA that encodes rRNAs, tRNAs, proteins for photosynthesis, and other essential components. As with mitochondria, many chloroplast genes have migrated out of the chloroplast to the cell nucleus, so the cell makes those corresponding proteins and transports them to the chloroplasts. With assistance from the two sets of genes, chloroplasts can reproduce by division just like mitochondria and bacteria.

Chloroplasts appear to be directly related to cyanobacteria, bacteria that produce chlorophyll and use it for photosynthesis, and that are thus often regarded as the simplest form of algae. Presumably some cyanobacteria got stuck inside a larger host cell once upon a time, decided to offer their photosynthetic services in exchange for free room and board in the cell, and then a billion years of botany happened.

In the photosynthesis pathway, chlorplasts absorb sunlight and convert that energy into carbohydrate fuels. Those carbohydrate fuels are stored in the cell for later use by the mitochondria, so plants can basically live on light, whereas animals must find external sources of carbohydrates to eat. Figure 22 shows the photosynthetic pathway in a plant chloroplast:

- In light reactions in the chloroplast's thylakoids, light energy splits water (H_2O) into hydrogen plus oxygen. As the name suggests, these reactions can only happen during daylight.
- In dark reactions outside the thylakoids in the chloroplast, that hydrogen is combined with CO_2 to make half-sugars (glyceraldehyde, $C_3H_6O_3$). As the name suggests, these reactions do not need light and can happen at night (or also during the day).
- In dark reactions in the plant cell cytosol outside the chloroplast, those half-sugars are converted into glucose ($C_6H_{12}O_6$) and other saccharides.

Note that the photosynthetic pathway in chloroplasts is basically the respiratory pathway in mitochondria being run in reverse.

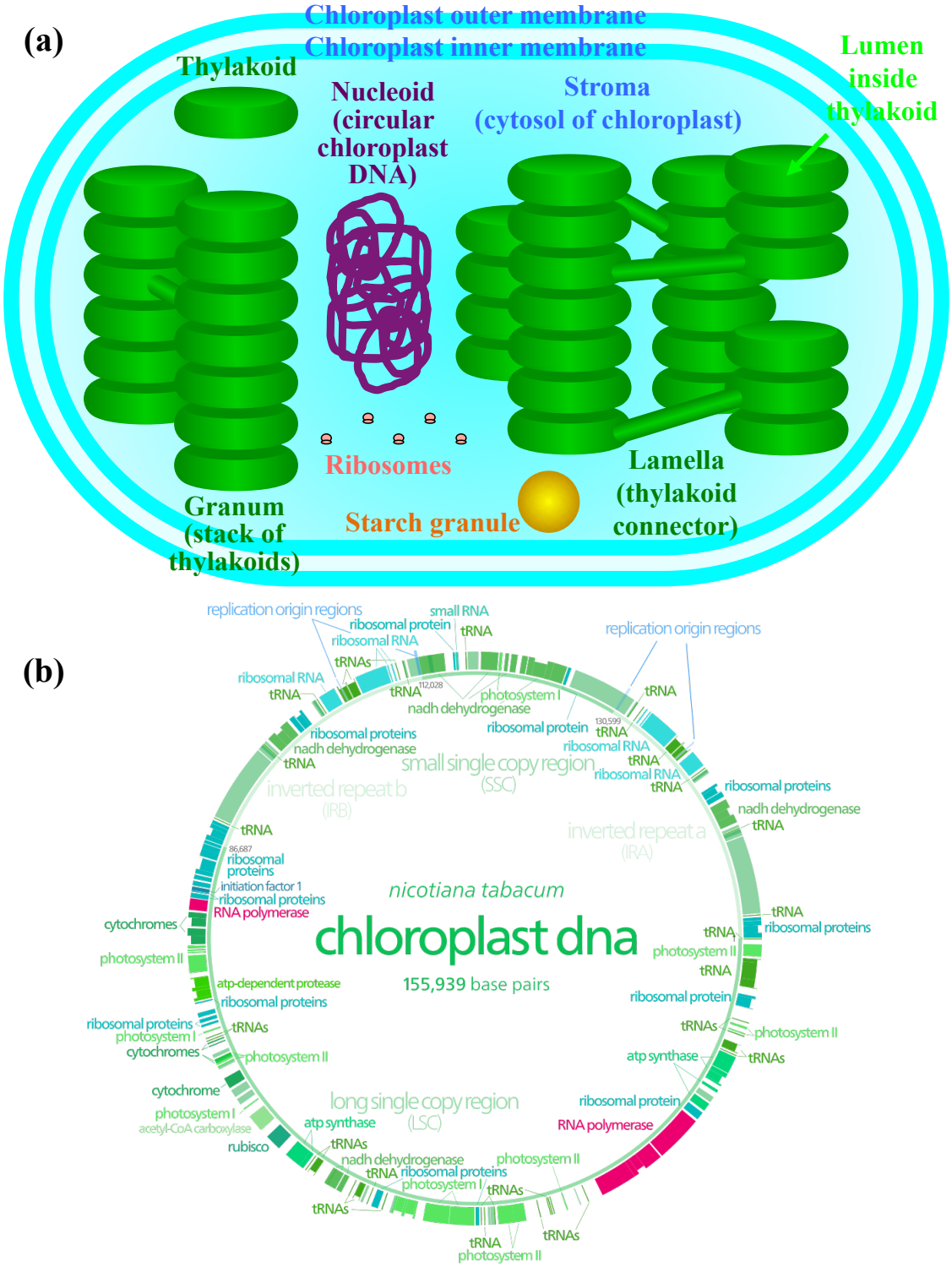


Fig. 21. Plant chloroplast, showing (a) typical structure including double membranes and light-absorbing thylakoid discs, and (b) the chloroplast's genome, a circular piece of DNA that forms a nucleoid within the chloroplast. [Image in (b) from https://en.wikipedia.org/wiki/Chloroplast.]

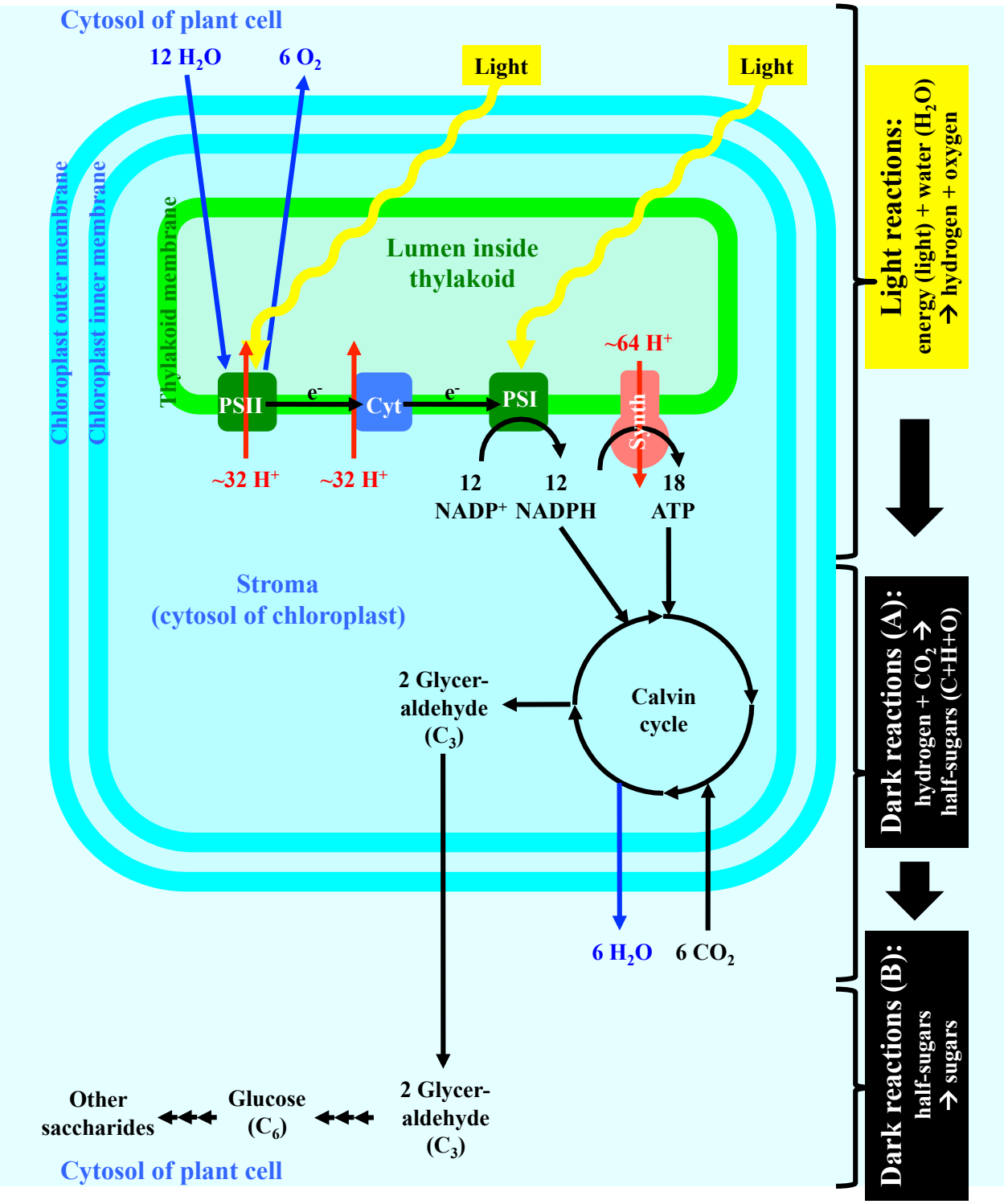


Fig. 22. Photosynthetic pathway in a plant chloroplast. In light reactions in the chloroplast's thylakoids, light energy splits water (H_2O) into hydrogen plus oxygen. In dark reactions outside the thylakoids in the chloroplast, that hydrogen is combined with CO_2 to make half-sugars (glyceraldehyde, $C_3H_6O_3$). In dark reactions in the plant cell cytosol outside the chloroplast, those half-sugars are converted into glucose and other saccharides.

1.10 Cytoskeleton

The cytoskeleton is an internal spiderweb-like network within the cell. A typical eukaryotic cytoskeleton is composed of three different types of protein filaments, as shown in Fig. 23(a):

- **Microtubules** are the widest cytoskeletal components. They are hollow tubes with a diameter of approximately 25 nanometers (nm, or billions of a meter or 10^{-9} m). Microtubules are composed of two protein subunits: α-tubulin and β-tubulin. Because of their relatively large diameter and tubular construction, microtubules are similar to structural columns in a building, and able to withstand compressive forces. They generally run from a central location called the **centrosome** near the nucleus out to the edges of the cell in all directions.
- **Intermediate filaments**, as the name suggests, are medium-sized cytoskeletal components. They are solid fibers with a diameter of roughly 10 nm composed of keritins or other fibrous protein subunits. Intermediate filaments tend to run across the cell between anchoring proteins in different locations on the plasma membrane.
- **Actin microfilaments** are the thinnest cytoskeletal components, roughly 7 nm in diameter. They have two intertwined strands made of actin subunits. They can appear throughout the cell, but they are especially numerous just inside the plasma membrane, where they create a dense web-like structure to support the plasma membrane. Closely related laminin microfilaments support the inside of the nuclear membrane, as discussed in Section 1.4.

In addition to physically holding the cell together, the cytoskeleton serves as train tracks to guide molecules, vesicles, and organelles to the right locations in the cell. As shown in Fig. 23(b), motor proteins grab receptors on cargo, and then drag that cargo along microtubules. **Kinesin** motor proteins generally move in the outbound or + direction, and **dynein** motor proteins generally move in the inbound or − direction. These motor proteins have two feet and literally "walk" along the microtubule, with each step powered by consumption of ATP, the cell's ubiquitous energy source.

This same motor protein/microtubule trick can be used to wave appendages on the cell's surface. Many single-celled eukaryotes have a **flagellum** (plural flagella) that wiggles back and forth like a motor to propel them as they swim around. The main use of a flagellum in mammals is in sperm cells. However, a wide variety of mammalian cells have **cilia**, waving finger-like appendages on the surface that tend to be much shorter and much more numerous than flagella. Cells from the respiratory tract to the gastrointestinal tract use cilia to sweep along substances that are passing by the cell, and most cells have at least one cilium to sense fluid motion around the cell.

Apart from differences in length, eukaryotic flagella and cilia look and work the same way [Fig. 24]. Microtubules come in pairs, and one pair is connected to the next pair by both dynein motor proteins and **crosslinking proteins**. When the flagellum or cilium is flooded with ATP, the dynein motors try to slide one pair of the microtubules relative to the other pair, like extending the arm of a crane. However, the crosslinking proteins hold the adjacent pairs of microtubules together, so they are not free to slide very far. All of the stress of trying to slide but not being able to causes the microtubules to bend, sort of like the stress of trying to escape biology and not being able to.

Eukaryotic flagella and cilia have a complex arrangement of nine microtubule pairs and two central individual microtubules, all connected by dynein motors and crosslinking proteins, and all surrounded by a protrusion of the cell's plasma membrane. Flagella and cilia are approximately 250 nm or 0.25 μm (μm = micrometer, micron, millionth of a meter, or 10^{-6} m) wide. Flagella tend to be around 100-200 μm long, whereas cilia tend to be around 2-20 μm long.

Prokaryotic flagella work very differently and will be covered in *Microbiology*.

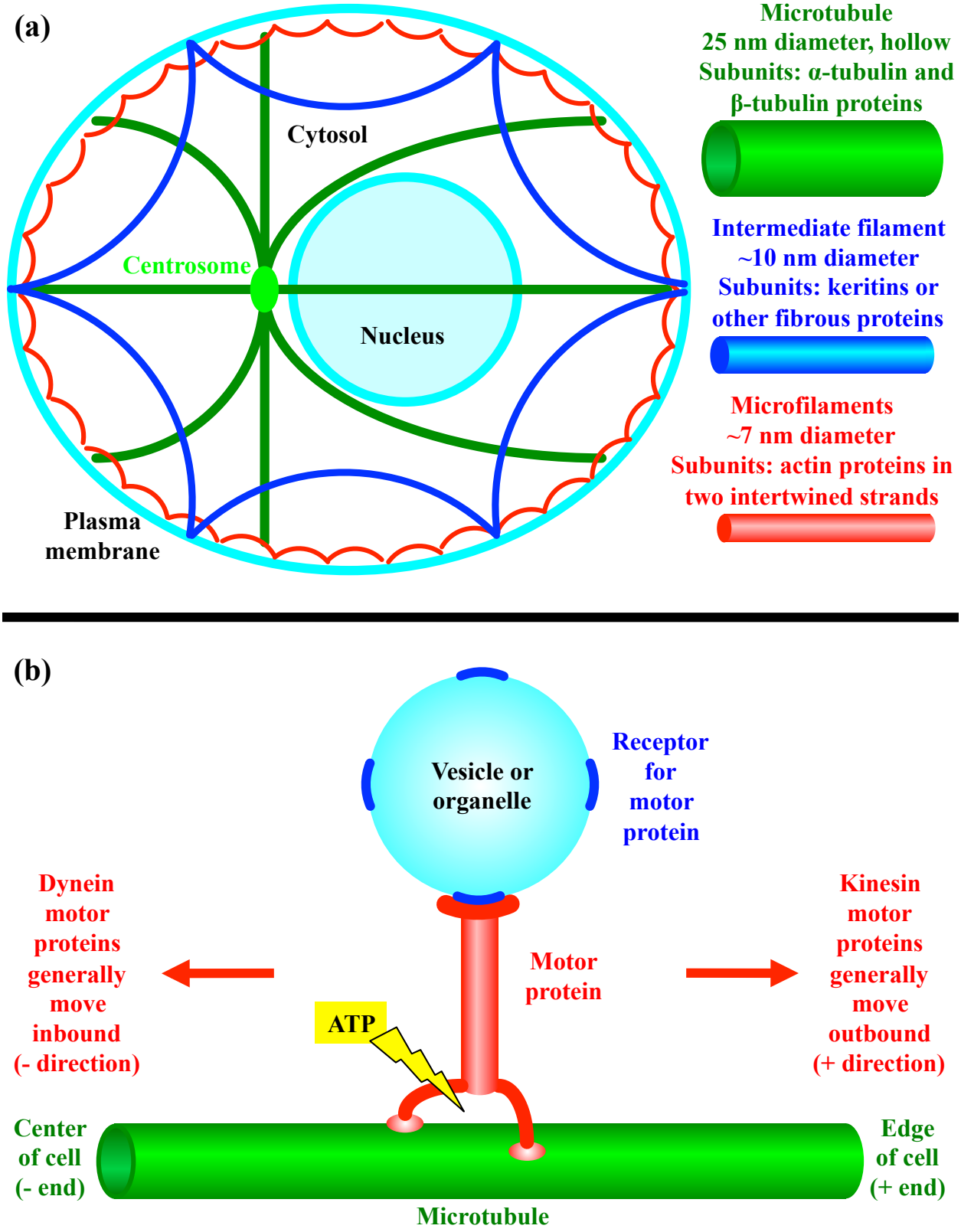


Fig. 23. Cytoskeleton. **(a)** Microtubules, intermediate filaments, and microfilaments in a eukaryotic cell. **(b)** Motor proteins move along microtubules to deliver cargo.

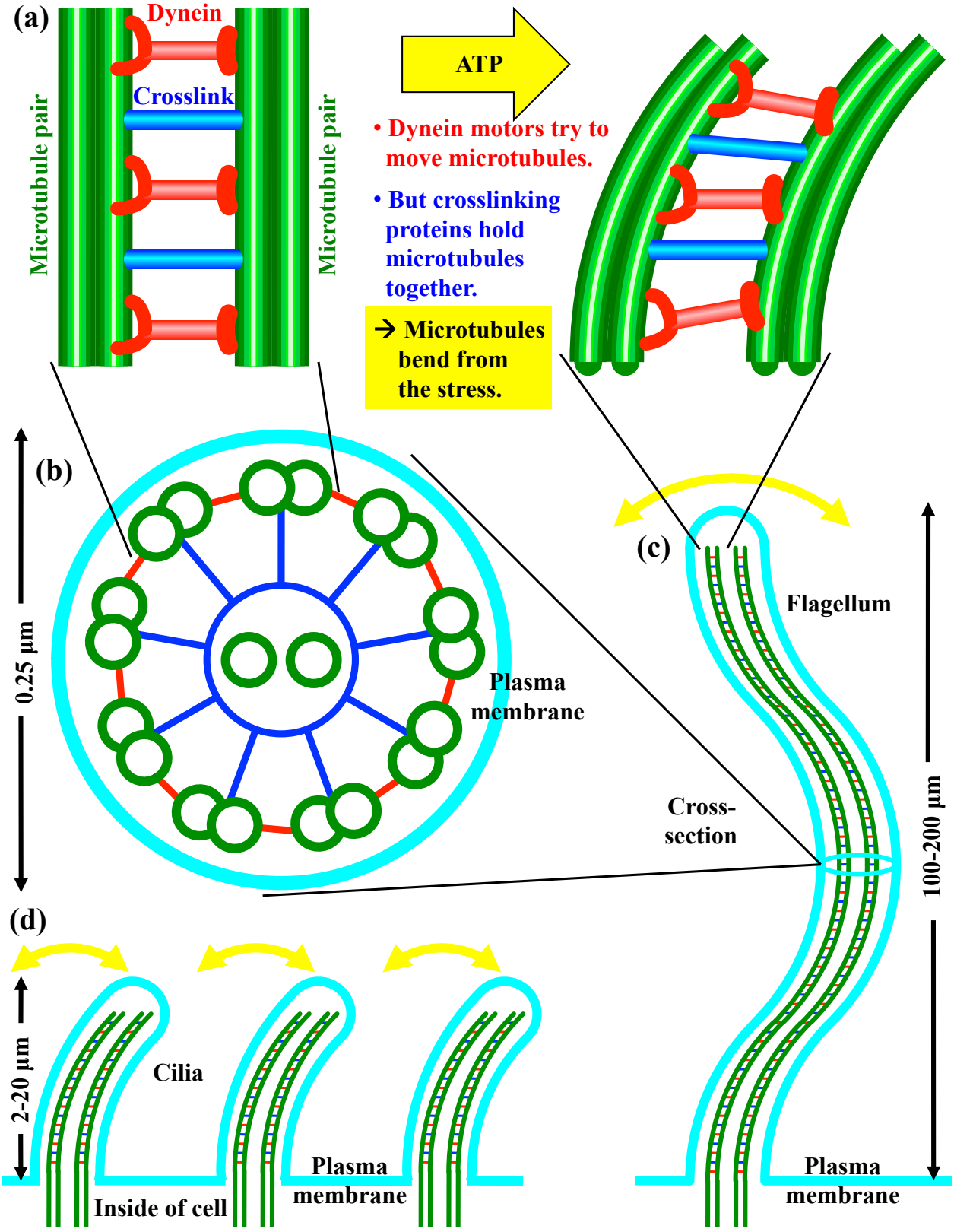


Fig. 24. Cilia and flagella on eukaryotic cells use microtubules and dynein motor proteins to generate oscillatory motion.

1.11 Cell Adhesion Molecules and the Extracellular Matrix

The individual cells in your body are connected to each other in organized ways; otherwise you would collapse into a puddle of single-celled goo. **Cell adhesion molecules** are Velcro-like sticky molecules on the surface of a cell that attach to molecules on other cells and/or the **extracellular matrix**, a spiderweb-like net of molecules running between cells.

As shown in Fig. 25, major types of cell adhesion molecules include:

- **Cadherins**, hook-shaped molecules that come in pairs and bind to cadherins on neighboring cells. Cadherins require bound calcium ions to work (hence their name); they lose their rigid hook shapes if calcium ions are removed from the extracellular medium.
- **Immunoglobin-superfamily cell adhesion molecules**, which bind to immunoglobin-superfamily cell adhesion molecules on neighboring cells. As the name suggests, these molecules are related to immunoglobulins or antibodies, important adhesion molecules in the immune system (see *Immunology*), but they include many other cell adhesion molecules with the same general structure.
- **Selectins**, which bind to glycans (sugars) on the surfaces of neighboring cells. Sugars form branching structures that are very sticky (and thus very handy for cell adhesion), just like a kid who has had too much cotton candy.
- **Integrins**, which bind to extracellular matrix glycoproteins, part of the web between cells.

The extracellular matrix is composed of webs of glycoproteins (e.g., fibronectin and laminin) and fibrous proteins (e.g., collagens and elastin) crosslinked by glycoproteins (e.g., nidogen) and proteoglycans (e.g., perlecan). Note that glycoproteins and proteoglycans are both categories of molecules that are part protein and part sugar (glycan). The component listed second in each name is more dominant, so glycoproteins are more protein than sugar, and proteoglycans are more sugar than protein. In both cases, the sugars form very sticky branching structures.

Some cells are only briefly attached to each other, for example to communicate with each other in the immune system; such transient interactions are often facilitated by immunoglobulin-superfamily cell adhesion molecules or selections. On the other hand, many cells use cell adhesion molecules such as cadherins to settle down in a nice neighborhood and form long-lived cell-cell junctions with their neighboring cells. Figure 26 shows the major types of cell-cell junctions:

(a) In an **anchoring junction**, extracellular cadherins couple the intracellular actin filaments (for an adherens anchoring junction) or intermediate filaments (for a desmosome anchoring junction) of one cell to those of another, such that fluid can still pass between the cells. Various adaptor proteins connect the cadherins to the filaments.

(b) In a **gap junction**, connexin (or similar innexin or pannexin) pores allow small molecules to pass from one cell to another, while still permitting fluid to pass between the cells (around the connexins). Connexins are important for passing chemical signals between cells, for example so that your heart muscle cells all beat at the same time, and also for passing metabolic nutrients between cells.

(c) In a **tight junction**, M-shaped transmembrane proteins called occludins and claudins fasten together parts of the membranes of two cells so tightly that fluid cannot pass between those cells. That conveniently ensures that all of your insides stay on the inside.

Through these sorts of junctions and adhesion molecules, what happens outside a cell can be sensed and have effects inside a cell, and vice versa, as will be discussed in Sections 2 and 3.

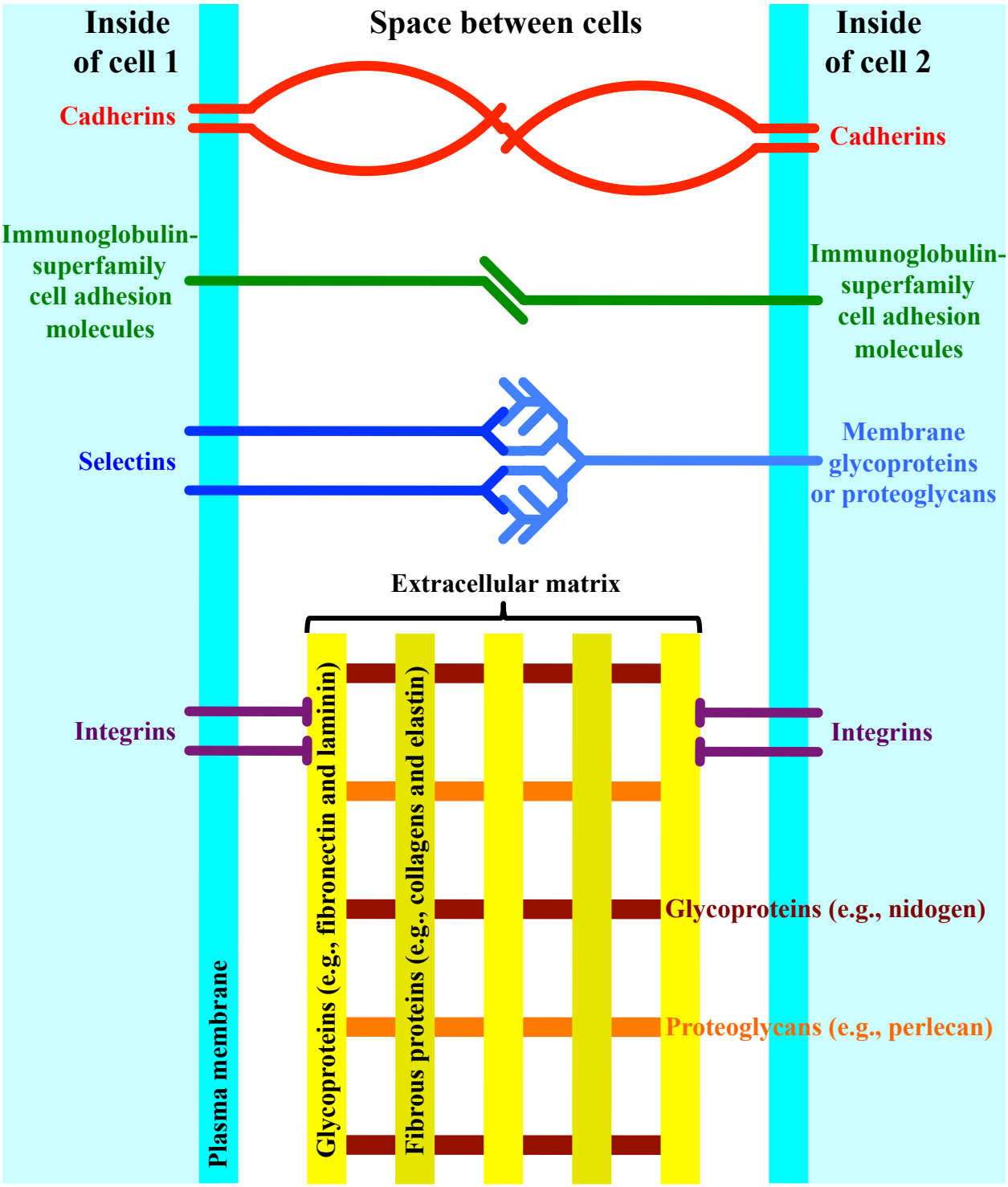


Fig. 25. Cell adhesion molecules and extracellular matrix. Cell adhesion molecules include cadherins (which bind to other cadherins), immunoglobin-superfamily cell adhesion molecules (which bind to members of the same family), selectins (which bind to glycans on a neighboring cell), and integrins (which bind to extracellular matrix glycoproteins). The extracellular matrix is composed of webs of glycoproteins (e.g., fibronectin and laminin) and fibrous proteins (e.g., collagens and elastin) crosslinked by glycoproteins (e.g., nidogen) and proteoglycans (e.g., perlecan).

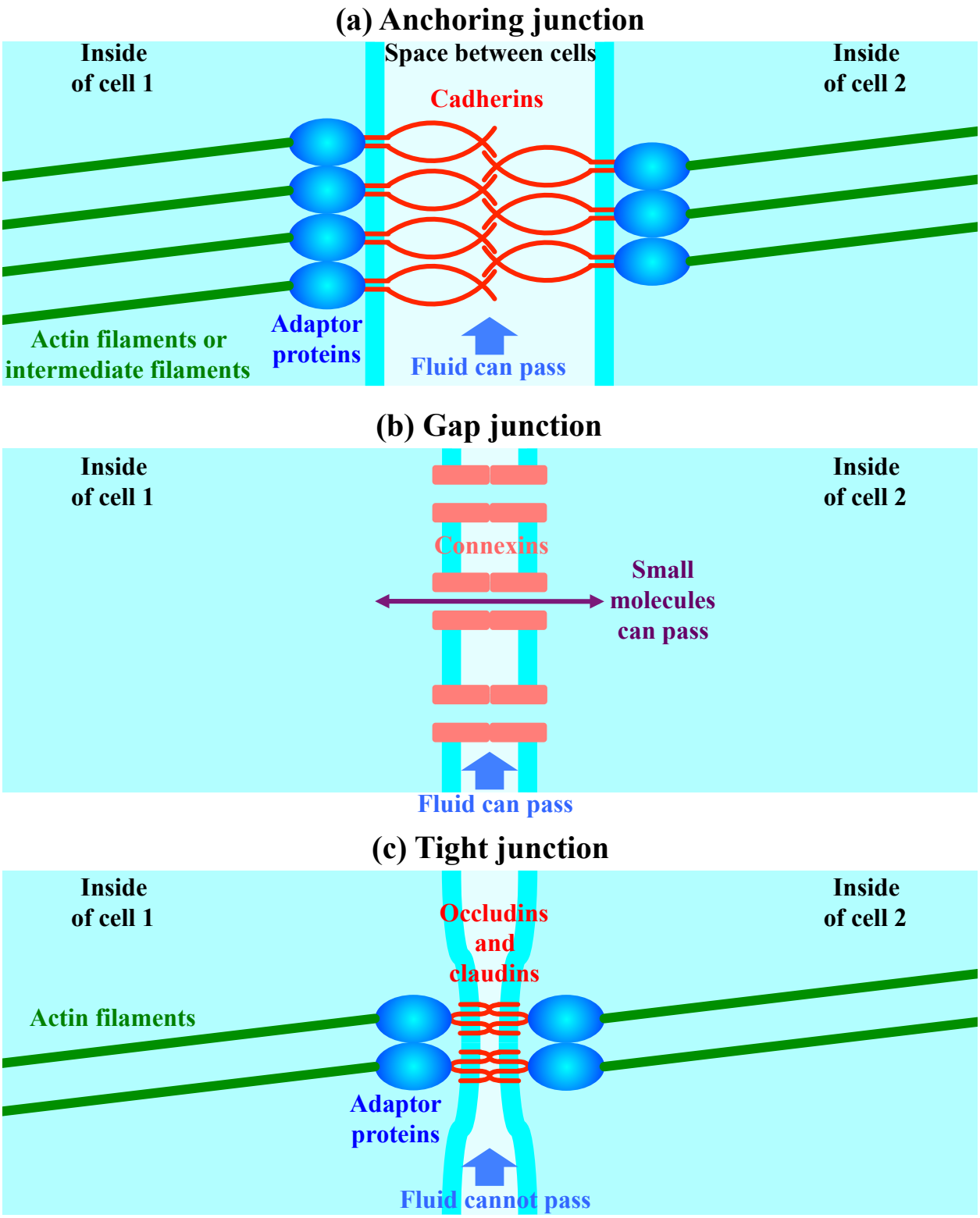


Fig. 26. Cell junction types. **(a)** Anchoring junction formed by cadherins. **(b)** Gap junction formed by connexins. **(c)** Tight junction formed by occludins and claudins.

2 Cell Pathways

Just as cells are like cities and organelles are like parts of those cities, cellular pathways that involve multiple organelles are like city-wide services that involve many different parts of the city. As shown in Fig. 27 and covered in the section numbers indicated below, major cellular pathways include:

2.1. Transcription and translation pathways are like the education system of the cell, reading blueprints from genes and then creating, educating, and polishing protein workers to carry out the tasks shown in those blueprints.

2.2. Metabolic pathways are like the city services that provide electricity, water, and food to all parts of the city, and then collect the resulting waste from all parts of the city.

2.3. Intercellular signaling methods are like the internet and phone lines that allow communications between different cities.

2.4. Intracellular signaling methods are like the internet and phone lines that allow communications within a city.

2.5. Heat shock and unfolded protein response pathways are like the cell's fire and ambulance services, responding to help cellular proteins that are threatened by excess heat, toxic metals, or other problems.

2.6. Interferon and inflammatory pathways are like the police department of the cell, constantly looking for dangerous pathogens or chemicals that invade the cell.

2.7. Cell death pathways are like an emergency self destruct system for the cell, a last line of defense in case the city is invaded by zombies or aliens.

3. Cell division pathways are like the ways that cities that became too populous could send some of their people off to found new cities on another continent in the past, or maybe new cities on other planets in the future. Technically cell division is just one more pathway within cells, but it is so complex and so important that its talent agent demanded that it get top billing in its own separate section.

- **Cell type differentiation pathways** that lead cells to become heart, lung, bone, or other types of cells are like the ways that different cities can specialize to become movie-making areas like Hollywood, high-tech entrepreneurial areas like Silicon Valley, or giant piles of red tape like Washington, DC. To learn more about these, you will have to wait breathlessly for the *Reproductive and Developmental Biology* summary.

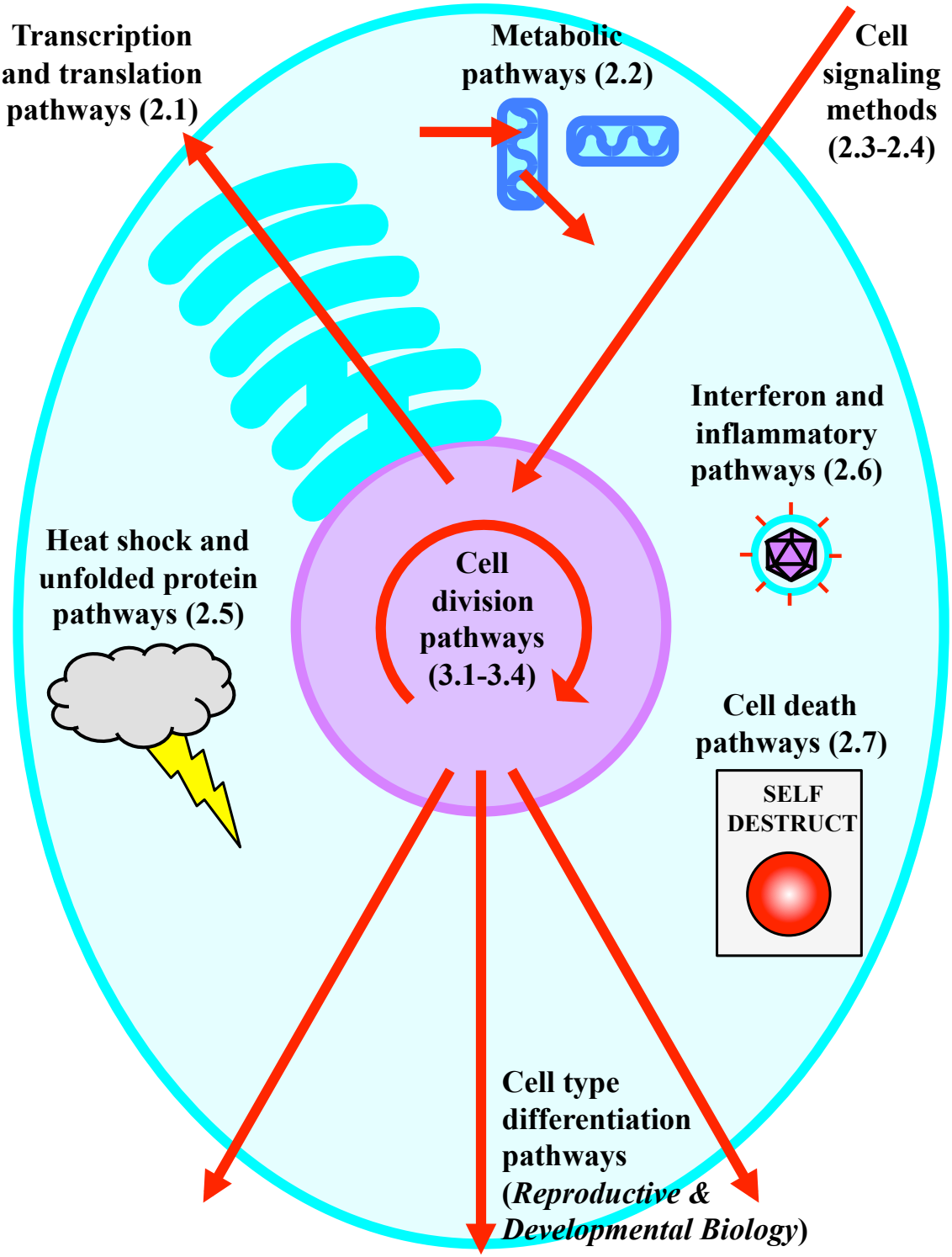


Fig. 27. Cellular pathways to be covered include: (Section 2.1) transcription and translation pathways, (2.2) metabolic pathways, (2.3) intercellular signaling methods, (2.4) intracellular signaling methods, (2.5) heat shock and unfolded protein response pathways, (2.6) interferon and inflammatory response pathways, (2.7) cell death pathways, (3.1-3.4) cell division pathways, and (some other time!) cell type differentiation pathways.

2.1 Transcription and Translation Pathways

Figure 28 shows the main pathways for transcription and translation from genes to proteins:

- DNA is a natural biological linear polymer containing a sequence of four possible subunits (bases or nucleotides). DNA is a relatively long-lived and precise molecule for encoding large amounts of information, and thus it is used in the cell nucleus (or nucleoid in prokaryotes) to store, replicate, and control the genes in all organisms, except some viruses. DNA regions may be classified as exons or introns (which both end up being copied to RNA), promoters (which control how many RNA copies to make), and intermediate regions that serve as spacers or perform other functions. DNA is **replicated** when a cell divides to become two cells, as will be discussed in Section 3.

- RNA is chemically very similar to DNA and also has a sequence of four possible subunits (bases or nucleotides), but it is a less long-lived and somewhat more error-prone biomolecule for encoding information. However, inside the nucleus, cells **transcribe** their individual genes from DNA to RNA to make temporary working copies of genes, and some viruses only store their genes as RNA.

- Still inside the nucleus, after a cell makes messenger RNA (mRNA) copies of individual genes, those mRNAs undergo **post-transcriptional modification**, including splicing to remove their introns yet leave their exons, and addition of a 5' cap on one end and 3' poly-adenosine tail on the other end to stabilize them. Then the mRNAs are shipped out of the nucleus.

- As described in Section 1.5, ribosomes outside the nucleus **translate** the RNA nucleotide sequences of individual genes to create proteins of the correct corresponding amino acid sequences. Proteins are polymers containing sequences of at least 20 possible subunits (amino acids or residues), and they function as specialized molecular machines to perform most of the essential tasks in and around cells.

- To prepare for their new jobs, some proteins require **post-translational modification** in the endoplasmic reticulum (Section 1.5) and Golgi apparatus (Section 1.6). These modifications include glycosylation or adding glycan (sugar) groups, creating disulfide bridges, phosphorylation or adding phosphate groups, and any other modifications required to help the proteins fold up into their final functional form.

In addition to these natural mechanisms, there are a number of modern technologies that can analyze or modify DNA, RNA, and proteins for various applications. For lots more information on both the natural pathways and the technological methods, see the *Molecular Biology* summary.

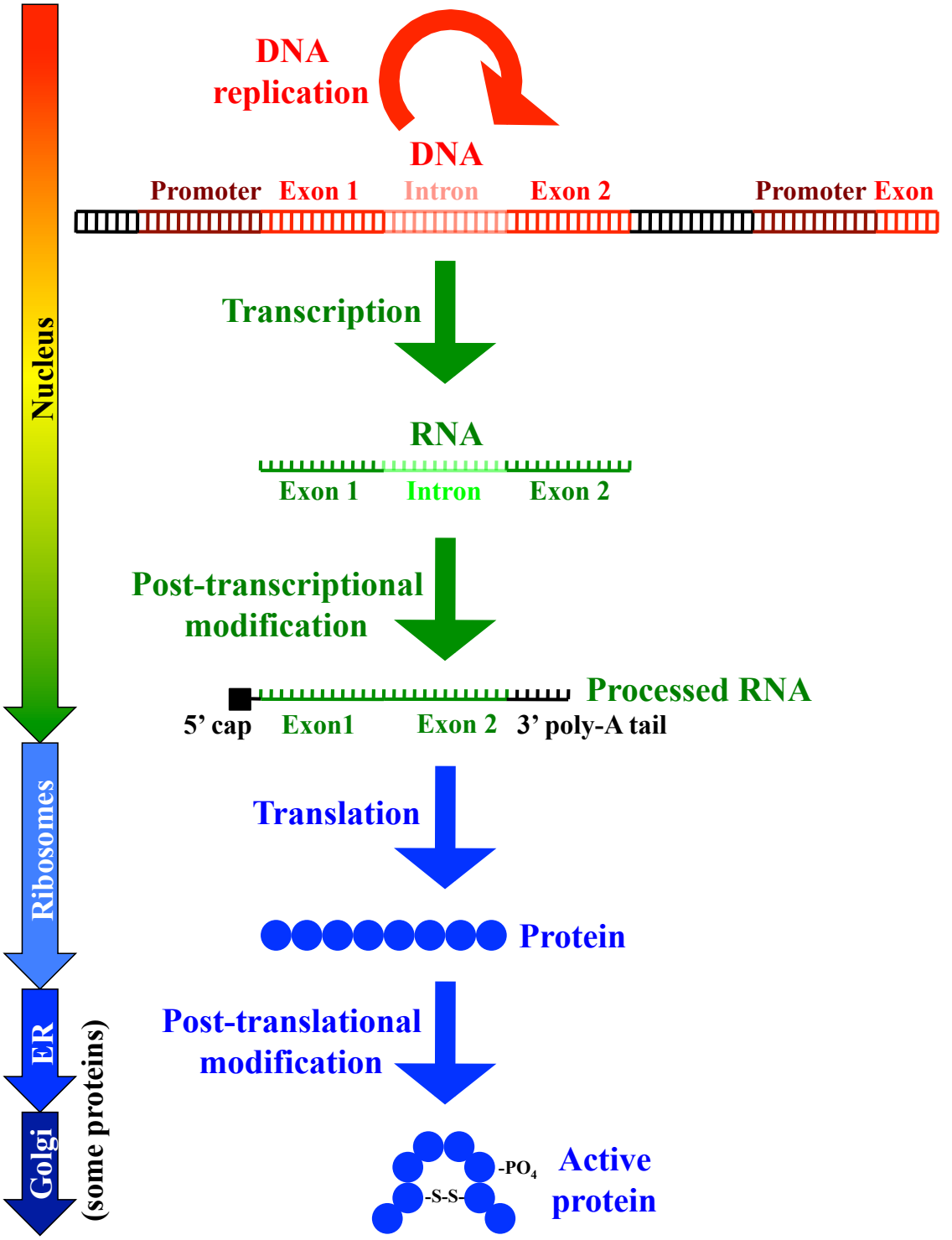


Fig. 28. Transcription and translation. In the nucleus, cells transcribe their individual genes from DNA to RNA to make temporary working copies of genes. Outside the nucleus, ribosomes translate the RNA nucleotide sequences of individual genes to create proteins of the correct corresponding amino acid sequences. Some newly translated proteins are processed into their final forms inside the endoplasmic reticulum and in the Golgi apparatus.

2.2 Metabolic Pathways

Figure 29 shows an overview of major metabolic pathways in cells. Important pathways include:

1. **Synthesis** (production) or **catabolism** (degradation) of biomolecules including:

    - **Nucleotides for DNA and RNA.** As needed, new nucleotides are built by combining monosaccharides (simple sugars) and amino acids. Old nucleotides are either recycled to form new stretches of DNA and RNA, or degraded to form uric acid.
    - **Amino acids for proteins.** Amino acids may be derived by breaking apart old proteins (or proteins that an animal has eaten) into their component amino acids, or by building them from scratch using parts and pieces kidnapped from the sugar-consumption pathways (glycolysis and citric acid cycle). Unwanted amino acids are broken down to form urea, from which urine gets its name.
    - **Lipids such as fatty acids, triglycerides, phospholipids, cholesterol, etc.** Lipids may be derived from consumed food or built from scratch (lipogenesis). Excess lipids may be stored (as many of us do!), dismantled and reformed into new lipids, or used as fuel for the respiratory pathway to power the cell.
    - **Carbohydrates.** Individual simple sugars can be strung together in various ways to make complex carbohydrates ranging from starch to glycogen to cell walls, or those complex carbohydrates can be split apart into their component simple sugars. Simple sugars make great fuel for the respiratory pathway.
    - **Porphyrins.** These frequently overlooked biomolecules are key catalytic components of a number of energy conversion pathways including respiration and photosynthesis. They contain iron or magnesium metal ions and turn lots of different colors like mood rings, from green in plant chlorophyll to red in oxygen-rich blood hemoglobin to blue in oxygen-deprived hemoglobin. Porphyrins are very complicated flower-shaped molecules that cells build from scratch. Old porphyrins are broken down to form bilirubin, a toxic waste product that makes urine yellow and poop brown. Too much information!

2. **Respiration**, in which energy is produced by combining hydrogen from biomolecules with oxygen from the air to form water. Section 1.8 gave an overview of the end stages of respiration in the mitochondria. If oxygen is not available (for example in anaerobic bacteria growing without fresh air), fermentation is an alternative process that produces a much smaller amount of energy by converting sugars to lactic acid and/or ethyl alcohol.

3. **Photosynthesis** (in plant cells), the reverse process in which light energy is absorbed and stored by splitting water into more oxygen for the air and more hydrogen in biomolecules. Section 1.9 gave an overview of the initial stages of photosynthesis in chloroplasts.

Good news–you don't have to know any more about these metabolic pathways right now! Bad news–they will be covered in nauseating detail in the *Biochemistry* summary!

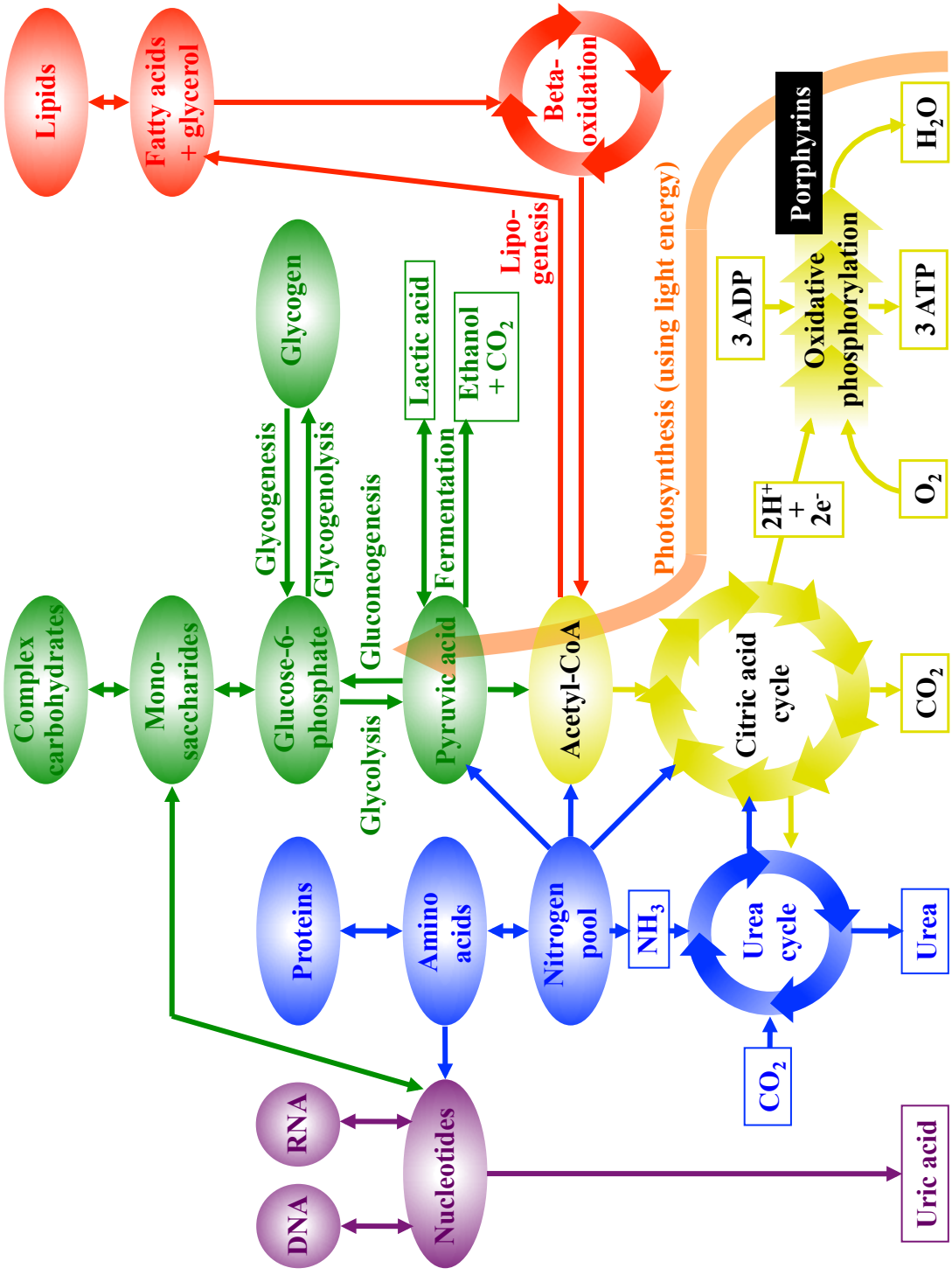


Fig. 29. Major metabolic pathways in cells. Important pathways include: (1) synthesis (production) or catabolism (degradation) of nucleic acids, proteins, lipids, carbohydrates, and porphyrins; (2) respiration, in which energy is produced by combining hydrogen from biomolecules with oxygen from the air to form water; and (3) photosynthesis (in plant cells), the reverse process in which light energy is absorbed and stored by splitting water into more oxygen for the air and more hydrogen in biomolecules. Porphyrins play catalytic roles in respiratory/photosynthetic pathways.

2.3 Intercellular Signaling

Before diving into more specific cellular pathways, we will discuss general methods that cells use to send signals. In the specific pathways to be covered in the rest of Sections 2 and 3, you will see many examples of these general methods. If your eyes don't glaze over, we will describe intercellular (externally from one cell to another) signaling methods in Section 2.3 and intracellular (internally from one part of a cell to another part of the same cell) signaling methods in Section 2.4:

(a) Cells can produce and send out intercellular signaling molecules, as shown for cell 1 in Fig. 30.

(b) Receptors on cells can receive those intercellular signals, as shown for cell 2 in Fig. 30.

(c) In response, intracellular signaling proteins or small-molecule second messengers carry those signals from one regions within the cell to another region within the same cell, with one protein or molecule activating the next, which activates the next, and so on [Fig. 30]. Having several steps allows signal amplification–each active molecule in one step can activate several molecules in the next step, and each of those can activate several molecules in the following step. It also allows an initial signal to branch out and have several different effects in the cell, or to interact with signals from another signaling pathway as the cell decides which of several possible courses of action it should take.

(d) As a result, as shown in Fig. 30, transcription factor proteins turn genes on or off (up-regulate or down-regulate the expression of certain genes, if you want to spout technobabble like a card-carrying biologist).

We will now go into these processes in more detail. You'll thank me later if you are still awake.

As shown in Fig. 31, cells have several methods of sending intercellular signals to other cells, including:

(a) **Secreted molecules** ranging from proteins to small chemical molecules can be spat out by cells to communicate with other cells. In **synaptic** signaling, those molecules are sent across a synapse (gap) to one specific neighboring cell, for example by one neuron (brain cell) communicating with another. In **paracrine** signaling, those molecules are sent to several nearby cells, for example by a cell secreting interferon proteins to warn nearby cells of an infection. In **endocrine** signaling, those molecules are sent through the bloodstream to cells far away, as is the case with **hormones**. In **autocrine** signaling, the cell is narcissistic and just wants to talk to itself, sending out and then receiving its own molecular signals.

(b) **Cell-surface molecules** such as cell adhesion molecules (Section 1.11) on one cell can grab those on an adjacent cell, letting a cell know that it is surrounded by neighbors and should stop growing, passing signals between cells in the immune system, or conveying other messages.

(c) **Electrical signals** transmitted between two cells whose membranes are in contact with each other, or that are connected by gap junctions (Section 1.11). Since cells keep different concentrations of positive and negative ions inside versus outside and have pumps and channels to transport those ions (Section 1.3), they can generate an electrical voltage across their plasma membranes, or an electrical current when ions are flowing. Those electrical signals can be detected by voltage-gated ion channels on nearby cells, which then create ion flow and electrical signals in those cells too.

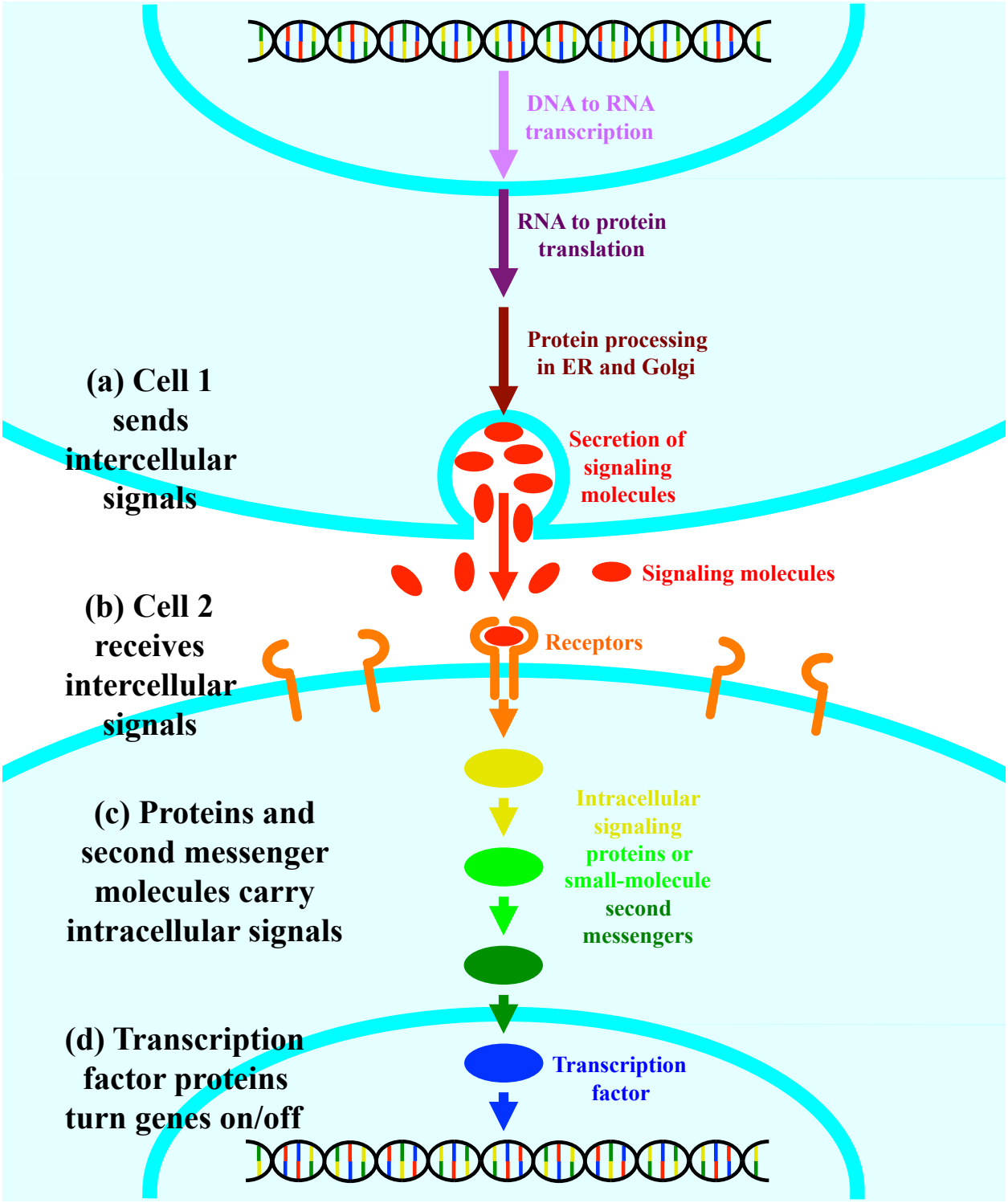


Fig. 30. Cell signaling overview. **(a)** Cell 1 sends intercellular signals. **(b)** Cell 2 receives those intercellular signals. **(c)** In response, intracellular signaling proteins or small-molecule second messengers carry those signals from one part of the cell to another. **(d)** As a result, transcription factor proteins turn genes on or off.

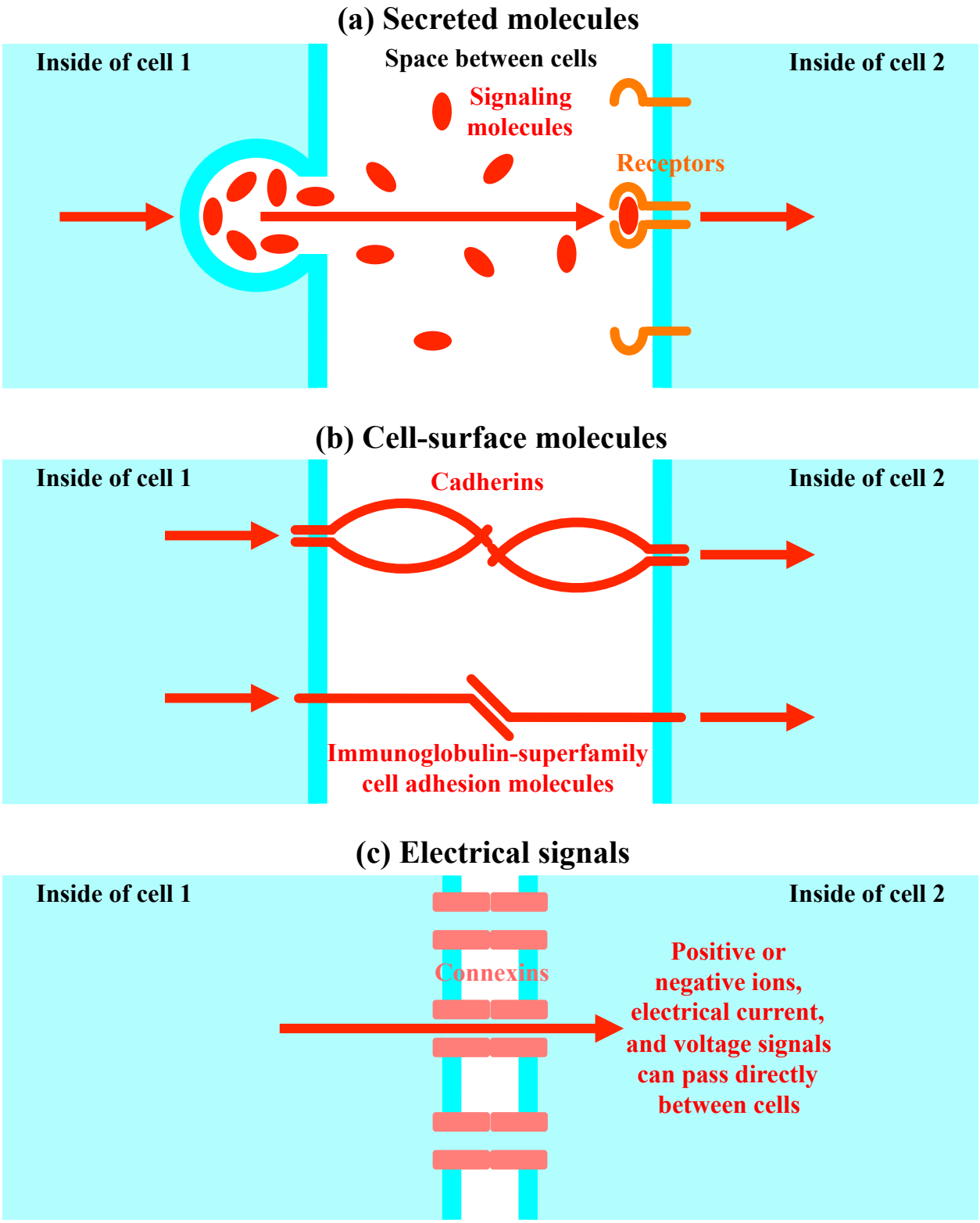


Fig. 31. Methods of sending intercellular signals. **(a)** Secreted molecules. **(b)** Cell-surface molecules. **(c)** Electrical signals.

Those intercellular signals can be received by a variety of receptors on other cells. Figure 32 shows the major categories of receptors:

(a) Cell-surface ion-channel-coupled receptors in the plasma membrane of a cell detect signals from other cells, and in direct response open ion channels in the plasma membrane, letting certain types of ions in or out of the cell for a short period of time until the channels close. Neurons and muscle cells are especially fond of receiving signals this way.

(b) Cell-surface enzyme-coupled receptors normally float around individually in the plasma membrane of a cell, but when they find an extracellular signaling molecule that they recognize, several of the receptors all bind to the same molecule. That brings all of the receptors into close physical proximity with each other, letting enzymes that are part of or bound to the intracellular ends of the receptors act on each other. Usually the enzymes are kinases that glue phosphate groups on each other, but sometimes the enzymes are proteases that cut up each other. Immune system cells are particularly fond of this sort of signaling.

(c) Cell-surface G-protein-coupled receptors (GPCRs) involve several different membrane-bound proteins and are Rube Goldberg's method of detecting intercellular signaling molecules. Normally the intracellular domain of the GPCR is hanging on to three other membrane-bound proteins, called G-alpha (Gα, which is munching on a GDP), G-beta (Gβ), and G-gamma (Gγ). When a signaling molecule binds to the extracellular domain of a GPCR that is specific for it, the intracellular domain of the GPCR changes shape causing Gα to swap its soggy old GDP for a crunchy new GTP and go off one way, and Gβ and Gγ together to go off another way. Gα and/or Gβ/Gγ can activate other proteins (often ones that make cyclic adenosine monophosphate or cAMP) to send signals inside the cell. Eventually the GTP in the jaws of the Gα protein turns into GDP like old gum, and the Gα, Gβ, and Gγ proteins go back home to the intracellular domain of the GPCR and wait for something interesting to happen again.

(d) Intracellular receptors detect steroid hormones or other small hydrophobic molecules that are sent by other cells and can penetrate through the plasma membrane to the inside of a cell. Most intracellular receptors hang out in the cytosol; if the steroid hormone for which they are specific (e.g., testosterone or estrogen) gets inside the cell and binds to the receptors, the activated receptors head into the nucleus and serve as transcription factors to turn certain genes on or off. Note that while hydrophobic hormones are great at passing through the plasma membrane, they are lousy at hanging out in the water-rich space between cells, so they are usually escorted by carrier proteins that protect them from the scary water until they reach their destination.

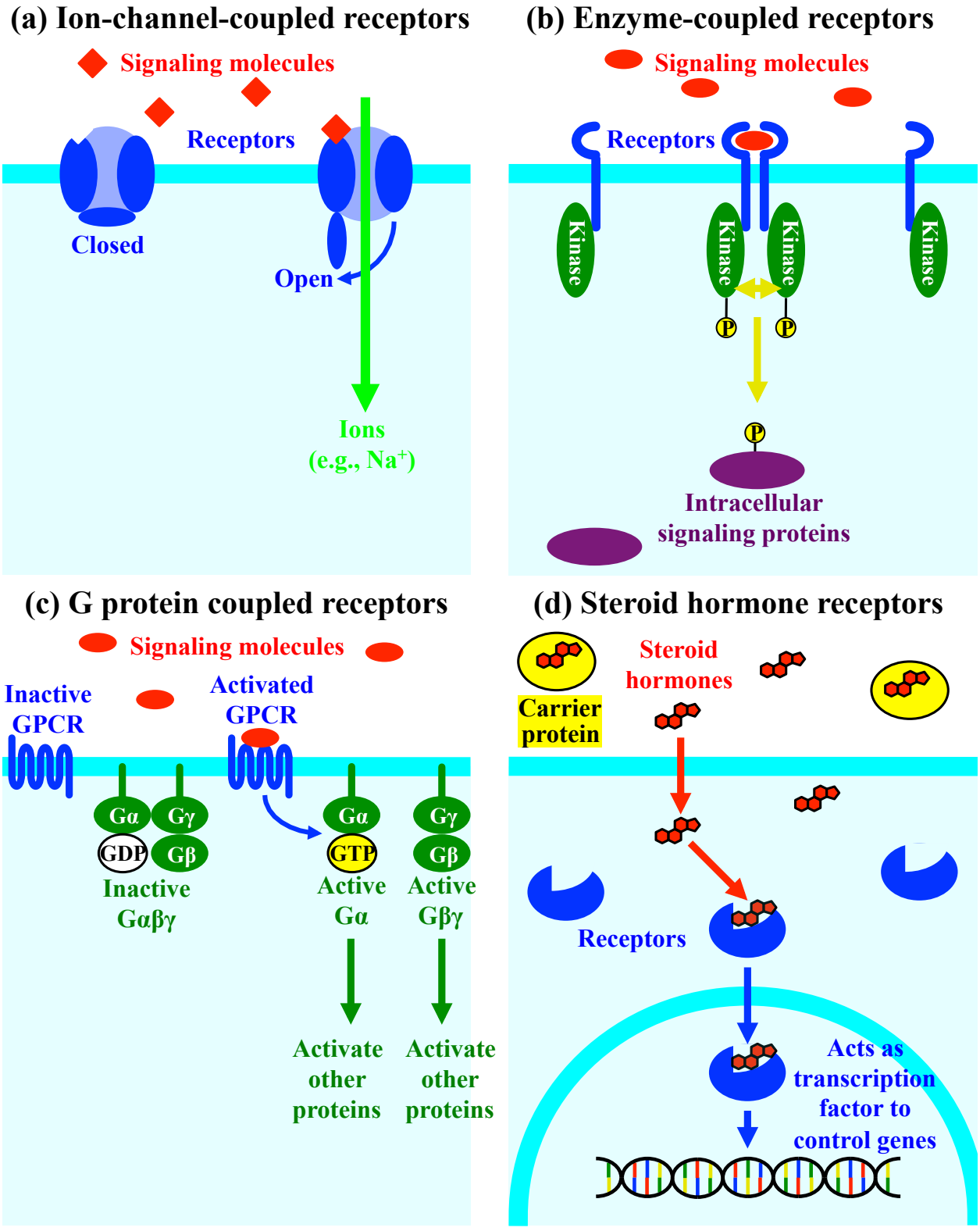


Fig. 32. Categories of receptors for intercellular signals. **(a)** Cell-surface ion-channel-linked receptors. **(b)** Cell-surface enzyme-linked receptors. **(c)** Cell-surface G-protein-coupled receptors (GPCRs). **(d)** Intracellular receptors.

2.4 Intracellular Signaling

In addition to sending intercellular signals from one cell to another, cells can send intracellular signals within a cell from one part to another.

As shown in Fig. 33, intracellular signaling often involves changes to proteins. For some proteins, these changes make the protein go from inactive to active. For other proteins, these changes make the protein go from active to inactive. Some common changes to intracellular signaling proteins include:

(a) **Phosphorylation**, or attachment of phosphate (PO_3^{2-}) groups to certain amino acids in a protein by other phosphate-attaching protein enzymes called **kinases**. The phosphate group is negatively charged, and its presence on a protein can affect how the protein folds up (for example by attracting positively charged amino acids and repelling negatively charged amino acids on the protein) and does its job. Other enzymes called **phosophatases** act in the opposite way to remove phosphate groups from certain target proteins. Biologists tend to talk about kinases much more than phosphatases, but rest assured that the corresponding phosphatates are there, like dust bunnies lurking under the bed.

(b) **Metal ion binding** to a protein. Like phosphates, metal ions are electrically charged, so their presence or absence can affect the folded shape and hence the function of a protein. Calcium ions are the most commonly added and removed metal ions, but zinc, magnesium, iron, and others are used by certain proteins.

(c) **GDP vs. GTP binding** to a protein. Converting guanosine triphosphate (GTP) to guanosine diphosphate (GDP) releases the energy stored in one phosphate bond. These reactions are used to power some enzymes in a cell, but whether a protein is bound to a fully charged GTP or a spent GDP is also used as a signal that can activate or deactivate the protein. To switch between the two states, the triphosphate bond can be broken to a diphosphate plus energy, or the protein can release the spent GDP and grab a fresh GTP. Lurking in the background are Guanosine Exchange Factors (GEFs), which help to switch out the old GDP for a new GTP, and sometimes GTPase-Accelerating Proteins (GAPs) that speed the conversion of GTP to GDP to limit how long the GTP-binding protein is active.

(d) **Cleavage** or cutting of the protein by **proteases**, protein enzymes that cut up other proteins for a living. Most signaling-related proteases only cut certain proteins at certain amino acids under certain conditions, rather than randomly gnawing on everything.

(e) **Multimerization**, or clumping together of two or more proteins (called **subunits** in this context) to form a larger protein **multimer** or **complex**. More specifically, something with two subunits is called a **dimer** (and its formation is called **dimerization**), something with three subunits is called a **trimer** (and its formation is called **trimerization**), etc. In some cases the subunits are different from each other (e.g., a **heterodimer**), and in other cases they are identical (e.g., a **homodimer**). Fortunately that is all legal now.

(f) **Translocation** or travel by a protein from one region to another within the cell. This process is most common with **transcription factors** that often hang out in the cytosol when they are inactive, then when activated move into the nucleus and turn certain genes on or off (increase or decrease the number of proteins made by those genes).

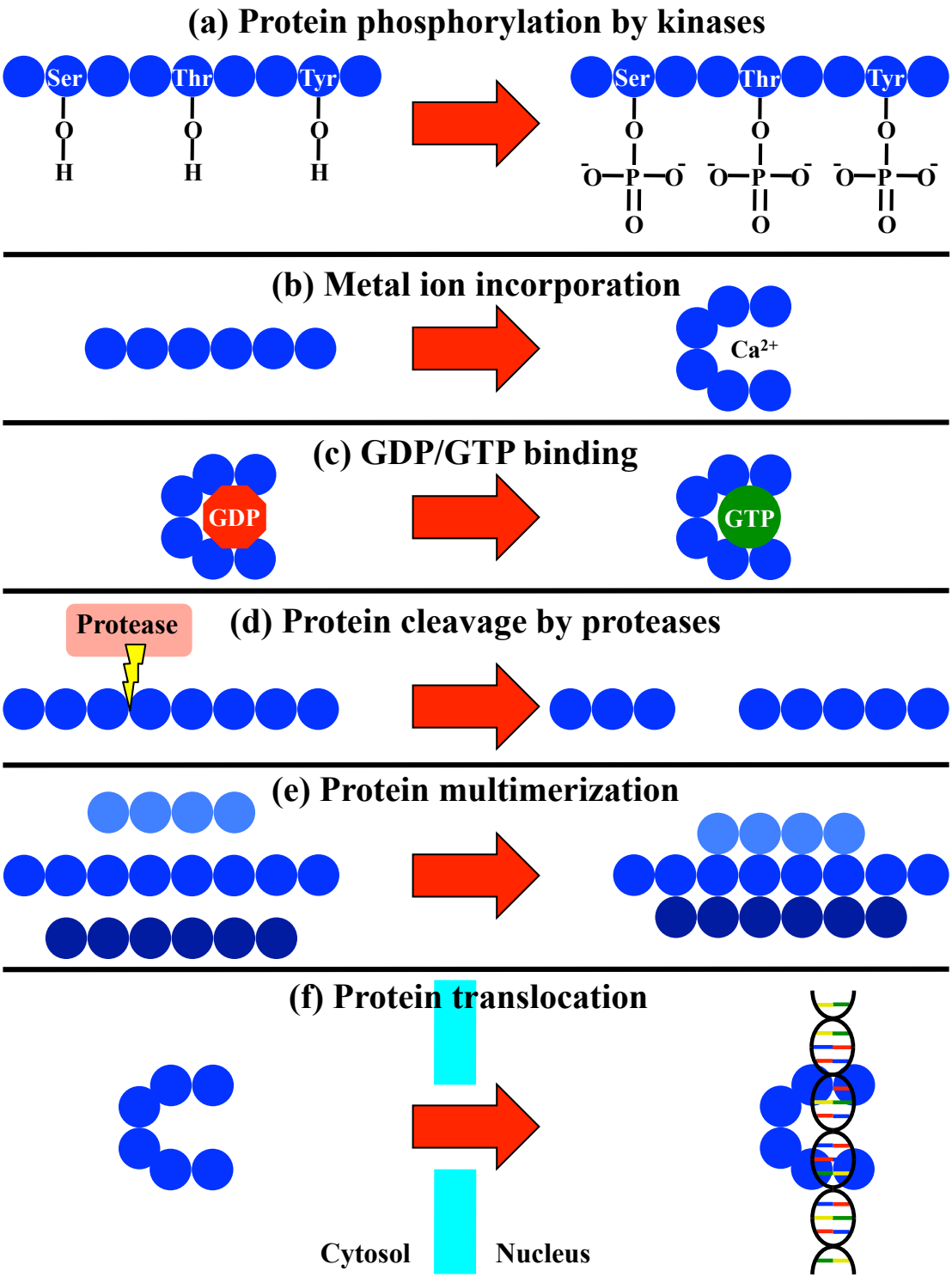


Fig. 33. Intracellular signaling can involve changes to proteins including (a) phosphorylation by kinases, (b) metal ion incorporation, (c) GDP vs. GTP binding, (d) cleavage by proteases, (e) multimerization, and (f) translocation to a different region of the cell.

As shown in Fig. 34, intracellular signaling also frequently involves release and detection of small molecules or **second messengers** (the "first messenger" being the intercellular signal) including:

(a) Cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP) are individual nucleotides or bases of RNA that are linked in a circle to themselves, instead of linked to other nucleotides as in a strand of RNA. The enzyme adenylyl cyclase converts adenosine triphosphate (ATP) into cAMP, and similarly the enzyme guanylyl cyclase converts guanosine triphosphate (GTP) into cGMP. Upstream, cAMP or cGMP production can be stimulated (or in some cases inhibited) by Gα proteins from activated G protein coupled receptors (GPCRs). Downstream, cAMP activates protein kinase A and cGMP activates protein kinase G (with the letters in the kinases' names corresponding to the nucleotide type).

(b) Inositol triphosphate (IP_3) and diacyl glycerol (DAG) are second messengers that can be created by the enzyme phospholipase C (PLC). PLC gnaws on phosphatidyl inositol diphosphate (PIP_2) phospholipids in the plasma membrane, releasing the hydrophilic head of the phospholipid (IP_3) into the cytosol, and leaving the hydrophobic twin tails of the phospholipid (DAG) floating around in the membrane. IP_3 opens gated calcium ion channels to flood the cytosol with calcium. DAG helps to activate protein kinase C (PKC), which also requires the calcium released by IP_3 (hence the C in the kinase's name). If this sounds dull, chemicals like phorbol esters that mimic DAG but are always "on" are very potent at causing cancer, which shows how important these pathways are for normal operation of cells.

(c) Calcium ions (Ca^{2+}) are normallly scarce in the cytosol of cells, so their presence is a strong signal. Cells keep most of the calcium ions pumped out of the cell or pumped into the endoplasmic reticulum for storage. However, if other signaling molecules (such as IP_3) open gated calcium-selective ion channels in the plasma membrane and endoplasmic reticulum membrane, all of that calcium rapidly floods into the cytosol. A number of proteins change their shape and hence their activity when one or more charged calcium ions bind to them; these target proteins include protein kinase C, calmodulin (which in turn activates many other proteins, including calmodulin kinases), and troponin (which makes muscle cells contract).

(d) Arachidonic acid is one of the long hydrophobic lipid tails from the phospholipids in plasma membranes. The enzyme phospholipase A_2 can whack it off of a complete phospholipid in the membrane, or the enzyme DAG lipase can whack it off of a membrane diacyl glycerol (DAG) that has been previously pruned by phospholipase C. Either way, the arachidonic acid can serve as a second messenger floating around the cytoplasm. Cycloxygenase enzymes (COX-1 and COX-2) can convert arachidonic acid into prostaglandins or thromboxanes, hormones that can have a variety of effects. Alternatively lipoxygenase enzymes can convert arachidonic acid into leukotrienes, which are used to send certain signals in the immune system.

Cellular pathways basically act as analog computers to weigh various inputs and decide on the best course of action. As shown in Fig. 35, pathways may contain any or all of the following features:

(a) Signal amplification, in which each active signaling molecule in one step activates several molecules in the next step, and each of those activates several molecules in the following step.

(b) Positive or negative feedback, in which activation of a signaling molecule either stimulates or inhibits activation of more copies of that signaling molecule.

(c) Branching, in which an initial signal has several different effects in the cell.

(d) Convergence, in which stimulatory or inhibitory signals from different pathways converge on the same target molecules, as the cell decides among several possible courses of action.

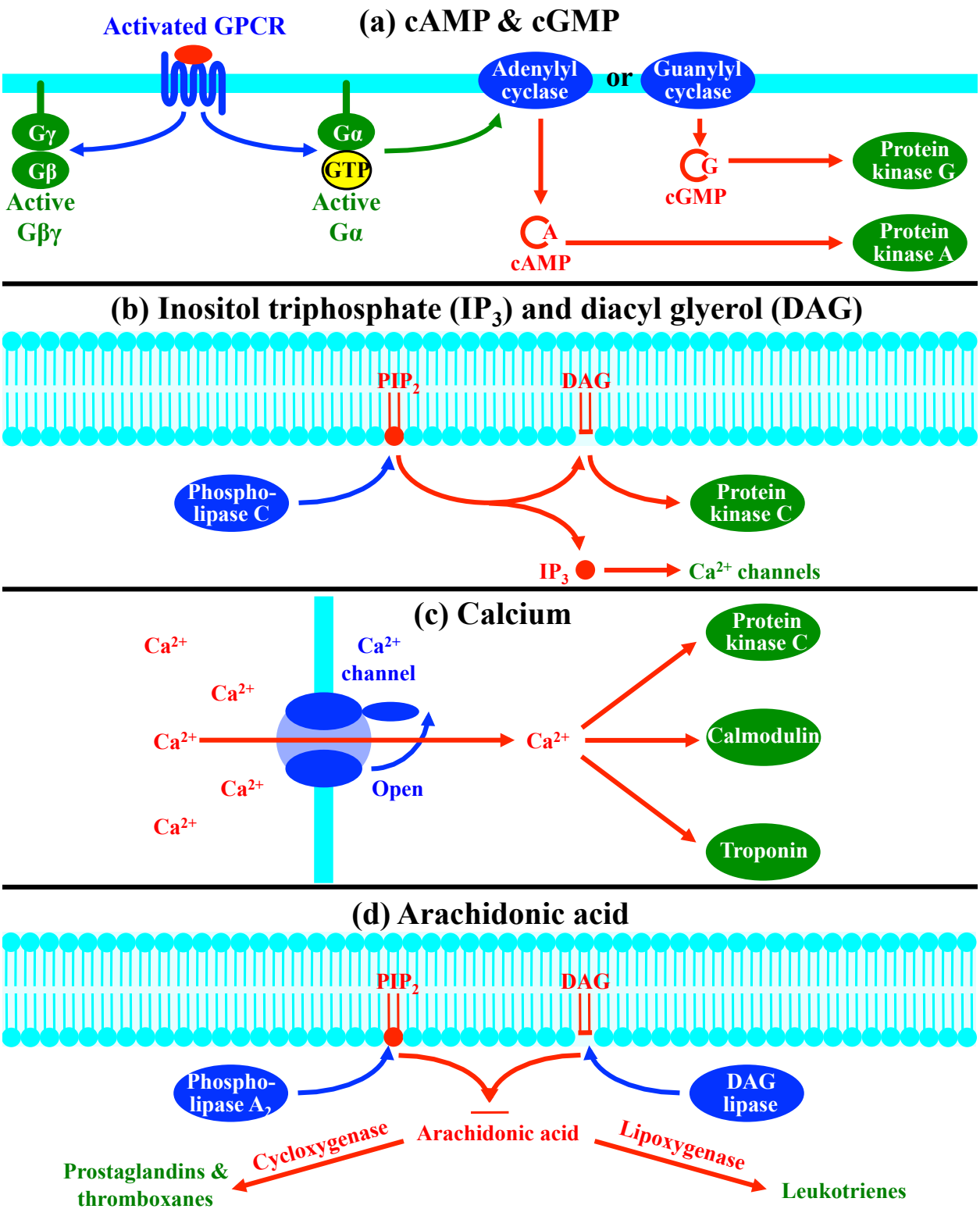


Fig. 34. Intracellular signaling can involve release and detection of small molecules: **(a)** cyclic adenosine or guanosine monophosphate (cAMP or cGMP), **(b)** inositol triphosphate (IP_3) and diacyl glycerol (DAG), **(c)** calcium ions (Ca^{2+}), and **(d)** arachidonic acid.

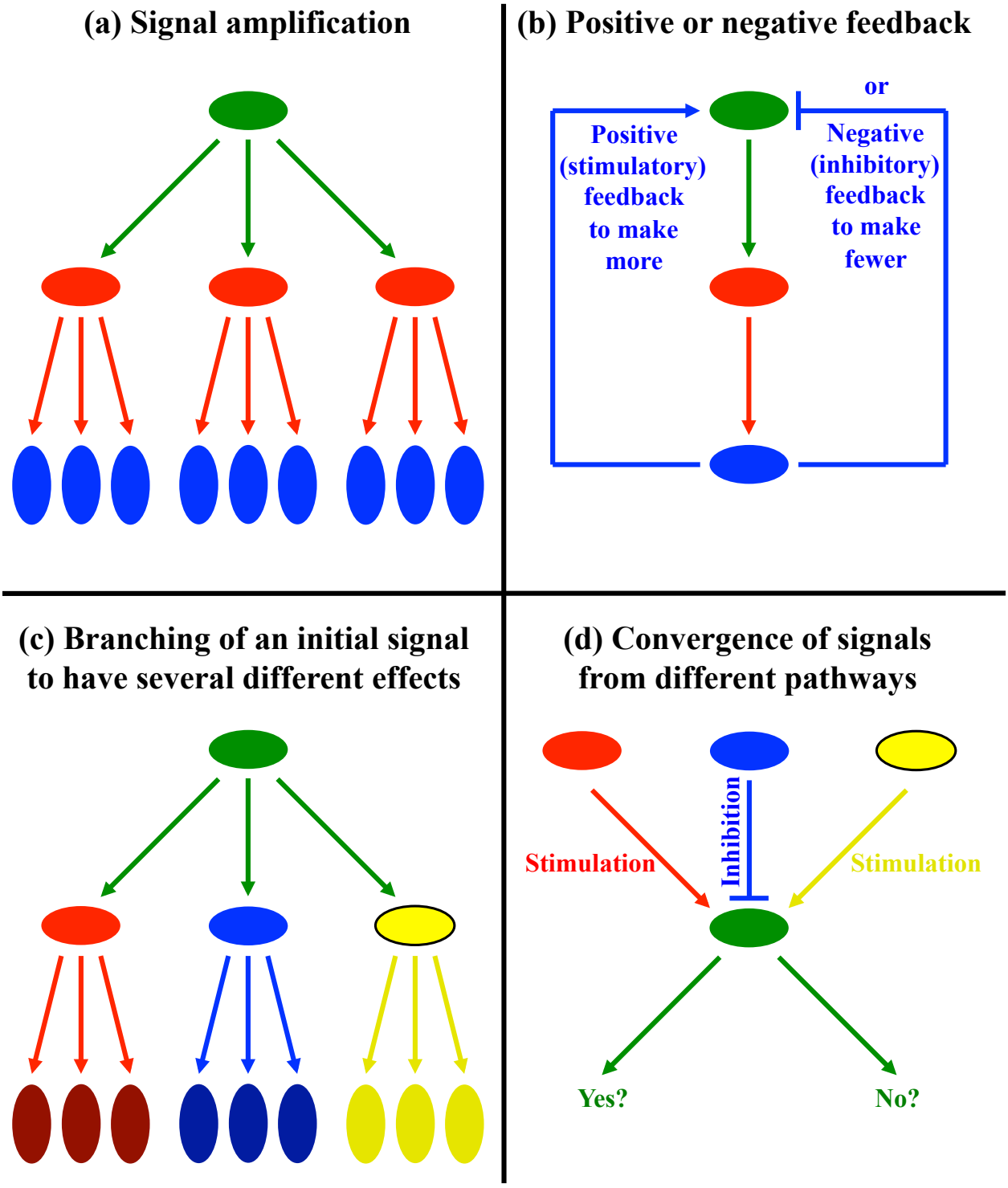


Fig. 35. Cellular pathways may include analog computing features such as: **(a)** signal amplification, **(b)** positive or negative feedback, **(c)** branching of an initial signal to have several different effects, and **(d)** convergence of stimulatory or inhibitory signals from different pathways on the same target molecules.

2.5 Heat Shock and Unfolded Protein Response Pathways

Cells have several pathways that help them survive stressful conditions that deviate from the comfy physical and chemical environmental conditions that they expect. These include the heat shock and unfolded protein response pathways.

Proteins must fold up correctly to do their individual jobs in a cell. As shown in Fig. 36, if elevated temperatures, heavy metal poisoning, or other environmental stresses make proteins unfold or misfold, various heat shock proteins (including HSP40, HSP70, and HSP90, where the number indicates the approximate size in kilodaltons, or thousands of protons + neutrons total) either refold the proteins or send the proteins to the proteasome for destruction. When HSPs grab unfolded proteins, they release Heat Shock Factor 1 (HSF1) subunits, which trimerize, enter the nucleus, and get phosphorylated (not necessarily in that order–the exact order of events is somewhat unclear) and activate genes in the nucleus to make more heat shock proteins. Eventually when there are plenty more HSPs than unfolded proteins, the idle HSPs grab all the HSF1 subunits, the alarm bells go off, and the system resets. Even under normal non-stressed conditions, HSPs are very important to help new proteins fold properly as they are being made by the ribosomes.

As shown in Fig. 36, unfolded or misfolded proteins can also occur in the endoplasmic reticulum (ER), which processes some fraction of the proteins produced by the ribosomes. The ER has its own heat shock proteins, most prominently one called BiP (Binding Immunoglobulin Protein, also called GRP78 just to be confusing–it is basically the ER equivalent of HSP70). BiP and other ER heat shock proteins either refold wayward proteins or send them off to the proteasome to be destroyed. By convention, the emergency response to misfolded proteins in the cytosol is called the heat shock response, and the emergency response to misfolded proteins in the ER is called the unfolded protein response, but they both involve the same problem and similar solutions.

Normally unneeded copies of BiP are bound to the internal ER domains of several sensor proteins, including PERK, IRE1, and ATF6. If BiP heat shock proteins get called away to deal with misfolded proteins in the ER, that sets off alarms with the three sensor proteins:

- **PERK** (Protein-kinase-R-like Endoplasmic Reticulum Kinase) receptors that are abandoned by BiP group together, allowing their outside cytosolic kinase domains to phosphorylate each other and eIF2α, an important subunit of the elongation initiation factor that helps ribosomes make proteins. Phosphorylated eIF2α stops production of most new proteins, allowing the ER's unfolded protein response pathway time to catch up and refold or destroy the misfolded proteins. However, phosphorylated eIF2α actually lets ribosomes make more ATF4 (Activating Transcription Factor 4) protein, a transcription factor that enters the nucleus and controls unfolded protein response genes to make more response proteins like BiP and minimize production of nonessential mRNAs and proteins until the problem is solved. ATF4 also induces production of CHOP (C/EBP Homology Protein), another transcription factor that can activate pro-apoptotic genes (e.g., Bax and Bid–we'll get there in Section 2.7) to kill the cell if the unfolded protein problem cannot be fixed in time.

- **IRE1** (Inositol-Requiring Enzyme 1–most of these names are gibberish, so don't worry about what the letters stand for) receptors that are left home alone by BiP also group together and also mutually phosphorylate their cytosolic kinase domains. Then they help splice XBP1 mRNA to make XBP1 protein, another transcription factor that controls unfolded protein response genes, and they help degrade most other mRNAs to minimize production of nonessential proteins for a while.

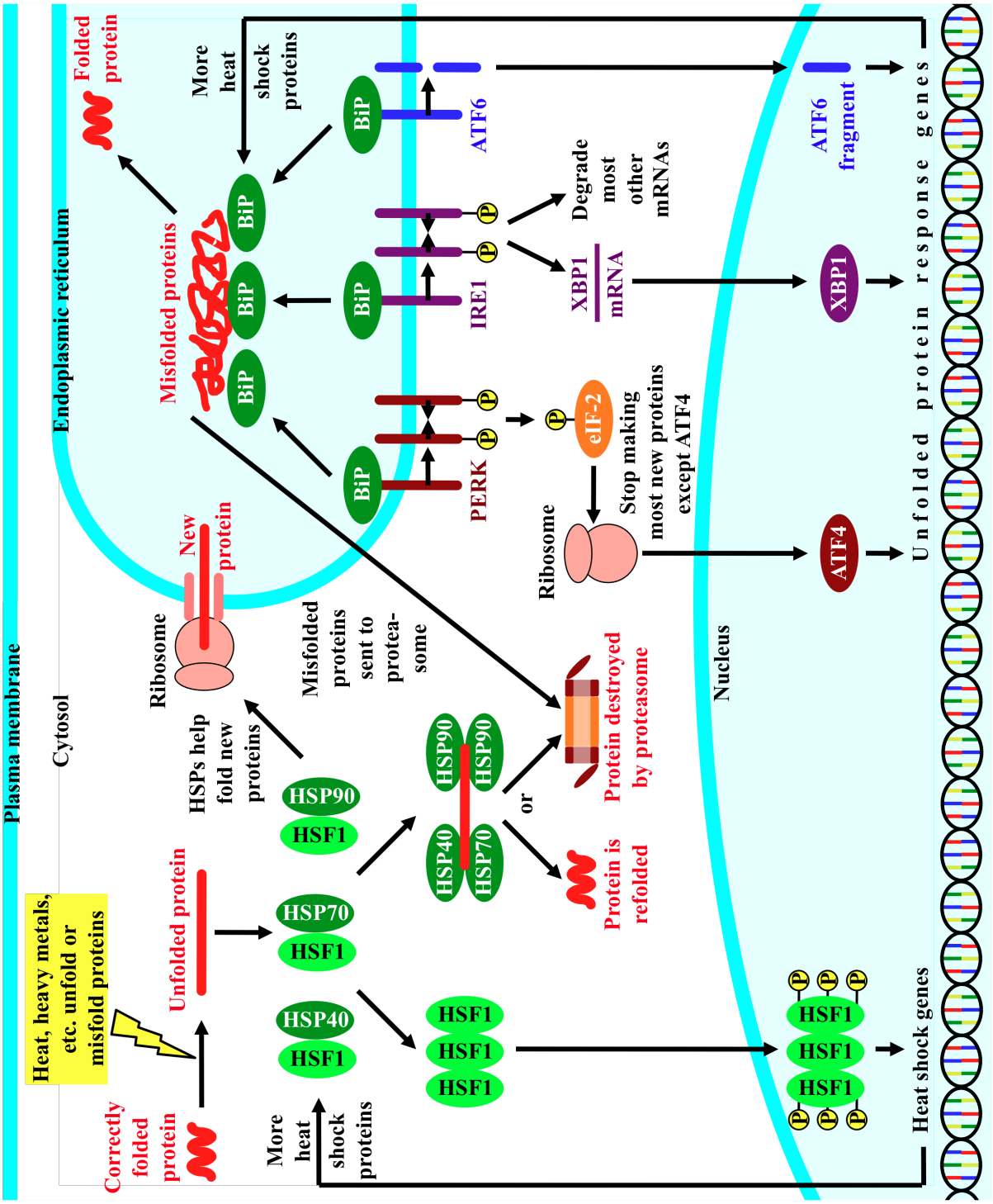


Fig. 36. Heat shock and unfolded protein response pathways. Proteins must fold up correctly to do their individual jobs in a cell. If elevated temperatures, heavy metal poisoning, or other environmental stresses make proteins unfold or misfold, various heat shock proteins (HSPs and BiP) either refold the proteins or send the proteins to the proteasome for destruction. When HSPs grab unfolded proteins, they release sensor proteins that activate genes in the nucleus to make more heat shock proteins until the problem is solved.

- **ATF6** (Activating Transcription Factor 6) receptors that are abandoned by BiP take a quick trip from the ER to the Golgi, where they are cut to release the cytoplasmic domain or fragment of ATF6. This ATF6 fragment becomes another transcription factor that controls unfolded protein response genes.

2.6 Interferon and Inflammatory Pathways

Cells have several pathways that help to protect them from infectious pathogens or from toxic chemicals, including the interferon and inflammatory pathways. The interferon pathway is a way for pathogen-infected cells (such as cell 1 in Fig. 37) to send interferon signaling proteins to nearby uninfected cells (like cell 2 in Fig. 37) to warn them that the Red Coats are coming and that they need to bolster their defenses.

Animal cells contain a number of Toll-Like Receptors (TLRs) that act as sensors to detect different broad classes of pathogens, including bacteria, viruses, fungi, and protozoa. Humans have ten TLRs as listed in Table 2. Note that some TLRs are located on the cell surface, where they can detect pathogens outside the cell. Other TLRs are located in endosomes (Fig. 37), where they can detect pathogens that try to use the endocytic pathway to sneak inside cells.

Toll-like receptor pair	Detects	Location
TLR1 + TLR2	Bacterial lipopeptides/peptidoglycans	Cell surface
TLR2 + TLR2	Gram+ bacterial peptidoglycans, fungal zymosan, protozoan GPI anchors	Cell surface
TLR3 + TLR3	Viral dsRNA	Endosome
TLR4 + TLR4	Gram- bacterial lipopolysaccharides	Cell surface
TLR5 + TLR5	Bacterial flagellin	Cell surface
TLR6 + TLR2	Bacterial lipopeptides	Cell surface
TLR7 + TLR7	Viral ssRNA	Endosome
TLR8 + TLR8	Viral ssRNA	Endosome
TLR9 + TLR9	Bacterial and viral DNA, protozoan hemozoin	Endosome
TLR10 + TLR10	Protozoan profilin	Endosome

Table 2. Human toll-like receptors (TLRs).

Pathogens or pathogen components activate TLRs by binding to and pulling together two TLRs (usually of the same type, but sometimes of different types as listed in Table 2). The interior cytoplasmic domains of the TLRs bind to and activate a series of proteins (MyD88, IRAK, TRAF6, and TAK1 in the particular case shown in Fig. 37). The last one, TGFβ-Activated Kinase 1 or TAK1, is a kinase that helps to phosphorylate and bring together two subunits of the Interferon Response Factor transcription factor (sometimes two IRF7 subunits, sometimes two IRF3 subunits, and sometimes an IRF7 and an IRF3, depending on the exact circumstances). The phosphorylated and dimerized IRF7/3 transcription factor enters the nucleus, activates genes for interferon alpha or beta (IFNα or IFNβ), and interferon proteins are produced and secreted by the infected cell to warn nearby uninfected cells.

In an alternative signaling pathway, activated TLRs can signal through TRIF and the TBK1 kinase to activate IRF7 or IRF3 transcription factors. In another alternative pathway, activated TLRs can signal through MyD88/IRAK/TRAF6/TAK1 to activate NF-κB transcription factors, which initiate an inflammatory response as will be discussed shortly. In any event, if TLRs find pathogens from any broad classes on the cell surface or in the endosomes, they set off a lot of alarm bells.

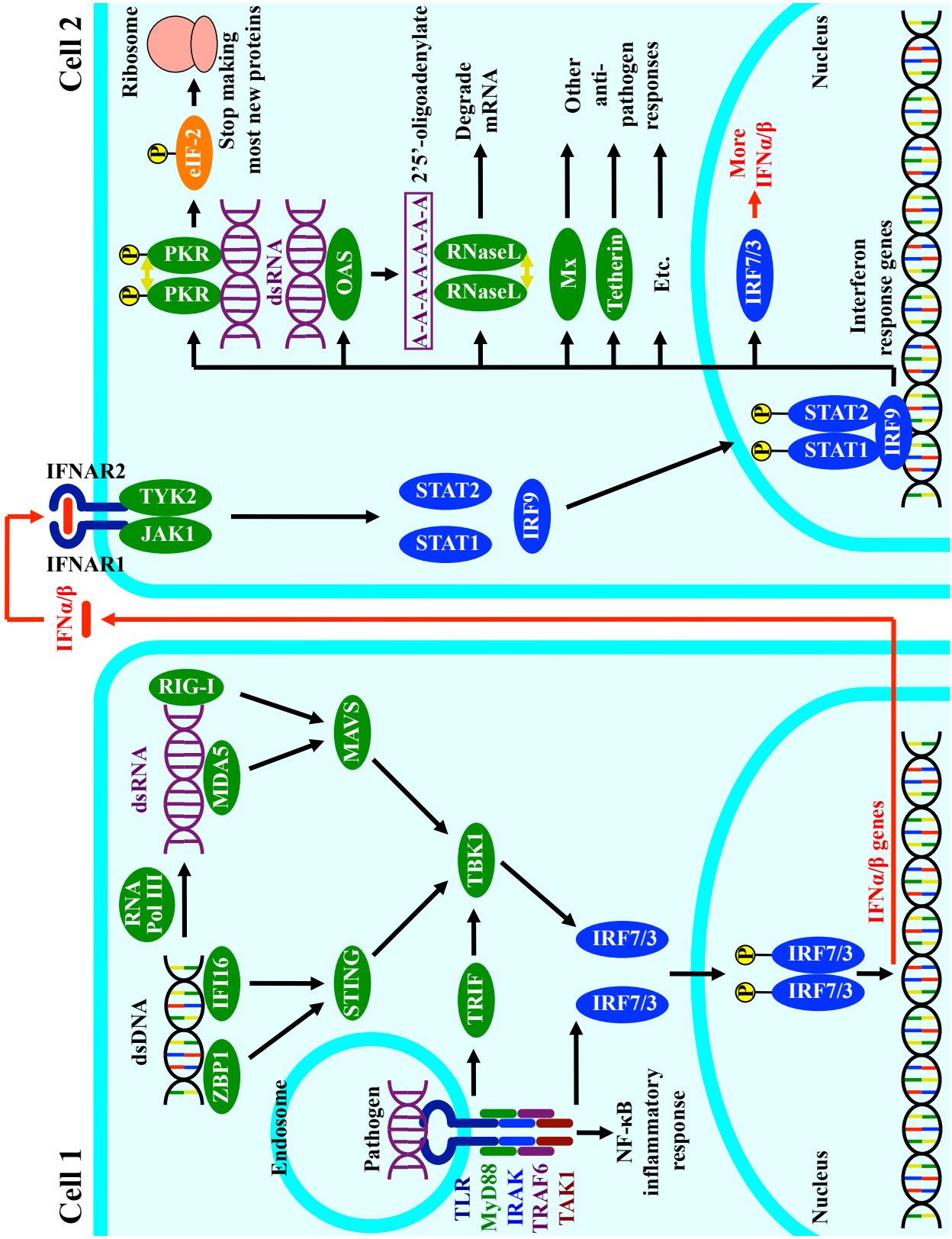


Fig. 37. Infected cell 1 produces interferon α or β to warn uninfected cell 2.

Animal cells also contain a number of sensors for pathogen DNA or RNA floating around in the cytosol, some of which are listed in Table 3:

Receptor	Detects
RIG-I	Uncapped 5' triphosphate ends of viral ssRNA or dsRNA
MDA5	Viral dsRNA
ZBP1/DAI	Cytoplasmic DNA
IFI16	Cytoplasmic DNA
Etc.	Cytoplasmic nucleic acids from pathogens

Table 3. Human cytosolic sensors for DNA or RNA from pathogens.

A cell's own DNA should be safely contained within its nucleus and mitochondria (or chloroplasts in plant cells), so any DNA floating around in the cytosol is a sign of a viral infection, other pathogen infection, or serious damage to that cell or nearby cells. As shown in Fig. 37, cytosolic DNA sensors like ZBP1 (also called DAI), IFI16, and others bind to cytosolic DNA and then signal through the STING protein and TBK1 kinase to activate IRF7/3 and interferon production.

Likewise, a cell's own RNAs in the cytosol should be single-stranded (or double-stranded but < 22 nucleotides long) and capped with a special structure at the upstream 5' end. MDA5 is a cytosolic sensor that recognizes pathogen RNA that is long and double-stranded, and RIG-I recognizes pathogen RNA that is single-stranded or double stranded but has uncapped 5' triphosphate ends. The cytosolic RNA polymerase III can even convert cytosolic pathogen DNA to RNA that then activates MDA5 or RIG-I. Once activated, MDA5 and RIG-I signal through the MAVS (Mitochondrial Antiviral Signaling) protein and TBK1 kinase to activate IRF7/3 and interferon production.

As shown on the right side of Fig. 37, nearby cells detect IFNα or IFNβ and respond by increasing the amounts of proteins that can inhibit pathogen infections. On a systemic level, the body's response to interferon is that feverish, tired, aching, run-over-by-a-bus feeling you sometimes get when you have just come down with a virus, even though you aren't yet that stuffed up from the actual virus. If interferon makes you feel that bad, just imagine how it makes the virus feel.

On a cellular level, IFNα or IFNβ binds to interferon alpha receptors 1 and 2 (IFNAR1 and IFNAR2) on the cell surface and pulls them together. Janus Kinase 1 (JAK1) and Tyrosine Kinase 2 (TYK2) that are bound to the internal cytosolic domains of the interferon receptors are brought close together, where they phosphorylate each other and then phosphorylate STAT1 and STAT2 proteins. Phosphorylated STAT1 and STAT2 plus IRF9 then join together to form a transcription factor, head for the nucleus, and activate interferon response genes (genes containing an Interferon Stimulated Response Element or ISRE sequence in their promoters). These genes encode a variety of defense proteins, including:

- **Protein kinase R (PKR)** binds to long dsRNA made by viruses; close proximity of multiple PKRs on the same dsRNA causes their kinase domains to phosphorylate each other and then eIF2α, an important subunit of the elongation initiation factor that helps ribosomes make proteins. Phosphorylated eIF2α stops production of most new proteins, including proteins that viruses are trying to produce.
- **Oligoadenylate synthases (OASs) and RNase L**. If any of several OASs binds to long dsRNA made by viruses, the OASs start to produce 2',5'-oligoadenylate (2-5A), a weird RNA-like second messenger. Multiple RNase Ls bind to 2-5A, dimerizing and activating their RNase (RNA-degrading) domains, which destroy most mRNAs, including viral mRNAs.
- **Mx proteins** are currently not well understood, but they appear to interfere with assembly of new viral protein capsids, the "body" of a virus that protects the virus's genes inside.

- **Interferon-stimulated gene 15 (ISG15)** is also not well understood, but it encodes a ubiquitin-like tag that is added to other proteins to increase the life span of antiviral proteins and/or interfere with viral proteins.
- **Tetherin and vipirin** proteins interact with the plasma membrane to make it harder for newly made viruses to leave an infected cell and infect other cells.
- There are > 300 other even less well understood interferon-stimulated defense genes!

Just to spill all the beans, there are other types of interferon. Interferons epsilon (ϵ), kappa (κ) and omega (ω) appear to be produced and used in very similar ways to interferon α and β. Interferon gamma (IFNγ) is produced by some immune system cells, binds to special receptors (IFNGR1 and IFNGR2) in nearby cells, signals through JAK1-JAK2 kinases and then STAT1-STAT1 transcription factors, and then activates defense genes that contain a Gamma Activated Sequence (GAS) in their promoters. Interferon λ appears to be use different receptors and cause somewhat different effects, but it is (you guessed it) currently not well understood.

Closely related to the interferon response is the inflammatory response, when tissues respond to infection or environmental stresses by becoming warmer, redder, and swollen. You may have experienced this response to a variety of stimuli, anything from an infected cut in the skin to a broken bone (even with no cuts) to an allergic reaction to something like homework. The inflammatory response overlaps with the interferon response yet differs, among other ways, by its ability to respond to a wide range of environmental stresses other than infectious pathogenic organisms. And whereas heat shock pathways try to fix damage caused by environmental stresses (e.g., unfolded proteins caused by elevated temperatures), inflammatory pathways respond to environmental stresses by initiating actions that can cause damage to that cell and even nearby cells (e.g., elevated temperature), but that in the end will hopefully eliminate the environmental factors.

Figure 38 shows an overview of the inflammatory pathways. Inflammatory signaling molecules called cytokines or interleukins sent by nearby cells are detected by receptors on a cell's surface. There are several different inflammatory cytokines and specialized receptors for each one, but Fig. 38 shows the specific example of interleukin-1β (IL-1β), which activates the IL-1β receptor by binding to and pulling together two identical subunits. The interior cytoplasmic domains of the IL-1β receptor bind to and activate a series of proteins (MyD88, IRAK, TRAF6, and TAK1 in this particular case). The last one, TAK1, is a kinase that helps to phosphorylate and bring together three subunits (IKKα, IKKβ, and NEMO–thanks, Disney!) to form a new functional kinase, IKK (Inhibitor of Kappa Kinase). IKK then phosphorylates IκB (Inhibitor of κ [Greek letter kappa] B), causing it to release the NF-κB (Nuclear Factor κ B) transcription factor. The phosphorylated IκB get ubiquitinated and destroyed by the proteasome, and NF-κB heads for the nucleus.

As shown in Fig. 38, the same response can be triggered by TLRs (which can also initiate the interferon response) that detect pathogens, or by cytosolic NOD (Nucleotide Oligomerization Domain, Table 4) receptors that detect a variety of pathogens and inflammation-inducing chemicals.

NOD	Detects	Activates
NOD1	Gram- bacterial diaminopimelic acid	NF-κB transcription factors
NOD2	Gram+ bacterial muramyl dipeptide	NF-κB transcription factors
NOD3/NLRC3	Inflammatory chemicals or pathogens	NF-κB transcription factors
NOD4/NLRC5	Inflammatory chemicals or pathogens	NF-κB transcription factors
NOD5/NLRX1	Inflammatory chemicals or pathogens	NF-κB transcription factors
CIITA	Digested pathogen components	RFX5 transcription factor

Table 4. Human NOD receptors.

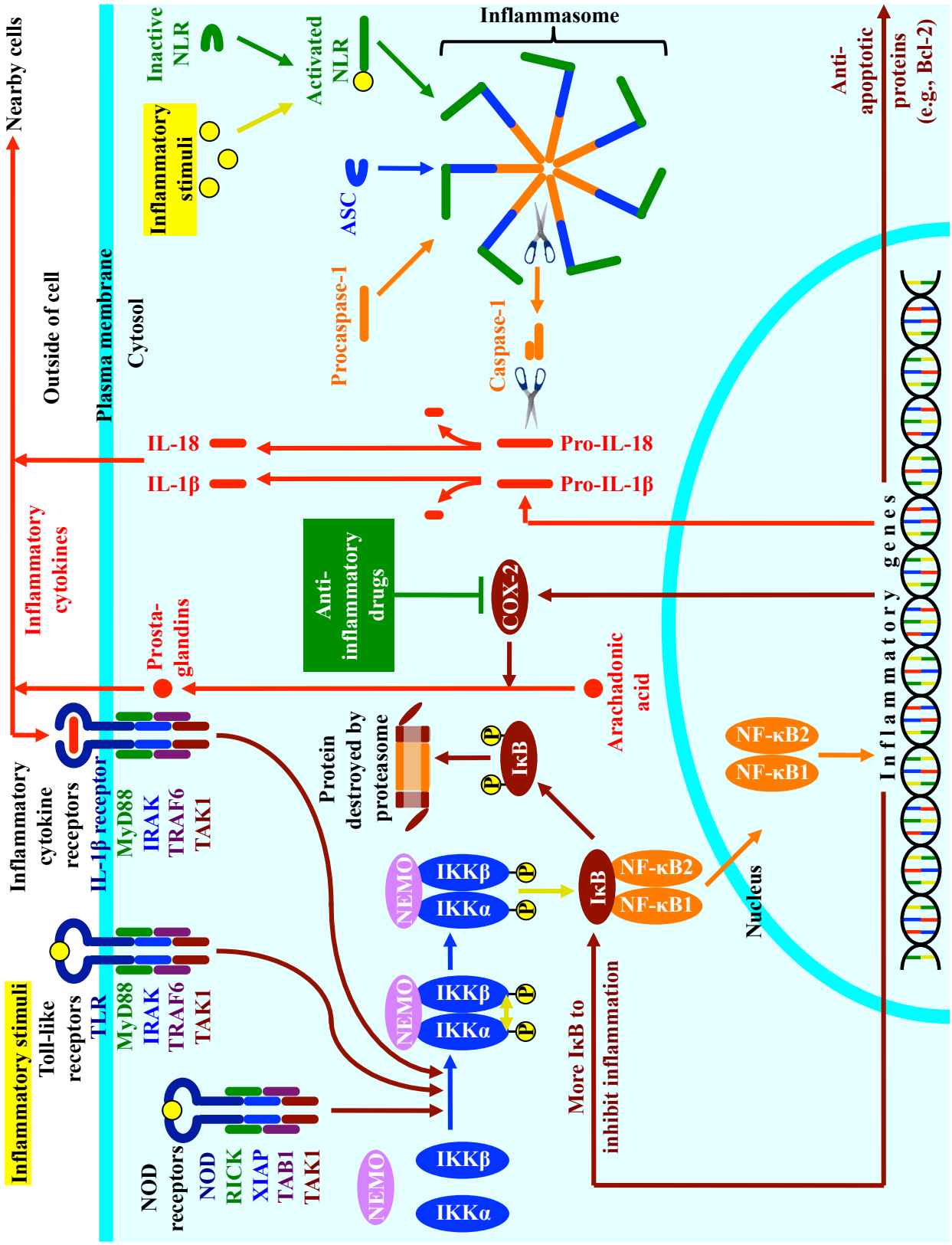


Fig. 38. Inflammatory pathways. Various inflammatory stimuli cause NF-κB to activate inflammatory genes, including cytokines that can trigger inflammatory responses in nearby cells.

There are five different NF-κB subunits in mammals (NF-κB1, NF-κB2, RelA, RelB, and c-Rel), which can form a bewildering number of homo- and hetero-dimers to control slightly different sets of inflammatory genes. Among other things, they can increase production of the three different versions of IκB proteins that normally bind and inhibit them (IκBα, IκBβ, and IκBγ), in order to ensure that the inflammatory response will be short-lived.

NF-κB inflammatory transcription factors also activate a gene to produce cyclo-oxygenase-2 (COX-2), a porphyrin-containing enzyme that converts arachidonic acid (a lipid derived from plasma membrane phosopholipids) into prostaglandins, inflammatory cytokines that are secreted by the cell and then detected by specialized G-protein-coupled receptors on the same cell or nearby cells. Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) like aspirin, ibuprofen, and acetaminophen inhibit COX-2. Corticosteroid antiflammatories like cortisone and COX-2 inhibitors like celecoxib also block COX-2, but can have a number of other often undesirable side effects.

As shown on the right side of Fig. 38, a wide variety of inflammatory stimuli ranging from irritating chemicals to components of invading microorganisms can bind to various corresponding NOD-Like Receptors (NLRs, Table 5). Activated NLRs then bind to ASC (Apoptosis-associated Speck-like protein containing a CARD–eyeroll!) and procaspase-1 to assemble a seven-spoked wheel called an inflammasome with the procaspases at the center. The **procaspases** are weakly active proteases that cleave or cut each other into their fully active forms, caspase-1. (We'll learn more about caspases in Section 2.7.)

If inflammatory stimuli have activated NF-κB, it will cause production of inactive inflammatory cytokines, including pro-IL-1β and pro-IL-18. If additional inflammatory stimuli have activated caspase-1, it will cleave these inactive cytokines into their active forms (e.g., IL-1β and IL-18), which are secreted and detected by the same cell or nearby cells.

NOD-like receptor	Detects	Adaptor	Activates
NLRP1	Gram+ bacterial components	ASC	Caspase-1
NLRP2	Inflammatory chemicals or pathogens	ASC	Caspase-1
NLRP3	Chemical crystals, pathogens	ASC	Caspase-1
NLRP4	Inflammatory chemicals or pathogens	ASC	Caspase-1
NLRP5	Inflammatory chemicals or pathogens	ASC	Caspase-1
NLRP6	Inflammatory chemicals or pathogens	ASC	Caspase-1
NLRP7	Inflammatory chemicals or pathogens	ASC	Caspase-1
NLRP8	Inflammatory chemicals or pathogens	ASC	Caspase-1
NLRP9	Inflammatory chemicals or pathogens	ASC	Caspase-1
NLRP10	Inflammatory chemicals or pathogens	ASC	Caspase-1
NLRP11	Inflammatory chemicals or pathogens	ASC	Caspase-1
NLRP12	Inflammatory chemicals or pathogens	ASC	Caspase-1
NLRP13	Inflammatory chemicals or pathogens	ASC	Caspase-1
NLRP14	Inflammatory chemicals or pathogens	ASC	Caspase-1
IPAF/NLRC4	Bacterial flagellin	Sometimes w/ NAIP	Caspase-1
NAIP	?	Sometimes w/ IPAF	Caspase-1
AIM2	DNA	ASC	Caspase-1

Table 5. Human NOD-like receptors (NLRs).

2.7 Cell Death Pathways

Cells can get depressed and commit suicide. If you watch too much reality TV, your neurons may lose hope and decide to end it all. The cell suicide pathway is called **apoptosis** or sometimes **programmed cell death**, and is shown in Fig. 39.

The key components in apoptosis are certain proteases (proteins that cleave or cut up other proteins for a living) called **caspases** or cysteine-aspartic proteases, since they recognize and only cut at certain cysteine and aspartic acid sequences of amino acids in proteins. There are at least half a dozen apoptosis-inducing caspases in mammalian cells. (There are other caspases that induce inflammation instead of apoptosis, as described in Section 2.6.) To avoid any accidents, caspases normally float around inside cells in a relatively inactive form, called procaspases. Procaspases are only weakly proteolytic (able to cleave proteins), but if multiple procaspases are brought close together, they cleave each other into two major pieces, reassemble into their fully active form, and then chew up everything in sight.

One method of triggering apoptosis is called the **intrinsic pathway**, since it can all happen inside the cell itself. If a cell becomes damaged or sick, its mitochondria may also be damaged and may leak cytochrome c molecules, one of the main components in the respiratory pathway (Section 1.8). If a cell is damaged but its mitochondria are not, protein channels called Bax (and Bak, Bad, Bid, Bok, and other close cousins) in the outer mitochondrial membrane may release cytochrome c molecules anyway. To make sure cytochrome c doesn't leak when it's not supposed to, rival proteins called Bcl-2 (and Bcl-xL, Bcl-w, and other kin) keep the Bax channels from opening. Many abnormalities in DNA and other cellular processes are detected by the protein p53, when then proceeds to activate pro-apoptotic genes in the nucleus, making more apoptosis-inducing proteins like Bax and fewer apoptosis-preventing proteins like Bcl-2 until the ship finally decides to sink. As will be discussed in Section 3.3, p53 and the intrinsic pathway are especially important for catching and killing misbehaving precancerous cells from the inside before they become fully cancerous cells; without them, cancer would be far more common than it is.

If cytochrome c molecules are released into the cell's cytosol, they wake up a dormant protein called Apaf-1 (Apoptotic Protease Activating Factor 1), which grabs both a cytochrome c and a procaspase-9. Seven cytochrome c/Apaf-1/procaspase-9 assemblies form a wheel-like structure called an **apoptosome**. The procaspase-9 proteins are at the center of the wheel, where they cleave or cut each other into their fully active caspase-9 forms.

Active caspase-9 proteins then cleave inactive procaspase-3 into active caspase-3 proteins. This is called a protealytic cascade or caspase cascade, since one active caspase can activate many other caspases in a chain reaction.

Active caspase-3 kills the cell by cutting up essential proteins in and around the cell nucleus. One protein that is destroyed by caspase-3 is ICAD (Inhibitor of Caspase Activated DNase). With ICAD history, CAD (Caspase Activated DNase) is then free to slice the DNA in the nucleus into confetti. To make sure that the DNA cannot be repaired, caspase-3 also destroys PARP (Poly-ADP Ribose Polymerase), an important DNA repair enzyme. Caspase-3 even cuts up lamin, which forms the nuclear lamina protein web that supports the nuclear membrane. Caspase-3 destroys a number of other targets too, but you get the idea–mass destruction.

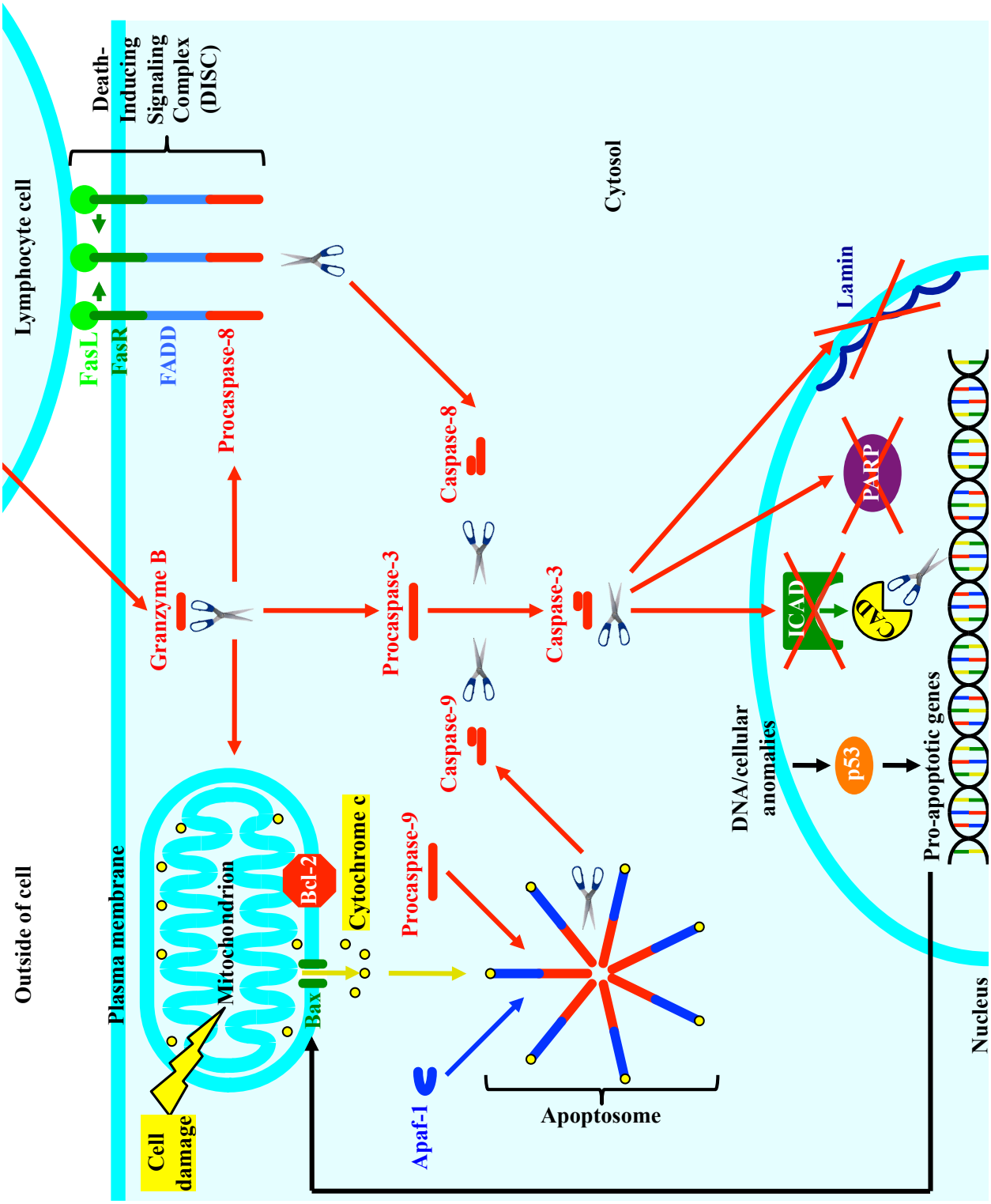


Fig. 39. Apoptosis cell death pathway.

Another method of triggering apoptosis is called the **extrinsic pathway**, since it requires intiation from something outside the cell. If lymphocytes or white blood cells in the immune system detect that a cell is infected with a virus or becoming cancerous, they can use the extrinsic pathway to order that cell to commit hara-kiri. FasL (Fas Ligand) proteins on the lymphocyte can bind to FasR (Fas Receptor) proteins on the plasma membrane of the target cell, generally in groups of three. Inside the target cell, FasR grabs a protein called FADD (FLICE Activated Death Domain– just go with it), which in turns grabs procaspase-8. When the FasR receptors outside the cell are bound and brought close together, the procaspase-8 proteins inside the cell are brought close enough together to cleave each other into their fully active forms. The clump of proteins that brings together multiple copies of procaspase-8 is called the Death-Inducing Signaling Complex or DISC. Hey, in science if you discover it, you get to name it whatever the heck you want.

Active caspase-8 cleaves and activates caspase-3, which kills the cell just as in the intrinsic pathway.

There are several different FasR-like receptors that respond to different pro-apoptotic signals from the immune system, including TNF-α (Tumor Necrosis Factor alpha), TRAIL cytokine, and others. But they all work in a very similar fashion, drawing together several cell-surface receptors that are linked by FADD and other adaptor proteins (with other silly names like TRADD, CRADD, RAIDD, etc.) to procaspase-8.

A more creative way for lymphocytes to kill a cell, especially if the cell is behaving so badly that it has eliminated its FasR and FasR-like receptors, is to inject the cell with granzyme B. Granzyme B is a protease that is very similar to caspases. When active granzyme B proteins are injected into a cell (often with help from another protein called perforin to get through the plasma membrane), they can cleave a number of targets that initiate apoptosis, including mitochondria and procaspases.

Although we have focused on caspases 8 and 9 as initiator caspases that can intially trigger apoptosis, caspases 2 and 10 can substitute for them or serve very similar roles. Likewise, caspase-3 is not the only effector caspase that carries out the final stages of apoptosis; caspases 6 and 7 can also do that. If you win an Oscar, you don't want to leave anyone out.

In addition to apoptosis, there are at least two other cell death pathways:

- **Necrosis** is cell death due to massive inflammation, basically the inflammatory pathway from Section 2.6 run amok.
- **Autophagy** is cell death by loading as much stuff into the autophagosomes and lysosomes (Section 1.7) as possible until the cell eats itself to death.

The pathways by which necrosis and autophagy are controlled and carried out are not currently well understood, so we will just sweep them under the rug for now and pretend that we really know everything.

3 Cell Division

Cells can divide to make more cells. Technically that is just another cellular pathway, but is so important and so complex that we will give it a whole section. Most cell division is **mitotic**, leading to two genetically identical copies of the original cell (Section 3.1). There are pathways for controlling cell division to ensure that it only happens when and how it is supposed to (Section 3.2), but when those pathways go haywire, cells can become cancer cells that divide and grow like weeds (Section 3.3). Finally, the special case of **meiotic** cell division leads to egg and sperm cells that are genetically different than the original parent cell (Section 3.4).

3.1 Mitotic Cell Division

One cell can divide into two cells, and then each of those can divide into two, and so forth. One round of cell division, the complete process in going from one cell to two and being ready for the next round, is called the **cell cycle**. Almost all cell division produces two cells that are genetically identical to the original parent cell (apart from any accidental mutations during DNA replication); this type of cell division is called **mitosis** or **mitotic cell division**. Figure 40 shows the cell cycle for mitosis. This discussion will focus on eukaryotic cell division, since prokaryotes (bacteria) just copy their DNA and split in two in a fairly simple fashion.

Cells that are just minding their business, not dividing, and not even thinking of dividing are said to be in the **Gap 0, G_0, resting, or quiescent phase**, depending on who you talk to.

If cells start thinking about dividing, they enter the **Gap 1 or G_1 phase**. Eventually they have to either change their minds and remain single, or commit to starting to divide.

Cells that commit to divide enter the **Synthesis or S phase**, in which all of their DNA is replicated. DNA is divided into several separate segments or chromosomes in the nucleus, and most cells are **diploid**, having two slightly different copies of each type of chromosome (and hence two copies of each gene). In the S phase, each chromosome is replicated, so now there are technically four copies of each chromosome, but the two genetically identical copies of each chromosome remain stuck together at a point called the **centromere**. This gives most replicated chromosomes an X shape if the centromere is somewhere in the middle, or a V shape if the centromere is at one end.

The cell enters the **Gap 2 or G_2 phase**, so named because nothing much seems to be happening, but in fact the cell is double-checking that all of the replicated DNA is correct, and growing in size to prepare for becoming two cells.

Finally, the cell enters the action-packed **Mitosis or M phase**. Most cells only have one centrosome, or center of the cytoskeletal fibers that criss-cross the inside of the cell. However, the centrosome got replicated when the DNA did, so now there are two centrosomes. Mitosis then proceeds through several steps:

- In **prophase**, the centrosomes move to opposite ends of the cell, and DNA tidies up to become well-organized chromosomes.
- In **metaphase**, the nuclear membrane disappears and cytoskeletal microtubule **spindle fibers** from each centrosome grab the chromosomes at their centromeres.
- In **anaphase**, the spindle fibers pull the replicated chromosomes apart, dragging a complete set of chromosomes to each side of the cell.
- In **telophase**, new nuclear membranes form around each complete set of chromosomes.
- In **cytokinesis**, the two nuclei each run off with half of the original cell's contents and plasma membrane, forming two new cells.

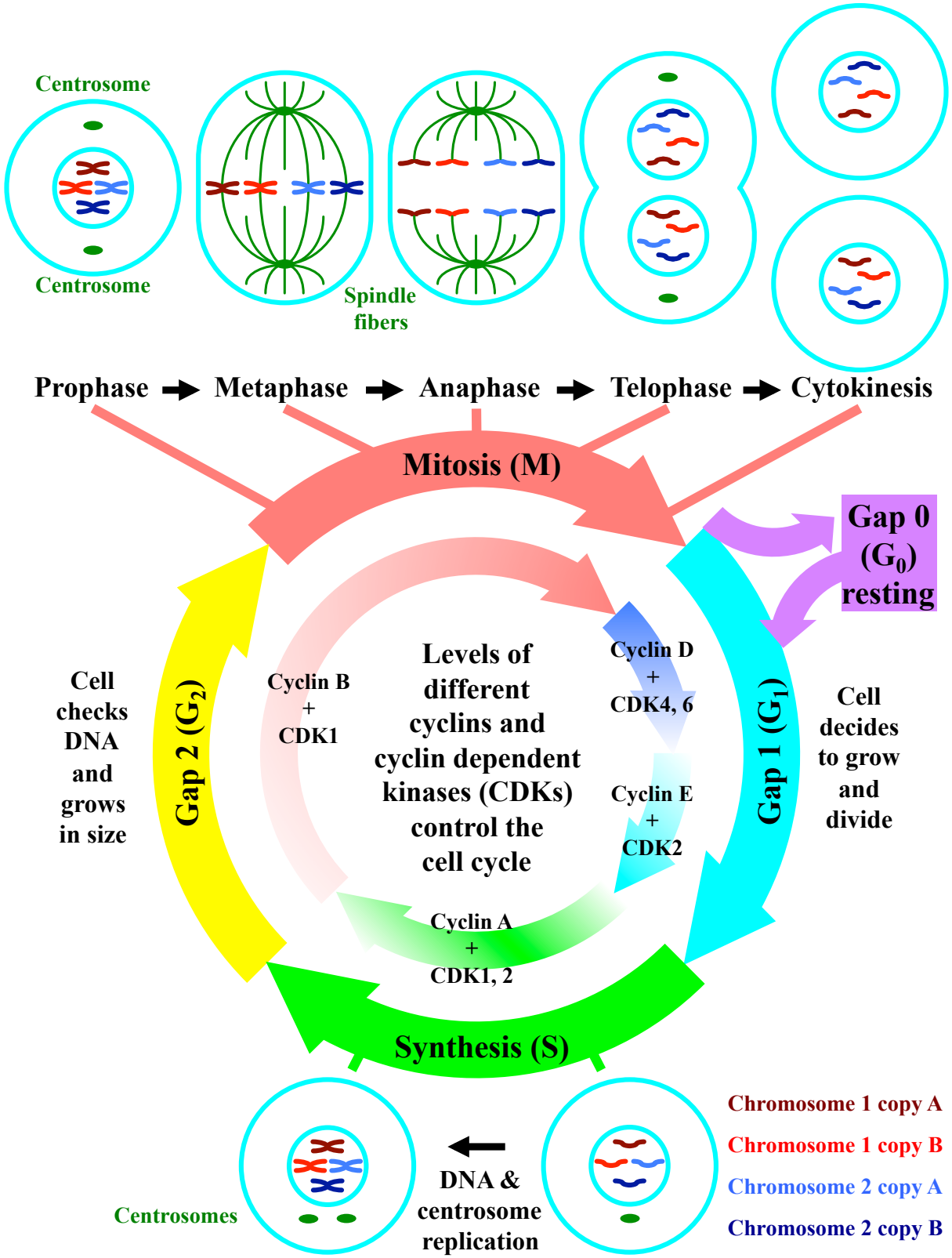


Fig. 40. Mitotic cell division proceeds through the stages of the cell cycle, which are controlled by levels of different cyclins and cyclin-dependent kinases (CDKs).

As shown in Fig. 40, the different phases of the cell cycle are controlled by different **cyclin** proteins, which are produced by the cell in preparation for the next phase and then immediately degraded by the proteasomes as soon as their phase is over. While each cyclin is around, it binds to and activates one or two corresponding **cyclin-dependent kinases (CDKs)**, which phosphorylate various signaling proteins and transcription factors to carry out that phase of the cell cycle. More details about those pathways for controlling the cell cycle will be discussed next.

3.2 Control of Mitotic Cell Division

The pathways that control cell division are not very creative–it seems as if almost every step is a protein kinase that phosphorylates the next kinase, and so on. However, understanding how these pathways work in normal cells is very important for understanding how to deal with cancer cells, in which these pathways are out of control, so do try to stay awake.

Figure 41 shows three of the major extracellular and cytoplasmic pathways that control cell growth and division:

(a) Contact-inhibited growth inhibition is the fancy name for the fact that if a cell is completely surrounded by other cells, it will usually decide that there isn't enough room for it to divide into two cells. For example, the cells in your liver won't keep making more liver cells if there isn't any available room in your liver for the extra cells. As discussed in Section 1.11, cells can physically contact adjacent cells via cell adhesion molecules such as cadherins. Contact inhibition is mediated by pathways such as the green one on the left side of Fig. 41. Cell-surface cadherins that interact with cadherins on a neighboring cell signal via proteins such as FRMD6, WWC1, and NF2 to phosphorylate MST, which is sometimes known as Hippo just to be confusing. MST then phosphorylates LATS, which is also known by unfortunate childhood nickname Warts. Anyhow, LATs then phosphorylates YAP (also known by the *nom de guerre* of Yorkie) and inactivates it. If the contact-mediated signaling had not done that, unphosphorylated YAP would have associated with TEAD to form a transcription factor, enter the nucleus, and activate genes for other transcription factors, cyclins, and other important stuff for cell growth and division. Thus physical contact with neighboring cells inhibits YAP and thereby inhibits cell growth and division.

(b) Growth factor pathways like the red one in the center of Fig. 41 ensure that the cell only divides when it is instructed to do so by certain growth factors sent out by other cells. Different types of cells (liver cells, skin cells, etc.) specifically detect and respond to different growth factors. Some of the most common growth factors are Vascular Endothelial Growth Factor (VEGF), Fibroblast Growth Factor (FGF), Platelet-Derived Growth Factor (PDGF), Epidermal Growth Factor (EGF), Colony-Stimulating Factor (CSF), and Stem Cell Factor (SCF). Binding to the growth factor brings together the two halves of the receptor specific for that growth factor, and close proximity makes the tyrosine kinases in the cytosolic domains of the receptors phosphorylate each other. The activated receptor acts via GRB2 and SOS proteins to activate Ras (Rat sarcoma) GTP/GDP binding protein by getting Ras to trade up its old GDP for a shiny new GTP. Ras helps phosphorylate Raf (Rapidly accelerated fibrosarcoma) kinase, which then causes a bewildering cascade of kinases (MEK, MKK, MEKK, ERK, JNK, etc.) phosphorylating each other. The ultimate result is to phosphorylate and dimerize two subunits for a transcription factor, Myc and Max together and/or Fos and Jun together. The phosphorylated, dimerized transcription factors enter the nucleus and activate genes for cell growth and division.

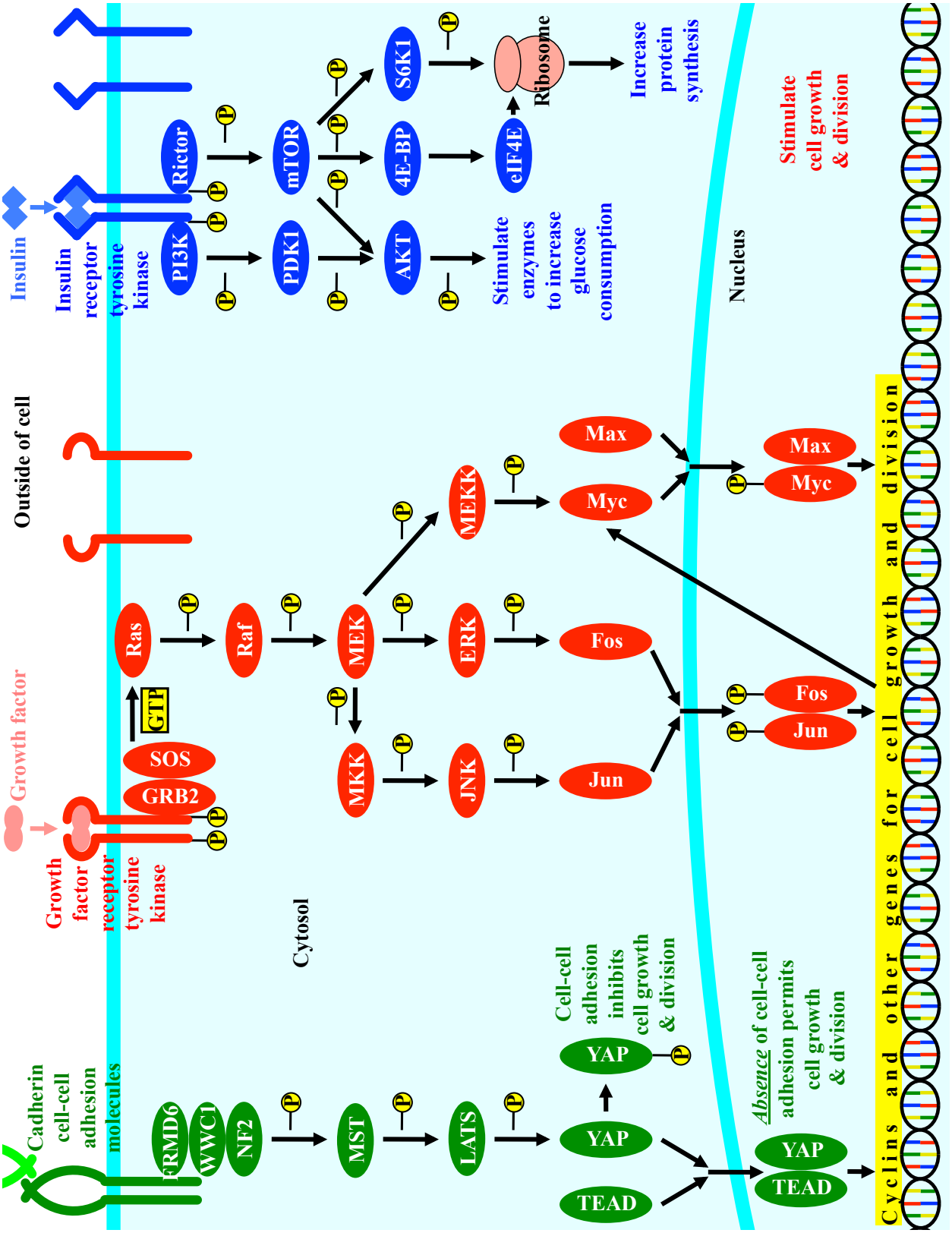


Fig. 41. Extracellular and cytoplasmic signaling pathways that control cell growth and division.

(c) Insulin and related pathways like the blue one on the right side of Fig. 41 control cell growth (how much a cell consumes and produces, and how large it gets), which isn't the same thing as cell division but is a necessary prerequisite for cell division. Insulin brings together the two halves of an insulin-binding receptor, thereby causing tyrosine kinases in the cytosolic domains of the receptor to phosphorylate each other and activate associated proteins such a PI3K (Phosphoinositide 3 Kinase) and Rictor. The subsequent chains of phosphorylation events activate AKT (Ak Thyoma or protein kinase B) kinase, which phosphorylates multiple targets to stimulate enzymes that increase the cell's glucose consumption, and mTOR (mammalian Target of Rapamycin), which phosphorylates multiple targets to increase the cell's level of protein synthesis.

Whereas Fig. 41 shows the cell growth and division pathways outside the cell and in the cytoplasm, it skimps on detail in the nucleus, but Fig. 42 shows the nuclear signaling pathways that control cell growth and division. As already mentioned, the different phases of the cell cycle are controlled by different cyclin proteins, which are produced by the cell in preparation for the next phase and then immediately degraded by the proteasomes as soon as their phase is over. While each cyclin is around, it binds to and activates one or two corresponding cyclin-dependent kinases (CDKs), which phosphorylate various signaling proteins and transcription factors to carry out that phase of the cell cycle.

Along the way in Fig. 42, there are several inhibitor proteins that prevent uncontrolled growth. One major example is the Rb (retinoblastoma) inhibitor, which normally binds to the E2F transcription factor to hold the cell in the G1 phase and prevent initiation of the next phases of the cell cycle. In the internal kinase cascade triggered by external growth factors, Rb gets phosphorylated and loses its grip on E2F. E2F is then free to activate transcription of the gene for cyclin E, the resulting cyclin E activates CDK2, and the train leaves the station.

Throughout the cell cycle, other inhibitor proteins are constantly checking for DNA damage, cell stress, or other problems, and they will pause the cell cycle if they find anything wrong. The M/R/N (MRE11/Rad50/Nbs1) complex and RPA (Replication Protein A) are key sensors for DNA damage. If they find damage, they activate ATM (Ataxia Telangiectasia M) and ATR (Ataxia Telangiectasia R) protein kinases, which both directly and indirectly activate a major inhibitor protein called p53. p53 is a transcription factor that can turn on genes to make p21 and other inhibitor proteins that stop most of the CDKs in their tracks and pause the cell cycle. If DNA repair enzymes cannot fix the problem within a limited period of time, p53 escalates the matter and turns on genes to make more pro-apoptotic proteins like Bax and Bid, causing the cell to kill itself. That may seem harsh, but in an organism composed of a gazillion cells, it is better for one cell with DNA damage to kill itself than to divide into two cells that may contain cancer-causing mutations.

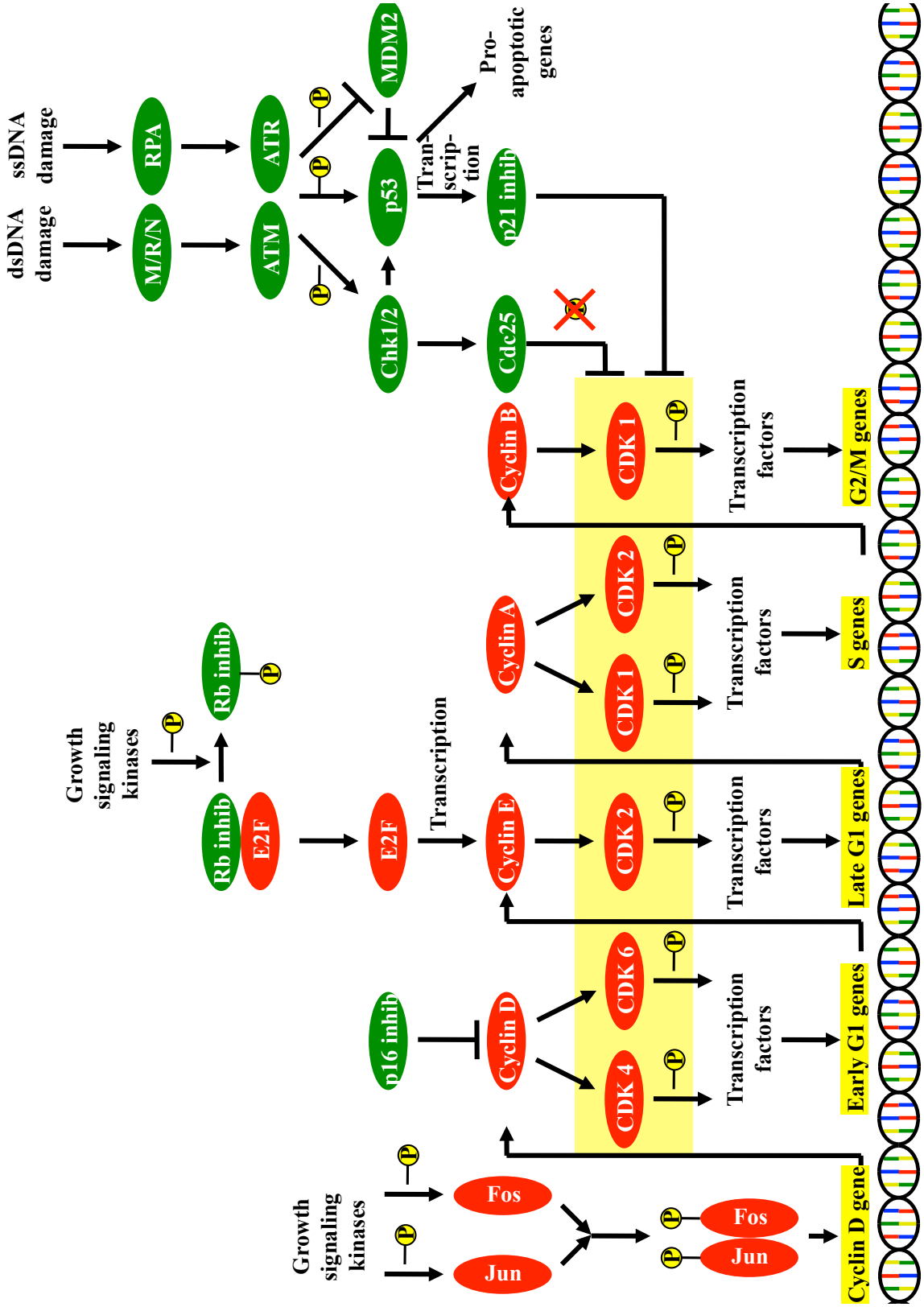


Fig. 42. Nuclear signaling pathways that control cell growth and division.

3.3 Uncontrolled Mitotic Cell Division–Cancer

Whereas normal cells only divide when they are supposed to, cancer cells divide uncontrollably, hogging space in the organ in which they originate and often then spreading to other parts of the body (a process called **metastasis**). Mutations in certain genes turn normal cells into cancer cells. Cancer-related genes are divided into two categories:

A. Proto-oncogenes stimulate cells to divide under the right conditions. If they are mutated to become **oncogenes** that are switched on all the time regardless of the conditions, they can contribute to a cell becoming a cancer cell. Oncogenes can be classified according to what role their products normally play in the cell growth pathway (Figs. 41-42). Some major human proto-oncogenes/oncogenes and the proteins they encode are listed in Table 6, along with treatments that inhibit each one. The treatments are either antibodies (proteins made by the immune system that specifically bind to certain other proteins) with names that end in -mab or small molecule drugs with names that usually (but not always) end in -nib.

B. Tumor suppressor proteins inhibit cells from dividing most of the time. If the genes encoding them are deleted or mutated to become inactive, the cell has fewer obstacles to becoming a cancer cell. Some major human tumor suppressors are listed in Table 7. The best treatments would be to insert functional tumor suppressor genes back into cancer cells, but unfortunately that is not yet practical with the current state of human gene therapy.

The mutation process is typically very slow and very random, and mutations in multiple genes are required for cancer, so cancer may or may not occur within specific people during their lifetimes. As will be discussed, a variety of environmental factors can create mutations and increase the probability of developing cancer.

Some people inherit cancer-promoting mutations from their parents. For example, a proto-oncogene might already be converted into an oncogene, or a tumor suppressor gene might already be knocked out. Usually those individual inherited mutations don't immediately cause cancer, but they put a person's cells one step closer to becoming cancer cells, and thus they increase the probability that that person will develop cancer at some point in their life.

Category	Oncogene	Therapeutics
Growth factor	PDGF/Sis	
	FGF/Int2	
	VEGF	Bevacizumab
Receptor tyrosine kinase	HER2/neu EGF receptor	Trastuzumab, pertuzumab
	ErbB1 EGF receptor	Panitumumab, cetuximab, gefitinib, erlotinib, afatinib
	Kit SCF receptor	Imatinib, dasatinib, nilotinib
	PDGF receptor	Sorafenib
	Fms CSF receptor	PLX3397
	VEGF receptor	Sorafenib
Intracellular receptor	Estrogen receptor	Tamoxifen, anastrozole, raloxifene
Regulatory GTPase	Ras	
	Gsα	
Kinase	Raf	Regorafenib, sorafenib
	B-Raf	Dabrafenib, vemurafenib
	Syk	
	Src	
	Btk	
	Abl	Imatinib
	MEK	Refametinib, selumetinib, trametinib
	Cyclin dependent kinase 1-6	
Cyclin	Cyclins A-E	
Apoptosis inhibitor	Bcl-2	
	Bcl-xL	
	MDM2	
Transcription factor	Fos	
	Jun	
	Myc	

Table 6. Some major human proto-oncogenes/oncogenes. Therapeutic antibodies end in -mab and therapeutic small molecules end in -nib or other endings. VEGF=Vascular Endothelial Growth Factor. FGF = Fibroblast Growth Factor. PDGF = Platelet-Derived Growth Factor. EGF = Epidermal Growth Factor. CSF = Colony-Stimulating Factor. SCF=Stem Cell Factor.

Category	Tumor suppressor	Therapeutics
Cell cycle	p53	
	Retinoblastoma (Rb)	
Contact inhibition	Cadherin 1 (CDH1)	
	Adenomatous Polyposis Coli (APC)	
DNA repair	Xeroderma Pigmentosum A-G	
	Ataxia Telangiectasia M	
	Ataxia Telangiectasia R	
	MLH1	
	MEN1	
	MSH2	
	Breast Cancer BRCA 1, 2	
Phosphatase	PTEN	

Table 7. Some major human tumor suppressors.

As listed in Table 7, tumor suppressors act in a variety of ways to inhibit cell division. Some facilitate cell-cell contact inhibition of division, some repair damaged DNA to prevent cancer-causing mutations, and some are phosphatases–protein enzymes that remove phosphates from other proteins (thus counteracting the cell-division-promoting effects of all the kinase proto-oncogenes listed in Table 6). However, two of the most important and most studied tumor suppressors directly help to control the cell cycle:

- The **Rb (retinoblastoma)** protein is a major tumor suppressor. Retinoblastoma (cancer of the retina at the back of the eye) develops if both copies of the Rb gene are defective, hence the name, but it plays a role in a wide variety of cancers. Random mutation during a person's lifetime may affect one copy of Rb, but rarely both copies. Inherited retinoblastoma is caused by already having a mutation that inactivates one copy of Rb. As shown in Fig. 42, the Rb protein binds to the E2F transcription factor to block the G1/S transition of the cell cycle. In normal cell proliferation, Rb is temporarily phosphorylated to transiently inactivate it and allow cell division. If the Rb protein is kidnapped by a tumor antigen or is defective due to a mutation, uncontrolled cell division can occur.

- **p53** is a multifunction tumor suppressor that is very important in preventing cancer. It recognizes a 10-nucleotide motif in some gene promoters, so it can activate or repress transcription of a variety of genes. As shown in Fig. 42, if p53 hears about any DNA damage, it will turn on genes to temporarily stop the cell cycle and repair the damage, or if that fails, activate genes to induce apoptotic cell death. Functional p53 transcription factor is a tetramer (composed of four identical subunits), so even if only one of the two gene copies is defective, tumor suppression ability is lost–most of the tetramers will contain at least one defective subunit. Loss of p53 allows cells with damaged DNA to divide, which enables pre-cancerous or cancerous cells to further mutate their genes and become even nastier.

Several different types of alterations to DNA can contribute to cancer:

- Mutations in proto-oncogenes that normally encode proteins that only induce cell division under the right conditions can create oncogenes that encode proteins that are always "switched on" and telling the cell to divide.
- Promoter and enhancer regions surrounding proto-oncogenes tell cells how much of the corresponding proteins to make, but mutations in those promoters or enhancers can cause cells to make too much of a growth-inducing protein.
- Cells can amplify or create extra copies of proto-oncogenes/oncogenes, causing production of larger amounts of the corresponding growth-inducing proteins.
- Cells can mutate tumor suppressor genes so that the proteins they make are inactive.
- Mutations in the promoter or enhancer regions for tumor suppressor genes can cause the cell to make too little of the corresponding tumor-suppressing protein.
- Deletions of tumor suppressor genes can entirely eliminate the tumor suppressors and give free reign to cancer.

Carcinogens are environmental factors that can cause or at least contribute to the development of cancer, including (A) radiation, (B) many chemicals, (C) a few viruses and at least one bacterium.

A. High-energy electromagnetic waves (ultraviolet, X-rays, and gamma rays) and high-energy particles (alpha, beta, and neutrons) can damage DNA by:

- Dimerizing adjacent thymine or other nucleotides in a DNA strand.
- Causing DNA strand breaks.
- Producing H_2O_2 or other reactive oxygen molecules that can cause oxidative damage to DNA.

Improper repair of DNA damage can lead to mutations, some of which may convert proto-oncogenes to oncogenes or inactivate tumor suppressor genes. Genetic defects in DNA repair pathways (such as xeroderma pigmentosum and ataxia telangiectasia) can make people especially susceptible to cancer.

B. Chemical carcinogens form a very long list and are difficult to classify into a few simple categories. Most (but not all) are initially safe and only become carcinogenic after they are metabolically activated by cytochrome P450 enzymes in a cell's endoplasmic reticulum or in the liver. Most (but not all) bind to DNA, causing mutations when cellular enzymes remove the carcinogenic molecules and repair the DNA. Some of the better known carcinogens are:

- Various polycyclic aromatic hydrocarbons in cigarette smoke.
- A number of heterocyclic amines in charred or smoked meat.
- Asbestos thermal insulation fibers that can cause lung inflammation.
- Various chemicals such as vinyl chloride that are associated with some plastics manufacturing or degradation.
- Some organic solvents such as benzene, gasoline, and formaldehyde.
- Some elements such as beryllium and arsenic.
- Some biological proteins such as aflatoxin produced by *Aspergillus* mold.

C. Tumor (or transforming) viruses and cancer-causing bacteria include:

- **Human papillomaviruses** can cause anything from warts to cervical cancer. Their DNA genome can integrate into cellular DNA chromosomes. Viral proteins E6 and E7 trigger degradation of p53 and RB tumor suppressors, respectively.
- **Merkel cell polyomavirus** causes some skin cancers. Its DNA genome can integrate into cellular chromosomes; its T antigens stimulate cell growth kinases and inhibit p53 and RB.
- **Epstein-Barr virus** can cause anything from brief mononucleosis to Burkitt's lymphoma or nasopharyngeal carcinoma. Its circular DNA genome can persist in infected cells, and its LMP1 protein stimulates growth signaling and inflammation and inhibits apoptosis.
- **Kaposi's sarcoma-associated herpesvirus** is best known for causing sarcoma in HIV patients. Its circular DNA genome can persist in infected cells. Its vCyclin protein stimulates cell division, its vBcl-2 protein inhibits apoptosis, and its LANA protein inhibits p53 and RB.
- **Hepatitis B virus** can cause liver cancer. All or part of its DNA genome can persist in infected cells. Its HBV X protein stimulates cell growth kinase signaling and inhibits p53-induced apoptosis, and virus-induced inflammation may promote mutation of liver cells.
- **Hepatitis C virus** can cause liver cancer and non-Hodgkin lymphoma. It is an RNA virus that can persist in cells; how it promotes cancer is currently not well understood.
- **Human T-lymphotropic virus** can cause leukemia. It is a retrovirus that copies its RNA genes into DNA and permanently inserts them into the genome of the white blood cells it infects. Its Tax protein in particular stimulates production of cellular growth factors and inhibits p53-induced apoptosis.
- ***Helicobacter pylori* bacteria** can cause anything from ulcers to stomach cancer. They can trigger inflammation and oxidative damage to DNA.

Viruses and bacteria will be covered in great gory detail in *Microbiology*.

3.4 Meiotic Cell Division

In mitotic cell division within an organism (Fig. 40 and left side of Fig. 43), the resulting cells have the exact same chromosomes as the original cell, barring any accidental mutations that occurred during DNA replication. Some organisms (most single-celled organisms, many plants, and many fungi) reproduce the whole organism that way, so that the descendants of that organism are **clones** or genetically identical copies of the original parent organism.

Cloning around makes it rather boring if everyone looks alike, though, so humans and lots of other critters are combinations of the chromosomes from their two parents. Most of these organisms are **diploid**–they have two copies of each chromosome, which have the same genes but are not necessarily genetically identical; the two chromosomes may contain slightly different versions of those genes, for example for different hair or eye color. Having two copies of each chromosome makes it very easy to get one copy from one parent and the other copy from the other parent. But you have four grandparents, and eight great-grandparents, and even more kinfolk further back in your family tree, and you may have some DNA from each one. How in the world does that math work out with only two copies of each chromosome?

The answer is that multiple chromosome copies from parents can mix and match pieces to create new versions of chromosomes for their children, through a special type of cell division called **meiosis**. Figure 43 shows meiosis on the right side, and for comparison old-fashioned mitosis on the left side. The chromosomes are contained in the nucleus most of the time, and each time the cells divide they go through all the individual steps of prophase/metaphase/anaphase/teletubby phase/etc. from Fig. 40. However, Fig. 43 is confusing enough as it is, so to keep things simple, we aren't showing the nucleus within the cells, and we aren't showing every little step of cell division along the way. You can fill in the details in your vivid imagination.

In both mitotis and meiosis, the process starts with a diploid cell having two copies of each chromosome. In both mitosis and meiosis, the first step is to replicate each chromosome. In mitosis, those replicated chromosomes are separated, and the cell divides into two cells having the same set of chromosomes as the original cell.

In contrast, in meiosis, after the chromosomes replicate, they do something weird. In a process called **crossing over**, the copies of chromosome 1 mix and match pieces with each other to create new patchwork versions of chromosome 1. Likewise, the copies of chromosome 2 mix and match pieces with each other, the copies of chromosome 3 mix and match with each other, and so on.

After all the chromosome hanky-panky is finished in meiosis, the chromosomes are divided up into two cells in the first meiotic cell division. But notice that the chromosomes are doled out in a very different way than in mitosis on the left. Then after the dust settles from the second meiotic cell division, there are four progeny cells. They are all **haploid** (having just one copy of each chromosome), and because of crossing over between chromosomes and random selection of which chromosome of each set goes where, these four cells are all genetically different.

These hapoid, genetically different cells are called **gametes** in general, or **egg** cells in females and **sperm** cells in males. Combining an egg from a mother and a sperm from a father yields a new dipolid cell that has two copies of each chromosome, with one copy from each parent, and portions of each chromosome copy derived randomly (through the magic of crossing over) from the grandparents without leaving anyone out. For information on how that one cell multiplies and becomes the whole you, you'll just have to wait until *Reproductive and Developmental Biology.* Hey, you always have to end with a cliffhanger...

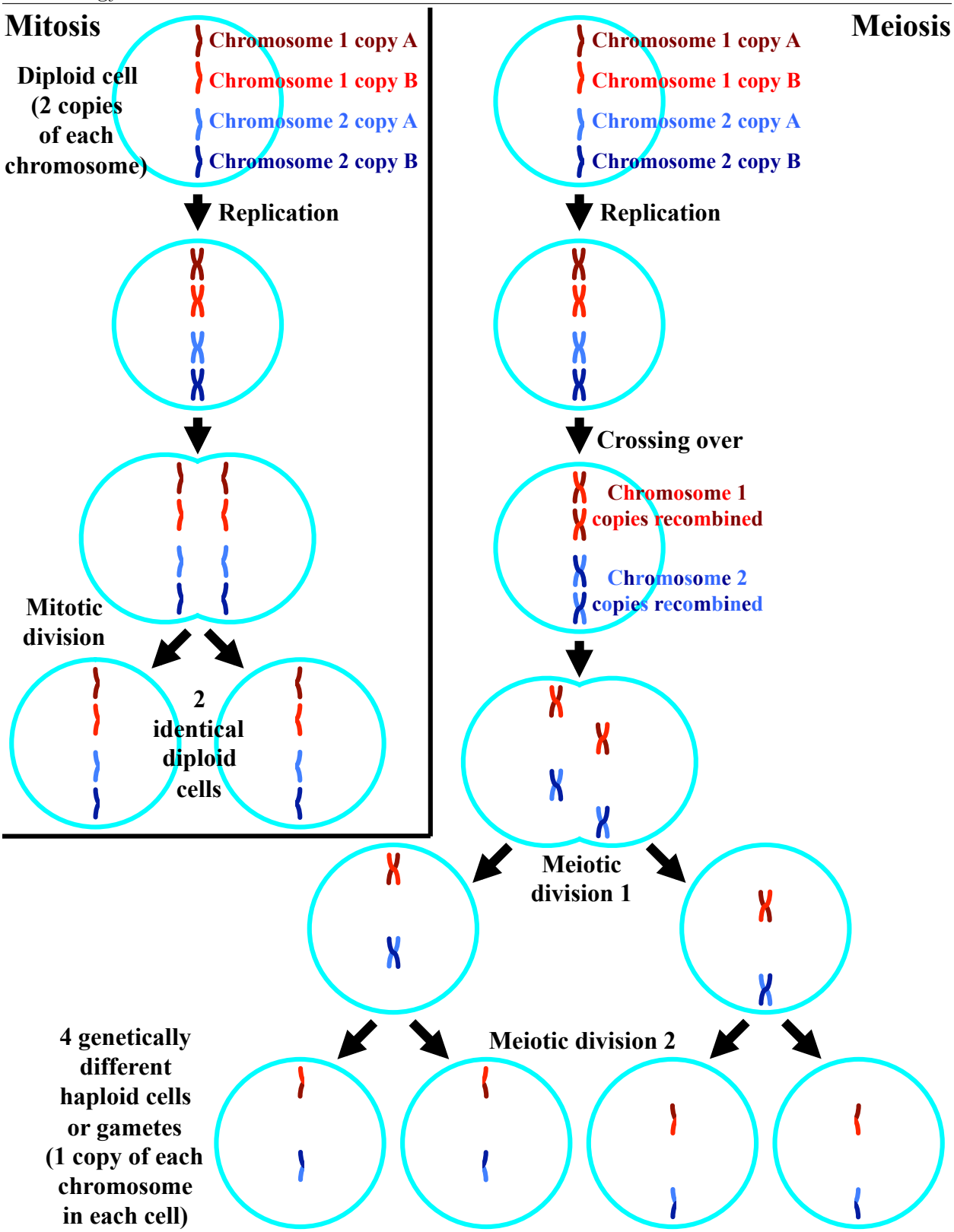


Fig. 43. Meiotic cell division (right) contrasted with mitotic cell division (left). For simplicity, nuclei are not shown and chromosomes are spread out.

References

[1] Bruce Alberts, Alexander Johnson, Julian Lewis, David Morgan, Martin Raff, Keith Roberts, and Peter Walter, *Molecular Biology of the Cell* (6th ed., Garland, 2014).

[2] Harvey Lodish, Arnold Berk, Chris A. Kaiser, Monty Krieger, Anthony Bretscher, Hidde Ploegh, Angelika Amon, and Matthew P. Scott, *Molecular Cell Biology* (7th ed., Freeman, 2012). These are the two major cell biology textbooks, which also give good overviews of molecular biology, biochemistry, and other related topics. In general, Alberts provides more detailed and comprehensive coverage than Lodish, but sometimes Lodish has something useful that is not in Alberts.

[3] Robert A. Weinberg, *The Biology of Cancer* (2nd ed., Garland, 2013).

[4] Lauren Pecorino, *Molecular Biology of Cancer: Mechanisms, Targets, and Therapeutics* (3rd ed., Oxford, 2012). These are the two major cancer textbooks. Pecorino is much shorter and easier to read, so Weinberg usually has more details, but sometimes Pecorino points out important things that Weinberg omits or obscures.

[5] Michael T. Madigan, John M. Martinko, Kelly S. Bender, Daniel H. Buckley, and David A. Stahl, *Brock Biology of Microorganisms* (14th ed., Benjamin Cummings, 2014).

[6] Joanne Willey, Linda Sherwood, Christopher J. Woolverton, *Prescott's Microbiology* (9th ed., McGraw-Hill, 2013). These are the two major microbiology textbooks, describing the functions and effects of bacterial cells in detail. They are fairly comparable, but sometimes one gives a better description of some aspect than the other.

[7] Russell Jones, Helen Ougham, Howard Thomas, and Susan Waaland, *The Molecular Life of Plants* (Wiley-Blackwell, 2012). This is the best book on plant cells, showing how their details are similar to and different from other types of cells.

[8] Gerhard Michal and Dietmar Schomburg (eds.), *Biochemical Pathways: An Atlas of Biochemistry and Molecular Biology* (2nd ed., Wiley, 2012). This book is invaluable for graphically showing the "wiring diagrams" of major pathways inside cells.

[9] Kathy Barker, *At the Bench: A Laboratory Navigator* (2nd ed., Cold Spring Harbor Laboratory Press, 2004). This is the best general introduction to biology lab methods, including common techniques for cell biology.

[10] Sean R. Gallagher and Emily A. Wiley (eds.), *Current Protocols: Essential Laboratory Techniques* (2nd ed., Current Protocols, 2012). This is probably the best single-volume collection of major biology lab methods, including techniques for cell biology.

[11] R. Ian Freshney, *Culture of Animal Cells: A Manual of Basic Technique and Specialized Applications* (7th ed., Wiley-Blackwell, 2016). This is the authoritative book on growing mammalian cells in the lab.

[12] Wojciech Pawlina, *Histology: A Text and Atlas: With Correlated Cell and Molecular Biology* (7th ed., LWW, 2015). Authored by Michael H. Ross for its earlier editions, this is the best book on histology, showing how different types of human cells and tissues look under the microscope and describing why they look that way.