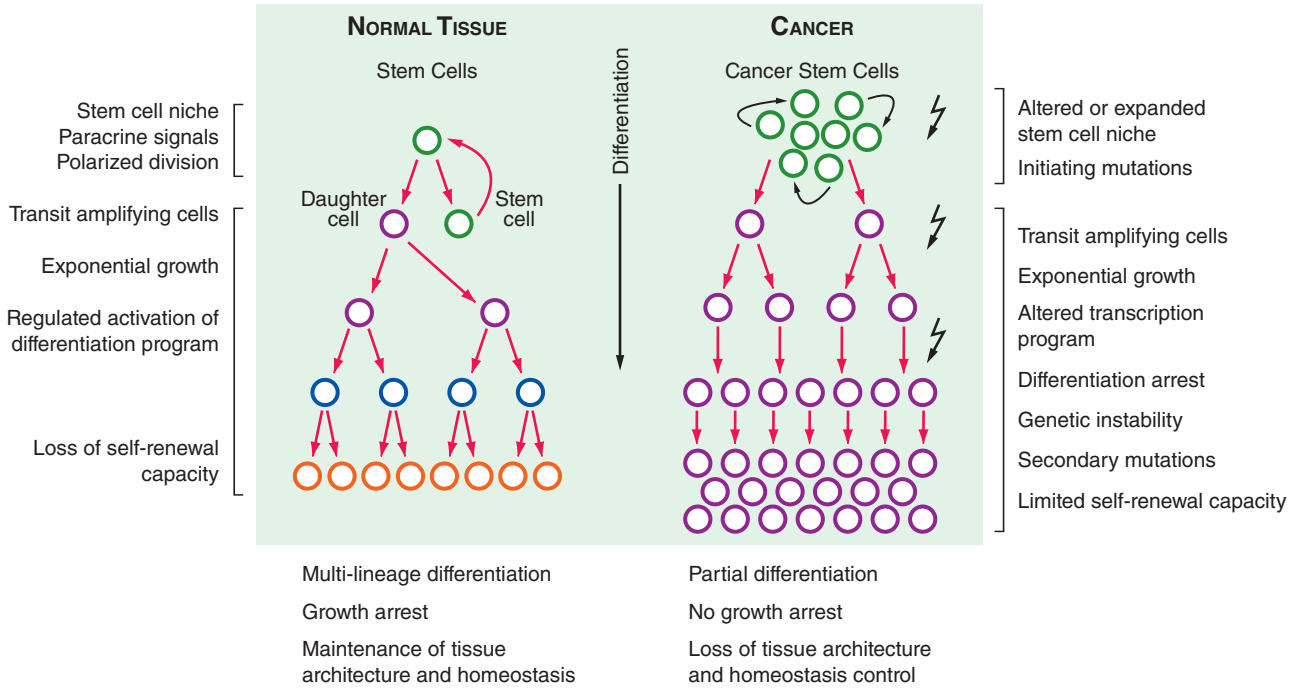


**FIGURE 102e-7 Cancer stem cells play a critical role in the initiation, progression, and resistance to therapy of malignant neoplasms.** In normal tissues (*left*), homeostasis is maintained by asymmetric division of stem cells, leading to one progeny cell that will differentiate and one cell that will maintain the stem cell pool. This occurs within highly specific niches unique to each tissue, such as in close apposition to osteoblasts in bone marrow, or at the base of crypts in the colon. Here, paracrine signals from stromal cells, such as sonic hedgehog or Notch ligands, as well as upregulation of β-catenin and telomerase, help to maintain stem cell features of unlimited self-renewal while preventing differentiation or cell death. This occurs in part through upregulation of the transcriptional repressor Bmi-1 and inhibition of the $p16^{Ink4a}$/Arf and p53 pathways. Daughter cells leave the stem cells niche and enter a proliferative phase (referred to as *transit-amplifying*) for a specified number of cell divisions, during which time a developmental program is activated, eventually giving rise to fully differentiated cells that have lost proliferative potential. Cell renewal equals cell death, and homeostasis is maintained. In this hierarchical system, only stem cells are long-lived. The hypothesis is that cancers harbor stem cells that make up a small fraction (i.e., 0.001–1%) of all cancer cells. These cells share several features with normal stem cells, including an undifferentiated phenotype, unlimited self-renewal potential, and a capacity for some degree of differentiation; however, due to initiating mutations (mutations are indicated by *lightning bolts*), they are no longer regulated by environmental cues. The cancer stem cell pool is expanded, and rapidly proliferating progeny, through additional mutations, may attain stem cell properties, although most of this population is thought to have a limited proliferative capacity. Differentiation programs are dysfunctional due to reprogramming of the pattern of gene transcription by oncogenic signaling pathways. Within the cancer transit-amplifying population, genomic instability generates aneuploidy and clonal heterogeneity as cells attain a fully malignant phenotype with metastatic potential. The cancer stem cell hypothesis has led to the idea that current cancer therapies may be effective at killing the bulk of tumor cells but do not kill tumor stem cells, leading to a regrowth of tumors that is manifested as tumor recurrence or disease progression. Research is in progress to identify unique molecular features of cancer stem cells that can lead to their direct targeting by novel therapeutic agents.



## PLASTICITY AND RESISTANCE

Cancer cells, and especially stem cells, have the capacity for significant plasticity, allowing them to alter multiple aspects of cell biology in response to external factors (e.g., chemotherapy, inflammation, immune response). Thus, a major problem in cancer therapy is that malignancies have a wide spectrum of mechanisms for both initial and adaptive resistance to treatments. These include inhibiting drug delivery to the cancer cells, blocking drug uptake and retention, increasing drug metabolism, altering levels of target proteins, acquiring mutations in target proteins, modifying metabolism and cell signaling pathways, using alternate signaling pathways, adjusting the cell replication process including mechanisms by which the cell deals with DNA damage, inhibiting apoptosis, and evading the immune system. Thus, most metastatic cancers (except those curable with chemotherapy such as germ cell tumors) eventually become resistant to the therapy being used. Overcoming resistance is a major area of research.

## CANCER METABOLISM

One of the distinguishing characteristics of cancer cells is that they have altered metabolism as compared with normal cells in supporting survival and their high rates of proliferation. These cells must focus a significant fraction of their energy resources on synthesis of proteins and other molecules while still maintaining sufficient ATP production to survive and grow. Although normal proliferating cells also have similar needs, there are differences in how cancer cells metabolize glucose and a number of other compounds, including glutamine, as compared to normal cells. Many cancer cells use aerobic glycolysis (the Warburg effect) (Fig. 102e-8) to metabolize glucose, leading to increased lactic acid production, whereas normal cells use oxidative phosphorylation in mitochondria under aerobic conditions, a much more efficient process. One consequence is increased glucose uptake by cancer cells, a fact used in fluorodeoxyglucose (FDG) positron emission tomography (PET) scanning to detect tumors. A number of proteins in cancer cells, including CMYC, HIF1, RAS, p53, pRB, and AKT, are all involved in modulating glycolytic processes and controlling the Warburg effect. Although these pathways remain difficult to target therapeutically, both the PI3 kinase pathway with signaling through mTOR and the AMP-activated kinase (AMPK) pathway, which inhibits mTOR complex 1 (mTORC1; a protein complex that includes mTOR), are important in controlling the glycolytic process and thus provide potential targets for inhibiting this process. The inefficient utilization of glucose also leads to a need for alternative metabolic pathways for other compounds as well, one of which is glutamine. Similar to glucose, this provides both a source for structural molecules as well as energy production. Glutamine is also inefficiently used by cancer cells.