Cell cycle and its role in repair

Learning objectives

- What is repair
- What is the role of cellular proliferation.
- Key elements in cellular proliferation.
- Definition and phases of cell cycle.
- Regulation of cell cycle.
- Checkpoints in cell cycle.

What is repair

Repair, also called healing, refers to the restoration of tissue architecture and function after an injury.

Repair of damaged tissues occurs by two processes:

- regeneration, which restores normal cells,
- and scarring, the deposition of connective tissue

The ability of tissues to repair themselves is determined, in part, by their intrinsic proliferative capacity and the presence of tissue stem cells.

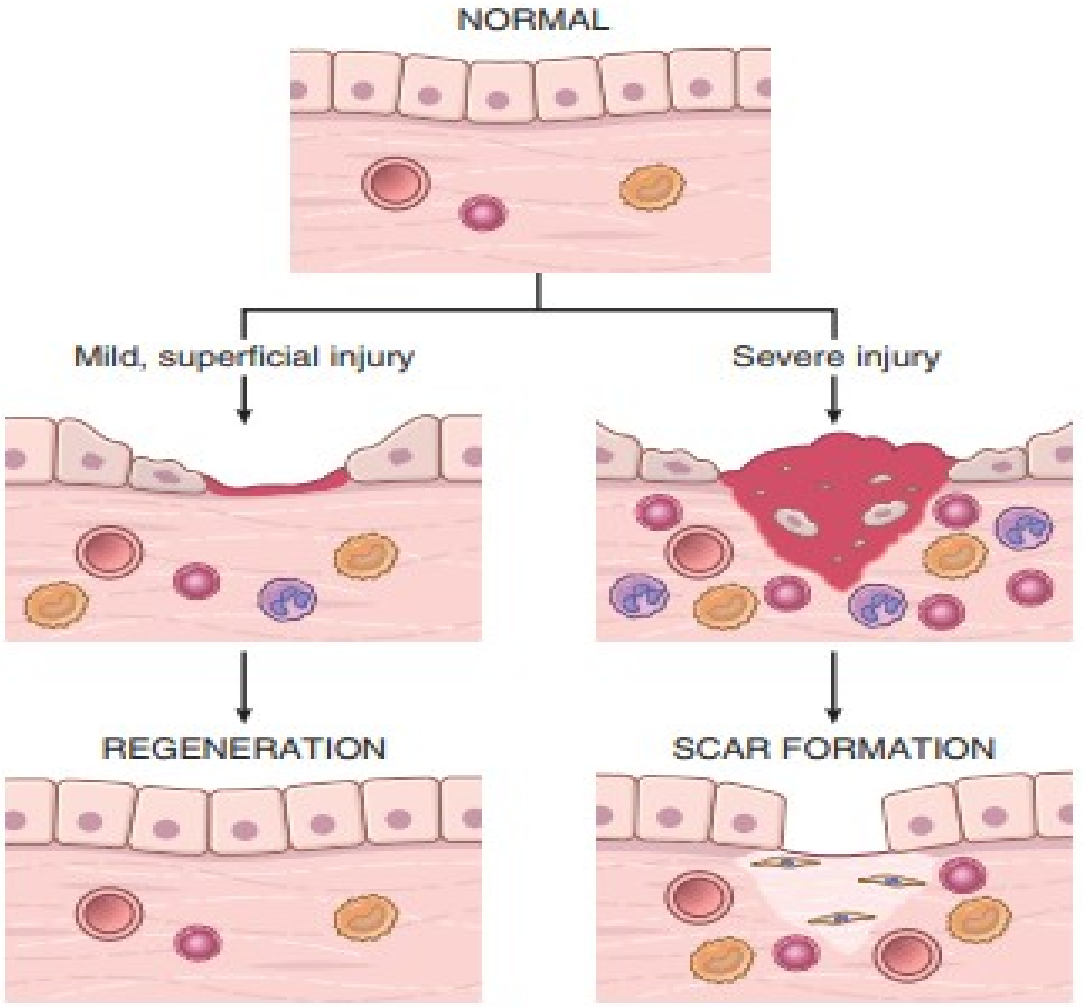


Figure 3.24 Mechanisms of tissue repair: regeneration and scar formation. Following mild injury, which damages the epithelium but not the underlying tissue, resolution occurs by regeneration, but after more severe injury with damage to the connective tissue, repair is by scar formation.

- In normal tissues—without healing, degeneration, or neoplasia—there is a homeostatic equilibrium between replication, self-renewal, and differentiation of stem cells and death of mature, fully differentiated cells.
- Cell proliferation is driven by signals provided by growth factors and from the ECM.
- During the phase of Repair or replication, numerous genes are activated; these include

1. genes encoding transcription factors,
2. cell cycle regulators,
3. regulators of energy metabolism

Role of cellular proliferation

Cellular proliferation is a base for

- development of organisms,
- to maintenance of steady-state tissue homeostasis, and
- to replacement of dead or damaged cells.

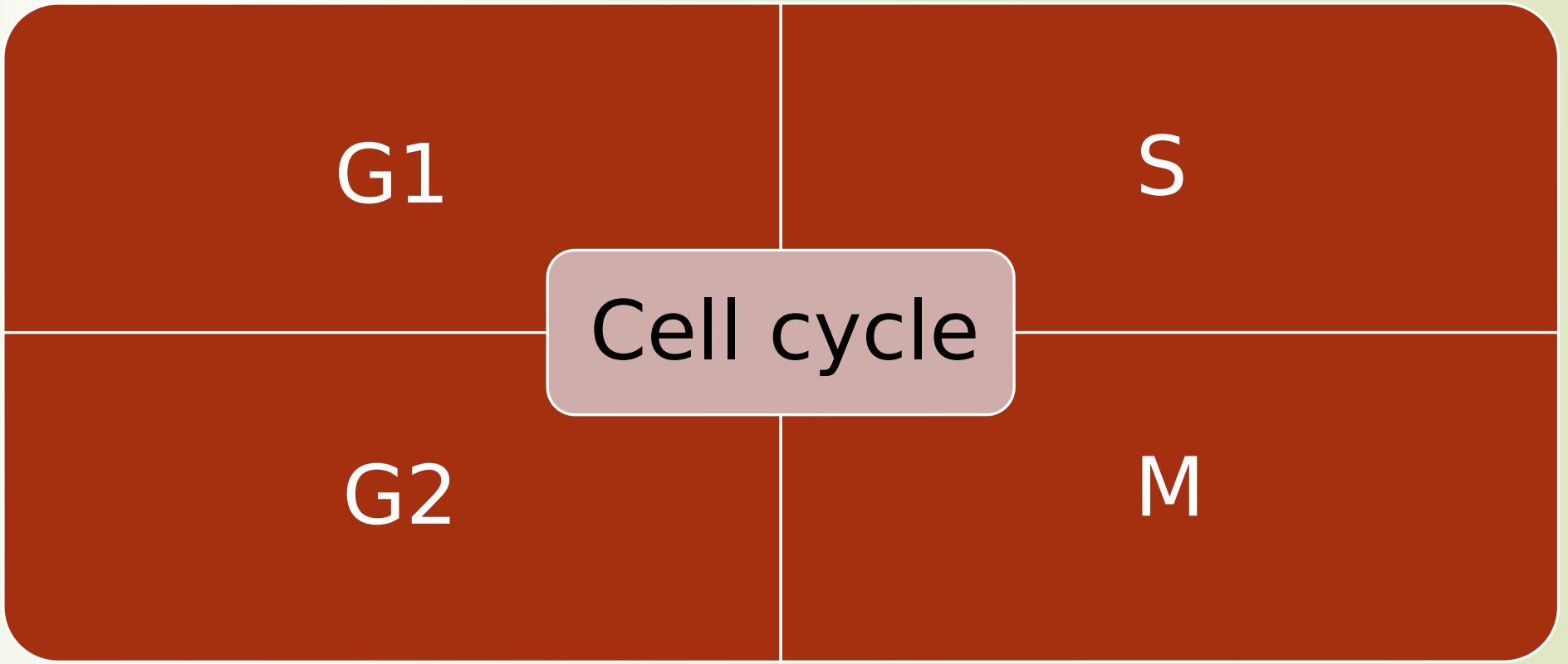
Elements in cell proliferation,

Key elements of cellular proliferation are

- Accurate DNA replication along with
- coordinated synthesis of other cellular components, and
- equal distribution of DNA and organelles to daughter cells through the processes of mitosis and cytokinesis.

Definition

- The sequence of events that results in cell proliferation is called the cell cycle.


G1
S
Cell cycle
G2
M

Phases of cell cycle

- It consists of
- G1 (gap 1),
- S (DNA synthesis),
- G2 (gap 2), and
- M (mitotic) phases;

Dormant or quiescent cells that are not actively cycling are in the G0 (gap 0) state.

How cell can enter the cycle

- Cells can enter G1 stage either from the G0 quiescent cell pool or after completing a round of mitosis. Each stage requires completion of the previous step, as well as activation of necessary factors.
- In accurate DNA replication or cofactor deficiency results in arrest at various transition points.

Regulation of cell cycle

- The cell cycle is regulated by activators and inhibitors. Cell cycle progression is chaperoned by proteins called cyclins named for the cyclic nature of their production and degradation and cyclin-associated enzymes called cyclin dependent kinases (CDKs) . Constitutively synthesized CDKs acquire kinase activity that is, the ability to phosphorylate protein substrates by forming complexes with the relevant cyclins. Transiently increased synthesis of a particular cyclin thus 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 CDK activity abates

So, as cyclin levels rise and fall, activity of associated CDKs will likewise get effected.

More than 15 cyclins have been identified; cyclins D, E, A, and B appear in a sequence during the cell cycle and bind to one or more CDKs.

Thus cell cycle resembles a relay race , and in this case every event is regulated by a distinct set of cyclins: as one collection of cyclins leaves the track, the next set takes over.

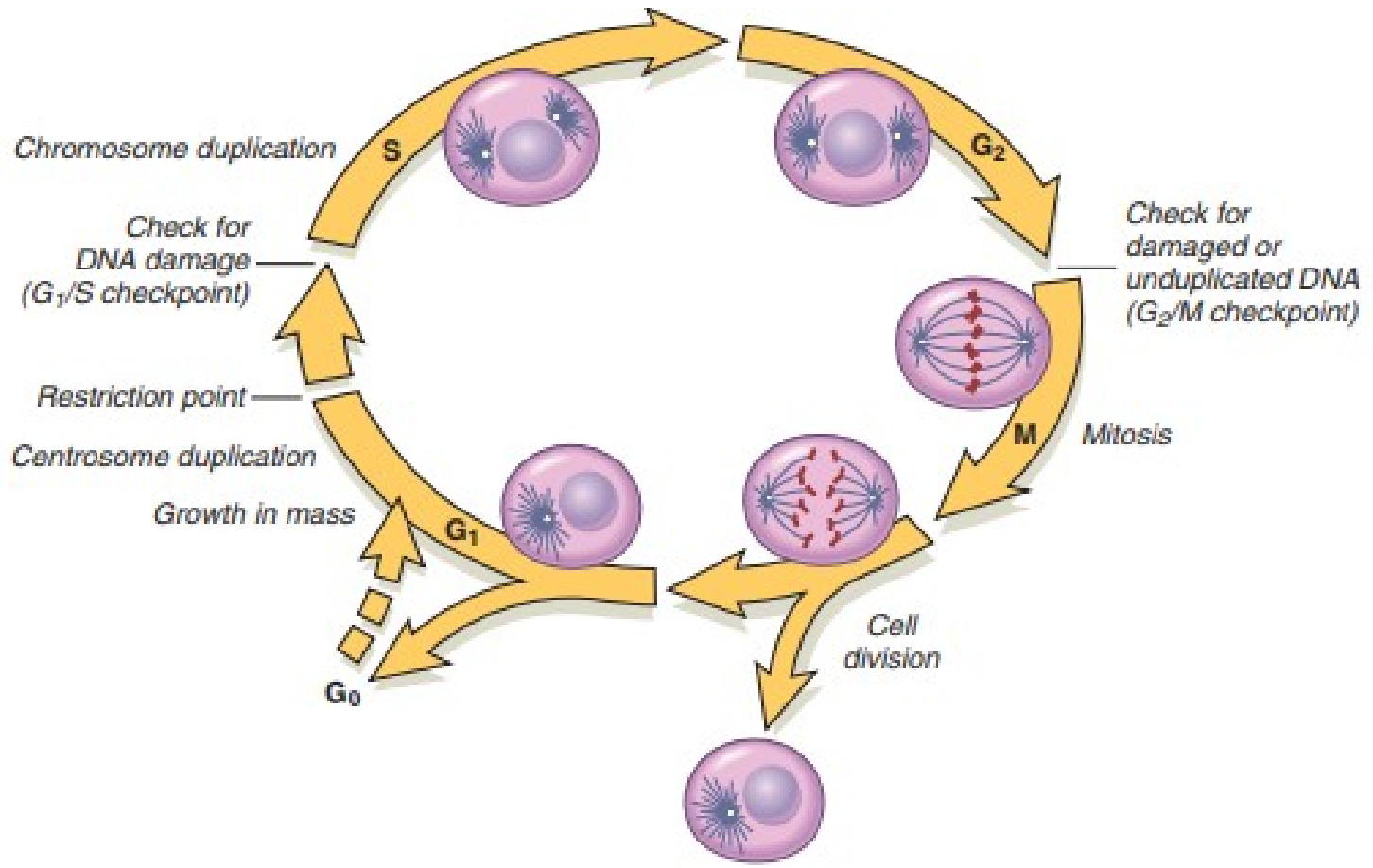


Figure 1.18 Cell cycle landmarks. The figure shows the cell cycle phases (G_0, G_1, G_2, S, and M), the location of the G_1 restriction point, and the G_1/S and G_2/M cell cycle checkpoints. *G_1 restriction point* refers to the stage in G_1 where the cell is committed to advance further into the cell cycle without requiring any more of the growth signal that initiated cell division. Cells from labile tissues such as the epidermis and the gastrointestinal 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, 2002, Saunders.)

Checkpoints in the cycle

- Surveillance mechanisms primed to sense DNA or chromosomal damage are embedded within the cell cycle. These quality control checkpoints ensure that cells with genetic imperfections do not complete replication.
- Thus the G1-S checkpoint monitors DNA integrity before irreversibly committing cellular resources to DNA replication.
- Later in the cell cycle, the G2-M restriction point insures 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, cells either undergo apoptosis or enter a nonreplicative state called senescence primarily through p53-dependent mechanisms.

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

- One family of CDKIs—composed of three proteins called p21 (CDKN1A), p27 (CDKN1B), and p57 (CDKN1C)—broadly inhibits multiple CDKs.
- Another family of CDKIs has selective effects on cyclin CDK4 and cyclin CDK6; these proteins are called p15 (CDKN2B), p16 (CDKN2A), p18 (CDKN2C), and p19 (CDKN2D).
- Defective CDKI checkpoint proteins allow cells with damaged DNA to divide, resulting in mutated daughter cells at risk for malignant transformation.

An equally important aspect of cell growth and division is the biosynthesis of the

- membranes,
- cytosolic proteins, and
- organelles

necessary to make two daughter cells. Thus as growth factor receptor signaling stimulates cell cycle progression, it also activates events that promote the metabolic changes that supports growth . Chief among these is the switching to aerobic glycolysis and with the counter-intuitive reduction in oxidative phosphorylation, also called the Warburg effect. These alterations in cell metabolism are an

Thank you