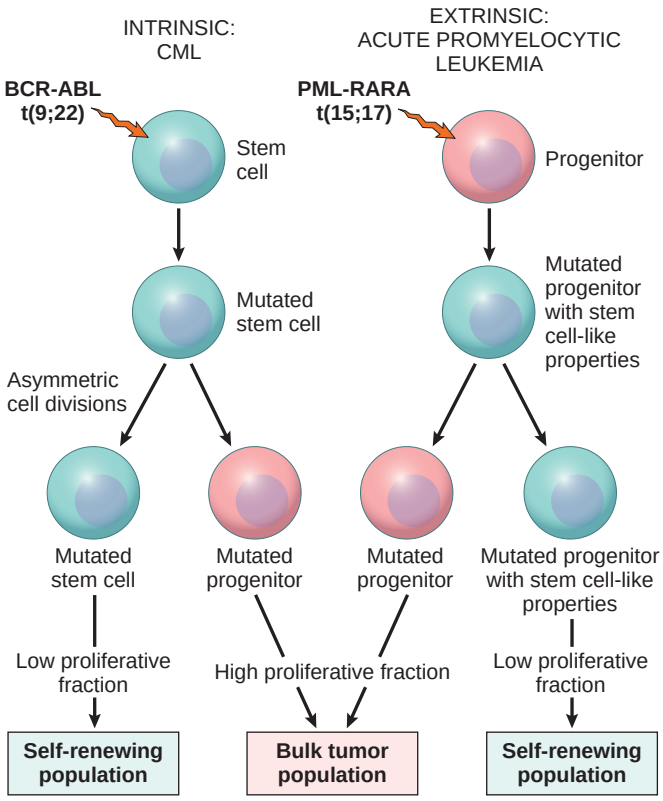

Figure 7-35 Origins of cells with self-renewing capacity in cancer. Cancer stem cells can arise from transformed tissue stem cells (e.g., hematopoietic stem cells in chronic myelogenous leukemia, CML) with intrinsic "stemness" or from proliferating cells that acquire a mutation that confers "stemness" (e.g., granulocyte progenitors in acute promyelocytic leukemia). In both instances, the cancer stem cells undergo asymmetric cell divisions that give rise to committed progenitors that proliferate more rapidly than the cancer stem cells; as a result, most of the malignant cells in both tumors lack self-renewing capacity.

differentiated somatic cell such as a fibroblast into a pluripotent stem cell. Thus, it is easy to imagine how mutations leading to misexpression of certain key transcription factors, such as MYC, might convert a somatic cell into a transformed cell with a capacity for self-renewal. A corollary of this idea is that, unlike normal stem cells and their more differentiated progeny, which have a fixed parent-offspring relationship, cancer cells within a tumor may be able to "de-differentiate" to a stem cell–like state. Indeed, there is evidence that cancers can repopulate their stem cell pools from non–stem cell populations, further complicating efforts to precisely define and selectively target cancer stem cells.

Despite these uncertainties, the concept of cancer stem cells has important implications for cancer therapy. Most notably, if cancer stem cells are essential for tumor persistence, it follows that these cells must be eliminated to eradicate the tumor. It is hypothesized that like normal stem cells, cancer stem cells have a high intrinsic resistance to conventional therapies due to a low rate of cell division and the expression of factors, such as multiple drug resistance-1 (MDR1), that counteract the effects of chemotherapeutic drugs. Thus, the limited success of current therapies may in part be explained by their failure to kill the malignant stem cells that lie at the root of cancer, an idea that is being actively tested in the laboratory.

KEY CONCEPTS

Limitless Replicative Potential

- At least some cells in all cancers must be stem cell–like; these cells are sometimes referred to as cancer stem cells. These may arise through transformation of a normal stem cell or through acquired genetic lesions that impart a stem-like state on a more mature cell.
- Cancer cells acquire lesions that inactivate senescence signals and reactivate telomerase, which act together to convey limitless replicative potential.

Angiogenesis

Even if a solid tumor possesses all of the genetic aberrations that are required for malignant transformation, it cannot enlarge beyond 1 to 2 mm in diameter unless it has the capacity to induce angiogenesis. Like normal tissues, tumors require delivery of oxygen and nutrients and removal of waste products; presumably the 1- to 2-mm zone represents the maximal distance across which oxygen, nutrients, and waste can diffuse from blood vessels. Growing cancers stimulate neoangiogenesis, during which vessels sprout from previously existing capillaries (Chapter 3). Neovascularization has a dual effect on tumor growth: perfusion supplies needed nutrients and oxygen, and newly formed endothelial cells stimulate the growth of adjacent tumor cells by secreting growth factors, such as insulin-like growth factors (IGFs) and PDGF. While the resulting tumor vasculature is effective at delivering nutrients and removing wastes, it is not entirely normal; the vessels are leaky and dilated, and have a haphazard pattern of connection, features that can be appreciated on angiograms. By permitting tumor cells access to these abnormal vessels, angiogenesis also contributes to metastasis. Angiogenesis is thus an essential facet of malignancy.

How do growing tumors develop a blood supply? The current paradigm is **that angiogenesis is controlled by a balance between angiogenesis promoters and inhibitors; in angiogenic tumors this balance is skewed in favor of promoters.** Early in their development, most human tumors do not induce angiogenesis. Starved of nutrients, these tumors remain small or in situ, possibly for years, until an *angiogenic switch* terminates this stage of vascular quiescence. The molecular basis of the angiogenic switch involves increased production of angiogenic factors and/or loss of angiogenic inhibitors. These factors may be produced by the tumor cells themselves or by inflammatory cells (e.g., macrophages) or other stromal cells associated with the tumors. Proteases, either elaborated by the tumor cells or by stromal cells in response to the tumor, are also involved in regulating the balance between angiogenic and antiangiogenic factors. Many proteases can release proangiogenic basic fibroblast growth factors (bFGF) that are stored in the ECM; conversely, the angiogenesis inhibitors angiostatin and endostatin are produced by proteolytic cleavage of plasminogen and collagen, respectively.

The local balance of angiogenic and antiangiogenic factors is influenced by several factors:

www.PTools.ir