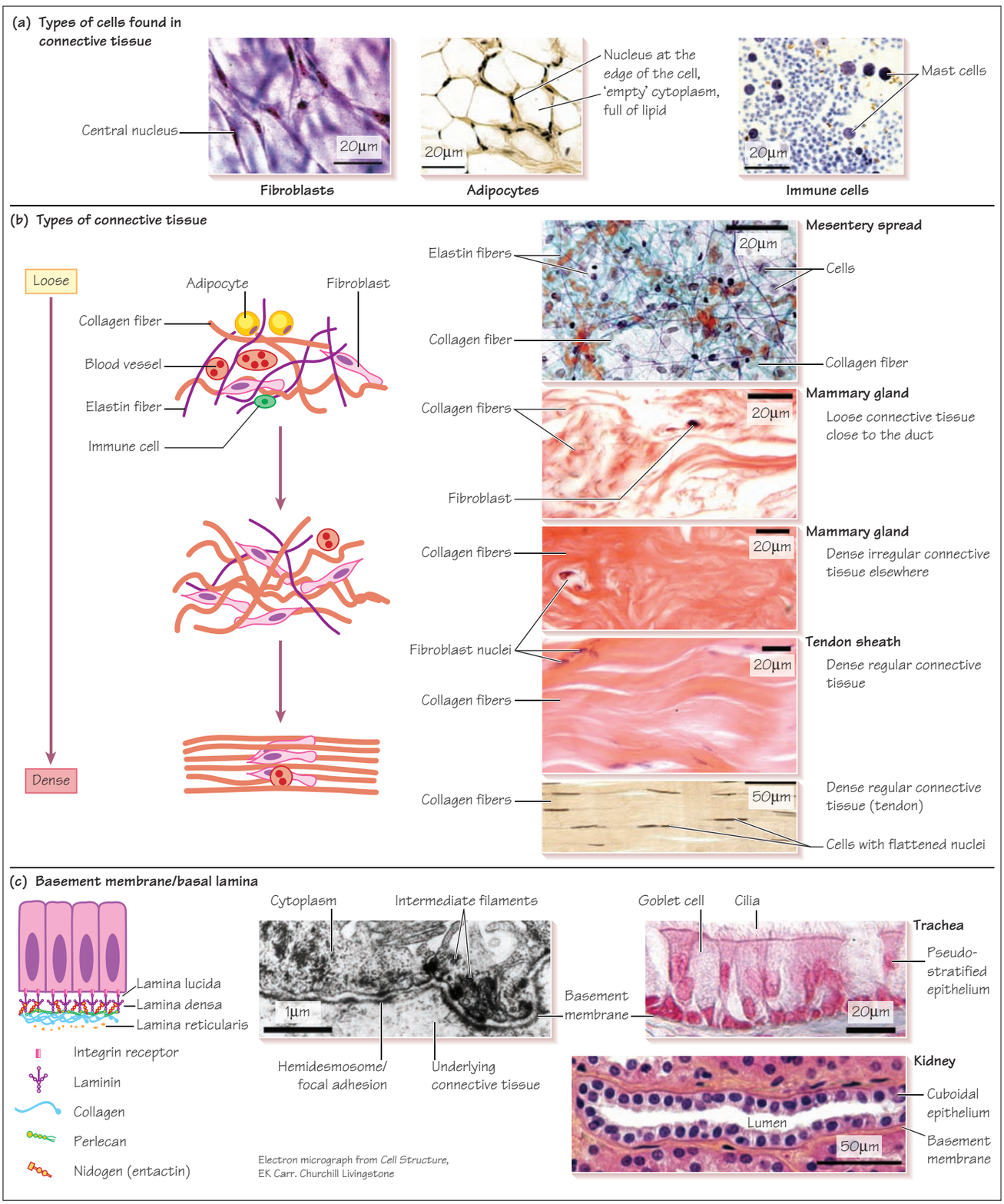
12 Connective tissue



Connective tissue lies under the epithelia of all tissues and organs. It provides both structural and metabolic support for the surrounding tissue, as it contains the blood vessels, and can also contain adipocytes. Adhesion of cells to the underlying connective tissue is essential for their survival. The extracellular matrix also regulates cell proliferation, migration, and differentiation.

Types of cell in connective tissue

• **Fibroblasts:** Fibroblasts (Fig. 12a) secrete the extracellular matrix that makes up the connective tissue.
• **Adipocytes:** These cells store fat. They usually look 'empty' in histology sections because lipid stored in these cells is extracted during the process of making the sections (Fig. 12a).
• **Immune cells:** These include macrophages, mast cells (Fig. 12a), and plasma cells.

Extracellular matrix in connective tissue

The extracellular matrix contains a mixture of proteoglycans, adhesive glycoproteins, and fibrous proteins.

Proteoglycans

• **Proteoglycans** contain repeating disaccharide units (glycosaminoglycans, or 'GAGs') bound to a protein core. (GAGs used to be known as 'ground substance'.) **GAGs** are highly negatively charged, hydrophilic, and heavily hydrated.
• There are four main groups of GAG: (1) hyaluronan (the simplest, which does not covalently link with proteins to form a proteoglycan); (2) chondroitin sulfate and dermatan sulfate; (3) heparan sulfate and heparin; (4) keratan sulfate.
• The large amount of water bound to GAGs gives connective tissue a high turgor, which means that it is good at resisting compressive forces.
• Proteoglycans are made by virtually all cells, and are secreted.

Adhesive glycoproteins

Adhesive glycoproteins are secreted extracellular proteins, which include various types of laminin and fibronectin. They bind to integrins in the cell membrane, and therefore help cells to adhere to the underlying extracellular matrix.

Fibrous proteins

Fibrous proteins include collagen and elastin (of which there are many types). Both collagen and elastin are secreted as precursor molecules (tropocollagen and tropoelastin). Mature elastic fibers consist of an inner core of cross-linked elastin and an outer coat of fibrillin (a glycoprotein). Collagen fibers consist of trimers, which can then assemble into higher-order structures.

The diversity of connective tissue arises from the variations in amount and type of components of the extracellular matrix.

Tendons, cartilage, and bone are specialized forms of extracellular matrix (see Chapters 15 and 16). In bone and teeth, the extracellular matrix becomes calcified.

Types of connective tissue

The organization of the extracellular matrix (Fig. 12b) varies from:
• **loose irregular** (where the numbers of cells and fibrous proteins are relatively low); to
• **dense irregular** (where there are more cells, and fibers); to
• **dense regular** (where the fibers are densely packed, and regularly arranged).

There is a continuous spectrum between these different types of connective tissue.

Basal lamina/basement membrane

The basal lamina is a specialized form of extracellular matrix. It consists of a thin layer, containing a dense meshwork of extracellular matrix proteins (laminin, type IV collagen, entactin, and proteoglycans, e.g., perlecan) (Fig. 12c). The specific content varies from tissue to tissue. These proteins bind to each other and form a highly dense, cross-linked extracellular matrix.

The cells in the epithelium are connected to the underlying basement membrane by integrins. Integrins are dimeric transmembrane proteins, which bind to laminin and fibronectin in the underlying basal lamina. Specialized integrins (bullous pemphigoid antigen (BPAG) 1 and 2, or $\alpha 6\beta 4$ integrin) are found in hemidesmosomes. These are anchored to keratin (intermediate) filaments on the intracellular side of the plasma membrane.

The basement membrane is found:
• directly underneath epithelial cells;
• surrounding neuronal, muscle and fat cells;
• separating two sheets of cells, such as the endothelium of blood vessels and the epithelium of adjacent ducts in the kidney.

Connections between the cells and their underlying basement membrane are very important for their integrity and survival. For example, blistering skin diseases are caused by mutations in *BPAG1*. Muscular dystrophy is caused by mutations in the protein dystrophin in striated muscle. Dystrophin is involved in connecting the muscle cytoskeleton to the basal lamina.

The basal lamina is often difficult to see by light microscopy, unless it is thick or special stains are used, as shown here (Fig. 12c).

Electron microscopy (Fig. 12c) shows that it has three layers: **lamina lucida**, a clear layer between the cell and the underlying **lamina densa**, and the **lamina reticularis** (reticular lamina), which contains type III collagen or reticular fibers and is continuous with the underlying connective tissue).