Formation of Embryonic Blood Vessels

The early embryo is devoid of blood vessels. Although blood islands appear in the wall of the yolk sac and extraembryonic vascular channels form in association with them (see Figure 6-17), much of the vasculature of the embryonic body is derived from intraembryonic sources. During the early period of somite formation, networks of small vessels rapidly appear in many regions of the embryonic body.

The formation of blood vessels in the embryo consists of several phases (Figure 17-6). The first is the specification of a population of vascular precursors, called **angioblasts**. These cells then become organized into a **primary capillary plexus** through a process known as **vasculogenesis**. To keep pace with rapidly growing embryo,

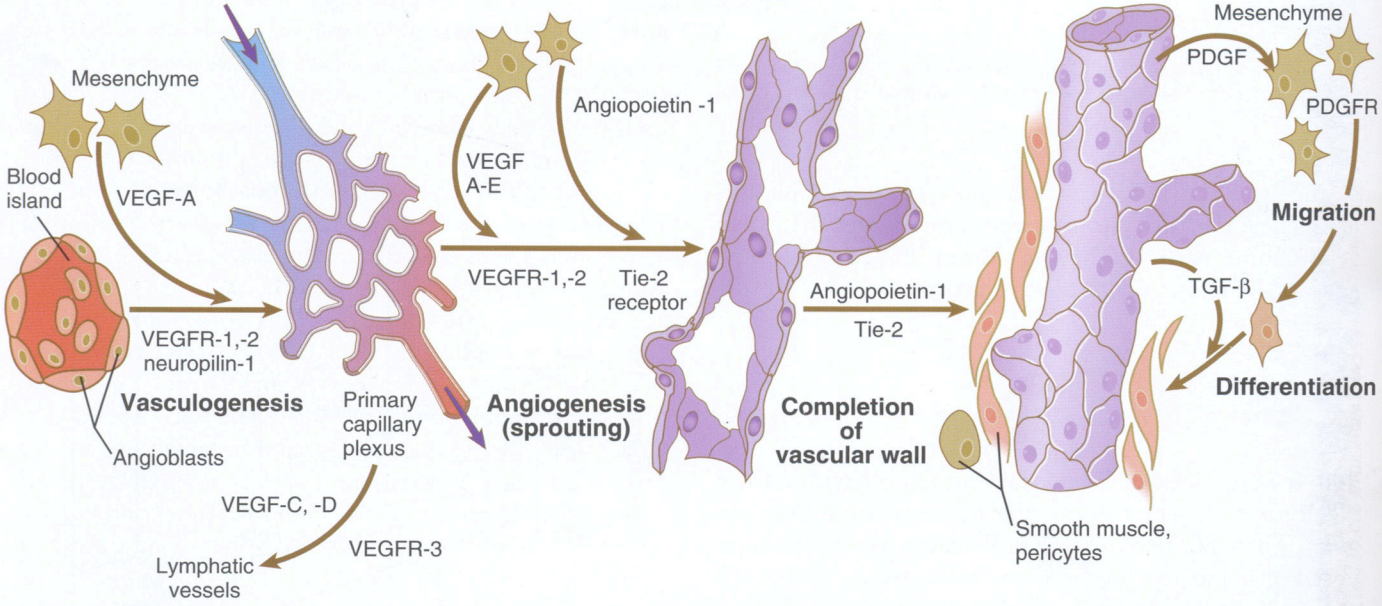

FIGURE 17-6 Scheme illustrating vasculogenesis, angiogenesis, and assembly of the vascular wall. Angioblasts, initially expressing vascular endothelial growth factor receptor (VEGFR-2), are stimulated by VEGF-A, secreted by the surrounding mesenchyme, to form the primary capillary plexus by the process of vasculogenesis. Under additional stimulation by growth factors, competent endothelial cells of the primary capillary plexus form vascular sprouts in the earliest stages of angiogenesis. This is followed by the recruitment of surrounding mesenchymal cells to form the cellular elements of the vascular wall. Early in vasculogenesis, endothelial cells that express VEGFR-3 respond to VEGF stimulation by differentiating into the precursors of the lymphatic vessels. *PDGF,* platelet-derived growth factor; *PDGFR,* platlet-derived growth factor receptor.

the primary capillary plexus must rapidly undergo reorganization through the resorption of existing vessels and the sprouting of new branches to support the expanding vascular network. This latter process is called **angiogenesis.** Angiogenesis continues not only in the prenatal period, but throughout adult life, as tissues and organs continually adapt to changing conditions of life, whether normal or pathological.

Detailed descriptive studies and transplantation experiments involving intrinsic cellular labels or graft-specific monoclonal antibody labels have shown that **angioblasts** arise from most mesodermal tissues of the body except notochord and prechordal mesoderm (Table 17-2). Embryonic blood vessels form from angioblasts by three main mechanisms. Many of the larger blood vessels, such as the dorsal aortae, are formed by the coalescence of angioblasts in situ. Other equally large channels, such as the endocardium, are formed by angioblasts migrating into the region from other sites. Other vessels, especially the intersegmental vessels of the main body axis and vessels of the central nervous system, arise as vascular sprouts from existing larger vessels. Many of the angioblasts of the trunk are originally associated with the splanchnic mesoderm.

All stages in the formation of the vascular system occur in response to the influence of powerful growth factors and their receptors. The initial phase of recruitment of a population of angioblasts from the mesoderm is characterized by the appearance of a transmembrane **vascular endothelial growth factor receptor** (VEGFR-2) on their surfaces (see Figure 17-6). Soon, in response to the production of **vascular endothelial growth factor** (VEGF-A) by the surrounding mesenchyme, the phase of vasculogenesis takes place, and the angioblasts form the cellular tubes that become the basis for the primary capillary plexus.

TABLE 17-2 *Distribution of Endogenous Angioblasts in Embryonic Tissues*

Tissues	Angioblasts
CEPHALIC	
Paraxial mesoderm	+
Lateral mesoderm	+
Prechordal mesoderm	−
Notochord	−
Brain	−
Neural crest	−
TRUNK	
Whole somites	+
Dorsal half somites	+
Segmental plate mesoderm	+
Lateral somatic mesoderm	+
Lateral splanchnic mesoderm	+
Spinal cord	−

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The formation of vascular endothelial sprouts, the cellular basis for angiogenesis, occurs against a background of VEGF/VEGFR-1 and -2 interactions, but with a new set of players added. A sprouting factor, **angiopoietin-1,** interacts with its receptor, **Tie-2,** on the endothelial cells at sites where endothelial sprouts will occur. The **Notch** signaling pathway is also strongly tied to the formation of vascular sprouts (a common denominator with other organ systems that display branching morphogenesis), but its connection to the angiopoietin-1/Tie-2 mechanism remains unclear.

The next step in building a blood vessel is formation of the vascular wall, which in the trunk and extremities is derived from local mesoderm that becomes associated with the endothelial lining of the vessel. In the head and many areas of the aortic arch system, mesenchyme derived from neural crest ectoderm is a major contributor to the connective tissue and smooth muscle of the vascular wall. The neural crest, however, does not give rise to endothelial cells.

Two-way molecular signaling is involved in building up the walls of blood vessels. In response to the angiopoietin-1/Tie-2 interaction that occurs during angiogenesis, the endothelial cells release their own signaling molecule, **platelet-derived growth factor** (PDGF), which stimulates the migration of mesenchymal cells toward the vascular endothelium. The release of other growth factors (possibly transforming growth factor-β [TGF-β]) by the endothelial cells stimulates the differentiation of the mesenchymal cells into vascular smooth muscle or pericytes.

Recent research has shed considerable light on the differentiation of the arterial vs. venous system. In contrast to previous assumptions that physiological and local environmental factors determine whether a developing vessel will become an artery or a vein, it is now known that the arterial or venous identity of endothelial cells is established very early in their development—prior to angiogenesis and before the onset of circulation. Endothelial cells of developing arteries express the membrane-bound ligand **Ephrin-B2,** whereas those of developing veins express the receptor **Eph-B4** on their surface membranes. These characteristic phenotypes appear to be the result of earlier signaling by the Notch system. **Notch** and its ligands **Delta** and **Jagged** are expressed in arterial endothelium, and experimental evidence suggests that Notch signaling in developing arteries may act to suppress the venous identity of endothelial cells.

As with myoblasts, angioblasts appear to react to local environmental cues that determine the specific

morphological pattern of a blood vessel. An unexpected recent finding is that in the skin, at least, the pattern of the peripheral innervation determines the pattern of the smaller arteries and that the effective patterning agent is the secretion of VEGF by the nerves. Tracing studies of transplanted angioblasts have shown that some can migrate long distances. Angioblasts that have migrated far from the place into which they were grafted become integrated into morphologically normal blood vessels in the areas where they settle.

Local factors also influence the initiation of vasculogenesis. In some organs (e.g., the liver) or parts of organs (e.g., the bronchi of the respiratory system), the blood vessels supplying the regions arise from local mesoderm, whereas other organs (e.g., the metanephric kidneys) or parts of organs (e.g., the alveoli of the lungs) are supplied by blood vessels that grow into the mesenchyme from other tissues. In the latter type of vascularization mechanism, evidence is increasing that these organ primordia produce their own **angiogenesis factors** that stimulate the growth of vascular sprouts (by promoting mitosis of endothelial cells) into the glandular mesenchyme.