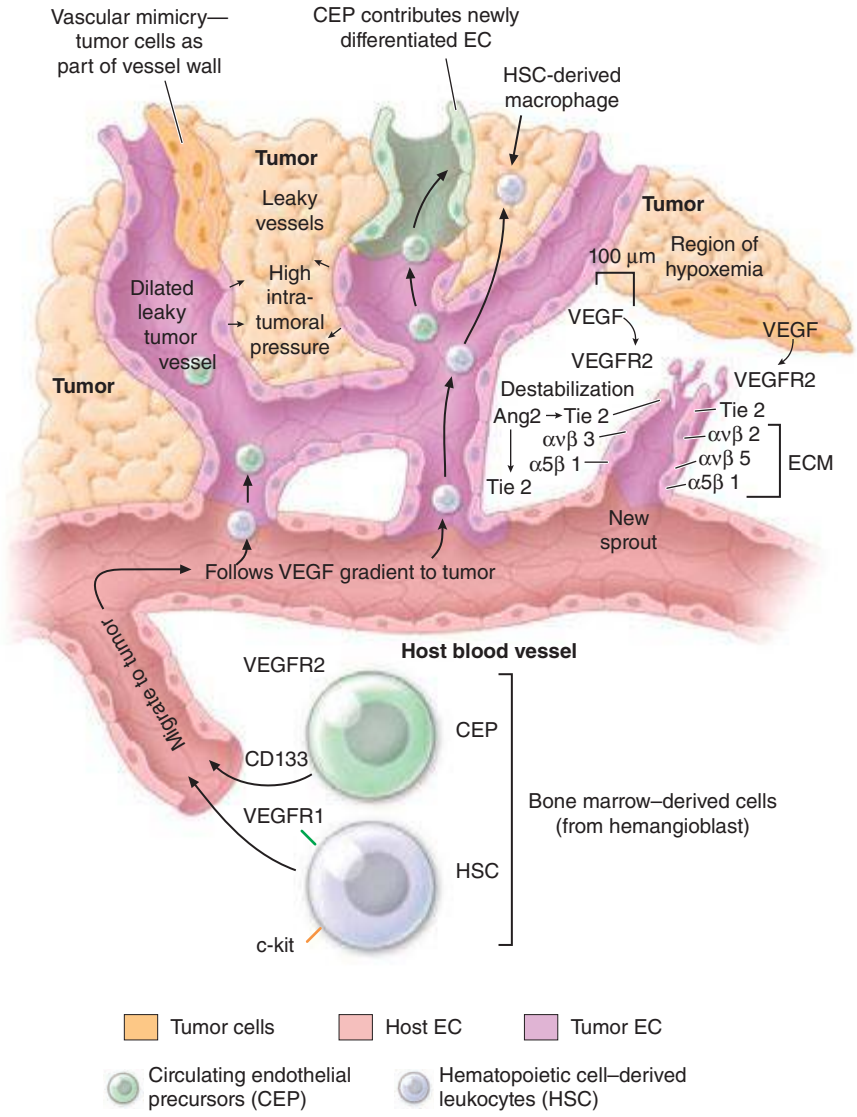

FIGURE 102e-9 Tumor angiogenesis is a complex process involving many different cell types that must proliferate, migrate, invade, and differentiate in response to signals from the tumor microenvironment. Endothelial cells (ECs) sprout from host vessels in response to VEGF, bFGF, Ang2, and other proangiogenic stimuli. Sprouting is stimulated by VEGF/VEGFR2, Ang2/Tie2, and integrin/extracellular matrix (ECM) interactions. Bone marrow–derived circulating endothelial precursors (CEPs) migrate to the tumor in response to VEGF and differentiate into ECs, while hematopoietic stem cells differentiate into leukocytes, including tumor-associated macrophages that secrete angiogenic growth factors and produce matrix metalloproteinases (MMPs) that remodel the ECM and release bound growth factors. Tumor cells themselves may directly form parts of vascular channels within tumors. The pattern of vessel formation is haphazard: vessels are tortuous, dilated, and leaky and branch in random ways. This leads to uneven blood flow within the tumor, with areas of acidosis and hypoxemia (which stimulate release of angiogenic factors) and high intratumoral pressures that inhibit delivery of therapeutic agents.

angiogenic molecules, the most potent being vascular endothelial growth factors (VEGF), that induce the proliferation and migration of host ECs into the tumor. Sprouting in normal and pathogenic angiogenesis is regulated by three families of transmembrane receptor tyrosine kinases (RTKs) expressed on ECs and their ligands (VEGFs, angiopoietins, ephrins; Fig. 102e-10), which are produced by tumor cells, inflammatory cells, or stromal cells in the tumor microenvironment.

When tumor cells arise in or metastasize to an avascular area, they grow to a size limited by hypoxemia and nutrient deprivation. Hypoxemia, a key regulator of tumor angiogenesis, causes the transcriptional induction of the gene encoding VEGF. VEGF and its receptors are required for embryonic *vasculogenesis* (development of new blood vessels when none preexist) and normal (wound healing, corpus luteum formation) and pathologic angiogenesis (tumor angiogenesis, inflammatory conditions such as rheumatoid arthritis). VEGF-A is a heparin-binding glycoprotein with at least four isoforms (splice variants) that regulates blood vessel formation by binding to the RTKs VEGFR1 and VEGFR2, which are expressed on all ECs in addition to a subset of hematopoietic cells (Fig. 102e-9). VEGFR2 regulates EC proliferation, migration, and survival, whereas VEGFR1 may act as an antagonist of R2 in ECs but is probably also important for angioblast differentiation during embryogenesis. Tumor vessels may be more dependent on VEGFR signaling for growth and survival than normal ECs. Although VEGF signaling is a critical initiator of angiogenesis, this is a complex process regulated by additional signaling pathways (Fig. 102e-10). The angiopoietin, Ang1, produced by stromal cells, binds to the EC RTK Tie2 and promotes the interaction of ECs with the ECM and perivascular cells, such as pericytes and smooth-muscle cells, to form tight, nonleaky vessels. Platelet-derived growth factor (PDGF) and basic fibroblast growth factor (bFGF) help to recruit these perivascular cells. Ang1 is required for maintaining the quiescence and stability of mature blood vessels and prevents the vascular permeability normally induced by VEGF and inflammatory cytokines.