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Pathology

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Sheet Slides

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Tissue Repair

Inflammation may cause injury and repair is critical after eliminating the enemy. Repair can be achieved by:

1. Regeneration (if possible, lost tissue will be replaced).
2. Scar & fibrosis: replacing tissue is connective (only structural) → loss of function.

*Both require:

- **Mediators** (many repair mediators also mediate inflammation, but, in the case of repair, can be termed **G**rowth **F**actors)
- **Cellular proliferation**
- **Interactions with the ECM**. Interaction between parenchymal cells and the ECM are more important in repair than with the intravascular compartment.

Regeneration:

The ability of tissues to repair themselves is determined, in part, by their intrinsic proliferative capacity.

Tissue types:

1. **Labile tissue**: where cells are continuously lost and regenerated. ex. epithelia of mucosal surfaces or the skin
2. **Stable tissue**: made up of cells that are normally in the G_0 stage, but are capable of dividing in response to injury. ex. liver, kidney, pancreas

   Liver regeneration**:** either by:

   - Hepatocyte proliferation
   - Progenitor cells are activated → proliferation + differentiation

   * Both need growth factors, cytokines and ECM interactions.
3. **Permanent tissue**: consist of terminally differentiated nonproliferative cells (most form during embryogenesis). ex. neurons (not all brain tissue), cardiac & skeletal muscle

Healing by **first intention**: when injury is superficial or mild / surgical wound →

(a) minimal tissue loss
(b) complete & quick repair
(c) return of function
(d) no or minimal granulation tissue

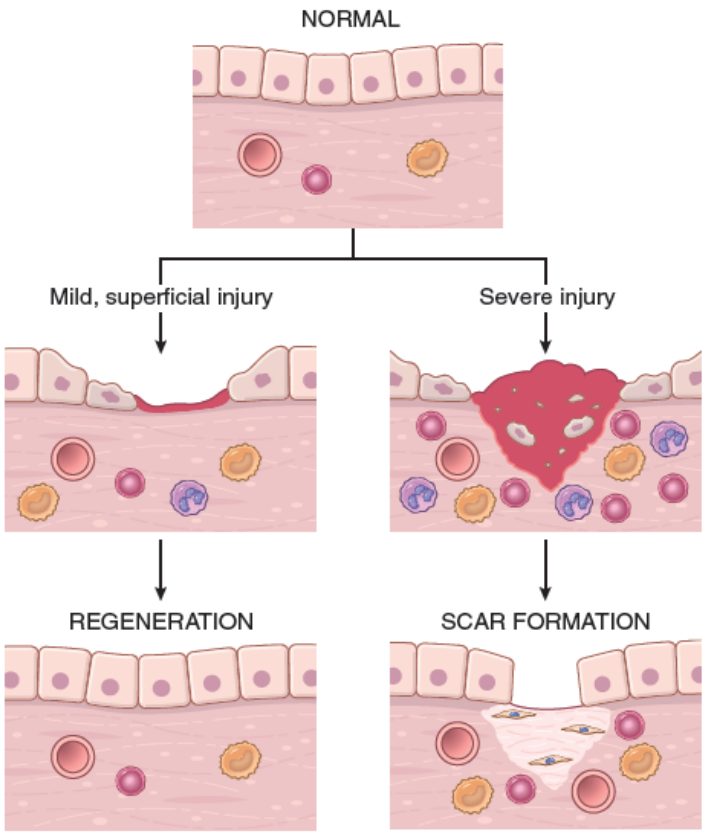

Fig. 3.23 Mechanisms of tissue repair: regeneration and scar formation. Following mild injury, which damages the epithelium but not the underlying tissue, resolution occurs by regeneration, but after more severe injury with damage to the connective tissue, repair is by scar formation.

Healing by **second intention**: when injury is severe →

(a) scar formation
(b) granulation tissue formed

Scarring and Fibrosis:

- Happens when tissue injury is severe or chronic and results in damage to parenchymal cells, epithelia, and connective tissue framework.
- Scarring is a response that 'patches' instead of 'restores'.
- Healing is by **first** and **second intention** (regeneration + scarring).
- Steps of scar formation:

1. Within minutes after injury, a **haemostatic plug** comprised of platelets & fibrin is formed to stop the bleeding. (Initial Platelet Haemostatic Plug).
2. **Inflammation**: 6 to 48 hrs – recruitment of macrophages (M1 and M2) which are the most important cells in the process of repair.
3. **Cell proliferation**: up to 10 days – starts with angiogenesis (discussed later and in the next sheet) and formation of **granulation tissue** (*the combination of proliferating fibroblasts, loose connective tissue, new blood vessels and scattered chronic inflammatory cells, this term derives from its pink, soft, granular gross appearance, such as that seen beneath the scab of a skin wound*).
4. **Remodelling**: 2 to 3 weeks – replacing granular tissue with stronger connective tissue (scar).

   When newly formed, scars look pink, then get whiter as they mature. Scar maturation occurs by replacing Collagen III with Collagen I & increased matrix connections/intersections + tissue retraction → tissue becomes tighter (this is presented by dips in epithelial tissue - observe image below).

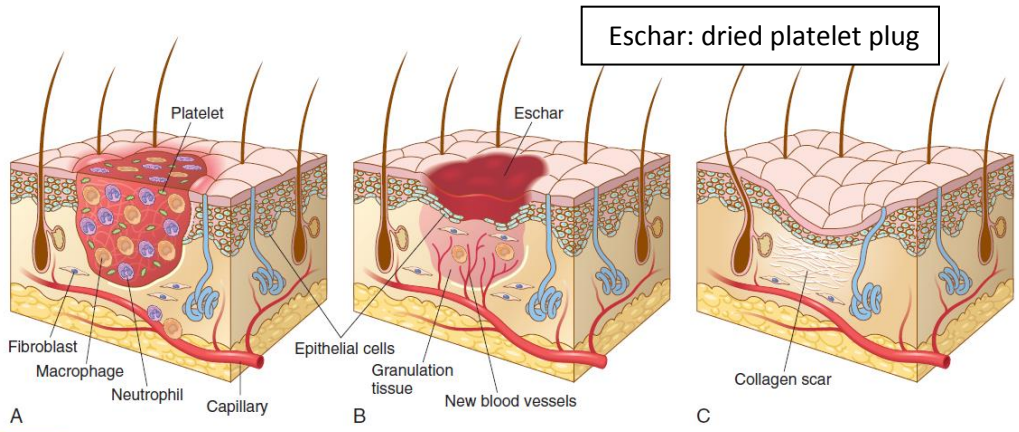

Fig. 3.24 Steps in repair by scar formation: healing of a large wound in the skin. This is an example of healing by second intention. (A) Hemostatic plug and inflammation. (B) Proliferation of epithelial cells; formation of granulation tissue by vessel growth and proliferating fibroblasts. (C) Remodeling to produce the fibrous scar.

Angiogenesis:

- The process of new blood vessel development from existing vessels and has a central role in healing.
- More important in **second intention** healing but important in both intentions.
- The process of angiogenesis involves several signalling pathways, cell to cell interactions, ECM proteins, and tissue enzymes.
    - **Growth factors:**
        - *VEGFs*, mainly VEGF-A (Vascular Endothelial Growth Factor-A), thus initiating the process of capillary sprouting in angiogenesis.
        - *FGFs* (Fibroblast Growth Factors), mainly FGF-2.
        - TransformingGF-β suppresses endothelial proliferation and migration and enhances the production of ECM proteins by recruiting fibroblasts.

          TGF-β is the most important cytokine for the synthesis and deposition of connective tissue proteins and plays an important role in scirrhous (a pathological subtype of breast cancer), pancreatic, and biliary cancers where a lot of **scarring and fibrosis occurs.*
    - **Notch Signalling:** regulation of sprouting BVs.
    - **ECM proteins.**
    - **Enzymes** for final remodelling.

Fibrosis in the **brain is termed **gliosis** because the brain's fibroblasts are called glial cells.*