Cell-cell desmosomal junctions are formed by homotypic association of transmembrane glycoproteins called *cadherins*. In spot desmosomes, the cadherins are called *desmogleins* and *desmocollins*; they are linked to intracellular intermediate filaments and allow extracellular forces to be mechanically communicated (and dissipated) over multiple cells. In belt desmosomes, the transmembrane adhesion molecules are called *E-cadherins* and are associated with intracellular actin microfilaments, by which they can influence cell shape and/or motility. In hemidesmosomes, the transmembrane connector proteins are called *integrins*; like cadherins, these attach to intracellular intermediate filaments, and thus functionally link the cytoskeleton to the extracellular matrix. *Focal adhesion complexes* are large (>100 proteins) macromolecular complexes that can be localized at hemidesmosomes, and include proteins that can generate intracellular signals when cells are subjected to increased shear stress, such as endothelium in the bloodstream, or cardiac myocytes in a failing heart.

- *Communicating junctions (gap junctions)* mediate the passage of chemical or electrical signals from one cell to another. The junction consists of a dense planar array of 1.5- to 2-nm pores (called *connexons*) formed by hexamers of transmembrane proteins called *connexins*. These pores permit the passage of ions, nucleotides, sugars, amino acids, vitamins, and other small molecules; the permeability of the junction is rapidly reduced by lowered intracellular pH or increased intracellular calcium. Gap junctions play a critical role in cell-cell communication; in cardiac myocytes, for example, cell-to-cell calcium fluxes through gap junctions allow the myocardium to behave like a functional syncytium capable of coordinated waves of contraction—the beating of the heart.

Biosynthetic Machinery: Endoplasmic Reticulum and Golgi

The structural proteins and enzymes of the cell are constantly renewed by ongoing synthesis tightly balanced with intracellular degradation. The endoplasmic reticulum (ER) is the site for synthesis of all the transmembrane proteins and lipids for plasma membrane and cellular organelles, including ER itself. It is also the initial site for the synthesis of all molecules destined for export out of the cell. The ER is organized into a meshlike interconnected maze of branching tubes and flattened lamellae forming a continuous sheet around a single lumen that is topologically equivalent to the extracellular environment. The ER is composed of contiguous but distinct domains, distinguished by the *presence* (rough ER or RER) or *absence* (smooth ER or SER) of ribosomes (Fig. 1-5).

Membrane-bound ribosomes on the cytosolic face of RER translate mRNA into proteins that are extruded into the ER lumen or become integrated into the ER membrane. This process is directed by specific *signal sequences* on the N-termini of nascent proteins. For proteins lacking a signal sequence, translation occurs on free ribosomes in the cytosol. Typically, such transcripts are read simultaneously by multiple ribosomes (*polyribosomes*) and the vast majority of such proteins remain in the cytoplasm. Proteins inserted into the ER fold and can form polypeptide complexes (*oligomerize*); in addition, disulfide bonds are formed, and *N-linked oligosaccharides* (sugar moieties attached to asparagine residues) are added. *Chaperone molecules* retain proteins in the ER until these modifications are complete and the proper conformation is achieved. If a protein fails to appropriately fold or oligomerize, it is retained and degraded within the ER. The most common pathogenic mutation involving the CFTR protein, a membrane transporter that is defective in cystic fibrosis (Chapter 5), illustrates this quality control mechanism. This mutation causes the absence of a single amino acid (phe_{508}), which leads to misfolding, ER retention, and degradation of the CFTR protein. Moreover, excess accumulation of misfolded proteins—exceeding the capacity of the ER to edit and degrade them—leads to the *ER stress response* (also called the *unfolded protein response* or *UPR*) that triggers cell death through *apoptosis* (Chapter 2).

From the RER, proteins and lipids destined for other organelles or for extracellular export are shuttled into the *Golgi apparatus*. This organelle consists of stacked cisternae that progressively modify proteins in an orderly fashion from *cis* (near the ER) to *trans* (near the plasma membrane); macromolecules are shuttled between the various cisternae within membrane-bound vesicles. As molecules move from *cis* to *trans*, the *N-linked oligosaccharides* originally added to proteins in the ER are pruned and further modified in a step-wise fashion; *O-linked oligosaccharides* (sugar moieties linked to serine or threonine) are also appended. Some of this glycosylation is important in directing molecules to lysosomes (via the *mannose-6-phosphate receptor*, Chapter 5); other glycosylation adducts may be important for cell-cell or cell-matrix interactions, or for clearing senescent cells (e.g., platelets and red cells). In addition to the stepwise glycosylation of lipids and proteins, the *cis Golgi network* can recycle proteins back to the ER; the *trans Golgi network* sorts proteins and lipids and dispatches them to other organelles (including the plasma membrane), or to secretory vesicles destined for extracellular release. The Golgi complex is especially prominent in cells specialized for secretion, including goblet cells of the intestine, bronchial epithelium (secreting large amounts of polysaccharide-rich mucus), and plasma cells (secreting large quantities of antibodies).

The SER in most cells is relatively sparse and primarily exists as the transition zone from RER to transport vesicles moving to the Golgi. However, in cells that synthesize steroid hormones (e.g., in the gonads or adrenals), or that catabolize lipid-soluble molecules (e.g., in the liver), the SER may be particularly conspicuous. Indeed, repeated exposure to compounds that are metabolized by the SER (e.g., phenobarbital catabolism by the cytochrome P-450 system), can lead to a reactive SER hyperplasia. The SER is also responsible for sequestering intracellular calcium; subsequent release from the SER into the cytosol can mediate a number of responses to extracellular signals (including apoptotic cell death). In addition, in muscle cells, specialized SER called *sarcoplasmic reticulum* is responsible for the cyclical release and sequestration of calcium ions that regulates muscle contraction and relaxation, respectively.

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