inflammatory cells), thus promoting recruitment of the cells into areas of inflammation and tissue injury.

Vascular Endothelial Growth Factor. Vascular endothelial growth factors (VEGFs)—VEGF-A, -B, -C, and -D, and PlGF (placental growth factor)—are a family of homodimeric proteins. VEGF-A is generally referred to simply as VEGF; it is the major *angiogenic* factor (inducing blood vessel development) after injury and in tumors. In comparison, VEGF-B and PlGF are involved in embryonic vessel development, and VEGF-C and -D stimulate both angiogenesis and lymphatic development (*lymphangiogenesis*). VEGFs are also involved in the maintenance of normal adult endothelium (i.e., not involved in angiogenesis), with the highest expression in epithelial cells adjacent to fenestrated epithelium (e.g., podocytes in the kidney, pigment epithelium in the retina, and choroid plexus in the brain). VEGF induces angiogenesis by promoting endothelial cell migration, proliferation (capillary sprouting), and formation of the vascular lumen. VEGFs also induce vascular dilation and increased vascular permeability. As might be anticipated, hypoxia is the most important inducer of VEGF production, through pathways that involve intracellular hypoxia-inducible factor (HIF-1). Other VEGF inducers—produced at sites of inflammation or wound healing—include PDGF and TGF-α.

VEGFs bind to a family of receptor tyrosine kinases (VEGFR-1, -2, and -3); VEGFR-2 is highly expressed in endothelium and is the most important for angiogenesis. Antibodies against VEGF are approved for the treatment of several tumors such as renal and colon cancers since they require angiogenesis for their spread and growth. Anti-VEGF antibodies are also being used for a number of ophthalmic diseases including "wet" age-related macular degeneration (AMD is a disorder of inappropriate angiogenesis and vascular permeability that causes adult-onset blindness); the angiogenesis associated with retinopathy of prematurity; and the leaky vessels that lead to diabetic macular edema. Finally, increased levels of soluble versions of VEGFR-1 (s-FLT-1) in pregnant women may cause preeclampsia (hypertension and proteinuria) by "sopping up" the free VEGF required for maintaining normal endothelium.

Fibroblast Growth Factor. Fibroblast growth factor (FGF) is a family of growth factors with of more than 20 members. Acidic FGF (aFGF, or FGF-1) and basic FGF (bFGF, or FGF-2) are the best characterized; FGF-7 is also referred to as keratinocyte growth factor (KGF). Released FGFs associate with heparan sulfate in the extracellular matrix, which serves as a reservoir for inactive factors that can be subsequently released by proteolysis (e.g., at sites of wound healing). FGFs transduce signals through four tyrosine kinase receptors (FGFR 1-4). FGFs contribute to wound healing responses, hematopoiesis, and development; bFGF has all the activities necessary for angiogenesis as well.

Transforming Growth Factor-β. TGF-β, which is distinct from TGF-α, has three isoforms (TGF-β1, TGF-β2, TGF-β3), each belonging to a family of about 30 members that includes bone morphogenetic proteins (BMPs), activins, inhibins, and müllerian inhibiting substance. TGF-β1 has the most widespread distribution, and is more commonly referred to as TGF-β. It is a homodimeric protein produced by multiple cell types, including platelets, endothelium, and mononuclear inflammatory cells; TGF-β is secreted as a precursor that requires proteolysis to yield the biologically active protein. There are two TGF-β receptors (types I and II), both with serine/threonine kinase activity that induce the phosphorylation of a variety of downstream cytoplasmic transcription factors called *Smads*. Phosphorylated Smads form heterodimers with Smad4, allowing nuclear translocation and association with other DNA-binding proteins to activate or inhibit gene transcription. TGF-β has multiple and often opposing effects depending on the tissue and concurrent signals. Agents with such multiplicity of effects are called *pleiotropic*. Because of the bewildering diversity of TGF-β effects (see later), this growth factor is said to be "pleiotropic with a vengeance." Primarily, however, TGF-β drives scar formation, and applies brakes on the inflammation that accompanies wound healing.

- TGF-β stimulates the production of collagen, fibronectin, and proteoglycans, and it inhibits collagen degradation by both decreasing matrix metalloproteinase (MMP) activity and increasing the activity of tissue inhibitors of proteinases (TIMPs; discussed later). TGF-β is involved not only in scar formation after injury, but also drives fibrosis in lung, liver, and kidneys in the setting of chronic inflammation.
- TGF-β is an antiinflammatory cytokine that serves to limit and terminate inflammatory responses. It does this by inhibiting lymphocyte proliferation and the activity of other leukocytes. Animal models lacking TGF-β have widespread and persistent inflammation.

Interaction with the Extracellular Matrix

Extracellular matrix (ECM) is a network of interstitial proteins that constitutes a significant proportion of any tissue. **Cell interactions with ECM are critical for development and healing, as well as for maintaining normal tissue architecture** (Fig. 1-12). Much more than a simple "space filler" around cells, ECM serves several key functions:

- *Mechanical support* for cell anchorage and cell migration, and maintenance of cell polarity
- *Control of cell proliferation,* by binding and displaying growth factors and by signaling through cellular receptors of the integrin family. As discussed earlier, the ECM provides a depot for a variety of latent growth factors that can be activated within foci of injury or inflammation.
- *Scaffolding for tissue renewal*. Because maintenance of normal tissue structure requires a basement membrane or stromal scaffold, the integrity of the basement membrane or the stroma of parenchymal cells is critical for the organized regeneration of tissues. Thus, ECM disruption results in defective tissue regeneration and repair, as occurs in the development of liver cirrhosis following injury to the liver cells and the collapse of the hepatic stroma.
- *Establishment of tissue microenvironments*. Basement membrane acts as a boundary between epithelium and