- Relative lack of oxygen due to hypoxia stabilizes HIF1α, an oxygen-sensitive transcription factor mentioned earlier, which then activates the transcription of the pro-angiogenic cytokines VEGF and bFGF. These factors create an angiogenic gradient that stimulates the proliferation of endothelial cells and guides the growth of new vessels toward the tumor. VEGF also increases the expression of ligands that activate the Notch signaling pathway, which regulates the branching and density of the new vessels (Chapter 3).
- Mutations involving tumor suppressors and oncogenes in cancers also tilt the balance in favor of angiogenesis. For example, p53 can stimulate expression of antiangiogenic molecules, such as thrombospondin-1, and repress expression of proangiogenic molecules such as VEGF. Thus, loss of p53 in tumor cells not only removes cell cycle checkpoints and alters tumor cell metabolism but also provides a more permissive environment for angiogenesis.
- The transcription of VEGF is also influenced by signals from the RAS-MAP kinase pathway, and gain-of-function mutations in *RAS* or *MYC* upregulate the production of VEGF. bFGF and VEGF are commonly expressed in a wide variety of tumor cells, and elevated levels can be detected in the serum and urine of a significant fraction of cancer patients.

The idea that angiogenesis is essential if solid tumors are to grow to clinically significant sizes has provided a powerful impetus for the development of therapeutic agents that block angiogenesis. These agents are now a part of the armamentarium that oncologists use against cancers; a cardinal example is bevacizumab, a monoclonal antibody that neutralizes VEGF activity and is approved for use in the treatment of multiple cancers. However, angiogenesis inhibitors have not been nearly as effective as was hoped based on preclinical studies conducted using mouse models of cancer; they can prolong life, but usually for only a few months and at very high financial cost. The mechanisms that underlie the persistence and ultimate progression of cancers in the face of therapy with angiogenesis inhibitors are not yet clear. Perhaps there is emergence of tumor subclones that by virtue of greater invasive and metastatic potential gain ready access to existing host vessels. The modest benefit of anti-angiogenic therapy highlights the pernicious nature of advanced cancers, which can even elude therapies directed at stromal support cells such as endothelium that are genomically stable and thus presumably "immune" to the Darwinian pressures that lead cancer cells to acquire more malignant phenotypes over time. Improvements are only possible with greater understanding of the "escape routes" through which tumor cells sidestep the effects of the angiogenesis inhibitors that are now in use.

KEY CONCEPTS

Angiogenesis

- Vascularization of tumors is essential for their growth and is controlled by the balance between angiogenic and anti-angiogenic factors that are produced by tumor and stromal cells.
- Hypoxia triggers angiogenesis through the actions of HIF-1α on the transcription of the proangiogenic factor VEGF.
- Many other factors regulate angiogenesis; for example, p53 induces synthesis of the angiogenesis inhibitor thombospondin-1, while RAS, MYC, and MAPK signaling all upregulate VEGF expression and stimulate angiogenesis.
- VEGF inhibitors are used to treat a number of advanced cancers and prolong the clinical course, but are not curative.

Invasion and Metastasis

Invasion and metastasis are the results of complex interactions between cancer cells and normal stroma and are the major causes of cancer-related morbidity and mortality. Hence, they are the subjects of intense scrutiny. Studies in mice and humans reveal that although millions of cells are released into the circulation each day from a primary tumor, only a few metastases are produced. Indeed, tumor cells can be frequently detected in the blood and marrow of patients with breast cancer who have not, and do not ever, develop overt metastatic disease. Why is the metastatic process so inefficient? For tumor cells to emerge from a primary mass, enter blood vessels or lymphatics, and produce a secondary growth at a distant site, they must go through a series of steps (summarized in Fig. 7-36), each of which is inefficient and subject to a multitude of controls; hence, at any point in the sequence, the breakaway cells may not survive. In this discussion, the metastatic cascade is divided into two phases: (1) invasion of the extracellular matrix (ECM) and (2) vascular dissemination, homing of tumor cells, and colonization. Subsequently, the molecular genetics of the metastatic cascade, as currently understood, are presented.

Invasion of Extracellular Matrix

The structural organization and function of normal tissues is to a great extent determined by interactions between cells and the ECM. As discussed in Chapter 1, tissues are organized into compartments separated from each other by two types of ECM: basement membrane and interstitial connective tissue. Although organized differently, each of these components of ECM is made up of collagens, glycoproteins, and proteoglycans. As shown in Figure 7-36, tumor cells must interact with the ECM at several stages in the metastatic cascade. A carcinoma must first breach the underlying basement membrane, then traverse the interstitial connective tissue, and ultimately gain access to the circulation by penetrating the vascular basement membrane. This process is repeated in reverse when tumor cell emboli extravasate at a distant site. Invasion of the ECM initiates the metastatic cascade and is an active process that can be resolved into several steps (Fig. 7-37):

- "Loosening up" of tumor cell–tumor cell interactions
- Degradation of ECM
- Attachment to novel ECM components
- Migration and invasion of tumor cells

Dissociation of cancer cells from one another is often the result of alterations in intercellular adhesion molecules and is the first step in the process of invasion.