ECM-sequestered growth factors. Indeed, cleavage products of collagen and proteoglycans also have chemotactic, angiogenic, and growth-promoting effects. For example, MMP9 is a gelatinase that cleaves type IV collagen of the epithelial and vascular basement membrane and also stimulates release of VEGF from ECM-sequestered pools. Benign tumors of the breast, colon, and stomach show little type IV collagenase activity, whereas their malignant counterparts overexpress this enzyme. Concurrently, the concentrations of metalloproteinase inhibitors are reduced so that the balance is tilted greatly toward tissue degradation. Indeed, overexpression of MMPs and other proteases has been reported for many tumors.

The third step in invasion involves changes in attachment of tumor cells to ECM proteins. Normal epithelial cells have receptors, such as integrins, for basement membrane laminin and collagens that are polarized at their basal surface; these receptors help to maintain the cells in a resting, differentiated state. Loss of adhesion in normal cells leads to induction of apoptosis, while, not surprisingly, tumor cells are resistant to this form of cell death. Additionally, the matrix itself is modified in ways that promote invasion and metastasis. For example, cleavage of the basement membrane proteins collagen IV and laminin by MMP2 or MMP9 generates novel sites that bind to receptors on tumor cells and stimulate migration.

Locomotion is the final step of invasion, propelling tumor cells through the degraded basement membranes and zones of matrix proteolysis. Migration is a multistep process that involves many families of receptors and signaling proteins that eventually impinge on the actin cytoskeleton. Cells must attach to the matrix at the leading edge, detach from the matrix at the trailing edge, and contract the actin cytoskeleton to ratchet forward. Such movement seems to be stimulated and directed by tumor cell-derived cytokines, such as autocrine motility factors. In addition, cleavage products of matrix components (e.g., collagen, laminin) and some growth factors (e.g., IGFs I and II) have chemotactic activity for tumor cells. Furthermore, proteolytic cleavage liberates growth factors bound to matrix molecules. Stromal cells also produce paracrine effectors of cell motility, such as hepatocyte growth factor/scatter factor, which binds to the receptor tyrosine kinase MET on tumor cells. The concentration of hepatocyte growth factor/scatter factor is elevated at the advancing edge of the highly invasive brain tumor glioblastoma, supporting its role in motility.

It has become clear in recent years that the ECM and stromal cells surrounding tumor cells are not a mere static barrier for tumor cells to traverse but instead constitute a varied environment in which reciprocal signaling between tumor cells and stromal cells may either promote or prevent tumorigenesis and/or tumor progression. Stromal cells that interact with tumors include innate and adaptive immune cells (discussed later), as well as fibroblasts. A variety of studies have demonstrated that tumor-associated fibroblasts exhibit altered expression of genes that encode ECM molecules, proteases, protease inhibitors, and various growth factors. Thus, tumor cells reside in a complex and ever-changing milieu composed of ECM, growth factors, fibroblasts, and immune cells, with significant cross-talk among all the components. It is easy to imagine that tumors come to be dominated by subclones that are most successful at co-opting this environment to their own malignant purposes.

Vascular Dissemination and Homing of Tumor Cells

Once in the circulation, tumor cells are vulnerable to destruction by a variety of mechanisms, including mechanical shear stress, apoptosis stimulated by loss of adhesion (termed *anoikis*), and innate and adaptive immune defenses. The details of tumor immunity are considered later.

Within the circulation, tumor cells tend to aggregate in clumps. This is favored by homotypic adhesions among tumor cells as well as heterotypic adhesion between tumor cells and blood cells, particularly platelets (Fig. 7-36). Formation of platelet-tumor aggregates may enhance tumor cell survival and implantability. Tumor cells may also bind and activate coagulation factors, resulting in the formation of emboli. Arrest and extravasation of tumor emboli at distant sites involves adhesion to the endothelium, followed by egress through the basement membrane. Involved in these processes are adhesion molecules (integrins, laminin receptors) and proteolytic enzymes, discussed earlier. Of particular interest is the CD44 adhesion molecule, which is expressed on normal T lymphocytes and is used by these cells to migrate to selective sites in lymphoid tissues. Such migration is accomplished by the binding of CD44 to hyaluronate on high endothelial venules. Solid tumors also often express CD44, which appears to enhance their spread to lymph nodes and other metastatic sites.

The site at which circulating tumor cells leave the capillaries to form secondary deposits is related to the anatomic location and vascular drainage of the primary tumor and the tropism of particular tumors for specific tissues. Most metastases occur in the first capillary bed available to the tumor. Many observations, however, suggest that natural pathways of drainage do not wholly explain the distribution of metastases. For example, prostatic carcinoma preferentially spreads to bone, bronchogenic carcinomas tend to involve the adrenals and the brain, and neuroblastomas spread to the liver and bones. Such organ tropism may be related to the following mechanisms:

- Tumor cells may have adhesion molecules whose ligands are expressed preferentially on the endothelial cells of the target organ.
- Chemokines have an important role in determining the target tissues for metastasis. For instance, some breast cancer cells express the chemokine receptors CXCR4 and CCR7.
- In some cases, the target tissue may be a nonpermissive environment—"unfavorable soil," so to speak, for the growth of tumor seedlings. For example, although well-vascularized, skeletal muscle and spleen are rarely sites of metastasis.

Alas, tumor cells do not read textbooks of pathology, and there is still much to be learned about the factors that govern their spread. Despite their "cleverness" in escaping their tissue of origin, circulating tumor cells are quite inefficient in colonizing distant organs. Moreover, even when metastases are established, they may grow to only small, clinically insignificant sizes. Indeed, the concept of *dormancy*, referring to the prolonged survival