Tissue Repair

Repair refers to the restoration of tissue architecture and function after an injury .

there are two types of repair:-

1- *Regeneration:-* occur when some tissues are able to replace the damaged cells and return to a normal state .

2-Fibrosis (scar formation):- occur If the injured tissues are incapable of regeneration , or if the supporting structures of the tissue are severely damaged, repair occurs by laying down of connective (fibrous) tissue .

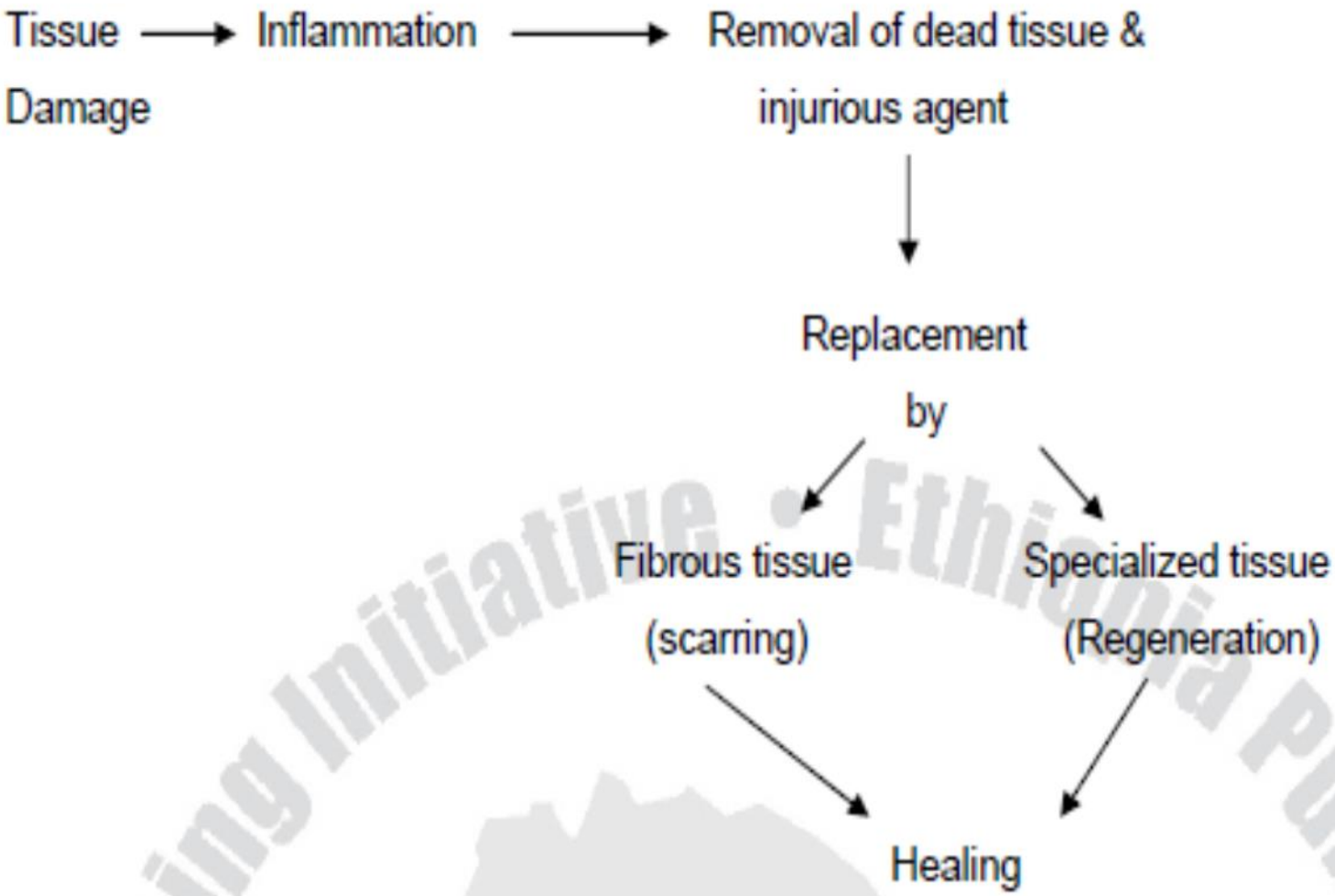

Figure 4.1 Processes of healing: Removal of dead tissue & injurious agent and replacement occur simultaneously.

The Cell Cycle

The sequence of events that control *the proliferation of cells are **DNA replication** and **mitosis**.*

The cycle consists of :-

1- the presynthetic growth phase 1 *(G_1).*

2-the DNA synthesis phase *(S).*

3-the premitotic growth phase 2 *(G_2).*

4- the mitotic phase *(M)*.

Non-dividing cells in the cell cycle are either arrest in G_1 or they exit the cycle to enter a phase called G_0 .

Growth factors are stimulate cells to transition from G0 into the G1 phase and beyond into DNA synthesis (S), premitotic growth phase 2 G2, and mitosis (M) phase.

Progression the cell cycle from G1 is regulated by proteins cyclins which form complexes with enzymes cyclin dependent kinases(CDKs) which lead to DNA replication . as their DNA is replicated , the cell enter the S phase and they progress through G2 and mitosis M .

Checkpoint controls prevent DNA replication or mitosis of damaged cells and either stop the cell cycle to allow for DNA repair or eliminate irreversibly damaged cells by apoptosis .

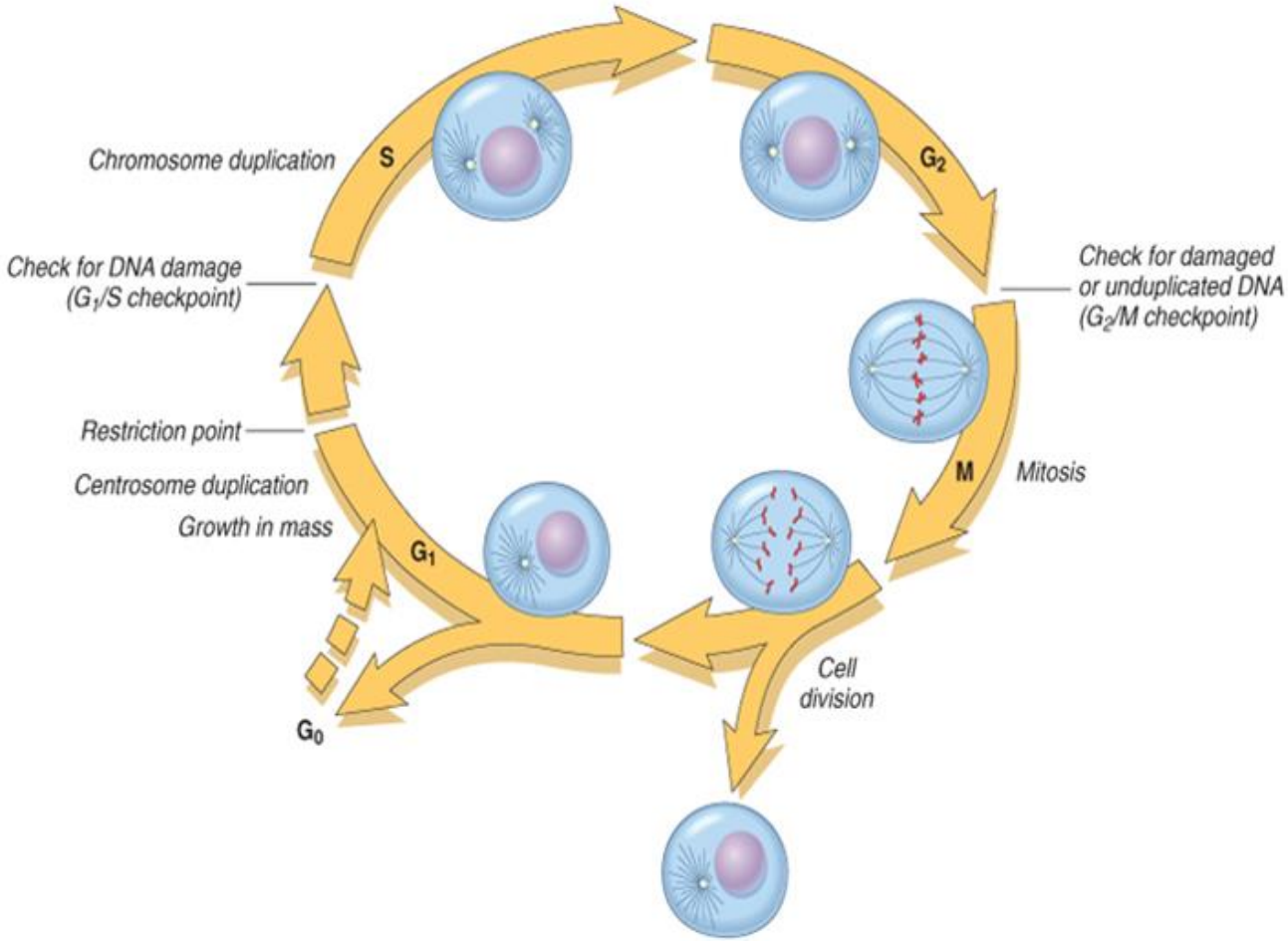

Figure 3-3 Cell populations and cycle landmarks. Note the cell cycle stages (G_0, G_1, S, G_2 and M), the G_1 restriction point, and the G_1/S and G_2/M checkpoints. While some cell populations continuously cycle and proliferate (e.g., epidermis, GI epithelium), others are quiescent (in G_0) but can enter the cell cycle (e.g., hepatocytes); permanent cells (e.g., neurons and cardiac myocytes) do not have the capacity to proliferate (see text). (Modified from Pollard TD, Earnshaw WC: Cell Biology. Philadelphia, WB Saunders, 2002.)

Proliferative Capacities of Tissues

The tissues of the body are divided into three groups on the basis their proliferative capacity .

1- Continuously Dividing Tissues (*labile tissues)*

Cells of these tissues are continuously being lost and replaced by proliferation and maturation of stem cells.

Labile cells include:-

A- hematopoietic cells in the bone marrow .

B- surface epithelia, such as :-

1-basal layers of the squamous epithelia of the skin, oral cavity, vagina, and cervix .

2- the cuboidal epithelia of the ducts draining exocrine organs (e.g., salivary glands, pancreas, biliary tract);

3- columnar epithelium of the gastrointestinal tract, uterus, and fallopian tubes;

4- the transitional epithelium of the urinary tract. These tissues can readily regenerate after injury as long as the stem cells are present.

Stem Cells

In most **continuously dividing tissues** the mature cells are terminally differentiated and short-lived . As mature cells die, the tissue is replenished by the differentiation of cells generated from stem cells .

Stem cells are characterized by :-

1- Self-renewal capacity .

2- Asymmetric replication .

means that when a stem cell divides, one daughter cell enters a differentiation pathway and gives rise to mature cells, while the other remains an undifferentiated stem cell that retains its self-renewal capacity .

3- They have very broad differentiation capabilities . Are able to generate any cell like fat, cartilage, bone, and muscle .

there are two kinds of stem cells:-

1- Embryonic stem cells (ES cells) are Stem cells with the capacity to generate multiple cell lineages (pluripotent stem cells) can be isolated from embryo . the normal function of ES cells is to give rise to all cells of the body

2- Adult stem cells, also called **tissue stem cells**, are stem cells with the capacity to generate multiple lineages but is restricted to the tissue or organ in which they are found such as **bone marrow** .

2- Stable Tissues (quiescent tissues)

Cells of these tissues are normally in the G0 stage of the cell cycle and hence not proliferating , but they are capable of dividing in response to injury .

Stable cells constitute:-

1.The parenchyma of most solid tissues (liver, kidney, and pancreas).

2.The endothelial cells.

3.The fibroblasts.

4.The smooth muscle cells are also normally quiescent but can proliferate in response to growth factors .

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 (non dividing tissues)

The cells of these tissues are terminally differentiated and non proliferative in postnatal life such as the **neurons and cardiac muscle cells** . Thus, injury to brain or heart is irreversible and results in a scar formation , because neurons and cardiac myocytes do not divide .

Skeletal muscle is usually classified as a permanent tissue, but satellite cells attached to the endomysial sheath provide some regenerative capacity for muscle.

CONTROL OF CELL PROLIFERATION

Several cell types proliferate during tissue repair. These include:-

1- the remnant cells 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).

The proliferation of these cell types is driven by signals provided by **growth factors** and from **the ExtraCellular Matrix (ECM)** .

The production of growth factors and the ability of cells to divide in response to these factors are important determinants of the adequacy of the repair process .

The normal size of organ is determined by a balance of cell proliferation, cell death by apoptosis, and new differentiated cells from stem cells .

GROWTH FACTORS

are proteins produced near the site of damage that stimulate the proliferation of cells, and may also promote migration , differentiation, and other cellular responses .

Most growth factors have **pleiotropic effects**; that is, in addition to stimulating cellular proliferation, they stimulate migration, differentiation and contractility, and enhance the synthesis of specialized proteins (such as collagen in fibroblasts).

growth factors that involved in repair are produced by :-

1- macrophages and lymphocytes that are recruited to the site of injury or are activated at this site, as part of the inflammatory process.

2- parenchymal cells or stromal (connective tissue) cells in response to cell injury.

MECHANISMS OF ACTION OF GROWTH FACTORS

1- stimulate the function of growth control genes called *protooncogenes* because mutations in these genes lead to un controlled cell proliferation that is the characteristic of cancer (oncogenesis).

2- stimulate proliferation of some cells and inhibit proliferation of other cells .

3- growth factor can have opposite effects on the same cell depending on its concentration. An example of such a growth factor is transforming growth factor-β (TGF-β).

Role of the Extracellular Matrix (ECM) in Tissue Repair

Tissue repair depends not only on growth factor activity but also on interactions between cells and ECM components . The ECM is a is a complex of several proteins that assembles into a network that surrounds cells and constitutes a significant proportion of any tissue. **ECM** sequesters water and minerals , providing turgor to soft tissues, giving rigidity to bone. It also regulates the proliferation, movement and differentiation of the cells living within it , and serving as a reservoir for growth factors .

ECM occurs in two basic forms: ***interstitial matrix*** *And* ***basement membrane*** *.*

Interstitial Matrix

This is present in the spaces between cells in connective tissue, and between epithelium and supportive vascular and smooth muscle structures ; it is synthesized by fibroblasts . Its major constituents are fibrillar and nonfibrillar collagens, as well as fibronectin, elastin, proteoglycans, hyaluronate .

Basement membrane

The basement membrane lies beneath the epithelium and is synthesized by overlying epithelium and underlying mesenchymal cells ; it tends to form a platelike mesh. Its major constituents are non fibrillar collagen type IV and laminin .

Components of the Extracellular Matrix

There are three basic components of ECM:

(1) fibrous structural proteins such as collagens and elastins .

(2) water-hydrated gels such as proteoglycans and hyaluronate .

(3) adhesive glycoproteins that connect the matrix elements to one another and to cells .

Function of the Extracellular Matrix

The ECM is not only fill the spaces around cells. Its various functions include:

1- ***Mechanical support*** for cell anchorage and cell migration .

2- ***Control of cell proliferation***. ECM components can regulate cell proliferation by signaling through cellular receptors .

3- ***Scaffolding for tissue renewal.*** The normal tissue requires a basement membrane or stromal scaffold. Disruption the basement membrane or the stroma results in a failure of the tissues to regenerate and repair by scar formation .

4-*Establishment of tissue microenvironments*. Basement membrane acts as a boundary between epithelium and underlying connective tissue .

Role of Regeneration in Tissue Repair

The importance of regeneration in the replacement of injured tissues varies in different types of tissues and with the severity of injury .

- In labile tissues, such as the epithelia of the intestinal tract and skin, injured cells are rapidly replaced by proliferation of residual cells and differentiation of tissue stem cells present intact to the basement membrane. The newly generated cells fill the defect created by the injury.

Loss of blood cells is corrected by proliferation of hematopoietic progenitors in the bone marrow and other tissues

- In stable tissue, regeneration can occur in parenchymal organs , whose cell proliferation is limited as in pancreas , adrenal, thyroid, and lung , but with the exception of the liver .

Regeneration of the liver occurs by two major mechanisms:

- **Proliferation of the remaining hepatocytes following partial hepatectomy** resection of up to 90% of the liver can be corrected by proliferation of the residual hepatocytes . is driven by cytokines (e.g. IL-6) and by growth factors such as Hepatocyte Growth Factor (HGF)

- **Repopulation from progenitor cells** .

REPAIR BY CONNECTIVE TISSUE (SCAR FORMATION)

If repair cannot be accomplished by regeneration alone, it occurs by replacement of the injured cells with connective tissue, leading to the formation of a scar, or by a combination of regeneration of some residual cells and scar formation .

Repair by connective tissue consists of sequential processes that follow the inflammatory response:

A- Formation of new blood vessels (angiogenesis).

B - Migration and proliferation of fibroblasts.

C - Deposition of ECM.

D - Maturation and reorganization of the fibrous tissue (remodeling) .

Repair begins within 24 hours of injury by the emigration of fibroblasts and the induction of fibroblast and endothelial cell proliferation .

By 3 to 5 days, a specialized type of tissue that is characteristic of healing, called ***granulation tissue,*** is apparent.

The term **granulation tissue** is the pink, soft, granular in gross appearance, that seen beneath the scab of a skin wound.

Its histologic appearance is characterized by:-

1-proliferation of fibroblasts .

2- new thin-walled, delicate capillaries (angiogenesis), with a loose ECM, with inflammatory cells, mainly macrophages.

Granulation tissue then accumulates more fibroblasts, which lay down collagen, eventually resulting in the formation of a scar .

A-Formation of new blood vessels (*angiogenesis*)

Angiogenesis, or *neovascularization,* is the process of new blood vessel development from existing vessels, primarily venules .

Angiogenesis involves sprouting of new vessels from existing vessels and consists of the following steps :-

- Vasodilation in response to Nitric Oxide (NO) and increased permeability induced by Vascular Endothelium Growth factor (VEGF).
- Separation of endothelial cells from the luminal surface of vessel. breakdown of the basement membrane to allow formation of a vessel sprout .
- Migration of endothelial cells toward the area of tissue injury .
- Proliferation of endothelial cells
- Remodeling into capillary tubes
- Recruitment of periendothelial cells (pericytes for small capillaries and smooth muscle cells for larger vessels) to form the mature vessel
- Suppression of endothelial proliferation and migration and deposition of the basement membrane .

Several growth factors contribute to angiogenesis; the most important are **vascular endothelial growth factor VEGF** and **basic fibroblast growth factor 2 (FGF-2).**

B ,C - Migration and proliferation of fibroblasts and scar formation

It occurs in two steps:

(1) migration and proliferation of fibroblasts into the site of injury (2) deposition of ECM (*scar formation*) by these cells .

(1) migration and proliferation of fibroblasts into the site of injury

- The recruitment and stimulation of fibroblasts to synthesize connective tissue proteins are driven by many growth factors, *including* **platelet-derived growth factor(*PDGF), basic fibroblast growth factor-2 (FGF-2)*** . One source of these factors is the activated endothelium and inflammatory cells .

*(2) deposition of ECM by these cells (*scar formation)

The fibroblasts are more synthetic for Collagen , and hence there is increased deposition of ECM . Collagen synthesis is critical to the development of strength in a healing site. Collagen synthesis by fibroblasts begins early in wound healing (days 3 to 5) and continues for several weeks, depending on the size of the wound. many of growth factors that involve ECM synthesis and Scar Formation including :-

- Fibroblast Growth Factor (FGF) Involved in Angiogenesis It also promotes the migration of fibroblasts to the damaged area, and stimulates epithelial cell migration to cover epidermal wounds .

- Platelet-derived growth factor (PDGF) cause migration and proliferation of fibroblasts.

- Transforming growth factor-β (TGF-β) It stimulates the production of collagen from fibroblasts .

D- Maturation and reorganization of the fibrous tissue (Remodeling)

After the scar is formed, it is remodeled to increase its strength and contract it .

Wound strength increases because of cross-linking of collagen and increased size of collagen fibers .

With time, the connective tissue is degraded and the scar shrinks. The *degradation* of collagens and other ECM components is accomplished by a family of matrix metalloproteinases (MMPs) . MMPs are produced from neutrophil s ,macrophages ,and fibroblast and some epithelial cells. and their synthesis and secretion are regulated by growth factors , cytokines .