Lecture 6

General pathology

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Healing and repair

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

the term repair →is used for parenchymal and connective tissues

the term healing →is for surface epithelia

Repair of damaged tissues occurs by *two processes*:

***1.regeneration*, which restores normal cells: occurs by**

a. Some tissues are able to replace the damaged components and essentially return to a normal state; this

process is called *regeneration.*

b. may occur by proliferation of differentiated cells that survive the injury and retain the capacity to proliferate, notably hepatocytes in the liver.

c. In other tissues, particularly the epithelia of the skin and intestines, tissue stem cells and their progenitors contribute to the restoration of damaged tissues

***2. scarring,* the deposition of connective tissue.**

a. if the injured tissues are incapable of regeneration, or if the supporting structures of the tissue are too severely damaged to support regeneration of the tissue cells, repair occurs by the laying down of connective (fibrous) tissue, a process that may result in scar formation.

Although the fibrous scar is not normal, it usually provides enough structural stability that the injured tissue is able to function.

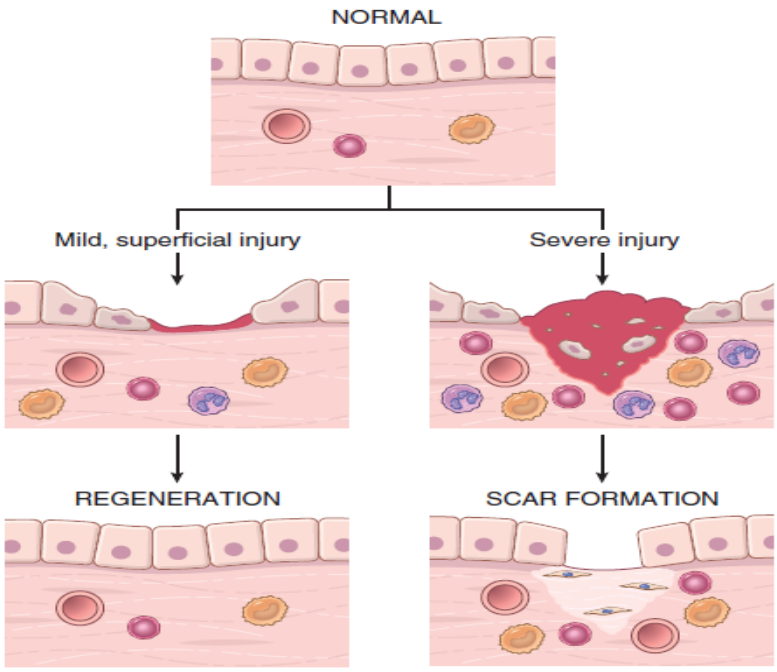
b. The term fibrosis is often used to describe the deposition of collagen that occurs in the lungs, liver, kidney, and other organs as a consequence of chronic inflammation or in the myocardium after extensive ischemic necrosis (infarction).

c. If fibrosis develops in a tissue space occupied by an inflammatory exudate, it is called organization (as in organizing pneumonia affecting the lung).

Factors That Influence Tissue Repair

1. **Infection**
2. **Diabetes**
3. **Nutritional status**
4. **Glucocorticoids (steroids)**
5. **Mechanical factors such as increased local pressure.**
6. **Poor perfusion, due to peripheral vascular disease, arteriosclerosis, and diabetes or due to obstructed venous drainage (e.g., in varicose veins).**
7. **Foreign bodies such as fragments of steel, glass etc.**
8. **The type and extent of tissue injury**

9. **The location of the injury.**



Cell and Tissue Regeneration:

The regeneration of injured cells and tissues involves cell proliferation, which is driven by

1. **growth factors and is critically dependent on the integrity of the ECM,**
2. **by the development of mature cells from tissue stem cells.**

Cell Proliferation: Signals and Control Mechanisms

Several cell types proliferate during tissue repair:

1. **the remnants of the injured tissue (which attempt to restore normal structure).**
2. **vascular endothelial cells (to create new vessels that provide the nutrients needed for the repair process.**

3. **fibroblasts (the source of the fibrous tissue that forms the scar to fill defects that cannot be corrected by regeneration).**

Cell proliferation is driven by signals provided by

1. growth factors and

2. from the ECM.

Functions of Growth factors and receptors:

Growth factors bind to specific receptors and, ultimately, influence expression of genes that:

1. Promote entry into the cell cycle.

2. Relieve blocks on cell cycle progression (thus promoting replication).

3. Prevent apoptosis.

4. Enhance synthesis of components (nucleic acids, proteins, lipids, carbohydrates) required for cell division.

5. They can also regulate a host of nongrowth activities including migration, differentiation, and synthetic capacity.

Table 1.1 Growth Factors Involved in Regeneration and Repair

Growth Factor	Sources
Epidermal growth factor (EGF)	Activated macrophages, salivary glands, keratinocytes, many other cells
Transforming growth factor-α (TGF-α)	Activated macrophages, keratinocytes, many other cells
Hepatocyte growth factor (HGF) (scatter factor)	Fibroblasts, stromal cells in the liver, endothelial cells
Vascular endothelial growth factor (VEGF)	Mesenchymal cells
Platelet-derived growth factor (PDGF)	Platelets, macrophages, endothelial cells, smooth muscle cells, keratinocytes
Fibroblast growth factors (FGFs) including acidic (FGF-1) and basic (FGF-2)	Macrophages, mast cells, endothelial cells, many other cell types
Transforming growth factor-β (TGF-β)	Platelets, T lymphocytes, macrophages, endothelial cells, epithelial cells, smooth muscle cells, fibroblasts
Keratinocyte growth factor (KGF) (i.e., FGF-7)	Fibroblasts

ECM, Extracellular matrix.

Extracellular matrix (ECM)

The ECM is a protein network that constitutes a significant proportion of any tissue. Cell interactions with the ECM are critical for development, healing, and maintenance of normal tissue architecture. the ECM functions as:

1. **Mechanical support for cell anchorage, cell migration, and maintenance of cell polarity.**
2. **Regulator of cell proliferation. by binding and displaying growth factors and by signaling via cellular integrin family receptors.**
3. **Scaffolding for tissue renewal Because maintenance of normal tissue structure requires a basement membrane or stromal scaffolds, integrity of the basement membrane or the stroma of parenchymal cells is critical for organized tissue regeneration.**
4. **Foundation for establishment of tissue microenvironments. Basement membrane acts as a boundary between epithelium and underlying connective tissue but often does more than just provide structural support; for example, in the kidney, it forms part of the filtration apparatus.**

The ECM occurs in two basic forms: interstitial matrix and basement membrane

1. ***Interstitial matrix*. Interstitial matrix occupies the spaces between stromal cells within connective tissue and between parenchymal epithelium and the underlying supportive vascular and smooth muscle structures in some organs. Interstitial matrix is synthesized by mesenchymal cells (e.g., fibroblasts),**

The major constituents are:

a. **fibrillar and nonfibrillar collagens**
b. **fibronectin,**
c. **elastin,**
d. **proteoglycans,**

e. hyaluronate,

f. other constituents.

2. *Basement membrane*. Which lies beneath the epithelium and is synthesized by overlying epithelium and underlying mesenchymal cells.

The major constituents are nonfibrillar type IV collagen and laminin.

Components of the Extracellular Matrix:

ECM components fall into three families:

• Fibrous structural proteins such as collagens and elastin that confer tensile strength and recoil

• Water-hydrated gels such as proteoglycans and hyaluronan that permit compressive resistance and lubrication

• Adhesive glycoproteins that connect ECM elements to one another and to cells.

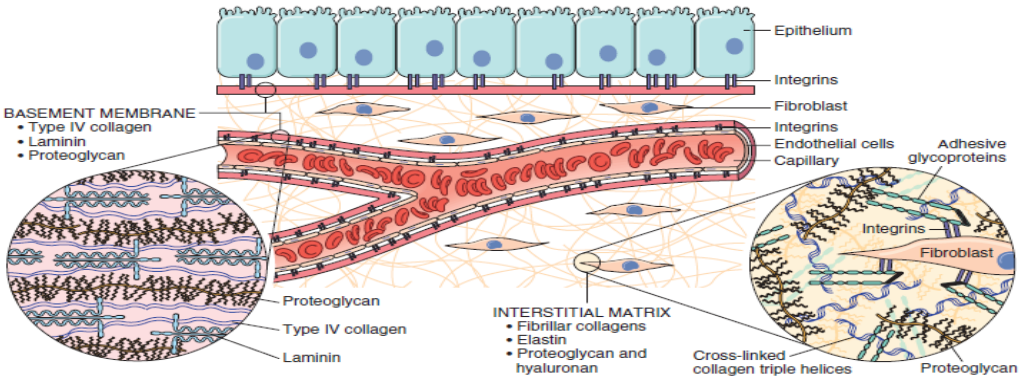


Figure 1.14 Main components of the extracellular matrix (ECM) including collagens, proteoglycans, and adhesive glycoproteins. Both epithelial and mesenchymal cells (e.g., fibroblasts) interact with ECM via integrins. Basement membranes and interstitial ECM have different architecture and general composition, although certain components are present in both. For the sake of clarity, many ECM components (e.g., elastin, fibrillin, hyaluronan, and syndecan) are not shown.

The tissues of the body are divided into three groups:

1. ***Labile (continuously dividing) tissues:*** **Cells of these tissues are continuously being lost and replaced by maturation from tissue stem cells and *by proliferation* of mature cells. Labile cells include:**
   - ***a.*** **hematopoietic cells in the bone marrow and**
   - ***b.*** **the majority of surface epithelia, such as the stratified squamous epithelia of the skin, oral cavity, vagina, and cervix.**
   - ***c.*** **the cuboidal epithelia of the ducts draining exocrine organs (e.g., salivary glands, pancreas, biliary tract);**
   - ***d.*** **the columnar epithelium of the gastrointestinal tract, uterus, and fallopian tubes; and the transitional epithelium of the urinary tract. These tissues can readily regenerate after injury as long as the pool of stem cells is preserved.**
2. ***Stable tissues.*** **Cells of these tissues are quiescent (in the G0 stage of the cell cycle) and have only *minimal proliferative activity* in their normal state. However, these cells are capable of dividing in response to injury or loss of tissue mass. Stable cells constitute**
   - ***a.*** **the parenchyma of most solid tissues, such as liver, kidney, and pancreas.**
   - ***b.*** **They also include endothelial cells, fibroblasts, and smooth muscle cells; the proliferation of these cells is particularly important in wound healing. *With the exception of liver, stable tissues have a limited capacity to regenerate after injury.***
3. ***Permanent tissues:*** **The cells of these tissues are considered to be terminally differentiated and non-proliferative in postnatal life. The majority of cells belong to this category include**
   - ***a.*** **neurons and**
   - ***b.*** **cardiac muscle.**

Thus, injury to the brain or heart is irreversible and results in a scar because neurons and cardiac

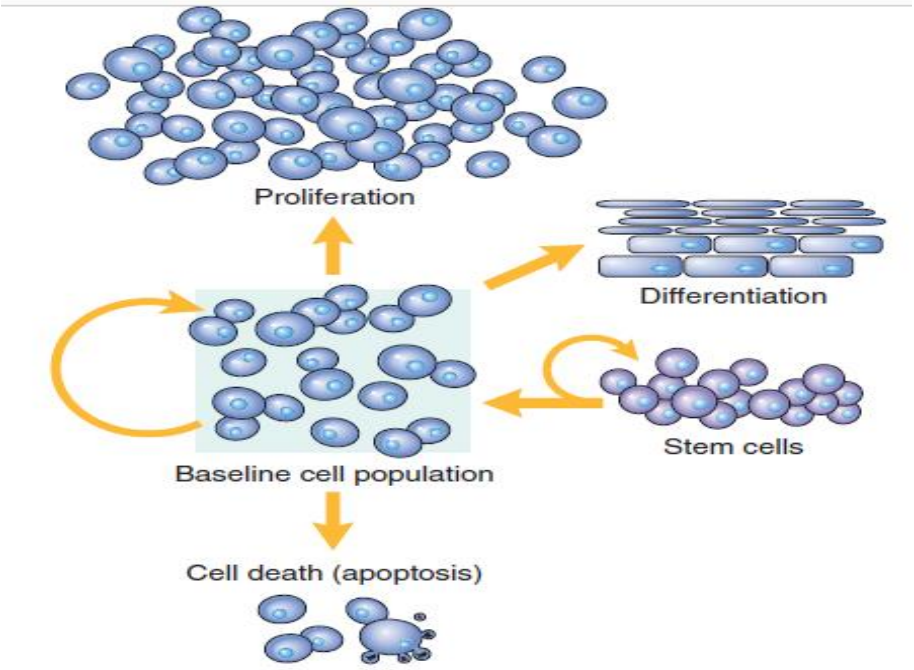
myocytes cannot regenerate. In permanent tissues, *repair is typically dominated by scar formation.*

Stem Cells

Stem cells have the dual property of being able to self-renew and to give rise to differentiated cells and tissues.

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.



Under conditions of homeostasis, stem cells are maintained by self-renewal, which can involve two types of cell division:

1. **Asymmetric division refers to cell replication 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.**
2. **Symmetric division occurs when both daughter cells retain self-renewal capacity. Such replication occurs early in embryogenesis—when stem cell populations are expanding—and under stress conditions, as in bone marrow repopulation after ablative chemotherapy. there are fundamentally only two varieties.**

   • Embryonic stem (ES) cells are the most undifferentiated.

   They are present in the inner cell mass of the blastocyst, have virtually limitless cell renewal capacity, and can give rise to every cell in the body; they are thus said to be totipotent.

   - **Tissue stem cells (also called adult stem cells) are found in intimate association with the differentiated cells of a given tissue.**

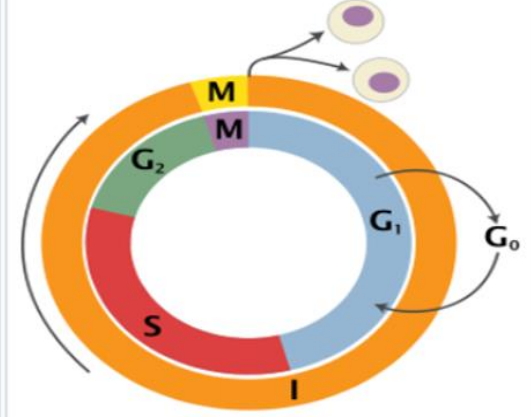
Cell cycle

The cell cycle, or cell-division cycle, is the series of events that take place in a cell that cause it to divide into two daughter cells. These events include the duplication of its DNA (DNA replication) and some of its organelles, and subsequently the partitioning of its cytoplasm and other components into two daughter cells in a process called cell division.

The cell cycle is a four-stage process in which the cell increases in size (gap 1, or G1, stage), copies its DNA (synthesis, or S, stage), prepares to divide (gap 2, or G2, stage), and divides (mitosis, or M, stage), quiescent cells that are not actively cycling are in the G0 (gap 0) state. Cells can enter G1 either from the G0 quiescent cell pool or after completing a round of mitosis.

The stages G1, S, and G2 make up interphase, which accounts for the span between cell divisions.

State	Phase	Abbreviation	Description
Resting	Gap 0	G_0	A phase where the cell has left the cycle and has stopped dividing.
Interphase	Gap 1	G_1	Cells increase in size in Gap 1. The *G_1 checkpoint* control mechanism ensures that everything is ready for DNA synthesis.
	Synthesis	S	DNA replication occurs during this phase.
	Gap 2	G_2	During the gap between DNA synthesis and mitosis, the cell will continue to grow. The *G_2 checkpoint* control mechanism ensures that everything is ready to enter the M (mitosis) phase and divide.
Cell division	Mitosis	M	Cell growth stops at this stage and cellular energy is focused on the orderly division into two daughter cells. A checkpoint in the middle of mitosis (*Metaphase Checkpoint*) ensures that the cell is ready to complete cell division.



Schematic of the cell cycle. Outer ring: I = Interphase, M = Mitosis; inner ring: M = Mitosis, G_1 = Gap 1, G_2 = Gap 2, S = Synthesis; not in ring: G_0 = Gap 0/Resting[2]

The cell cycle is regulated by activators and inhibitors.

Cell cycle progression is accompanied by proteins called cyclins—named for the cyclic nature of their production and degradation—and cyclin-associated enzymes called cyclin dependent kinases (CDKs).

Synthesized CDKs acquire kinase activity—that is, the ability to phosphorylate protein substrates—by forming complexes with the relevant cyclins. 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.

When cells do detect DNA irregularities, checkpoint (the G1-S checkpoint monitors DNA integrity) activation delays cell cycle progression and triggers DNA repair mechanisms. Later in the cell cycle, the (G2-M) restriction point insures that there has been accurate genetic replication before the cell actually divides. 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.

Defective CDKI checkpoint proteins allow cells with damaged DNA to divide, resulting in

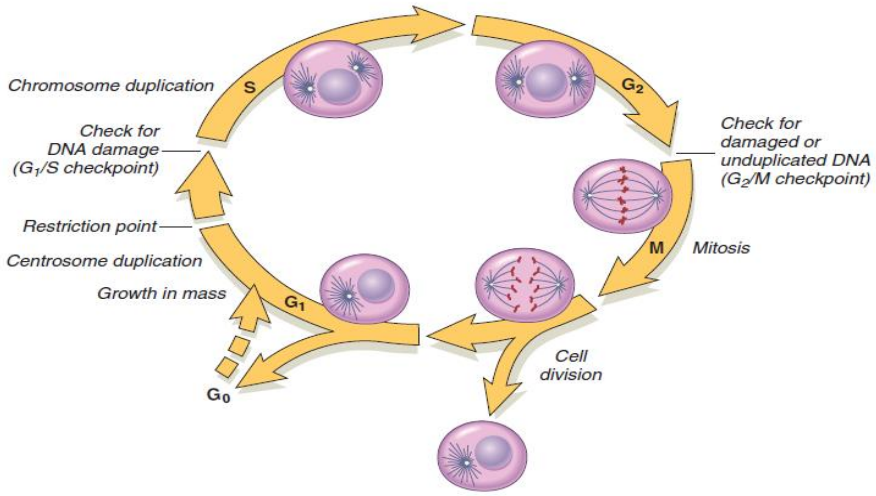


Figure 1.18 Cell cycle landmarks. The figure shows the cell cycle phases (G_0, G_1, G_2, S, and M), the location of the G_1 restriction point, and the G_1/S and G_2/M cell cycle checkpoints. *G_1 restriction point* refers to the stage in G_1 where the cell is committed to advance further into the cell 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.)

mutated daughter cells at risk for malignant transformation.