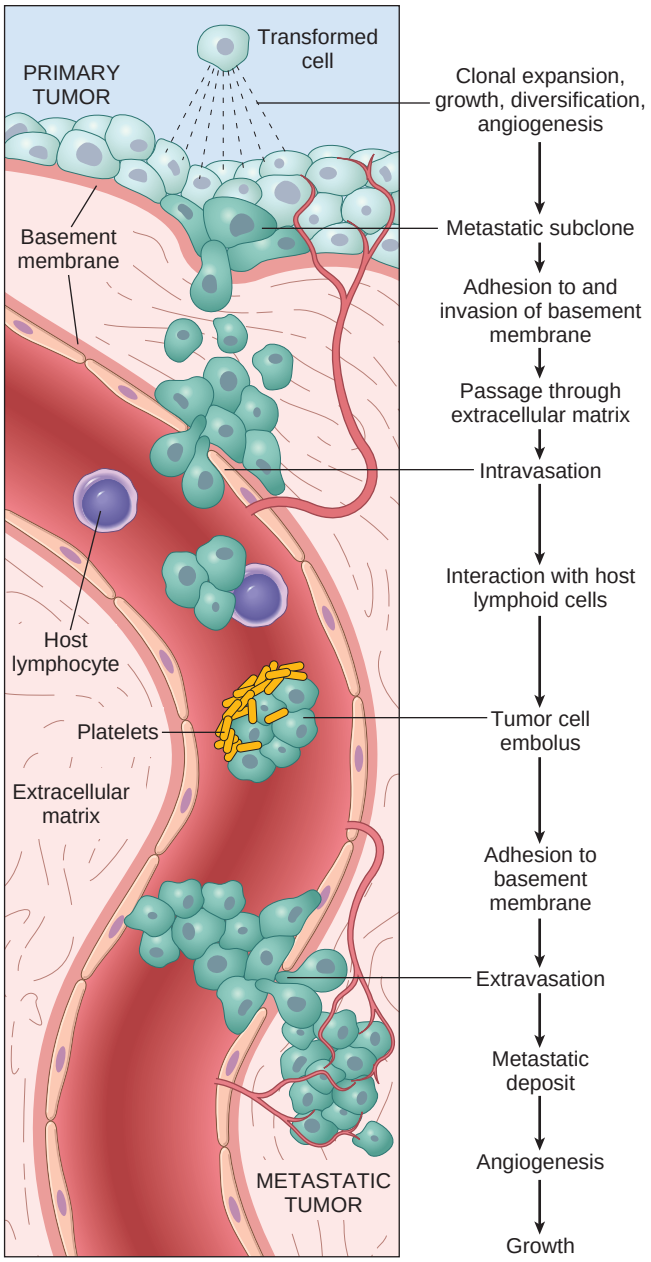

Figure 7-36 The metastatic cascade. Sequential steps involved in the hematogenous spread of a tumor.

Normal epithelial cells are tightly glued to each other and the ECM by a variety of adhesion molecules. Cell-cell interactions are mediated by the cadherin family of transmembrane glycoproteins. *E-cadherins* mediate the homotypic adhesion of epithelial cells, serving to both hold the cells together and to relay signals between the cells. In several epithelial tumors, including adenocarcinomas of the colon, stomach, and breast, E-cadherin function is lost. Presumably, this reduces the ability of cells to adhere to each other and facilitates their detachment from the primary tumor and their advance into the surrounding tissues.

Degradation of the basement membrane and interstitial connective tissue is the second step in invasion. Tumor cells may accomplish this by either secreting proteolytic enzymes themselves or by inducing stromal cells (e.g., fibroblasts and inflammatory cells) to elaborate proteases. Many different families of proteases, such as matrix metalloproteinases (MMPs), cathepsin D, and urokinase plasminogen activator, have been implicated in tumor cell invasion. MMPs regulate tumor invasion not only by remodeling insoluble components of the basement membrane and interstitial matrix but also by releasing

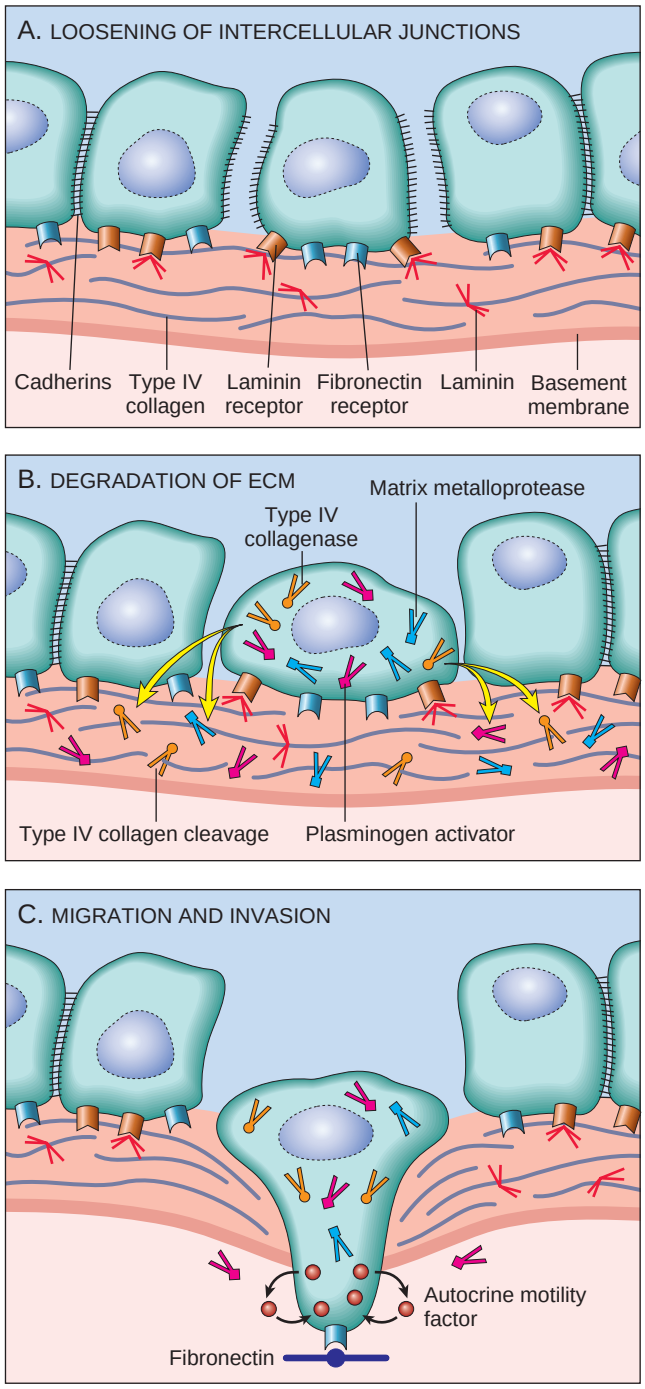

Figure 7-37 Sequence of events in the invasion of epithelial basement membranes by tumor cells. Tumor cells detach from each other because of reduced adhesiveness and attract inflammatory cells. Proteases secreted from tumor cells and inflammatory cells degrade the basement membrane. Binding of tumor cells to proteolytically generated binding sites and tumor cell migration follow.