The extracellular face of the plasma membrane is diffusely studded with carbohydrates, not only as complex oligosaccharides on glycoproteins and glycolipids, but also as polysaccharide chains attached to integral membrane proteoglycans. This *glycocalyx* functions as a chemical and mechanical barrier, and is also involved in *cell-cell* and *cell-matrix interactions*.

Passive Membrane Diffusion. Small, nonpolar molecules like O_2 and CO_2 readily dissolve in lipid bilayers and therefore rapidly diffuse across them; in addition, hydrophobic molecules (e.g., steroid-based molecules like estradiol or vitamin D) also cross lipid bilayers with relative impunity. Similarly, polar molecules smaller than 75 daltons in mass readily cross membranes (e.g., water, ethanol, and urea). However, in tissues where water is transported in large volumes (e.g., renal tubular epithelium), special integral membrane proteins called *aquaporins* augment passive water transport. In contrast, the lipid bilayer is an effective barrier to the passage of polar molecules of greater than 75 daltons in mass, even those that are only slightly larger, such as glucose. Lipid bilayers are also impermeant to ions, no matter how small, due to their charge and high degree of hydration. We will discuss next specialized mechanisms that regulate traffic across plasma membranes.

Carriers and Channels. For each of the larger polar molecules that must cross membranes to support normal cellular functions (e.g., for nutrient uptake and waste disposal), a unique plasma membrane protein is typically required. For low molecular weight species (ions and small molecules up to approximately 1000 daltons), *channel proteins* and *carrier proteins* may be used (although this discussion focuses on plasma membranes, it should be noted that similar pores and channels are needed for transport across organellar membranes). Each transported molecule (e.g., ion, sugar, nucleotide) requires a transporter, which are often highly specific for a select molecule in each class (e.g., glucose but not galactose):

- *Channel proteins* create hydrophilic pores, which, when open, permit rapid movement of solutes (usually restricted by size and charge, Fig. 1-7).
- *Carrier proteins* bind their specific solute and undergo a series of conformational changes to transfer the ligand across the membrane; their transport is relatively slow.

In most cases, a concentration and/or electrical gradient between the inside and outside of the cell drives solute movement via *passive transport* (virtually all plasma membranes have an electrical potential difference across them, with the inside negative relative to the outside). In some cases, *active transport* of certain solutes *against* a concentration gradient is accomplished by carrier molecules (not channels) using energy released by ATP hydrolysis or a coupled ion gradient. Transporter ATPases also include the infamous *multidrug resistance (MDR) protein*, which pumps polar compounds (e.g., chemotherapeutic drugs) out of cells and may render cancer cells resistant to treatment.

Because plasma membranes are freely permeable to water, it moves into and out of cells by osmosis, depending on relative solute concentrations. Thus, extracellular salt in excess of that in the cytosol (*hypertonicity*) causes a net movement of water out of cells, while *hypotonicity* causes a net movement of water into cells. Since the cytosol is rich in charged metabolites and protein species that attract a large number of counterions that tend to increase the intracellular osmolarity, cells need to constantly pump out small inorganic ions (e.g., Na^+ and Cl^-), typically through the activity of the membrane sodium-potassium ATPase, lest they become overhydrated. Loss of the ability to generate energy (e.g., in a cell injured by toxins or ischemia) therefore results in osmotic swelling and eventual rupture of cells. Similar transport mechanisms also regulate intracellular and intraorganellar pH; most cytosolic enzymes prefer to work at pH 7.4 whereas lysosomal enzymes function best at pH 5 or less.

Receptor-mediated and fluid-phase uptake (Fig. 1-7)**.** Uptake of fluids or macromolecules by the cell, called *endocytosis,* occurs by two fundamental mechanisms. Certain small molecules—including some vitamins—are taken up by invaginations of the plasma membrane called *caveolae*. For bigger molecules, uptake occurs after binding to specific cell-surface receptors; internalization occurs through a membrane invagination process driven by an intracellular coat of *clathrin* proteins. Clathrin is a hexamer of proteins that spontaneously assembles into a basket-like lattice to drive the invagination process. We shall come back to these later.

The process by which large molecules are exported from cells is called *exocytosis*; In this process, proteins synthesized and packaged within the RER and Golgi apparatus are concentrated in secretory vesicles, which then fuse with the plasma membrane and expel their contents.

Transcytosis is the movement of endocytosed vesicles between the apical and basolateral compartments of cells; this is a mechanism for transferring large amounts of intact proteins across epithelial barriers (e.g., ingested antibodies in maternal milk across intestinal epithelia) or for the rapid movement of large volumes of solute. In fact, increased transcytosis probably plays a role in the increased vascular wall permeability seen in healing wounds and in tumors.

We now return to the two forms of endocytosis mentioned earlier

- *Caveolae-mediated endocytosis.* Caveolae ("little caves") are *noncoated* plasma membrane invaginations associated with GPI-linked molecules, cyclic adenosine monophosphate (cAMP) binding proteins, SRC-family kinases, and the folate receptor. Caveolin is the major structural protein of caveole. Internalization of caveolae with any bound molecules and associated extracellular fluid is sometimes called *potocytosis*—literally "cellular sipping." Although caveolae likely participate in the transmembrane delivery of some molecules (e.g., folate), they are increasingly implicated in the regulation of transmembrane signaling and/or cellular adhesion via the internalization of receptors and integrins.
- *Pinocytosis and receptor-mediated endocytosis* (Fig. 1-7). *Pinocytosis* ("cellular drinking") describes a fluid-phase process during which the plasma membrane invaginates and is pinched off to form a cytoplasmic vesicle. Endocytosed vesicles may recycle back to the plasma

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