in the formation of a scar (Fig. 3-27*B*), which may remodel over time.

Macrophages play a central role in repair by clearing offending agents and dead tissue, providing growth factors for the proliferation of various cells, and secreting cytokines that stimulate fibroblast proliferation and connective tissue synthesis and deposition. The macrophages that are involved in repair are mostly of the alternatively activated (M2) type. It is not clear how the classically activated macrophages that dominate during inflammation, and are involved in getting rid of microbes and dead tissues, are gradually replaced by alternatively activated macrophages that serve to terminate inflammation and induce repair.

Repair begins within 24 hours of injury by the emigration of fibroblasts and the induction of fibroblast and endothelial cell proliferation. By 3 to 5 days, the specialized granulation tissue that is characteristic of healing is apparent.

We next describe the steps in the formation of granulation tissue and the scar.

Angiogenesis

Angiogenesis is the process of new blood vessel development from existing vessels. It is critical in healing at sites of injury, in the development of collateral circulations at sites of ischemia, and in allowing tumors to increase in size beyond the constraints of their original blood supply. Much work has been done to understand the mechanisms underlying angiogenesis, and therapies to either augment the process (e.g., to improve blood flow to a heart ravaged by coronary atherosclerosis) or inhibit it (to frustrate tumor growth or block pathologic vessel growth such as in diabetic retinopathy) are being developed.

Angiogenesis involves sprouting of new vessels from existing ones, and consists of the following steps (Fig. 3-28):

- Vasodilation in response to nitric oxide and increased permeability induced by vascular endothelial growth factor (VEGF)
- Separation of pericytes from the abluminal surface and breakdown of the basement membrane to allow formation of a vessel sprout
- Migration of endothelial cells toward the area of tissue injury
- Proliferation of endothelial cells just behind the leading front ("tip") of migrating cells
- Remodeling into capillary tubes
- Recruitment of periendothelial cells (pericytes for small capillaries and smooth muscle cells for larger vessels) to form the mature vessel
- Suppression of endothelial proliferation and migration and deposition of the basement membrane.

The process of angiogenesis involves several signaling pathways, cell-cell interactions, ECM proteins, and tissue enzymes.

- **Growth factors.** *Vascular endothelial growth factors (VEGFs)*, mainly VEGF-A (Chapter 1), stimulates both migration and proliferation of endothelial cells, thus initiating the process of capillary sprouting in angiogenesis. It promotes vasodilation by stimulating the production of NO and contributes to the formation of the vascular lumen. *Fibroblast growth factors (FGFs)*, mainly FGF-2, stimulates the proliferation of endothelial cells. It also promotes the migration of macrophages and fibroblasts to the damaged area, and stimulates epithelial cell migration to cover epidermal wounds. *Angiopoietins 1 and 2 (Ang 1 and Ang 2)* are growth factors that play a role in angiogenesis and the structural maturation of new vessels. Newly formed vessels need to be stabilized by the recruitment of pericytes and smooth muscle cells and by the deposition of connective tissue. Ang1 interacts with a tyrosine kinase receptor on endothelial cells called Tie2. The growth factors PDGF and TGF-β also participate in the stabilization process: PDGF recruits smooth muscle cells and TGF-β suppresses endothelial proliferation and migration, and enhances the production of ECM proteins.
- **Notch signaling.** Through "cross-talk" with VEGF, the Notch signaling pathway regulates the sprouting and branching of new vessels and thus ensures that the new vessels that are formed have the proper spacing to effectively supply the healing tissue with blood.

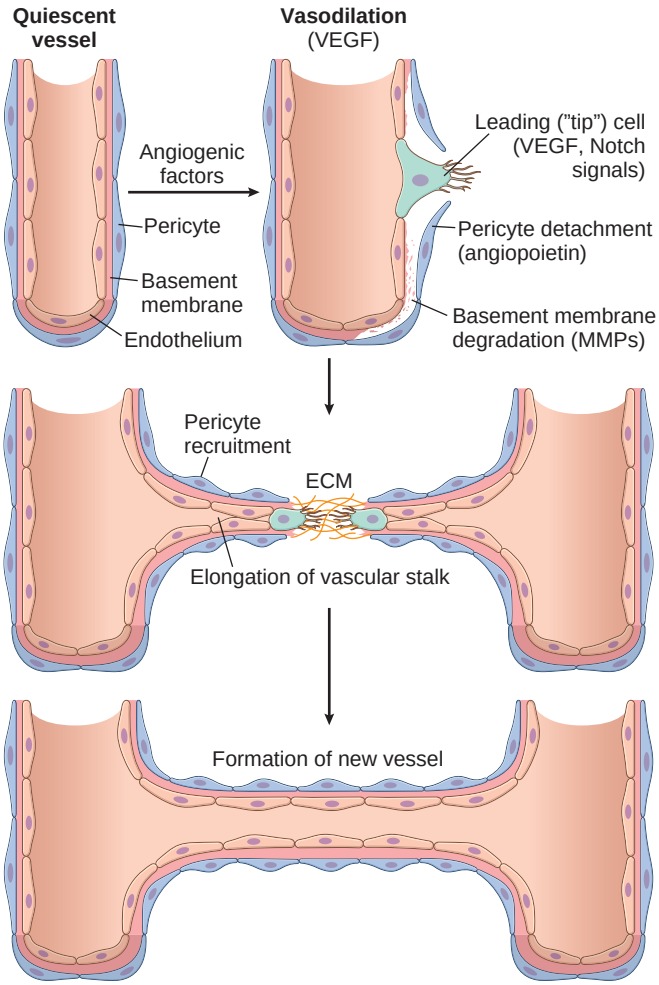

Figure 3-28 Angiogenesis. In tissue repair, angiogenesis occurs mainly by sprouting of new vessels. The steps in the process, and the major signals involved, are illustrated. The newly formed vessel joins up with other vessels (not shown) to form the new vascular bed.