



FIGURE 102e-6 Oncogene signaling pathways are activated during tumor progression and promote metastatic potential. This figure shows a cancer cell that has undergone epithelial to mesenchymal transition (EMT) under the influence of several environmental signals. Critical components include activated transforming growth factor β (TGF- β) and the hepatocyte growth factor (HGF)/c-Met pathways, as well as changes in the expression of adhesion molecules that mediate cell-cell and cell-extracellular matrix interactions. Important changes in gene expression are mediated by the Snail and Twist family of transcriptional repressors (whose expression is induced by the oncogenic pathways), leading to reduced expression of E-cadherin, a key component of adherens junctions between epithelial cells. This, in conjunction with upregulation of N-cadherin, a change in the pattern of expression of integrins (which mediate cell-extracellular matrix associations that are important for cell motility), and a switch in intermediate filament expression from cytokeratin to vimentin, results in the phenotypic change from adherent highly organized epithelial cells to motile and invasive cells with a fibroblast or mesenchymal morphology. EMT is thought to be an important step leading to metastasis in some human cancers. Host stromal cells, including tumor-associated fibroblasts and macrophages, play an important role in modulating tumor cell behavior through secretion of growth factors and proangiogenic cytokines, and matrix metalloproteinases that degrade the basement membrane. VEGF-A, -C, and -D are produced by tumor cells and stromal cells in response to hypoxemia or oncogenic signals and induce production of new blood vessels and lymphatic channels through which tumor cells metastasize to lymph nodes or tissues.

and OPG determines the activation state of RANK on osteoclasts. Many tumors increase osteoclast activity by secretion of substances such as parathyroid hormone (PTH), PTH-related peptide, interleukin (IL)-1, or Mip1 that perturb the homeostatic balance of bone remodeling by increasing RANK signaling. One example is multiple myeloma, where tumor cell-stromal cell interactions activate osteoclasts and inhibit osteoblasts, leading to the development of multiple lytic bone lesions. Inhibition of RANKL by an antibody (denosumab) can prevent further bone destruction. Bisphosphonates are also effective inhibitors of osteoclast function that are used in the treatment of cancer patients with bone metastases.

CANCER STEM CELLS

Only a small proportion of the cells within a tumor are capable of initiating colonies *in vitro* or forming tumors at high efficiency when injected into immunocompromised NOD/SCID mice. Acute and chronic myeloid leukemias (AML and CML) have a small population of cells (<1%) that have properties of stem cells, such as unlimited self-renewal and the capacity to cause leukemia when serially transplanted in mice. These cells have an undifferentiated phenotype (Thy1-CD34+CD38- and do not express other differentiation markers) and resemble normal stem cells in many ways, but are no longer under

homeostatic control (Fig. 102e-7). Solid tumors may also contain a population of stem cells. Cancer stem cells, like their normal counterparts, have unlimited proliferative capacity and paradoxically traverse the cell cycle at a very slow rate; cancer growth occurs largely due to expansion of the stem cell pool, the unregulated proliferation of an amplifying population, and failure of apoptosis pathways (Fig. 102e-7). Slow cell cycle progression and high levels of expression of antiapoptotic Bcl-2 family members and drug efflux pumps of the MDR family render cancer stem cells less vulnerable to cancer chemotherapy or radiation therapy. Implicit in the cancer stem cell hypothesis is the idea that failure to cure most human cancers is due to the fact that current therapeutic agents do not kill the stem cells. If cancer stem cells can be identified and isolated, then aberrant signaling pathways that distinguish these cells from normal tissue stem cells can be identified and targeted. Evidence that cells with stem cell properties can arise from other epithelial cells within the cancer by processes such as epithelial mesenchymal transition also implies that it is essential to treat all of the cancer cells, and not just those with current stem cell-like properties, in order to eliminate the self-renewing cancer cell population. The exact nature of cancer stem cells remains an area of investigation. One of the unanswered questions is the exact origin of cancer stem cells for the different cancers.