of micrometastases without progression, is well described in melanoma and in breast and prostate cancer. Although the molecular mechanisms of colonization are still being unraveled in mouse models, a consistent theme seems to be that tumor cells secrete cytokines, growth factors, and ECM molecules that act on the resident stromal cells, which in turn make the metastatic site habitable for the cancer cell. For example, breast cancer metastases to bone are osteolytic because of the activation of osteoclasts in the metastatic site. Breast cancer cells secrete parathyroid hormone-related protein (PTHRP), which stimulates osteoblasts to make RANK ligand (RANKL). RANKL then activates osteoclasts, which degrade the bone matrix and release growth factors embedded within it, like IGF and TGF-β. With a better molecular understanding of the mechanisms of metastasis our ability to target them therapeutically will be greatly enhanced.

Molecular Genetics of Metastasis Development

Why do only some tumors metastasize? What are the genetic and epigenetic changes that allow metastases? Why is the metastatic process so inefficient? Several competing theories have been proposed to explain how the metastatic phenotype arises.

- The *clonal evolution model* suggests that as mutations accumulate in genetically unstable cancer cells and the tumor become heterogeneous (Fig. 7-38*A*), a rare subset of tumor cell subclones acquires a pattern of gene expression that is permissive for all steps involved in metastasis.
- A subset of breast cancers has a metastatic gene expression signature similar to that found in metastases, although no clinical evidence for metastasis is apparent. It is hypothesized that in these tumors with a "*metastasis signature*" most if not all cells develop a predilection for metastatic spread during early stages of carcinogenesis (Fig. 7-38*B*).
- A third idea that combines the two above supposes that the metastatic signature is necessary but not sufficient for metastasis, and that additional mutations are needed for metastasis to occur (Fig. 7-38*C*).
- Finally, there is evidence the capacity for metastasis involves not only properties intrinsic to the cancer cells but also the characteristics of their microenvironment, such as the components of the stroma, the presence of infiltrating immune cells, and angiogenesis (Fig. 7-38*D*).

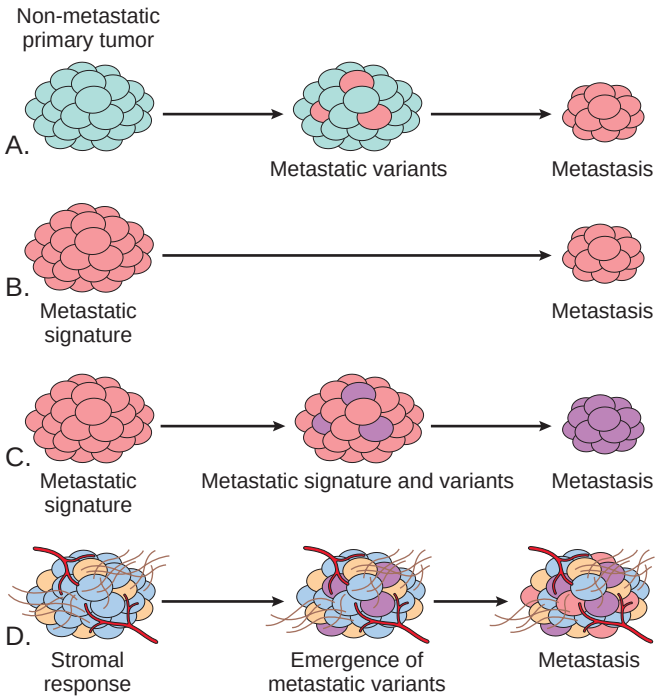

Figure 7-38 Mechanisms of metastasis development within a primary tumor. A nonmetastatic primary tumor is shown (light blue) on the left side of all diagrams. Four models are presented: **A,** Metastasis is caused by rare variant clones that develop in the primary tumor. **B,** Metastasis is caused by the gene expression pattern of most cells of the primary tumor, referred to as a metastatic signature. **C,** A combination of **A** and **B**, in which metastatic variants appear in a tumor with a metastatic gene signature. **D,** Metastasis development is greatly influenced by the tumor stroma, which may regulate angiogenesis, local invasiveness, and resistance to immune elimination, allowing cells of the primary tumor, as in **C**, to become metastatic.

One open question in the field is whether there are genes whose principal or sole contribution to tumorigenesis is to control metastasis. This question is of more than academic interest, because if altered forms of certain genes promote or suppress the metastatic phenotype, their detection in a primary tumor would have both prognostic and therapeutic implications. Because metastasis is a complex phenomenon involving a variety of steps and pathways, it is thought that "metastasis oncogenes" or "metastasis suppressor genes" are few in number. A metastasis suppressor gene is defined as a gene whose loss promotes the development of metastasis without an effect on the primary tumor. At least a dozen genes lost in metastatic lesions have been confirmed to function as "metastasis suppressors." Their molecular functions are varied and not completely clear; however, most appear to affect various signaling pathways.

Among candidates for metastasis oncogenes are *SNAIL* and *TWIST*, which encode transcription factors whose primary function is to promote epithelial-to-mesenchymal transition (EMT). In EMT, carcinoma cells downregulate certain epithelial markers (e.g., E-cadherin) and upregulate certain mesenchymal markers (e.g., vimentin and smooth muscle actin). These changes are believed to favor the development of a promigratory phenotype that is essential for metastasis. Loss of E-cadherin expression seems to be a key event in EMT, and SNAIL and TWIST are transcriptional repressors that downregulate E-cadherin expression. EMT has been documented mainly in breast cancers; whether it is a general phenomenon in other solid tumors remains to be established.

Role of Stromal Elements in Metastasis

In the preceding sections we have seen seen several examples of interaction between tumor cells and stromal elements. For example, macrophages in the stroma secrete matrix-degrading proteases, and cleavage of ECM proteins can release latent angiogenic factors and growth factors, such as TGFβ. Successful tumor cells must co-opt these and other interactions and use them to promote their growth and invasion, and it follows that these interactions, and the stromal cells themselves, are potential targets in cancer treatment. We have already discussed the use of