

Inflammation and Repair

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Lecture 7

TISSUE REPAIR:

- Inflammation may cause injury and repair is critical after eliminating the enemy
- Repair can be achieved by:
 - 1. Regeneration
 - 2. Scar & fibrosis

Both require mediators and cellular proliferation. And interactions with ECM

TISSUE REGENERATION:

- Regeneration requires growth factors and interactions between cells and matrix (ECM)
- Tissue types

Labile tissue	Continuous regeneration : epithelia of mucosal surfaces
Stable tissue	Normally in G₀, but can be stimulated to regenerate when injured (liver, Kidney, pancreas)
Permanent tissue	Terminally differentiated, non proliferative (neurons and cardiac muscle, skeletal muscle)

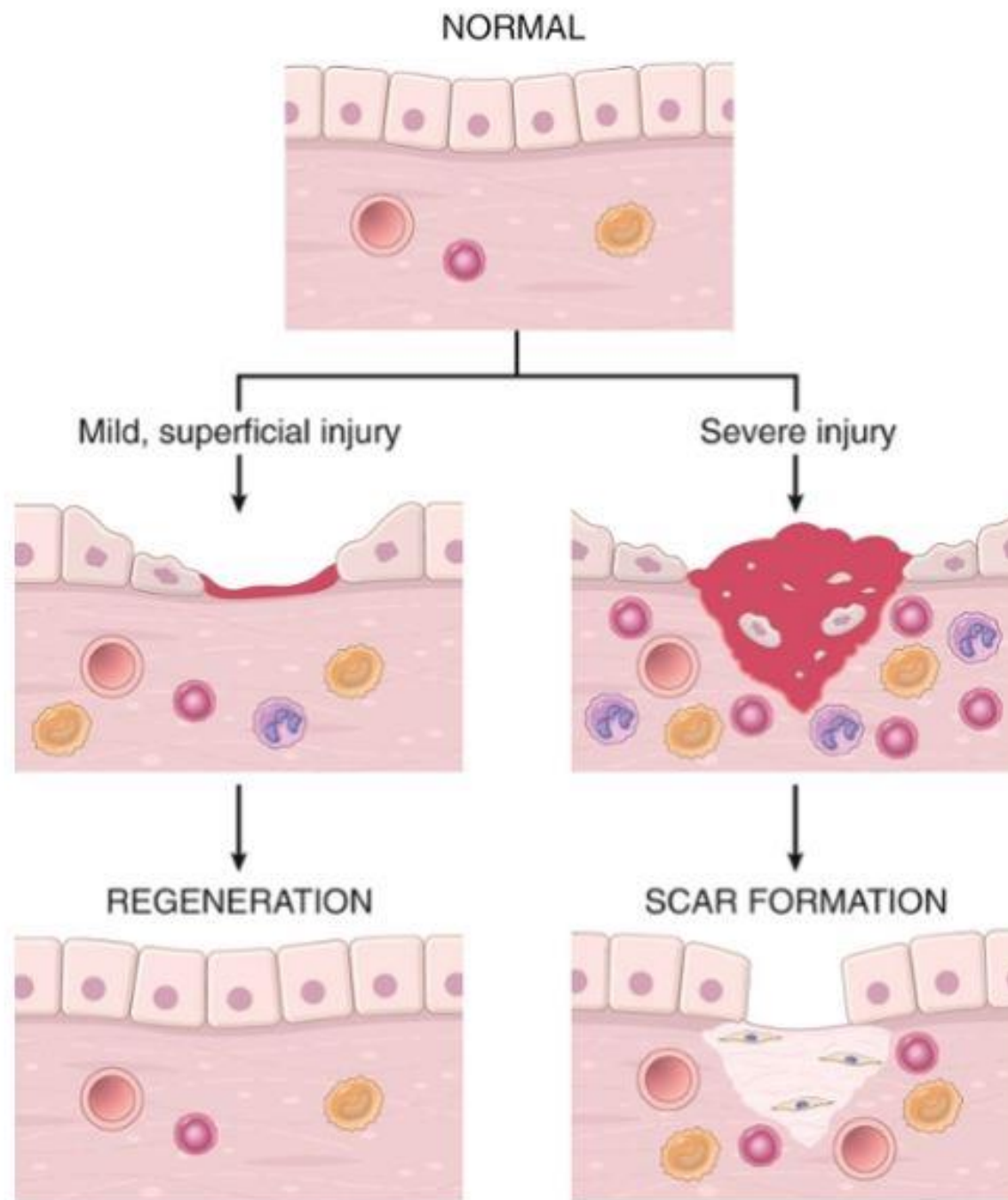


FIG. 3.23  Mechanisms of tissue repair: regeneration and scar formation. Following mil...

LIVER REGENERATION:

- **Liver can regenerate in 2 ways:**
 - 1. **Hepatocytes proliferation, post partial hepatectomy**
 - 2. **Progenitor cells gets activated and proliferate and differentiate**

Both need growth factors & cytokines and cell matrix interactions



Summary

Repair by Regeneration

- Different tissues consist of continuously dividing cells (epithelia, hematopoietic tissues), normally quiescent cells that are capable of proliferation (most parenchymal organs), and nondividing cells (neurons, skeletal and cardiac muscle). The regenerative capacity of a tissue depends on the proliferative potential of its constituent cells.
- Cell proliferation is controlled by the cell cycle, and is stimulated by growth factors and interactions of cells with the extracellular matrix.
- Regeneration of the liver is a classic example of repair by regeneration. It is triggered by cytokines and growth factors produced in response to loss of liver mass and inflammation. In different situations, regeneration may occur by proliferation of surviving hepatocytes or repopulation from progenitor cells.

REPAIR BY SCARRING:

- Large amount of tissue damage
- “Patching”, wound healing and Scarring
- Healing by first and second intention.
- Steps:
 - Hemostatic plug (platelets)...minutes
 - Inflammation (Macs, M1 and M2)...6-48 hours
 - Cell proliferation (granulation tissue)...10 days
 - Remodeling.... 2-3 weeks

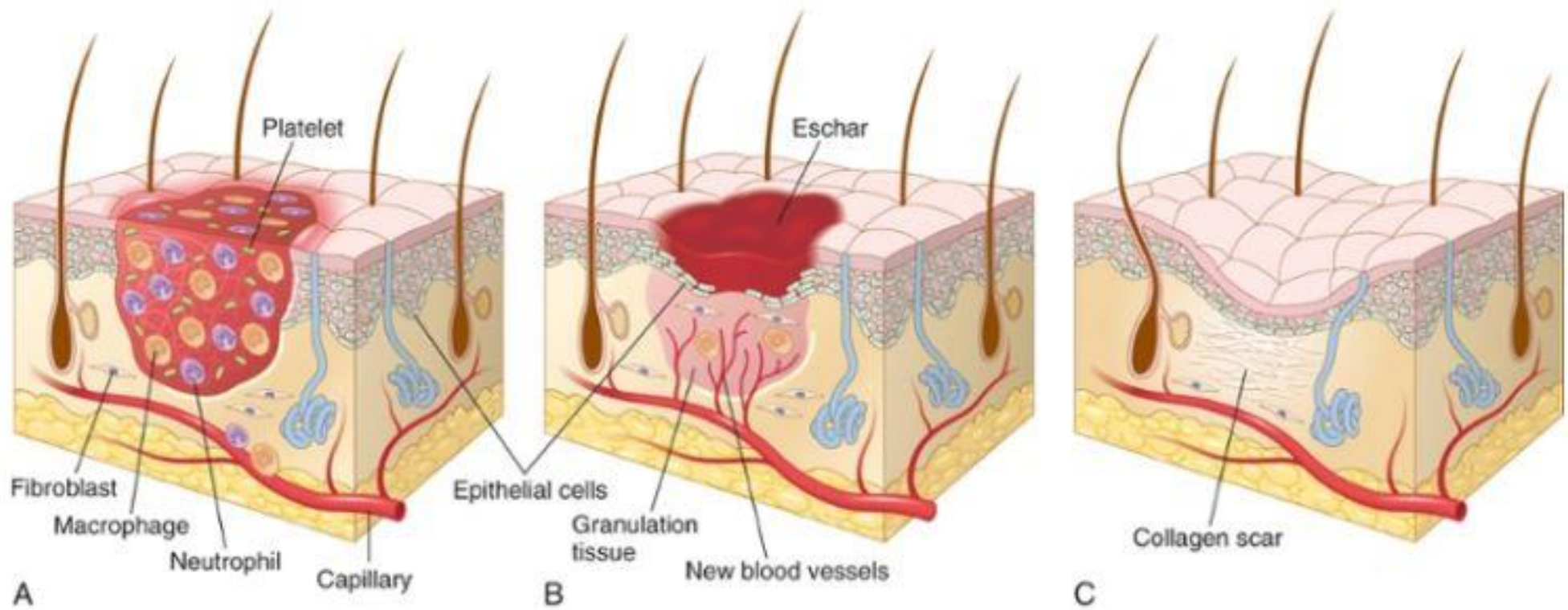


FIG. 3.24  Steps in repair by scar formation: healing of a large wound in the skin. This is ...

Lecture 8

ANGIOGENESIS:

- Central role in healing
- Requires multiple steps; signaling pathways, growth factors, cell-matrix interactions and enzymes of remodeling
 - GF: VEGF-A, FGFs mainly FGF-2, TGF- β
 - Notch signaling: sprouting
 - ECM proteins
 - Enzymes for final remodeling

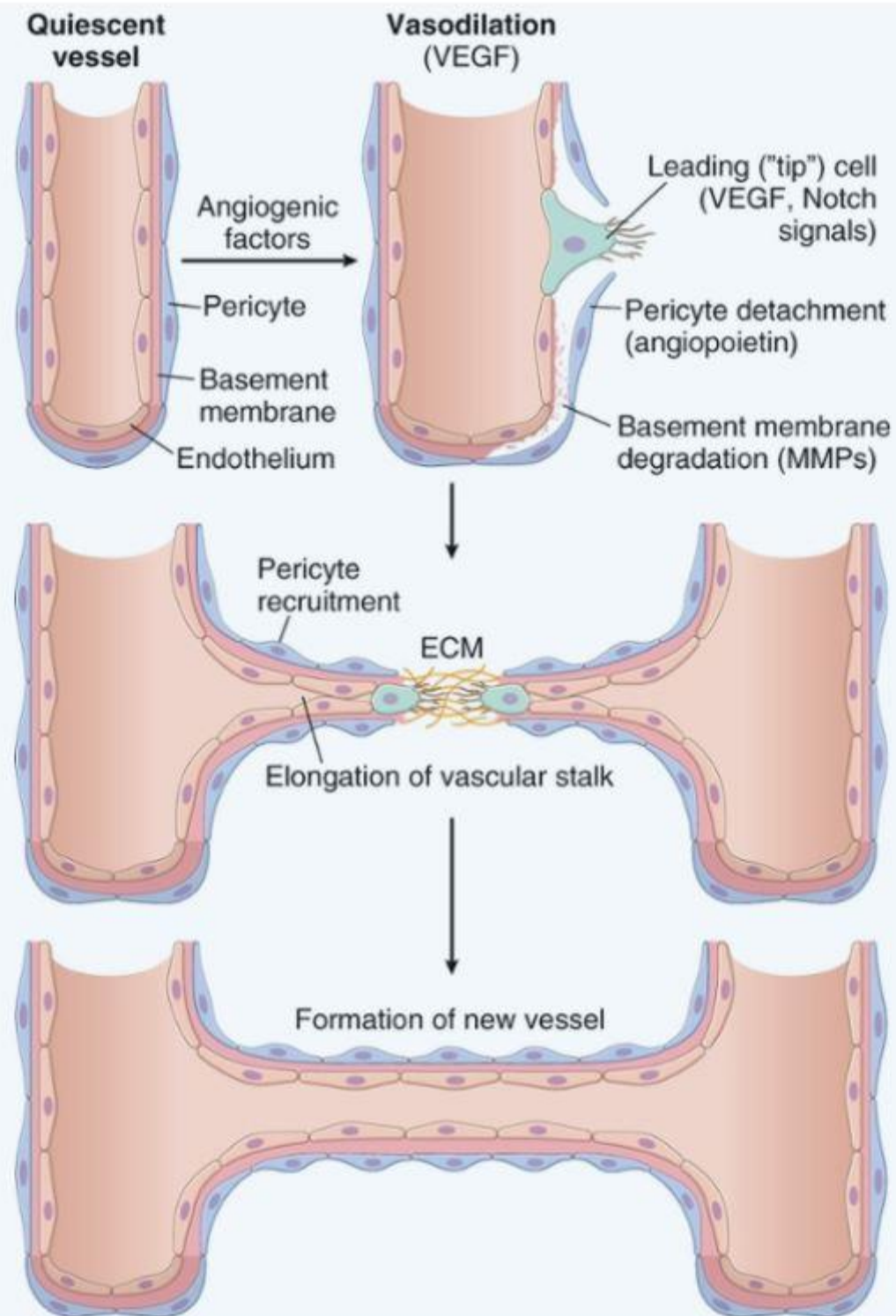


FIG. 3.25  Angiogenesis. In tissue repair, angiogenesis occurs mainly by the sprouting o...

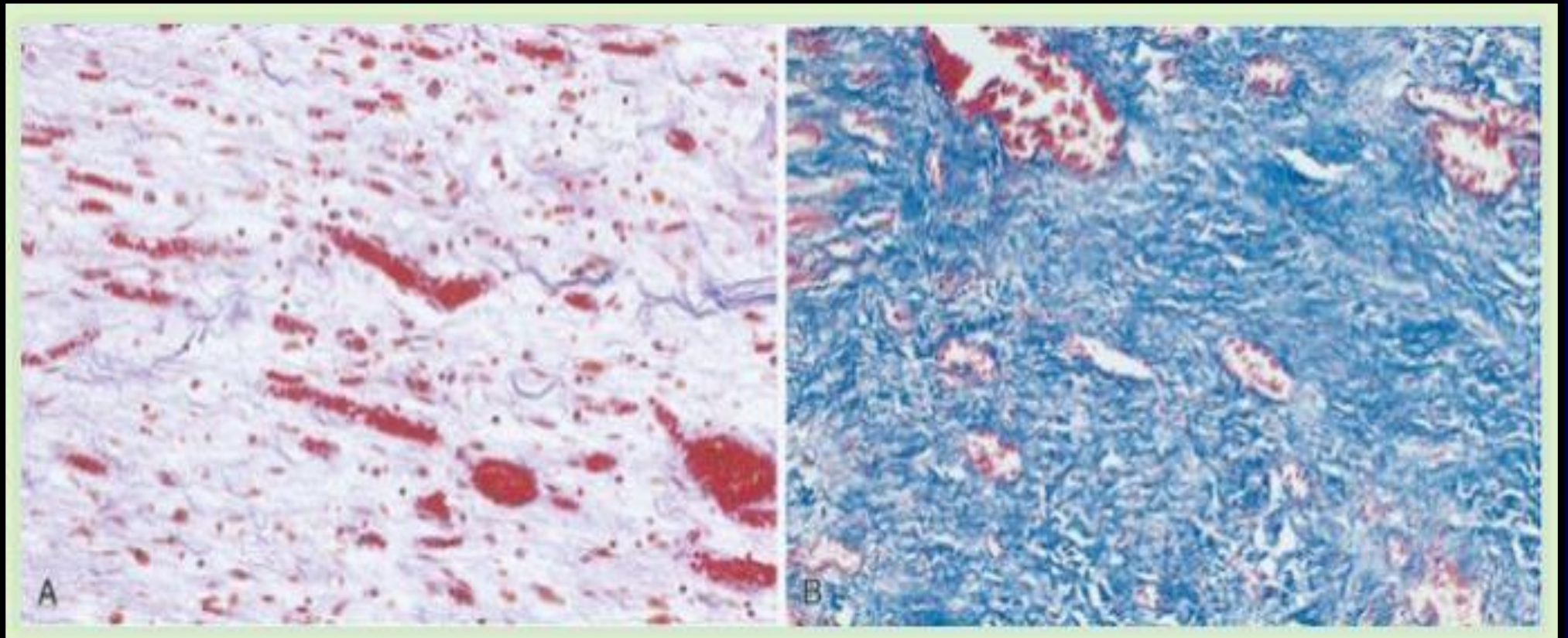
ACTIVATION OF FIBROBLASTS AND DEPOSITION OF MATRIX:

- 2 STEPS:
 - Migrations and proliferation of fibroblasts
 - Deposition of ECM proteins by these cells
- Need cytokines and GFs: PDGF, FGF-2, **TGF- β**
- Fibroblasts and myofibroblasts help lay down collagen to close the gap
- **TGF- β is the most important**

REMODELING OF CONNECTIVE TISSUE:

- **It is needed to make the scar strong and contract it**
- **Cross linking of collagen**
- **Switching type III to type I collagen**
- **Degradation of collagen by Matrix Metalloproteinases (MMPs) and balanced by their inhibitors (TIMPs)**

GRANULATIONS TISSUE VS MATURE SCAR





Summary

Repair by Scar Formation

- Repair occurs by deposition of connective tissue and scar formation if the injured tissue is not capable of regeneration or if the structural framework is damaged and cannot support regeneration.
- The main steps in repair by scarring are clot formation, inflammation, angiogenesis and formation of granulation tissue, migration and proliferation of fibroblasts, collagen synthesis, and connective tissue remodeling.
- Macrophages are critical for orchestrating the repair process, by eliminating offending agents and producing cytokines and growth factors that stimulate the proliferation of the cell types involved in repair.
- TGF- β is a potent fibrogenic agent; ECM deposition depends on the balance among fibrogenic agents, matrix metalloproteinases (MMPs) that digest ECM, and the tissue inhibitors of MMPs (TIMPs).

Lecture 9

FACTORS THAT IMPAIR TISSUE REPAIR (IMPORTANT):

- 1. Infections**
- 2. Diabetes mellitus**
- 3. Nutritional status**
- 4. Steroids**
- 5. Mechanical factors**
- 6. Poor perfusion**
- 7. Foreign body**
- 8. Type and extent of tissue injury**
- 9. Site of injury**

ABNORMAL HEALING

- Deficient scar formation
- Excessive repair
- Contractures

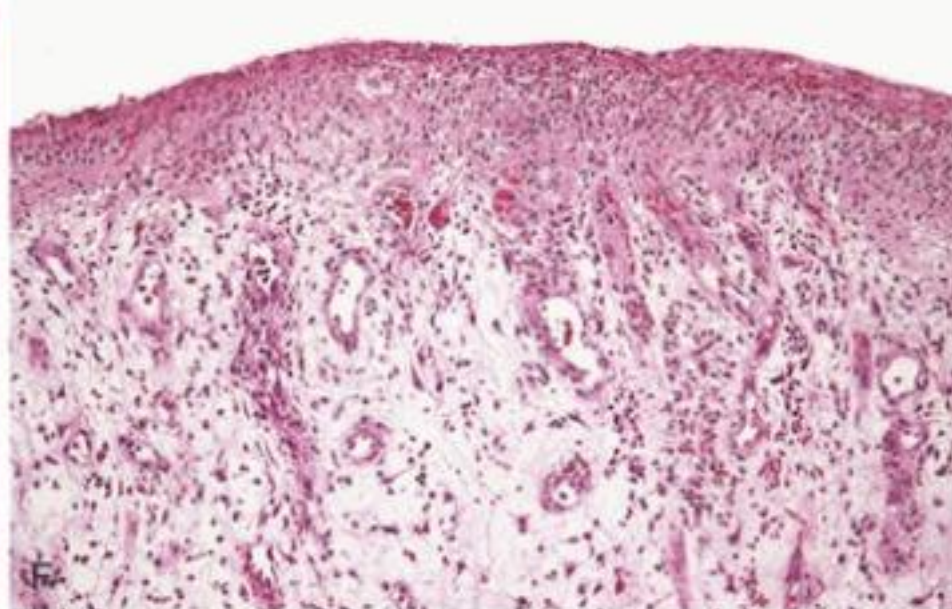
DEFICIENT HEALING:

- Venous leg ulcers
- Arterial ulcers
- Pressure sores
- Diabetic ulcers
- *** Wound dehiscence

Wound dehiscence:



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EXCESSIVE SCARRING:

- Hypertrophic scar
- Keloid
- Exuberant granulation tissue (proud flesh)
- Aggressive fibromatosis (desmoid tumor)
- Contractures

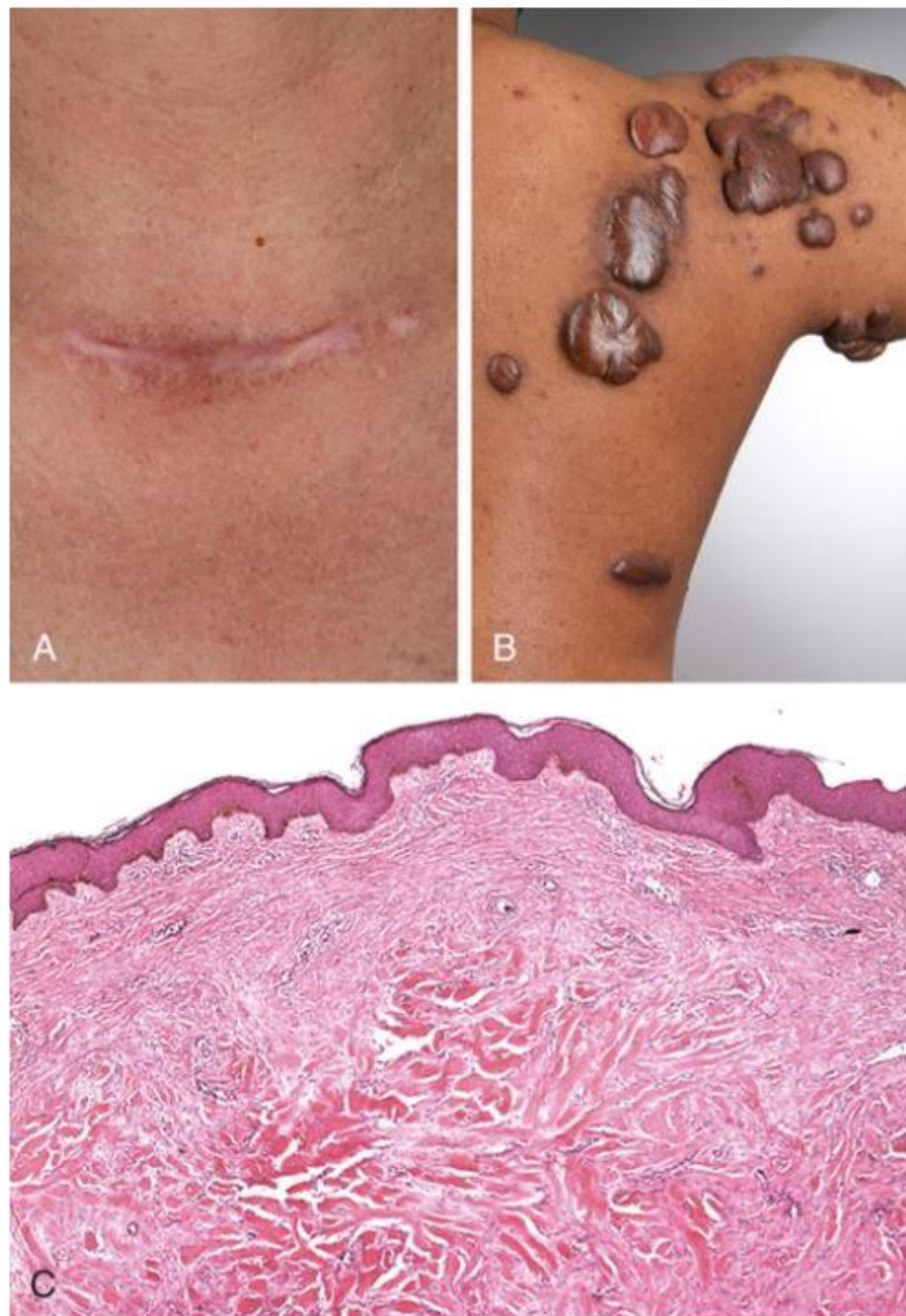



FIG. 3.28  Clinical examples of excessive scarring and collagen deposition. (A) Hypertro...

FIBROSIS OF ORGANS:

- Scar and fibrosis: excessive deposition of collagen and ECM.
- Continuous infections and immunologic injuries cause organ fibrosis and loss of function
- **TGF- β is the most common cytokine of fibrosis**
- Examples: liver cirrhosis, Idiopathic lung fibrosis, ESKD

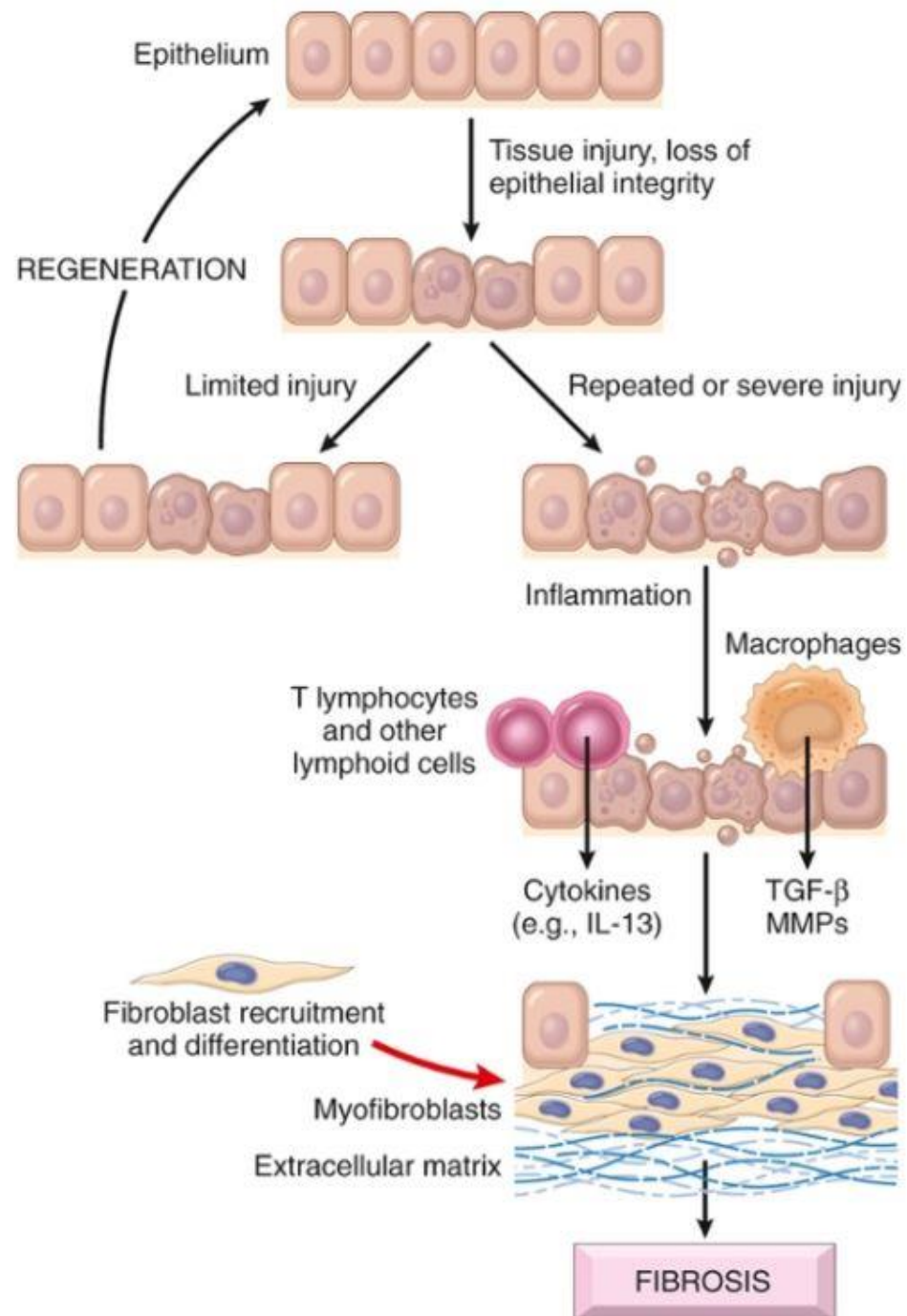


FIG. 3.29 Mechanisms of fibrosis. Persistent tissue injury leads to chronic inflammatio...



Summary

Cutaneous Wound Healing and Pathologic Aspects of Repair

- The main phases of cutaneous wound healing are inflammation, formation of granulation tissue, and ECM remodeling.
- Cutaneous wounds can heal by primary union (first intention) or secondary union (secondary intention); secondary healing involves more extensive scarring and wound contraction.
- Wound healing can be altered by many conditions, particularly infection and diabetes; the type, volume, and location of the injury are important factors that influence the healing process.
- Excessive production of ECM can cause keloids in the skin.
- Persistent stimulation of collagen synthesis in chronic inflammatory diseases leads to tissue fibrosis, often with extensive loss of the tissue and functional impairment.

Lecture 10

REVIEW

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