**Lecture 6 General pathology Dr. Ali H. Murad**

***Wound healing:***

Healing process in general involve:

(1) Inflammation

(2) Formation of granulation tissue

(3) ECM deposition and remodelling

Healing of any wound can occur by one of two types of repairs:

1-Healing by First Intention (primary union).

2-Healing by Second Intention (secondary union).

**1-Healing by First Intention (**primary union):

It is the healing of a clean, uninfected small wound or surgical incision approximated by surgical sutures. The incision causes only **focal disruption** of epithelial basement membrane continuity and death of a relatively **few** epithelial and connective tissue cells. As a result, epithelial **regeneration** predominates over fibrosis. A very small scar is formed, but there is minimal wound contraction.

**Steps of primary union:**

1- The narrow incisional space first fills with fibrin-clotted blood, which is rapidly invaded by granulation tissue and covered by new epithelium.

2- Within 24 hours, neutrophils are seen at the incision margin, migrating toward

the fibrin clots.

3- Basal cells at the cut edge of the epidermis show increased mitotic activity.

4- Within 24 to 48 hours, epithelial cells from both edges have begun to migrate

and proliferate along the dermis, depositing basement membrane components as they progress. The cells meet in the midline beneath the surface cut, yielding a thin but continuous epithelial layer.

5- By 3rd day, neutrophils have been largely replaced by macrophages, and granulation tissue progressively invades the incision space. Collagen fibers are now evident at the incision margins, but these are vertically oriented and do not bridge the incision. Epithelial cell proliferation continues, yielding a thickened epidermal covering layer.

6- By 5th day, neovascularization reaches its peak as granulation tissue fills theincisional space. Collagen fibrils become more abundant and begin to bridge the incision. The epidermis recovers its normal thickness as differentiation of surface cells yields a mature epidermal architecture with surface keratinization.

7- During the second week, there is continued collagen accumulation and fibroblast proliferation. The leukocytes infiltrate, edema, and increased vascularity are substantially diminished. The long process of "blanching"begins, accomplished by increasing collagen deposition within the incisional scar and the regression of vascular channels.

8- By the end of the first month, the scar comprises a cellular connective tissue largely devoid of inflammatory cells and covered by an essentially normal epidermis. However, the dermal appendages destroyed in the line of the incision are permanently lost.

**1. Healing by Second Intention (secondary union):**

When tissue loss is more extensive, such as in large wounds, abscess formation, and ulceration, the repair process is more complex. In second intention healing, the inflammatory reaction is more intense, there is abundant development of granulation tissue, and the wound contracts by the action of myofibroblasts. This is followed by accumulation of ECM and formation of a large scar.

Repair begins within 24 hours of injury by the emigration of fibroblasts and the induction of fibroblast and endothelial cell proliferation. By 3 - 5 days, a specialized type of tissue that is characteristic of healing, called **granulation tissue** is apparent.

The term granulation tissue derives from the pink, soft, granular gross appearance, such as that seen beneath skin wound.

Its **histologic appearance** is characterized by

1- proliferation of fibroblasts .

2- new thin-walled, delicate capillaries (angiogenesis).

3- with a loose ECM.

Granulation tissue then progressively accumulates connective tissue matrix, eventually resulting in the formation of a scar which may remodel over time.

***Steps of repair by connective tissue deposition:***

1- Formation of new blood vessels (angiogenesis).

2- Migration and proliferation of fibroblasts and deposition of ECM (scar formation).

3-Maturation and reorganization of the fibrous tissue (remodelling).

4-Wound contraction

***1. Formation of new blood vessels (Angiogenesis):***

Angiogenesis, or neovascularization,is a process of formation of new blood vessels in which preexisting vessels send out capillary sprouts to produce new vessels. Endothelial precursor cells may migrate from the bone marrow to areas of injury and participate in angiogenesis at these sites. Several growth factors induce angiogenesis, but the most important are vascular endothelial growth factor VEGF and fibroblast growth factor (FGF).

***2. Migration of Fibroblasts and ECM Deposition (Scar Formation)***

Scar formation occurs in two steps:

**(1)-Migration and proliferation of fibroblasts into the site of injury**.

The granulation tissue is started by formation of a framework of **new** **vessels and loose ECM** that develop early at the repair site.

Then the recruitment and stimulation of **fibroblasts i**s driven by many growth factors, including PDGF, FGF-2 and TGF-β. (Derived from activated endothelium and inflammatory cells).

\*\* **Macrophages**, in particular, are important cellular constituents of granulation tissue, and besides clearing extracellular debris and fibrin at the site of injury, they elaborate a host of mediators that induce fibroblast proliferation and ECM production.

\*\* Sites of inflammation are also rich in **mast cells**, and **lymphocytes**. These

can contribute directly or indirectly to fibroblast proliferation and activation.

**(2)-Deposition of ECM by fibroblasts:**

As healing progresses, the number of proliferating fibroblasts and new vessels decreases; however, the fibroblasts progressively assume a more synthetic phenotype, and hence there is increased deposition of ECM. 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 the same growth factors that regulate fibroblast proliferation also participate in stimulating ECM synthesis and scar formation including **TGF-β, PDGF, and FGF**. These are potent fibrogenic agent stimulating the production of collagen, fibronectin and proteoglycans, causes migration and proliferation of fibroblasts, smooth muscle cells, and macrophages.

**Cytokines** as mediators of inflammation and may also function as growth factors and participate in ECM deposition and scar formation. **IL-1** **and TNF**, for example, induce fibroblast proliferation and can have a fibrogenic effect. They are also chemotactic for fibroblasts and stimulate the synthesis of collagen by these cells.

The granulation tissue formed will evolves into a scar composed of largely **inactive,** spindle-shaped fibroblasts, dense collagen, fragments of elastic tissue, and other ECM components. Matured scar has vascular regression, which eventually transforms the highly vascularized granulation tissue into a **pale,** largely **avascular scar.**

***3-Maturation and reorganization of the fibrous tissue (remodeling)***

The transition from granulation tissue to scar involves shifts in the composition of the ECM; even after its synthesis and deposition, scar ECM continues to be modified and remodelled. The outcome of the repair process is, in part, a balance between ECM synthesis and degradation.

The degradation of collagens and other ECM components is accomplished by a family of matrix metalloproteinases (MMPs). MMPs are produced by a variety of cell types (fibroblasts, macrophages, neutrophils, synovial cells, and some epithelial cells), and their synthesis and secretion are regulated by growth factors, cytokines, and other agents.

***4-Wound contraction:***

Secondary healing involves wound contraction. Within 6 weeks, for example, large skin defects may be reduced to 5% to 10% of their original size, largely by contraction. This occurs due to the presence of **myofibroblasts,** which are modified fibroblasts exhibiting many of the ultrastructural and functional features of contractile smooth muscle cells.

***Differences between secondary healing and primary healing:***

1- A larger clot forms at the surface of the wound.

2- Inflammation is more intense because large tissue defects have a greater volume of necrotic debris, exudate, and fibrin that must be removed.

3- Large defects have a greater potential for secondary infections.

4- Much larger amounts of granulation tissue are formed to fill the gaps and provide the underlying framework for the regrowth of epithelium.

5- A greater volume of granulation tissue results in a greater mass of scar tissue.