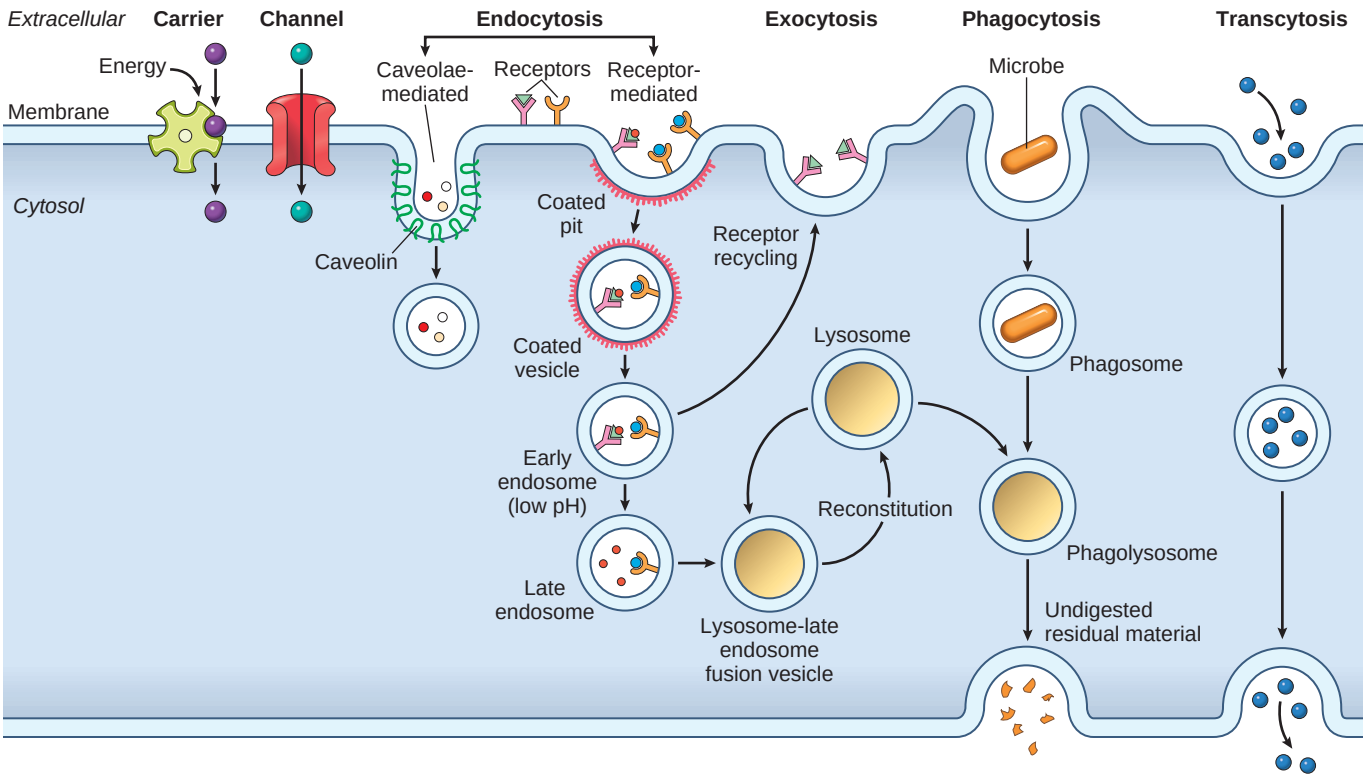

Figure 1-7 Movement of small molecules and larger structures across membranes. The lipid bilayer is relatively impermeable to all but the smallest and/or most hydrophobic molecules. Thus, the import or export of charged species requires specific transmembrane transporter proteins; the internalization or externalization of large proteins, complex particles, or even cells requires encircling them with segments of the membrane.

Small charged solutes can move across the membrane using either channels or carriers; in general, each molecule requires a unique transporter. *Channels* are used when concentration gradients can drive the solute movement. *Carriers* are required when solute is moved *against* a concentration gradient.

Receptor-mediated and fluid-phase uptake of material involves membrane bound vacuoles. *Caveolae* endocytose extracellular fluid, membrane proteins, and some receptor bound molecules (e.g., folate) in a process driven by caveolin proteins concentrated within lipid rafts (*potocytosis*). *Pinocytosis* of extracellular fluid and most surface receptor-ligand pairs involves *clathrin-coated pits and vesicles*. After internalization, the clathrin dissociates and can be re-used, while the resulting vesicle progressively matures and acidifies. In the early and/or late endosome, ligand can be released from its receptor (e.g., iron released from transferrin bound to the transferrin receptor) with receptor recycling to the cell surface for another round. Alternatively, receptor and ligand within endosomes can be targeted to fuse with lysosomes (e.g., epidermal growth factor bound to its receptor); after complete degradation, the late endosome-lysosome fusion vesicle can regenerate lysosomes. *Phagocytosis* involves the non-clathrin-mediated membrane invagination of large particles—typically by specialized phagocytes (e.g., macrophages or neutrophils). The resulting phagosomes eventually fuse with lysosomes to facilitate the degradation of the internalized material. *Transcytosis* involves the transcellular endocytotic transport of solute and/or bound ligand from one face of a cell to another. *Exocytosis* is the process by which membrane-bound vesicles fuse with the plasma membrane and discharge their contents to the extracellular space.

membrane (*exocytosis*) for another round of ingestion. Endocytosis and exocytosis must be tightly coupled since a cell will typically pinocytose 10% to 20% of its own cell volume each hour, or about 1% to 2% of its plasma membrane each minute. Pinocytosis and receptor-mediated endocytosis begin at a specialized region of the plasma membrane called the *clathrin-coated pit*, which rapidly invaginates and pinches off to form a *clathrin-coated vesicle*; trapped within the vesicle is a gulp of the extracellular milieu and in some cases receptor bound macromolecules described below. The vesicles then rapidly uncoat and fuse with an acidic intracellular structure called the *early endosome* where they discharge their contents for digestion and further passage to the lysosome.

Receptor-mediated endocytosis is the major uptake mechanism for certain macromolecules, as exemplified by transferrin and low-density lipoprotein (LDL). These macromolecules bind to receptors that are localized in clathrin coated pits. After binding to their specific receptors, LDL and transferrin are endocytosed in vesicles that fuse with lysosomes. In the acidic environment of the lysosome, LDL and transferrin release their cargo (cholesterol and iron, respectively), which is subsequently taken up into the cytoplasm. Remarkably, the LDL receptor and the transferrin receptor are resistant to the harsh environment of the lysosome, allowing them to be recycled back to the plasma membrane. Defects in receptor-mediated transport of LDL are responsible for familial hypercholesterolemia, as described in Chapter 5.

Cytoskeleton and Cell-Cell Interactions

The ability of cells to adopt a particular shape, maintain polarity, organize the relationship of intracellular organelles, and move about depends on the intracellular scaffolding of proteins called the *cytoskeleton* (Fig. 1-8). In eukaryotic cells, there are three major classes of cytoskeletal proteins: