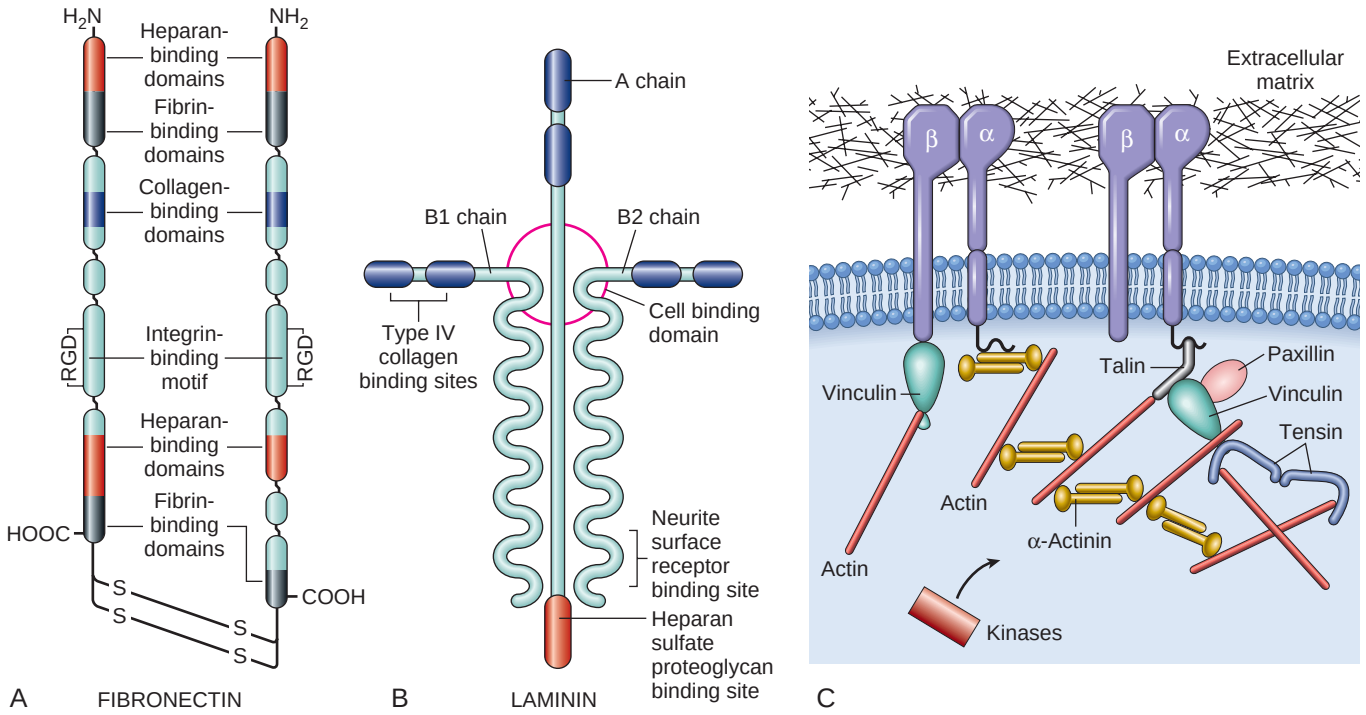

Figure 1-16 Cell and extracellular matrix (ECM) interactions: adhesive glycoproteins and integrin signaling. **A,** *Fibronectin* consists of a disulfide-linked dimer, with several distinct domains that allow binding to ECM and to integrins, the latter through arginine-glycine-aspartic acid (RGD) motifs. **B,** The cross-shaped *laminin* molecule is one of the major components of basement membranes; its multi-domain structure allows interactions between type IV collagen, other ECM components, and cell-surface receptors. **C,** Integrins and integrin-mediated signaling events at focal adhesion complexes. Each α-β heterodimeric integrin receptor is a transmembrane dimer that links ECM and intracellular cytoskeleton. It is also associated with a complex of linking molecules (e.g., vinculin, and talin) that can recruit and activate kinases that ultimately trigger downstream signaling cascades.

called *hyaluronan,* in a manner reminiscent of the bristles on a test tube brush. The highly negatively charged nature of the densely packed sulfated sugars pulls in cations (mostly sodium) that, in turn, osmotically attract water; the result is a viscous, gelatin-like matrix. Besides providing compressibility to tissues, proteoglycans also serve as reservoirs for growth factors secreted into the ECM (e.g., FGF and HGF). Some proteoglycans are integral cell membrane proteins that have roles in cell proliferation, migration, and adhesion, for example, by binding growth factors and chemokines and providing high local concentrations of these mediators (Fig. 1-14).

Adhesive glycoproteins and adhesion receptors are structurally diverse molecules variously involved in cell-to-cell adhesion, linking cells to the ECM, and the interactions between ECM components (Fig. 1-16). Prototypical adhesive glycoproteins include *fibronectin* (a major component of the interstitial ECM) and *laminin* (a major constituent of basement membrane). *Integrins* are representative of the adhesion receptors, also known as cell adhesion molecules (CAMs); the CAMs also include immunoglobulins, cadherins, and selectins.

- *Fibronectin* is a large (450 kD) disulfide-linked heterodimer that exists in tissue and plasma forms; it is synthesized by a variety of cells, including fibroblasts, monocytes, and endothelium. Fibronectin has specific domains that can bind to distinct ECM components (e.g., collagen, fibrin, heparin, and proteoglycans), as well as integrins (Fig. 1-16). In healing wounds, tissue and plasma fibronectin provide the scaffolding for subsequent ECM deposition, angiogenesis, and reepithelialization.
- *Laminin* is the most abundant glycoprotein in basement membrane. It is an 820-kD cross-shaped heterotrimer that connects cells to underlying ECM components such as type IV collagen and heparan sulfate (Fig. 1-16). Besides mediating attachment to basement membrane, laminin can also modulate cell proliferation, differentiation, and motility.
- *Integrins* are a large family of transmembrane heterodimeric glycoproteins (composed of α- and β-subunits) that allow cells to attach to ECM constituents such as laminin and fibronectin, thus functionally and structurally linking the intracellular cytoskeleton with the outside world. Integrins on the surface of leukocytes are also essential in mediating firm adhesion and transmigration across endothelium at sites of inflammation (Chapter 3), and they play a critical role in platelet aggregation (Chapter 4). Integrins attach to ECM components via a tripeptide arginine-glycine-aspartic acid motif (abbreviated RGD). Besides providing focal attachment to underlying substrates, binding through the integrin receptors can also trigger signaling cascades that can influence cell locomotion, proliferation, shape, and differentiation (Fig. 1-16).