protonation and deprotonation as the protons translocate through the pore into the lumen of the vacuole (Figure 11-14b). The rotation of the subunits closes access to the cytoplasm and traps the proton within the pump, and further rotation then releases the protons to the lumen of the vacuole.

ABC Proteins Export a Wide Variety of Drugs and Toxins from the Cell

About 50 different mammalian ABC proteins are now recognized, and mutations in these proteins have been linked to many human diseases (Table 11-3). In eukaryotic cells, ABC proteins localize not only to the plasma membrane but also to the membranes of many intracellular organelles. Several are expressed in abundance in the liver, intestines, and kidneys — sites where natural toxic and waste products are removed from the body. Substrates for these ABC proteins include sugars, amino acids, cholesterol, bile acids, phospholipids, peptides, proteins, toxins, and foreign substances. The normal function of ABCB1 most likely is to transport various natural and metabolic toxins into the bile or intestinal lumen for excretion or into the urine being formed in the kidney. During the course of its evolution, ABCB1 appears to have acquired the ability to transport drugs whose structures are similar to those of these endogenous toxins. Tumors derived from MDR-expressing cell types, such as hepatomas (liver cancers), are frequently resistant to virtually all chemotherapeutic agents and are thus difficult to treat, presumably because the tumors exhibit increased expression of ABCB1 or a related ABC protein.

TABLE 11-3 • Selected Human ABC Proteins

Protein	Tissue Expression	Function	Disease Caused by Defective Protein
ABCB1 (MDR1)	Many epithelia, blood-brain barrier	Exports glucosylceramides and lipophilic drugs	Inflammatory bowel disease
ABCB4 (MDR2)	Liver	Exports phosphatidylcholine into bile	
ABCB11	Liver	Exports bile salts into bile	Progressive familial intrahepatic cholestasis
CFTR	Exocrine tissue	Transports Cl ions	Cystic fibrosis
ABCDI	Ubiquitous in peroxisomal enzyme	Influences activity of peroxisomal enzyme that oxidizes very long chain fatty acids	Adrenoleukodystrophy (ADL)
ABCG5/8	Liver, intestine	Exports cholesterol and other sterols	β-Sitosterolemia
ABCA1	Ubiquitous	Exports cholesterol and phospholipid for uptake into high-density lipoprotein (HDL)	Tangier's disease
ABCA4	Retina	Transports N-retinyl-phosphatidylethanolamine	Stargardt's disease in photoreceptor cells (juvenile macular degeneration)

ABCA2	Brain, kidney, heart, lung	Exports cholesterol	Alzheimer's disease
ABCA3	Lung	Exports surfactant lipids	Surfactant metabolism dysfunction 3
ABCA12	Lung, skin	Exports lipids	Harlequin ichthyosis
ABCB4	Liver	Exports long-chain phosphatidylcholines	Progressive familial intrahepatic cholestasis 3
ABCC2	Liver, kidney, intestines	Exports bilirubin, bile salts	Dubin-Johnson
ABCD1	Ubiquitous	Exports very long chain fatty acids	Adrenoleukodystrophy
ABCG5	Liver, intestine	Exports cholesterol, plant sterols	Sitosterolemia
ABCG8	Liver, intestine	Exports cholesterol, plant sterols	Sitosterolemia, gallstones

As noted earlier, all members of the very large and diverse ABC superfamily of membrane transport proteins contain two transmembrane (TM) domains and two cytosolic ATP-binding (A) domains (see Figure 11-9). The TM domains, each built of 10 membrane-spanning α helices, form the pathway through which the transported substance (substrate) crosses the membrane (Figure 11-15a) and determine the substrate specificity of each ABC protein. The sequences of the A domains are approximately 30–

40 percent homologous in all members of this superfamily, indicating a common evolutionary origin.

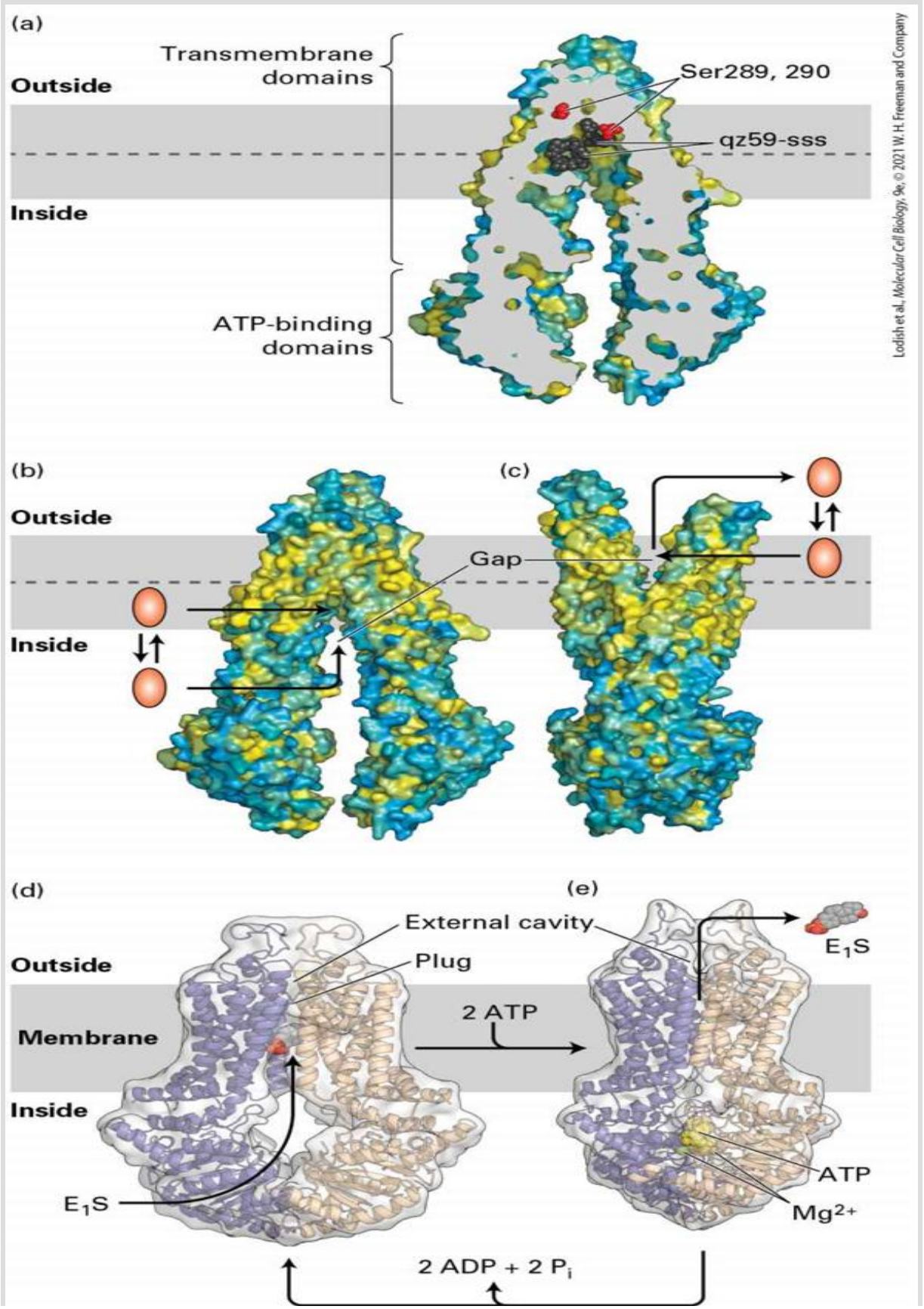

FIGURE 11-15 The multidrug transporter ABCB1 (MDR1): Structure and model of ligand export. (a) Cross-sectional view through the center of an ABCB1 protein bound to two molecules of a drug analog, qz59-sss (black), reveals the central location of the ligand-binding site in relation to the phospholipid bilayer: the central ligand-binding cavity is close to the leaflet-leaflet interface of the membrane. During transport, this binding cavity is alternately exposed to the exoplasmic and the cytosolic surface of the membrane. Serines 289 and 290 affect the ligand specificity of the transporter; they are shown as red spheres to highlight their juxtaposition to the bound ligand. Surface residues are colored yellow to denote hydrophobic and blue to denote hydrophilic amino acids. (b) Three-dimensional structure of ABCB1 with its ligand-binding site facing inward toward the cytosol. In this conformation, a hydrophilic ligand can bind directly from the cytosol. A more hydrophobic ligand can enter into the inner leaflet of the plasma membrane bilayer and then enter the ligand-binding site through a gap in the protein that is accessible directly from the hydrophobic core of the inner leaflet. (c) Model for the structure of ABCB1 with its ligand-binding site facing outward, based on the structures of homologous bacterial ABC proteins. When the protein assumes this conformation, the ligand can either diffuse into the exoplasmic leaflet or directly into the aqueous extracellular medium. (d) Cryo-electron microscopy structure of human ABCG2 in the ADP-bound, inward-facing state, revealing a large cavity facing the cytosol into which the substrate can enter. (e) Mg^{2+} ions, which are important for ATP binding and activity, are shown as light green spheres. ATP (yellow spheres) binding triggers rotation of the α helices, compression of the large cavity, and extrusion of the substrate outside of the cell.

[Data from S. G. Aller et al., 2009, *Science* **323**:1718–1722, PDB ID 3g61; and I. Manolaridis et al., 2018, *Nature* **563**:426–430, PDB ID 6FEQ.]

Description

The illustration shows a sliced view of the transmembrane protein. The protein has an upside-down V shape, where the apex points slightly out of the exterior of the membrane. The illustration labeled (a) shows two A T P binding domains in the interior of the cell. Near the mutual regions of the two leaflets, are a bound molecule of q z 59-s s s and two close by serine residues (289 and 290). The cell membrane is represented as a gray rectangle with the protein going through it. Outside the cell membrane is the label transmembrane domains. Inside of the membrane is the label A T P-binding

domains. The illustration labeled (b) shows the two space-filling three-dimensional models of the same protein. The protein looks like an upside-down V, arrows are labeled Gap, and two red circles are going from inside the membrane to the cytosol. The illustration labeled (c) shows the V-shaped protein. The gap is labeled, and the red circles are moving from the upper membrane to outside of the membrane. The illustration labeled (d) shows a ribbon diagram of the same protein. In this diagram, the left side of the protein is blue, the right side, pink, and the red circle is inside the gap and labeled E 1 S. The labels near and above the E 1 S reads, plug and external cavity. The illustration labeled (e) shows the same protein with the external cavity labeled E 1 S, which is in the outside of the cell membrane. Inside of the protein is labeled A T P and M g superscript 2 plus. Below both illustrations (d) and (e) is a shared arrow labeled 2 A D P plus 2 P subscript i.

The first eukaryotic ABC protein to be recognized was discovered during studies on tumor cells and cultured cells that exhibited resistance to several drugs with unrelated chemical structures. Such cells were eventually shown to express elevated levels of a *multidrug-resistance (MDR) transport protein* originally called *MDR1* and now known as *ABCB1*. This protein uses the energy derived from ATP hydrolysis to *export* a large variety of drugs from the cytosol to the extracellular medium. The *Mdr1* gene is frequently amplified in multidrug-resistant cells, resulting in a large overproduction of the ABCB1 protein. In contrast to bacterial ABC proteins, which are built of four discrete subunits, all four domains of mammalian ABCB1 are fused into a single 170-kDa protein.

The substrates of mammalian ABCB1 are primarily planar, lipid-soluble molecules with one or more positive charges; they all compete with one another for transport, which suggests that they bind to the same or

overlapping sites on the protein. Many drugs transported out of the cell by ABCB1 have earlier diffused into the cell cytosol from the extracellular medium across the plasma membrane, unaided by transport proteins. Once in the cell, they block various cellular functions. Two such drugs, used to treat certain cancers, are colchicine and vinblastine, which block assembly of microtubules (see Chapter 18). ATP-powered export of such drugs by MDR1 reduces their concentration in the cytosol. As a result, a much higher extracellular drug concentration is required to kill cells that express ABCB1 than those that do not. That ABCB1 is an ATP-powered small-molecule pump has been demonstrated with liposomes containing the purified protein. Different drugs enhance the ATPase activity of these liposomes in a dose-dependent manner corresponding to their ability to be transported by ABCB1.

The three-dimensional structure of ABCB1, together with those of homologous bacterial and eukaryotic ABC proteins, revealed the protein's mechanism of transport as well as the key to its ability to bind and transport a wide array of hydrophilic and hydrophobic substrates (see Figure 11-15). The two TM domains form a binding site in the center of the membrane that alternates between an inward-facing (Figure 11-15b) and an outward-facing (Figure 11-15c) orientation, conforming to the alternating access model. The alternation between these two conformational states is powered by ATP binding to the two A subunits and its subsequent hydrolysis to ADP and P_i.

The substrate-binding cavity formed by ABCB1 is large. Some of the amino acids that line the cavity — mainly tyrosine and phenylalanine —

have aromatic side chains, allowing ABCB1 to bind multiple types of hydrophobic ligands. Other segments of the cavity are lined with hydrophilic residues, allowing hydrophilic or amphipathic molecules to bind. In the inward-facing conformation, the binding site is open directly to the surrounding aqueous solution, allowing hydrophilic molecules to enter the binding site directly from the cytosol. In addition, a gap in the protein is accessible directly from the hydrophobic core of the inner leaflet of the membrane bilayer; through this gap hydrophobic molecules can enter the binding site directly from the inner leaflet (see Figure 11-15b). After the ATP-powered change to the outward-facing conformation, molecules can exit the binding site into the outer membrane leaflet or directly into the extracellular medium (see Figure 11-15c).

The human ABCG2 structure has recently been determined in substrate- and ATP-bound states. This structure provided additional insights into the mechanisms underlying ATP-driven substrate translocation (Figure 11-15d, e). ABCG2 is also known as the Breast Cancer Resistance Protein and its expression levels are correlated with a poor outcome in breast as well as other cancers. A clever experimental strategy made use of a mutant form of ABCG2 that exhibits decreased rates of transport and of ATP hydrolysis. High-resolution cryo-electron microscopy was used to capture the transporter bound to the substrate in the internal facing, pre-translocation state and bound to ATP in the post-translocation state. These studies revealed a large substrate-binding cavity in the internal-facing state, with a plug creating a smaller cavity toward the external-facing part of the protein. ATP binding triggered rotation of the α helices of the A domains, compressing the substrate-binding cavity and extruding the

substrate through the plug to the external cavity, with release of the substrate to the outside. While not clear, ATP hydrolysis may be required to return the protein transporter to the inward-facing state.

Certain ABC Proteins "Flip" Phospholipids and Other Lipid-Soluble Substrates from One Membrane Leaflet to the Other

As shown in Figure 11-15, ABCB1 and ABCG2 can move, or "flip," a hydrophobic or amphipathic substrate molecule from the inner leaflet of the membrane to the outer leaflet. This otherwise energetically unfavorable reaction is powered by the ATPase activity of the protein, and is required for maintaining the asymmetric distribution of phospholipids across the cytoplasmic and exoplasmic membrane leaflets (Chapter 10) and for transporting lipids across cellular membrane. Support for this so-called **flippase** model of transport by ABCB1 comes from experiments on ABCB4 (originally called *MDR2*), a protein homologous to ABCB1 that is present in liver cells in the region of the plasma membrane that faces the thin tubes (canaliculi) that collect bile. ABCB4 moves phosphatidylcholine from the cytosolic to the exoplasmic leaflet of the plasma membrane for subsequent release into the bile in combination with cholesterol and bile acids, which themselves are transported by other ABC superfamily members. Still other ABC superfamily members are also

flippases that export various lipids from cells, presumably by mechanisms similar to that of ABCB1 (see Table 11-3).

The flipping of lipids across membranes is required for the generation of glycoproteins within the endoplasmic reticulum in eukaryotic cells or the periplasm of prokaryotes (see Chapter 13). This process provides a way to get the hydrophilic oligosaccharides needed to form glycoproteins across the hydrophobic membrane. In this process, oligosaccharides are added to the cytosolic side of long polyisoprenol membrane lipids to form lipid-linked oligosaccharides (LLOs). These LLOs are then flipped across the membrane into the endoplasmic reticulum (or into the periplasm in prokaryotes) so that the oligosaccharides can be transferred to membrane and secreted proteins to generate glycoproteins. Recent x-ray crystal structures of a dimeric ABC transporter from *Campylobacter jejuni* (a bacteria that commonly causes food poisoning) that mediates flipping of LLOs across the membrane captured the transporter in inward- and outward-facing states. These structures revealed a novel lipid-flipping mechanism (Figure 11-16d). Initially, the lipid tail of a lipid-linked oligosaccharide (LLO) binds the extracellular-facing helix of one of the flippase subunits (step **1**). Its binding promotes exchange of ATP for ADP, triggering the dimer to convert to an outward-open state (step **2**) that allows the hydrophilic oligosaccharide head of the LLO to enter the positively charged pore of the transporter (step **3**). ATP hydrolysis drives the return of the dimer to an inward-open conformation, squeezing the LLO head to the outward side of the membrane (step **4**). The LLO lipid tail then dissociates from the flippase and extends into the cytosolic side of the membrane. In this mechanism, the transporter protects the

hydrophilic oligosaccharide head of the LLO from the hydrophobic milieu of the membrane, allowing the lipid tails to flip from one side of the membrane to the other.

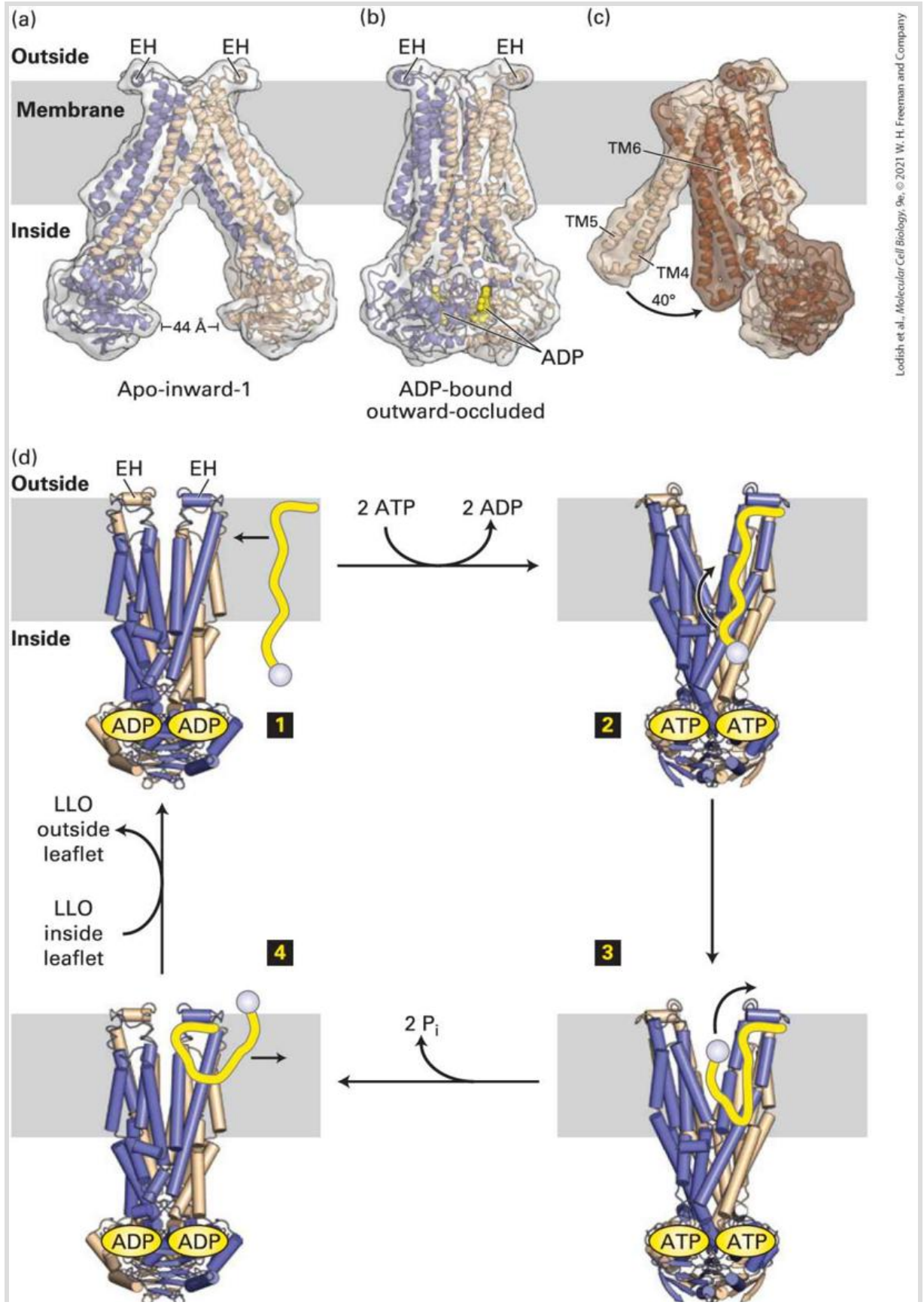

FIGURE 11-16 An ABC transporter from *Campylobacter jejuni* flips lipid-linked oligosaccharides across the membrane. (a) The inward-facing structure of the PglK ABC transporter, with a larger cavity facing the cytosol. Subunits are shown in peach and purple, with the extracellular-facing helix (EH) labeled. (b) The ADP-bound, outward-facing structure in which the cytosolic cavity is occluded. (c) The conversion of inward- to outward-facing states is associated with conformational changes. (d) In the proposed model for the flippase mechanism, the PglK subunits are shown as cartoon-like structures in peach and purple, with the EH labeled. The lipid tail of the LLO is yellow and the oligosaccharide head light purple. The lipid tail interacts with the EH (step 1–2); ATP replaces ADP, which opens the cytosolic cavity (step 2), into which the large oligosaccharide head of the LLO enters (step 3); ATP hydrolysis triggers conformational changes that achieve occlusion of the cytosolic cavity, dislodging and ejecting the oligosaccharide head into the periplasm (step 4) and flipping the direction of the lipid tail within the membrane.

[Information from C. Perez et al., 2015, *Nature* **524**:433–438.]

Description

The illustration labeled (a) shows a ribbon diagram of the transporter with an upside-down V shape. The cell membrane is represented as a gray rectangle with the ribbon diagram going through it. The bottom of the v shape outside the membrane is labeled E H on both parts. Below the diagram is the label Apo-inward-1. The illustration labeled (b) shows the same transporter but the angles of the v are close together. A D P is labeled in yellow toward the bottom inside the cell. The label reads A D P-bound outward-occluded. The illustration labeled (c) shows a V shaped ribbon diagram, where the V shape is turned and shows the third leg. The leftmost leg is labeled T M 5, T M 4. An arrow moving from this leg to the middle one is labeled 40 degrees. The right side has a label, T M 6. The illustration labeled (d) shows a cycle diagram of the protein in action. Step 1 is labeled with the cell membrane and the E H labels. It has 2 A D P at the bottom. There is a yellow ribbon separate from this transporter with an arrow indicates that it is moving toward the transporter. In step 2, the V has opened at the outside of the membrane and the two A D P ovals are converted into A T P. Between steps 1 and 2 is an arrow labeled 2 A T P to 2 A D P. The yellow ribbon has moved downward into the transporter. Step 3 shows the yellow ribbon moving out of the

transporter. No new labels. Step 4 shows the yellow ribbon coming out of the transporter and the two ovals are converted into A D P.

The ABC Cystic Fibrosis Transmembrane Regulator Is a Chloride Channel, Not a Pump

Several human genetic diseases are associated with defective ABC proteins (see Table 11-3). The most common (1 in 2500 births) is cystic fibrosis (CF), caused by a mutation in the gene encoding the *cystic fibrosis transmembrane regulator* (*CFTR*, also called *ABCC7*). Like other ABC proteins, CFTR has two transmembrane TM domains and two cytosolic ATP-binding domains (A domains). CFTR contains an additional R (regulatory) domain on the cytosolic face; R links the two homologous halves of the protein, creating an overall domain organization of TM1–A1–R–TM2–A2. CFTR is a Cl^- channel that opens upon phosphorylation and ATP binding to allow Cl^- anions to flow down their electrochemical gradient. It is expressed in the apical plasma membranes of epithelial cells in the lungs, sweat glands, pancreas, and other tissues, and mutations in the protein decrease the capacity of these membranes to transport Cl^-. For instance, CFTR protein is important for reuptake into the cells of sweat glands of Cl^- lost by sweating; babies with cystic fibrosis, if licked, often taste salty because this reuptake is inhibited. Over time, as a result of disrupted salt and water homeostasis, patients with cystic fibrosis accumulate dehydrated mucus in their lungs and other tissues, leading to

chronic respiratory infections and digestive system disorders, which can ultimately result in organ failure.

Until recently, our understanding of CFTR channel structure and function was derived from biochemical and biophysical studies, along with x-ray crystal structures of fragments of the CFTR protein. In 2017, however, the high-resolution structures of the full-length zebrafish and human CFTR channels were solved using cryo-electron microscopy (Figure 11-17). While it was known that the channel was gated by phosphorylation and ATP binding, comparison of the structure of open and closed CFTR channels revealed the major conformational changes produced by phosphorylation and ATP binding to open the channel. These structures show that channel gating is regulated by two processes: phosphorylation of the cytosolic R domain by cAMP-dependent protein kinase (PKA, discussed in Chapter 15), followed by binding of ATP to the cytosolic A domains. In the unphosphorylated state, the R domain is wedged between transmembrane α helices, keeping the A1 and A2 domains apart and blocking the anion channel. Phosphorylation by PKA triggers a conformational change that moves the R domain away from the A1 and A2 interface, and, following ATP binding, the two A domains dimerize, narrowing (but not closing) the opening of the channel on the cytosolic side and widening it on the extracellular side of the membrane, allowing the anions to flow through the channel. The ion channel pathway is lined with positively charged amino acids, making the channel specific for conductance of anions.

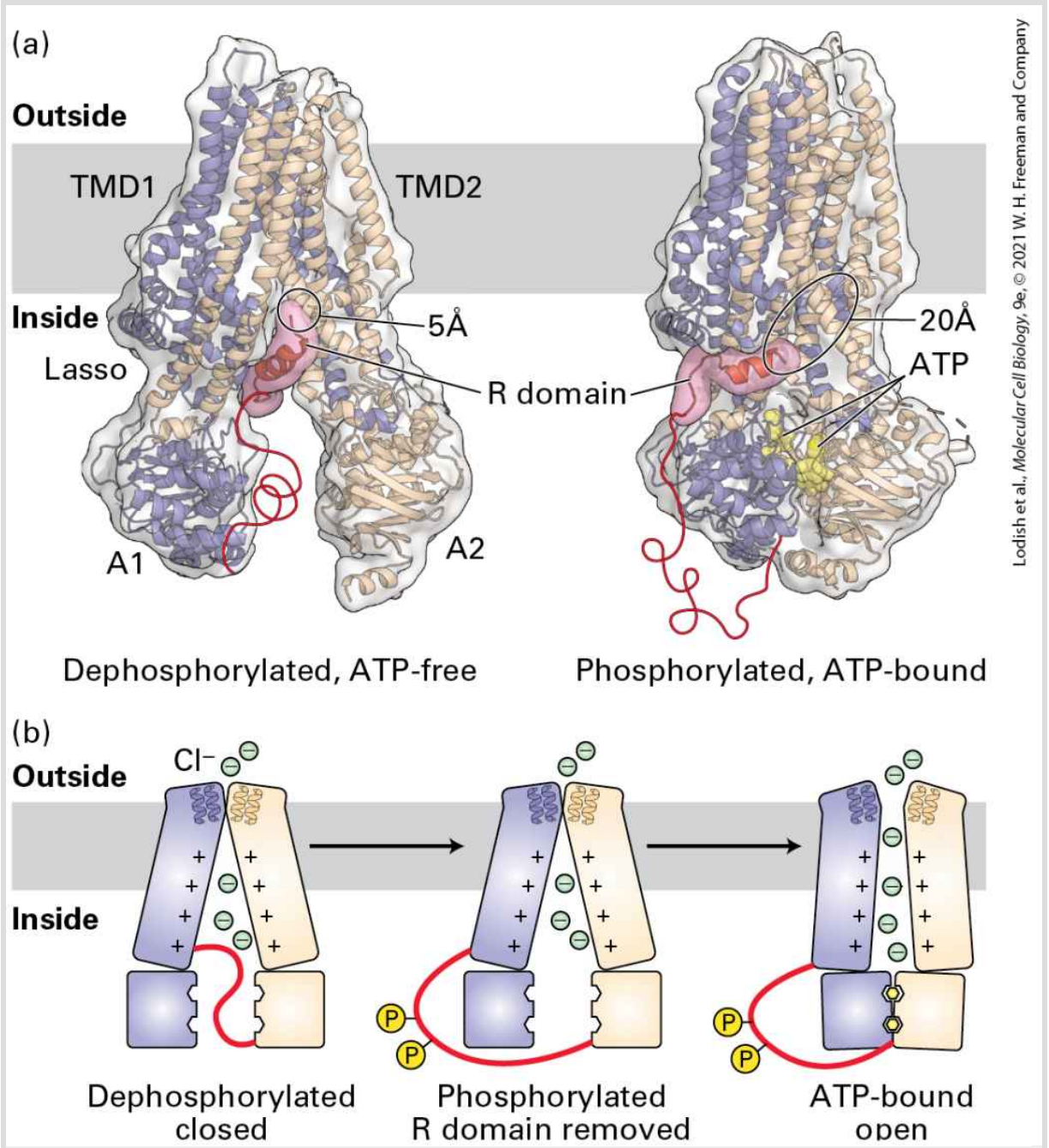

FIGURE 11-17 Structure and function of the cystic fibrosis transmembrane regulator (CFTR). (a) Ribbon structures of the human CFTR in the dephosphorylated, ATP-free state on the left and in the phosphorylated, ATP-bound state on the right. The unresolved regions of the structure are shown as thin red lines, and unstructured regions within the R domain are shown in pink. Phosphorylation of the R domain moves it out of the ATP-binding region and allows ATP binding and dimerization of the two ATP-binding (A) domains. This narrows the opening on the cytosolic side, with a widening of the pore on the extracellular

side of the membrane. (b) A cartoon of the CFTR, with each subunit of the dimer shown in purple and peach. In the unphosphorylated, ATP-free state, the R-domain (shown as a red line) is wedged between the two subunits. Phosphorylation of R moves it out of the region between the two subunits, ATP binds and the two ATP-binding (A) sites dimerize. Dimerization narrows the channel on the cytosolic face and opens the channel on the extracellular face so that the chloride ions can travel through the pore (lined with positively charged amino acid residues) down its electrochemical gradient.

[Data from Z. Zhang et al., 2017, *Cell* **170**:483; and Z. Zhang et al., 2018, *Proc. Nat'l Acad. Sci. USA* **115**:12757.]

Description

The illustration labeled (a) shows ribbon diagrams of the transmembrane regulator. The cell membrane is represented as a gray rectangle with the ribbon diagram going through it. Outside is labeled above the cell membrane and inside is labeled below the cell membrane. The ribbon structure is labeled T M D 1 on the left and T M D 2 on the right. Also labeled in the cytosol area of this regulator on the left is Lasso and A 1. On the right side, 5 angstroms are labeled along with the R domain and A 2. Text below the diagram reads, dephosphorylated, A T P free. Right side of the illustration shows the same structure with the R domain labeled and 20 angstroms. The ATP is yellow and labeled. Text below the diagram reads, phosphorylated, A T P bound. A red tiny ribbon comes out of the R domain on both diagrams. The illustration labeled (b) shows a three-step pattern of action for this regulator. Outside is labeled above the cell membrane and inside is labeled below the cell membrane. In the left diagram, there is the label Dephosphorylated closed. There are circles with negative charges, 3 inside the inverted V shape, and 3 above it with the label C l minus. The tiny red ribbon is between the halves of the inverted V inside the cytosol. The center diagram is labeled phosphorylated R domain removed. The tiny red ribbon is now moving around the outside of one leg to the other one and has two yellow circles labeled P on it. The last diagram shows the inverted V closed up with the top split open to the outside of the cell. It is labeled A T P-bound open.

About two-thirds of all CF cases can be attributed to a single mutation in CFTR: deletion of Phe 508 (F508del) in the ATP-binding A1 domain. At body temperature, the mutant protein fails to fold properly and to move to the cell surface, where it normally functions. Interestingly, if cells expressing the mutant protein are incubated at room temperature, the protein folds and accumulates normally on the plasma membrane, where it functions nearly as well as the wild-type CFTR channel. Recently, a series of small molecules have been chemically synthesized that bind to this mutant CFTR protein in CF patients and stabilize the folded form at 37 °C, allowing it to traffic normally to the cell surface and partially reverse the effects of the disease. These molecules are known as *CFTR correctors*. They only promote the cell surface trafficking of a fraction of CFTR channels and thus only partially reverse the effects of the disease. Another CFTR mutation, Gly 551 to Asp (G551D), accounts for approximately 5 percent of CF cases and results in a channel that folds normally and accumulates normally on the plasma membrane but is defective in Cl^- transport because the mutation disrupts ATP binding. In 2012, a small molecule drug called *Ivacaftor*, which increases the flow of Cl^- ions through the mutant channel, was approved by the U.S. Food and Drug Administration (FDA) to treat CF patients whose disease is caused by this mutation. This drug, known as a *CFTR potentiator*, represents one of the first successful personalized therapies resulting from a molecular understanding of the disease-causing protein. Recently, the FDA has approved treatment of F508del cystic fibrosis patients with a combination of CFTR correctors and the CFTR potentiator Ivacaftor, which increases the flow of Cl^- ions through those channels that do reach the plasma

membrane. This drug combination exemplifies the use of targeted combination drug therapies resulting from detailed molecular understanding of how specific mutations cause disease. ■

KEY CONCEPTS OF SECTION 11.3

ATP-Powered Pumps and the Intracellular Ionic Environment

- Four classes of transmembrane proteins couple the energy-releasing hydrolysis of ATP with the energy-requiring transport of substances against their concentration gradients: P-, V-, and F-class pumps and ABC proteins (see Figure 11-9).
- The combined action of P-class Na^+/K^+ ATPases in the plasma membrane and homologous Ca^{2+} ATPases in the plasma membrane or SR creates the usual ionic milieu of animal cells: high K^+, low Ca^{2+}, and low Na^+ in the cytosol; low K^+, high Ca^{2+}, and high Na^+ in the extracellular fluid.
- In P-class pumps, phosphorylation of the α (catalytic) subunit and changes in conformational states are essential for coupling ATP hydrolysis to transport of H^+, Na^+, K^+, or Ca^{2+} ions (see Figures 11-10 through 11-13).
- V- and F-class ATPases, which transport protons exclusively, are large, multisubunit complexes with a proton-conducting channel in the transmembrane domain and ATP-binding sites in the cytosolic domain.
- V-class proton pumps in animal lysosomal and endosomal membranes and plant vacuolar membranes are responsible for maintaining a lower pH inside the organelles than in the surrounding cytosol (see Figure 11-14).
- V- and F-class ATPases transport protons across the membrane using a rotary motor mechanism.
- All members of the large and diverse ABC superfamily of membrane transport proteins contain four core domains: two transmembrane domains, which form a pathway for solute movement and determine substrate specificity, and two cytosolic ATP-binding domains (see Figure 11-15).
- The two T domains of the multidrug transporter ABCB1 form a ligand-binding site in the middle of the plane of the membrane; ligands can bind directly from the cytosol or from the inner-membrane leaflet through a gap in the protein.
- The ABC superfamily includes about 50 mammalian proteins (e.g., ABCB1, ABCA1) that transport a wide array of substrates, including toxins, drugs, phospholipids, peptides, and proteins, into or out of the cell.

- Biochemical experiments directly demonstrate that ABCB4 (MDR2) possesses phospholipid flippase activity (see Figure 11-16).
- High resolution cryo-electron microscopy of a flippase from *Campylobacter jejuni* reveals a novel mechanism by which an ABC transporter flips a lipid-linked oligosaccharide across the membrane.
- CFTR, an ABC protein, is a Cl^- channel, not a pump. Channel opening is triggered by protein phosphorylation and by binding of ATP to the two A domains (see Figure 11-17).
- Mutations in CFTR cause cystic fibrosis; small molecules targeting these mutations, classified as CFTR correctors and CFTR potentiators, are used to treat cystic fibrosis patients.