Maintaining Cell Populations

Proliferation and the Cell Cycle

Cell proliferation is fundamental to development, maintenance of steady-state tissue homeostasis, and replacement of dead or damaged cells. The key elements of cellular proliferation are accurate DNA replication accompanied by the coordinated synthesis of all other cellular constituents, followed by equal apportionment of DNA and other cellular constituents (e.g., organelles) to daughter cells through mitosis and cytokinesis.

The sequence of events that results in cell division is called the *cell cycle;* it consists of G_1 (presynthetic *growth*), S (DNA *synthesis*), G_2 (premitotic *growth*), and M (*mitotic*) phases (Fig. 1-17). Quiescent cells that are not actively cycling are said to be in the G_0 state. Cells can enter G_1 either from the G_0 quiescent cell pool, or after completing a round of mitosis, as for continuously replicating cells. Each stage requires completion of the previous step, as well as activation of necessary factors (see later); nonfidelity of DNA replication, or cofactor deficiency result in arrest at the various transition points.

The cell cycle is regulated by activators and inhibitors. Cell cycle progression is driven by proteins called *cyclins*—named for the cyclic nature of their production and degradation—and cyclin-associated enzymes called *cyclin-dependent kinases* (CDKs) (Fig. 1-18). CDKs acquire the ability to phosphorylate protein substrates (i.e., kinase activity) by forming complexes with the relevant cyclins. Transiently increased synthesis of a particular cyclin leads to increased kinase activity of the appropriate CDK binding partner; as the CDK completes its round of phosphorylation, the associated cyclin is degraded and the CDK activity abates. Thus, as cyclin levels rise and fall, the activity of associated CDKs likewise wax and wane.

More than 15 cyclins have been identified; cyclins D, E, A, and B appear sequentially during the cell cycle and bind to one or more CDKs. The cell cycle can thus be conceived as a relay race in which each leg is regulated by a distinct set of cyclins: as one collection of cyclins leaves the track, the next set takes over.

Embedded in the cell cycle are surveillance mechanisms primed to sense DNA or chromosomal damage. These quality control *checkpoints* ensure that cells with genetic imperfections do not complete replication. Thus, the G_1-S checkpoint monitors the integrity of DNA before irreversibly committing cellular resources to DNA replication. Later in the cell cycle, the G_2-M restriction point ensures that there has been accurate genetic replication before the cell actually divides. When cells do detect DNA irregularities, checkpoint activation delays cell cycle progression and triggers DNA repair mechanisms. If the genetic derangement is too severe to be repaired, the cells will undergo apoptosis; alternatively, they may enter a nonreplicative state called *senescence*—primarily through p53-dependent mechanisms (see later).

Enforcing the cell cycle checkpoints is the job of *CDK inhibitors (CDKIs);* they accomplish this by modulating CDK-cyclin complex activity. There are several different CDKIs:

- One family—composed of three proteins called *p21* (CDKN1A), *p27* (CDKN1B), and *p57* (CDKN1C)—broadly inhibits multiple CDKs.
- The other family of CDKI proteins has selective effects on cyclin CDK4 and cyclin CDK6; these proteins are called *p15* (CDKN2B), *p16* (CDKN2A), *p18* (CDKN2C), and *p19* (CDKN2D).

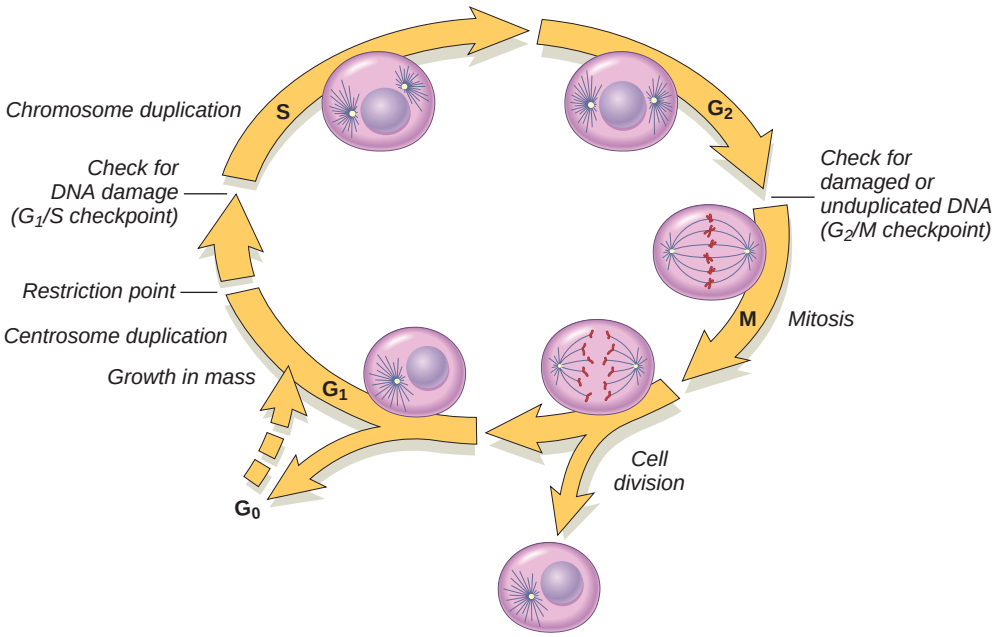

Figure 1-17 Cell cycle landmarks. The figure shows the cell cycle phases (G_0, G_1, G_2, S, and M), the location of the G_1 restriction point, and the G_1/S and G_2/M cell cycle checkpoints. Cells from labile tissues such as the epidermis and the GI tract may cycle continuously; stable cells such as hepatocytes are quiescent but can enter the cell cycle; permanent cells such as neurons and cardiac myocytes have lost the capacity to proliferate. (Modified from Pollard TD, Earnshaw WC: Cell Biology. Philadelphia, Saunders, 2002.)