**Lec.no.3/ Tissue Repair**

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**Cutaneous Wound Healing**

Cutaneous wound healing is divided into **three** phases:: Inflammation, proliferation and maturation.

The initial injury causes platelet adhesion and aggregation and the formation of a clot in the surface of the wound, leading to **inflammation.** **In the proliferative phase** there is formation of granulation tissue, proliferation and migration of connective tissue cells, and re-epithelialization of the wound surface.

**Maturation** involves ECM deposition, tissue remodeling, and wound contraction.

The simplest type of cutaneous wound repair is the healing of a clean, uninfected surgical incision approximated by surgical sutures.Such healing is called **healing by primary union or by first intention.**

This incision causes death of a limited number of epithelial and connective tissue cells and disruption of epithelial basement membrane continuity.**Re-epithelialization to close the wound occurs with formation of a relatively thin scar.**

The second form of healing is **healing by secondary union or by second intention,** the repair process is more complicated in excisional wounds that create large defects on the skin surface, causing extensive loss of cells and tissue.**The healing of these wounds involves a more intense inflammatory reaction, the formation of abundant granulation tissue, and extensive collagen deposition, leading to the formation of a large scar, which generally contracts** (fig 1, table 1).

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**Formation of Blood Clot**

Wounding causes the rapid activation of coagulation pathways, which results in **the formation of a blood clot on the wound surface**. In addition to entrapped red cells, the clot contains fibrin, fibronectin, and complement components. **The clot serves to stop bleeding and also as a scaffold for migrating cells**.

**Release of VEGF leads to**:

1-Increase vessel permeability and edema.

2-Stimulate endothelial cells migration and proliferation.

3- Promote angiogenesis .

The dehydration occurs at the external surface of the clot, forming **a scab** that covers the wound. In wounds causing large tissue deficits, the fibrin clot is larger, and there is more exudate and necrotic debris in the wounded area.

**Within 24 hours, neutrophils appear at the margins of the incision**.They release proteolytic enzymes that clean out debris and invading bacteria.

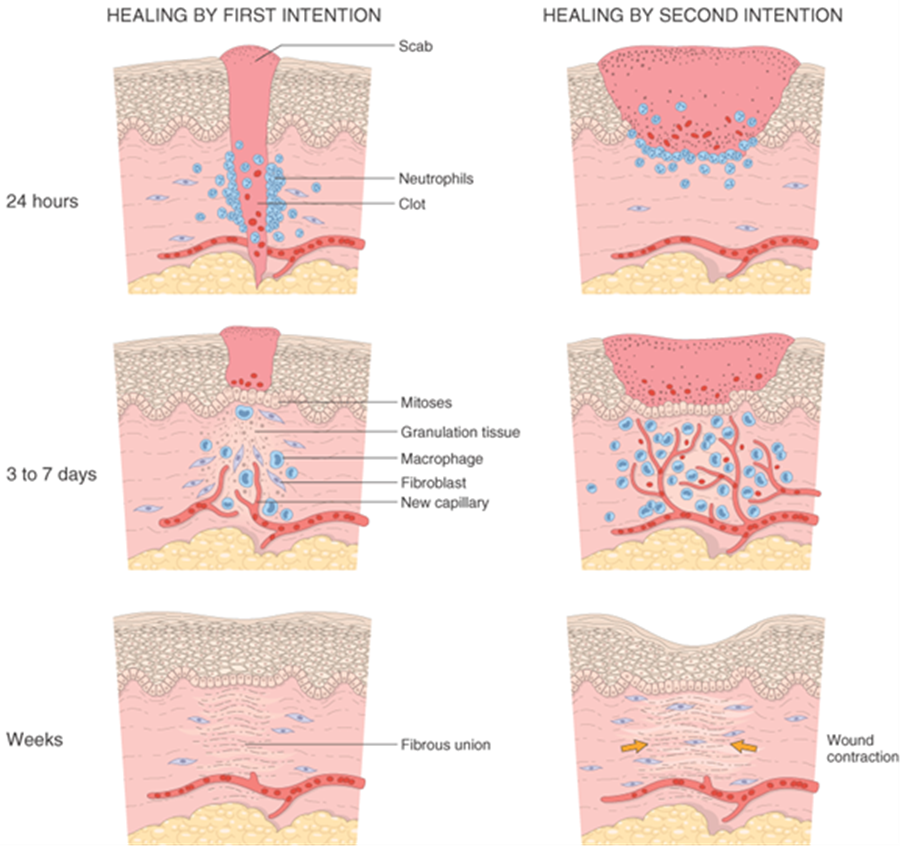
**Formation of Granulation Tissue**

**In the first 24-72 hours of the repair process ,**fibroblasts and vascular endothelial cells proliferate to form a specialized type of tissue called **granulation tissue**, which is a hallmark of tissue repair. **Its pink, soft, granular appearance on the surface of wounds.The characteristic histological feature is the presence of new small blood vessels (angiogenesis) and the proliferation of fibroblasts** .Granulation tissue progressively invades the incision space; the amount of granulation tissue is formed depending on the size of the tissue deficit created by the wound and the intensity of inflammation, this much more prominent in healing by secondary union. **By 5-7 days, granulation tissue fills the wound area and neovascularization is maximal.**

**Cell Proliferation and Collagen Deposition**

**In 48-96 hours, the neutrophils are largely replaced by macrophages, macrophages are key cellular constituents of tissue repair,** clearing extracellular debris, fibrin, and other foreign material at the site of repair, and promoting angiogenesis and ECM deposition. **Migration of fibroblasts to the site of injury is driven by chemokines,** TNF, PDGF, TGF-β, and FGF*.* Collagen fibers are now present at the margins of the incision, but at first these are vertically oriented and do not bridge the incision.

**In 24 to 48 hours, spurs of epithelial cells move from the wound edge (initially with little cell proliferation) along the cut margins of the dermis, depositing basement membrane components as they move.** They fuse in the midline beneath the surface scab, producing a thin, continuous epithelial layer that closes the wound. Full epithelialization of the wound surface is much slower in healing by secondary uncion because the gap to be bridged is much greater.



**Figure 1: Healing by primary union secondary union**

**Table 1:Differences between primary and secondary healing**

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| **Features** | **Primary** | **Secondary** |
| **Clean wound** | Clean | Not clean |
| **Infection** | Not Infected | Infected |
| **Margins** | Surgical wound | Irregular |
| **Sutures** | Used | Not used |
| **Granulation tissue** | Small amount | Large amount |
| **Scar** | Thin small scar | Large scar |
| **Complication** | Not frequent | Frequent |
| **Contraction** | Un common | Common |

**Scar Formation**

During the second week ,the leukocyte, edema and increased vascularity largely disappear.Blanching begins, accomplished by the increased accumulation of collagen within the wound area and regression of vascular channels. Finally, **the original granulation tissue scaffolding is converted into a pale, avascular scar, composed of spindle-shaped fibroblasts, dense collagen, fragments of elastic tissue, and other ECM components.**

**By the end of the first month,** the scar is made up of a cellular connective tissue devoid of inflammatory infiltrate, covered by intact epidermis.

**Wound Contraction**

**Wound contraction is an important feature in healing by secondary union.**The contraction helps to close the wound by decreasing the gap between its dermal edges and by reducing the wound surface area so the initial steps of wound contraction involve the formation of a network of myofibroblasts that express smooth muscle α-actin and vimentin at the edge of the wound.These cells have ultrastructural characteristics of smooth muscle cells, contract in the wound tissue, and may produce large amounts of ECM components.

**Connective Tissue Remodeling**

The replacement of granulation tissue with a scar involves changes in the composition of the ECM. **The balance between ECM synthesis and degradation results in remodeling of the connective tissue framework – an important feature of tissue repair.** Some of the growth factors that stimulate synthesis of collagen and other connective tissue molecules also modulate the synthesis and activation of metalloproteinases, enzymes that degrade these ECM components.

**Degradation of collagen and other ECM proteins is achieved by matrix metalloproteinases (MMPs),** a family of enzymes that includes more than 20 members MMPs are produced by fibroblasts, macrophages, neutrophils, synovial cells, and some epithelial cells.Their secretion is induced by growth factors (PDGF, FGF), cytokines (IL-1, TNF), and phagocytosis in macrophages, and is inhibited by TGF-β and steroids.

**Recovery of Tensile Strength**

Fibrillar collagens (mostly type I collagen) form a major portion of the connective tissue in repair sites and are essential for the development of strength in healing wounds. **Net collagen accumulation, depends not only on increased collagen synthesis but also on decreased** **degradation.** When sutures are removed from an incisional surgical wound, **usually at the end of the first week, wound strength is approximately 10% that of unwounded skin. Wound strength increases rapidly over the next 4 weeks,** Wound strength reaches approximately 70% to 80% of normal by 3 months but usually does not substantially improve beyond that point.The recovery of tensile strength results from the excess of collagen synthesis over collagen degradation during the first 2 months of healing, and, at later times, from structural modifications of collagen fibers (cross-linking, increased fiber size) after collagen synthesis ceases.

**Local and Systemic Factors that Influence Wound Healing**

**Local Factors that Influence Wound Healing**

**1-Infection** is the single most important cause of delay in healing process because of the persistent tissue injury and inflammation.

**2- Mechanical Factors** such as early motion of wounds can delay wound healing.

**3-Foreign bodies** such as fragments of steel, glass, or even bone delay healing.

**4- Size ,Location and the Type of Wound.**

Wounds in richly vascularized areas, such as the face, heal faster than those poorly vascularized once , such as the foot.

**Systemic Factors that Influence Wound Healing**

**1-Nutrition** has profound effects on wound healing; protein deficiency & vitamin C deficiency, inhibits collagen synthesis and delays healing.

**2-Hormons** such as glucocorticoids (steroids ) have anti -inf lammatory effects, and their administration may result in poor wound strength due to diminished fibrosis.

**3-Circulatory status** can effect on wound healing. Inadequate blood supply usually caused by arteriosclerosis or venous abnormalities (e.g. invaricose veins), impairs healing .

**4-Metabolic status** can change wound healing e.g. diabetes mellitus is associated with delay wound healing .

**Pathological Aspects of Repair**

Complications in wound healing can arise from abnormalities in any of the basic components of the repair process. These are divided into **three** general categories:

(1) Deficient scar formation.

(2) Excessive formation of the repair components.

(3) Formation of contractures.

**1-Deficient scar formation: Inadequate formation or assembly of a scar can lead to wound dehiscence**

Wound dehiscence is a surgical complication in which a wound ruptures along a surgical incision. Risk factors include age, collagen disorder such as Ehlers–Danlos syndrome, diabetes, obesity and trauma to the wound after surgery.

**2- Excessive formation of the repair components process can give rise to** **Hypertrophic scar and keloids.**

**Hypertrophic scar**: its excessive accumulation of collagen amounts may give rise to a raised scar within the incision, it develops after thermal or traumatic injury that involves the deep layers of the dermis.

**Keloid :** refers to the accumulation of excessive amounts of collagen that give rise to prominent, raised scars tissue grows beyond the boundaries of the original wound and does not regress.There appears to be a heritable predisposition and the condition its more common in blacks.

**3-Exuberant granulation** :its the formation of excessive amounts of granulation tissue, which protrudes above the level of the surrounding skin and blocks re-epithelialization.

**4-Exaggerated contraction** gives rise to **contracture** and results in deformities of the wound and the surrounding tissues.Contractures are particularly prone to develop on the palms, the soles. Contractures are commonly seen after serious burns and can compromise the movement of joints.

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