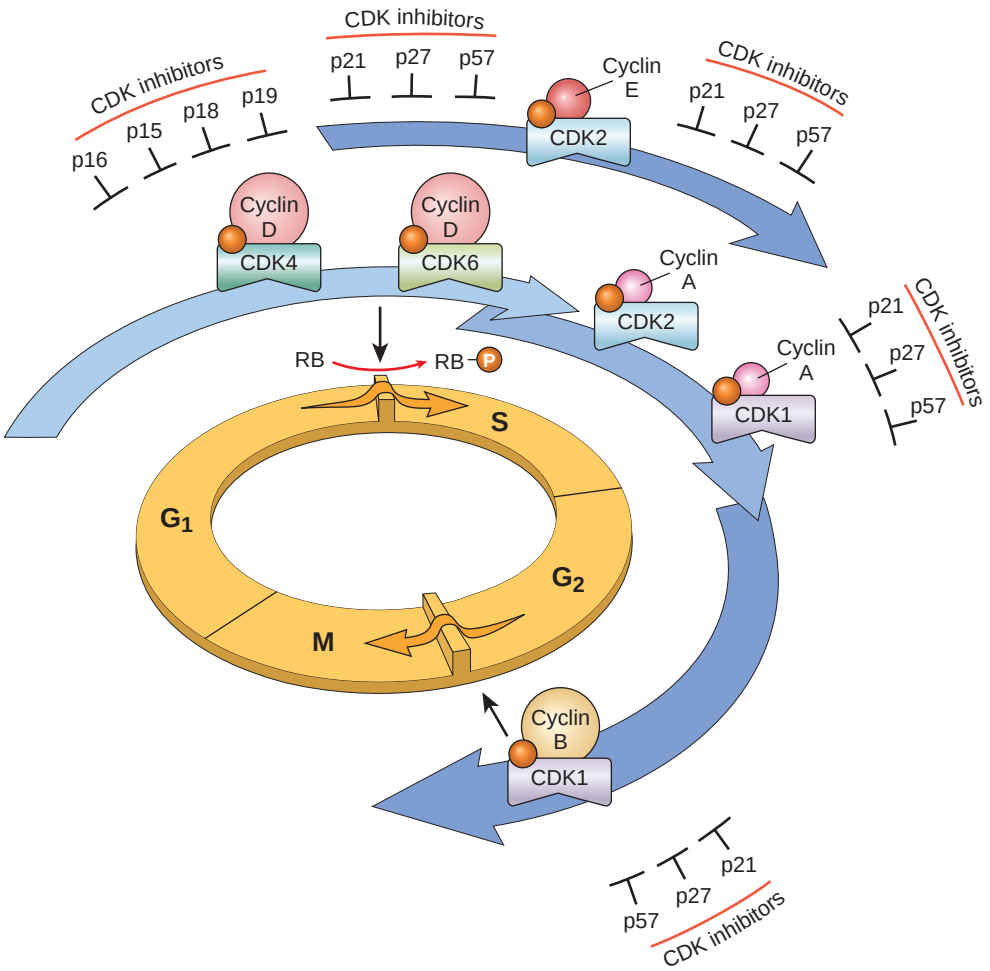

Figure 1-18 Role of cyclins, cyclin-dependent kinases (CDKs), and CDK inhibitors in regulating the cell cycle. The *shaded arrows* represent the phases of the cell cycle during which specific cyclin-CDK complexes are active. As illustrated, cyclin D-CDK4, cyclin D-CDK6, and cyclin E-CDK2 regulate the G_1-to-S transition by phosphorylating the Rb protein (pRb). Cyclin A-CDK2 and cyclin A-CDK1 are active in the S phase. Cyclin B-CDK1 is essential for the G_2-to-M transition. Two families of CDK inhibitors can block activity of CDKs and progression through the cell cycle. The so-called INK4 inhibitors, composed of p16, p15, p18, and p19, act on cyclin D-CDK4 and cyclin D-CDK6. The other family of three inhibitors, p21, p27, and p57, can inhibit all CDKs.

Defective CDKI checkpoint proteins allow cells with damaged DNA to divide, resulting in mutated daughter cells with the potential of developing into malignant tumors.

An equally important aspect of cell growth and division is the biosynthesis of other cellular components needed to make two daughter cells, such as membranes and organelles. At the same time that growth factor receptor signaling stimulates cell cycle progression, it also activates events that promote changes in cellular metabolism that support growth. Chief among these is the Warburg effect, mentioned earlier, which is marked by increased cellular uptake of glucose and glutamine, increased glycolysis, and (counter-intuitively) decreased oxidative phoshorylation. These changes become fixed in cancer cells and are discussed in greater detail in Chapter 7.

Stem Cells

During development, stem cells give rise to all the various differentiated tissues; in the adult organism, stem cells replace damaged cells and maintain tissue populations as individual cells within them undergo replicative senescence due to attrition of telomeres (described in chapter 2). There is a homeostatic equilibrium between the replication, self-renewal, and differentiation of stem cells and the death of the mature, fully differentiated cells (Fig. 1-19). The dynamic relationship between stem cells and terminally differentiated parenchyma is particularly evident in the continuously dividing epithelium of the skin. Thus, stem cells at the basal layer of the epithelium progressively differentiate as they migrate to the upper layers of the epithelium before dying and being shed.

Stem cells are characterized by two important properties:

- *Self-renewal*, which permits stem cells to maintain their numbers.
- *Asymmetric division,* in which one daughter cell enters a differentiation pathway and gives rise to mature cells, while the other remains undifferentiated and retains its self-renewal capacity.