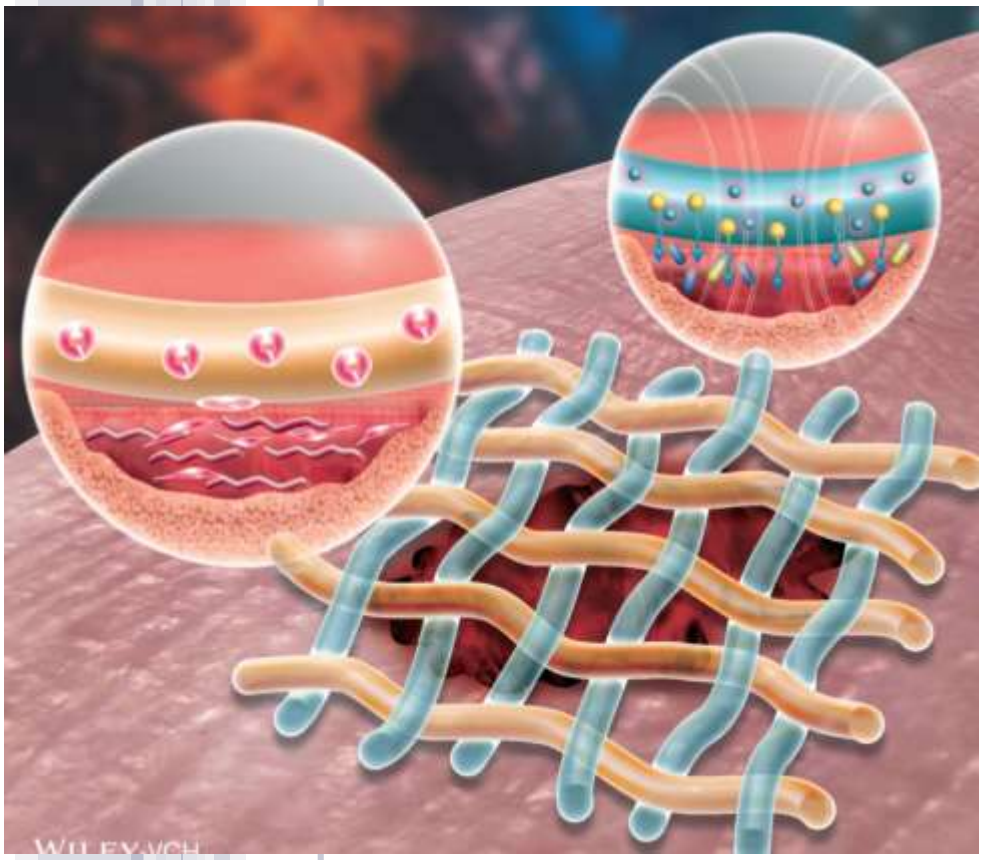
TISSUE REPAIR 1



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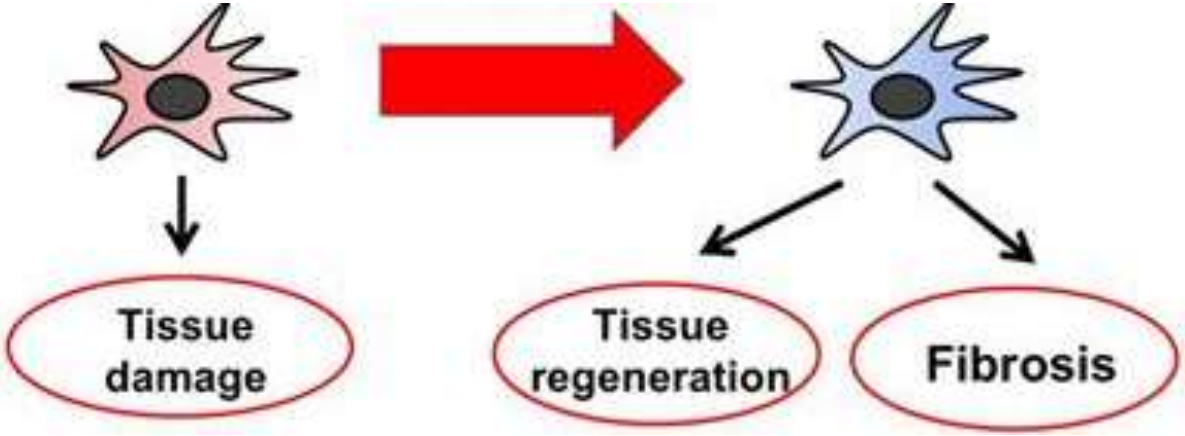
- The ability of an organism to repair the damage caused by toxic insults and inflammation is critical to the survival .

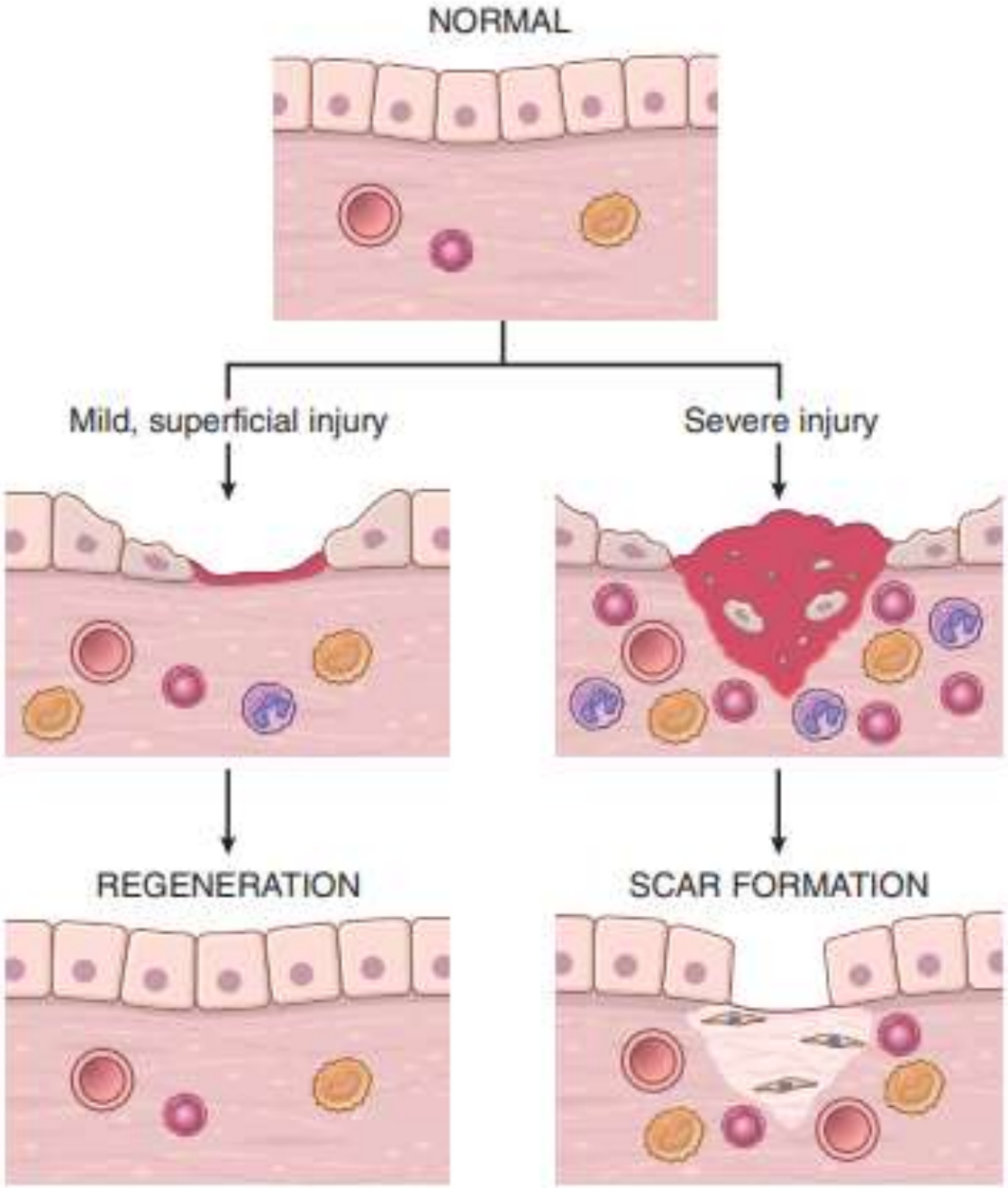
- In fact, the inflammatory response to microbes and injured tissues not only serves to eliminate these dangers but also sets into motion the process of repair.

Overview of Tissue Repair

- Repair of damaged tissues occurs by two types of reactions:

- Regeneration by proliferation of residual (uninjured) cells and maturation of tissue stem cells.
- Deposition of connective tissue to form a scar.




NORMAL
Mild, superficial injury
Severe injury
REGENERATION
SCAR FORMATION

1.REGENERATION

- Proliferation of cells that survive the injury and retain the capacity to proliferate leading to restoration of damaged tissues, may seen in:

- Rapidly dividing epithelia of the skin and intestines.
- Some parenchymal organs, notably the liver.
- Tissue stem cells.

2.Connective tissue deposition (scar formation)

- Repair occurs by the laying down of connective (fibrous) tissue, a process that may result in formation of a scar, it occur in:

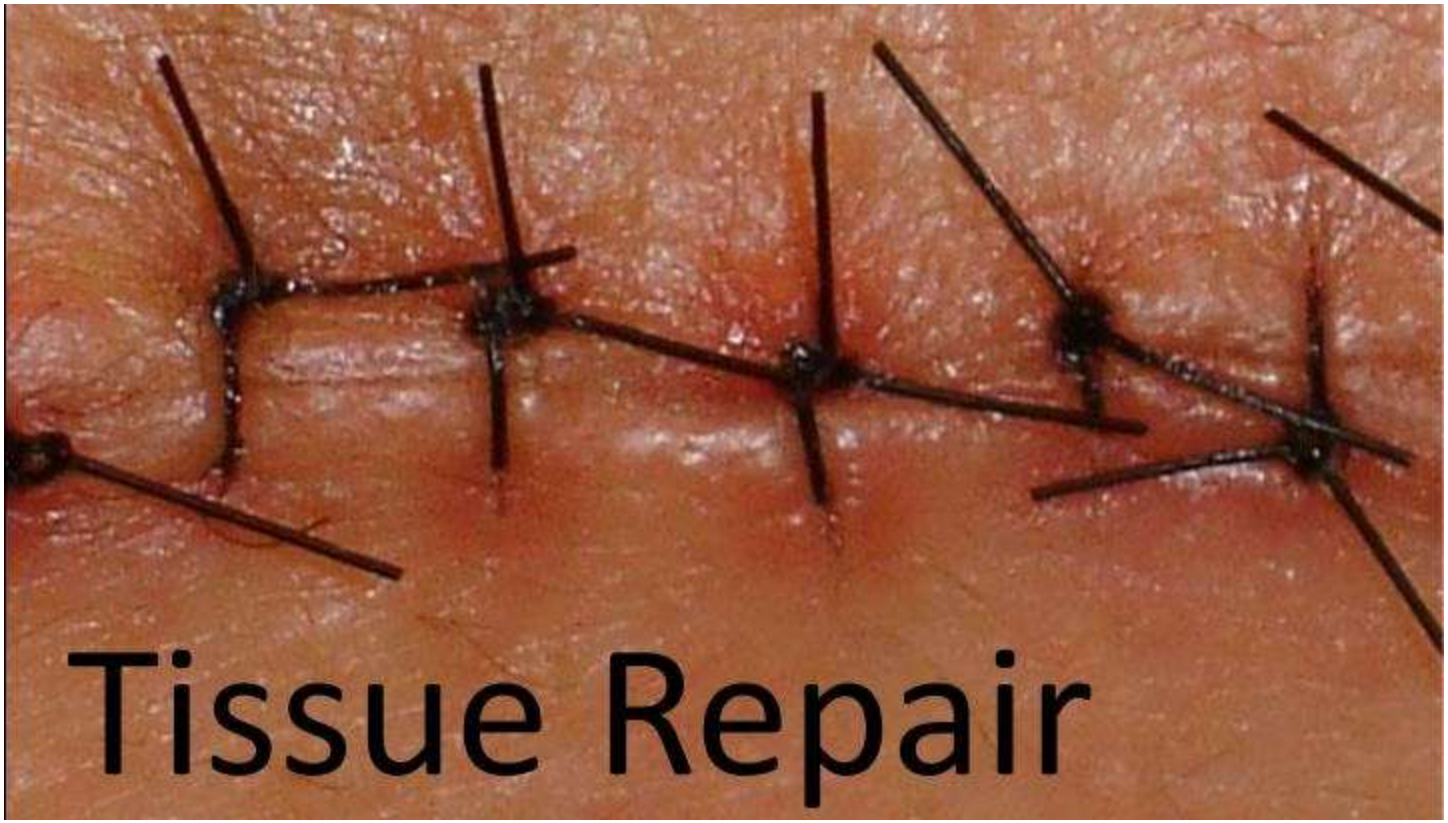
- injured tissues are incapable of complete restitution.
- if the supporting structures of the tissue are severely damaged

❖FIBROSIS

- Extensive deposition of collagen that occurs in:
- lungs, liver, kidney, and other organs as a consequence of chronic inflammation.
- In the myocardium after extensive ischemic necrosis (infarction).

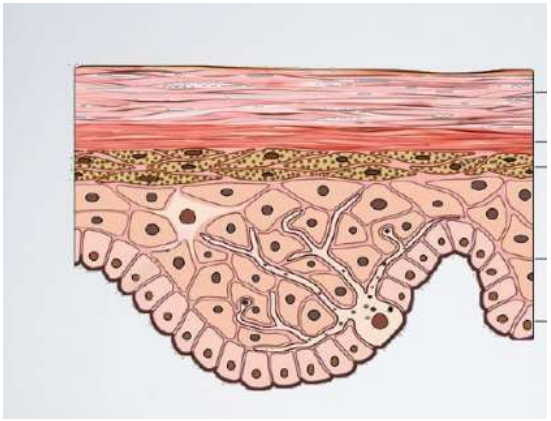
➢Although the fibrous scar is not normal, it provides enough structural stability that the injured tissue is usually able to function.

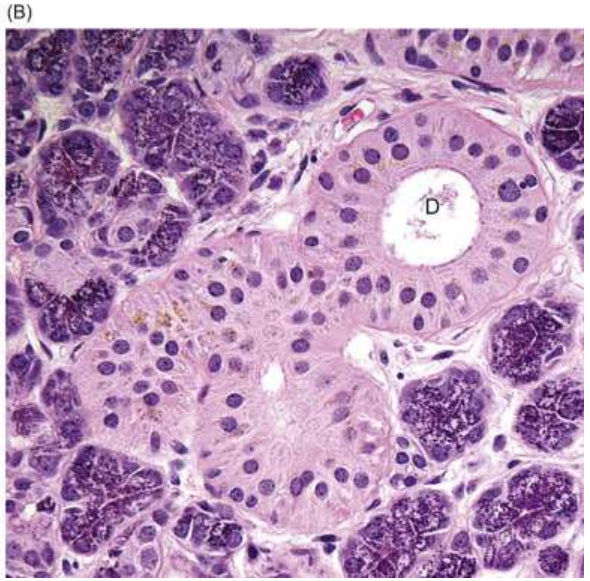
- The ability of tissues to repair themselves is determined, in part, by their intrinsic proliferative capacity.

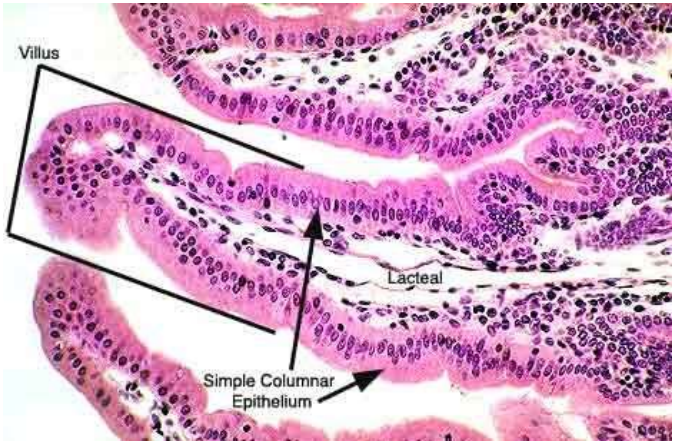


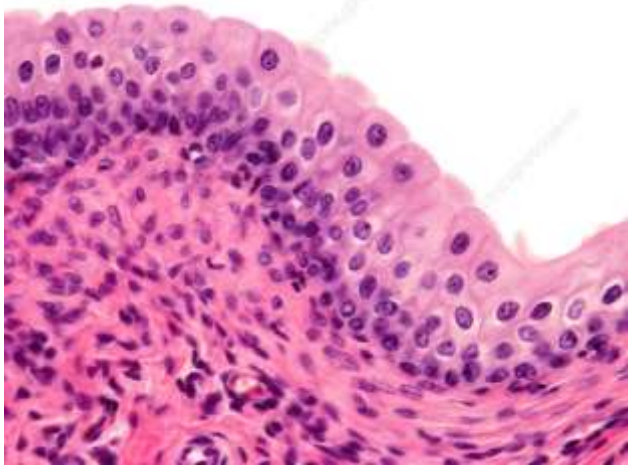
➢ *1.labile tissues: **

cells are constantly being lost and must be continually replaced by new cells that are derived from tissue stem cells and rapidly proliferating immature progenitors.

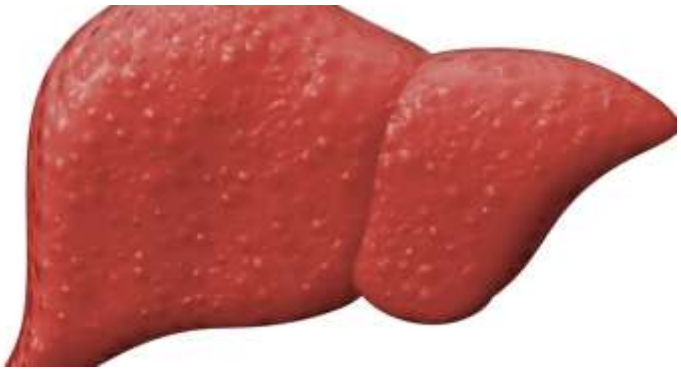


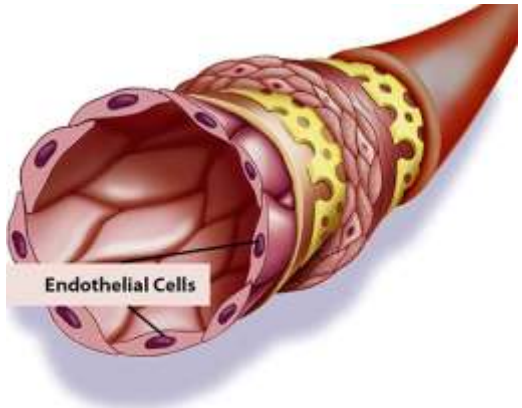


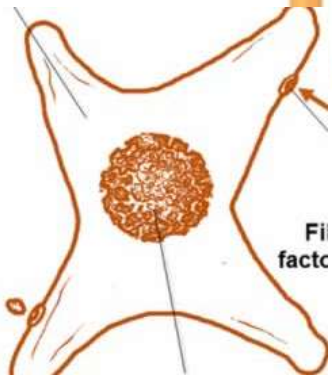




- 2.stable tissues
- Made up of cells that are normally in the G0 stage of the cell cycle and hence not proliferating, but they are capable of dividing in response to injury or loss of tissue mass.



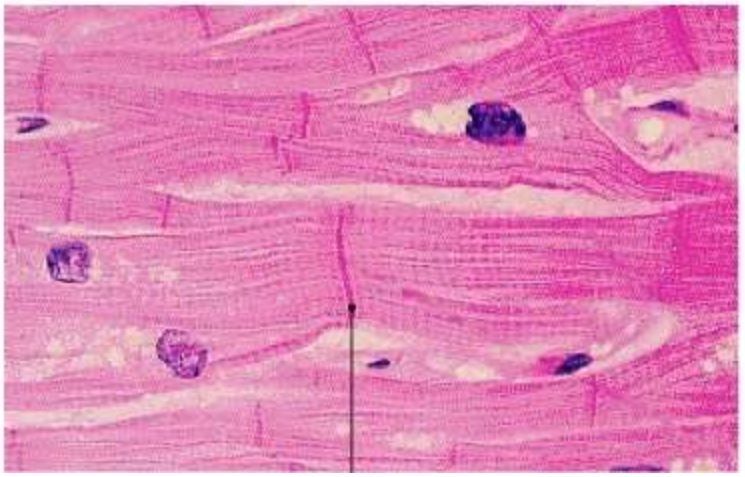




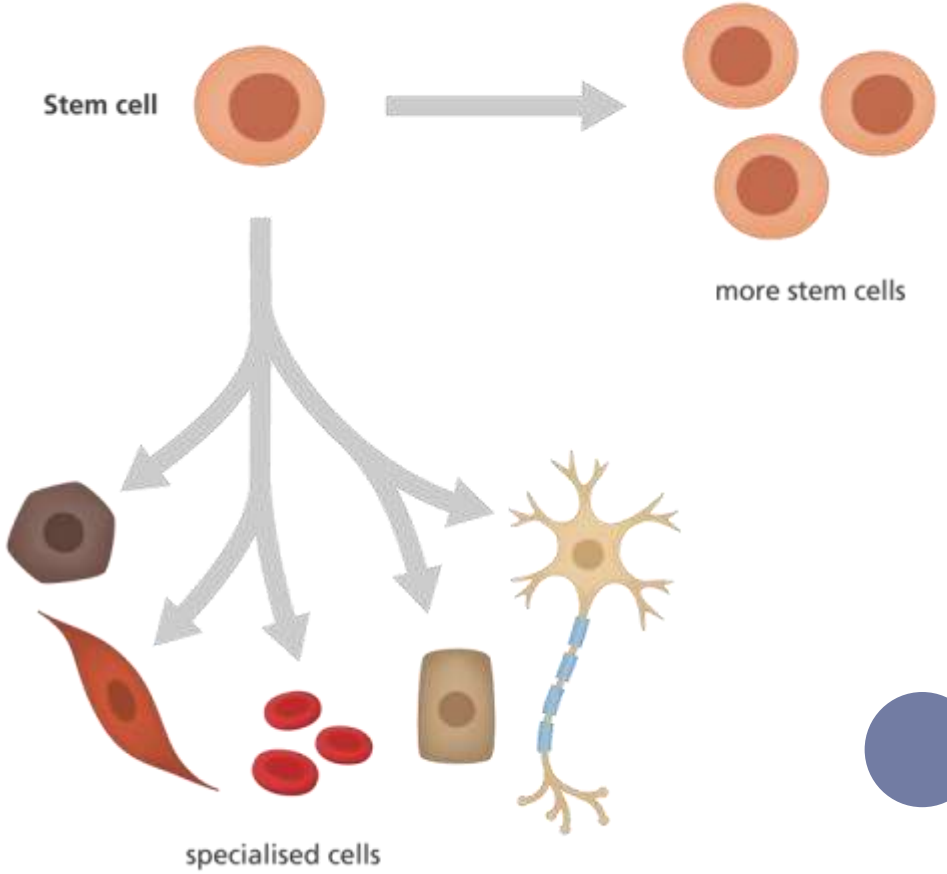
➢3.PERMANENT TISSUES

- consist of terminally differentiated nonproliferative cells, such as the majority of neurons and cardiac muscle cells.

- Injury to these tissues is irreversible and results in a scar, because the cells cannot regenerate.



- In the process of regeneration, proliferation of residual cells is supplemented by development of mature cells from stem cells



❖Liver Regeneration

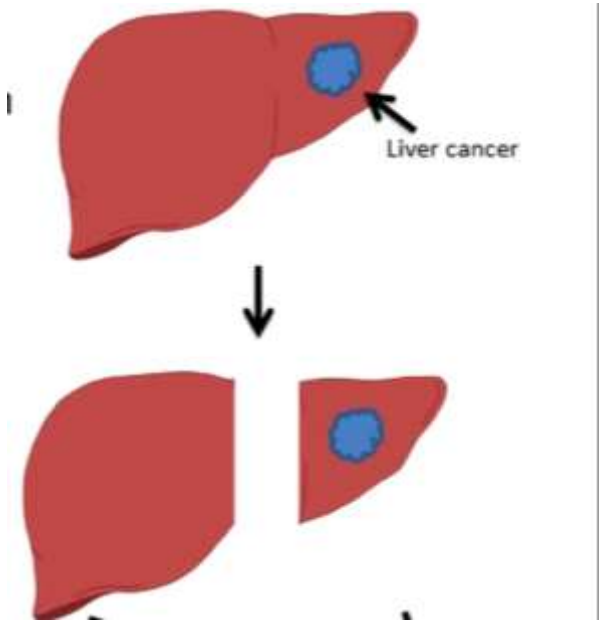
- The human liver has a remarkable capacity to regenerate, as demonstrated by its growth after partial hepatectomy,

- Regeneration of the liver occurs by two major mechanisms:

  - proliferation of remaining hepatocytes.

  - repopulation from progenitor cells.

- Restoration of normal tissue architecture can occur only if the residual tissue is structurally intact.
- if the entire tissue is damaged, regeneration is incomplete and is accompanied by scarring.



partial surgical resection

liver abscess

- 1.Proliferation of hepatocytes following partial hepatectomy.

- In humans, resection of up to 90% of the liver can be corrected by proliferation of the residual hepatocytes.

- This process is driven by
  - cytokines such as IL-6 produced by Kupffer cells.
  - hepatocyte growth factor (HGF) produced by many cell types.

- 2.Liver regeneration from progenitor cells.

- In situations in which the proliferative capacity of hepatocytes is impaired, progenitor cells in the liver contribute to repopulation, such as:

  - after chronic liver injury.
  - inflammation.

Repair by Scarring

- 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.

- The term scar is most used in connection to wound healing in the skin.
- Replacement of parenchymal cells in any tissue by collagen, as in the heart after myocardial infarction.

Steps in Scar formation

Injury

Hemostatic plug → Inflammation → Cell proliferation → Formation of **granulation tissue**

Stops bleeding, provides scaffold for deposition of fibrin

To eliminate offending agent

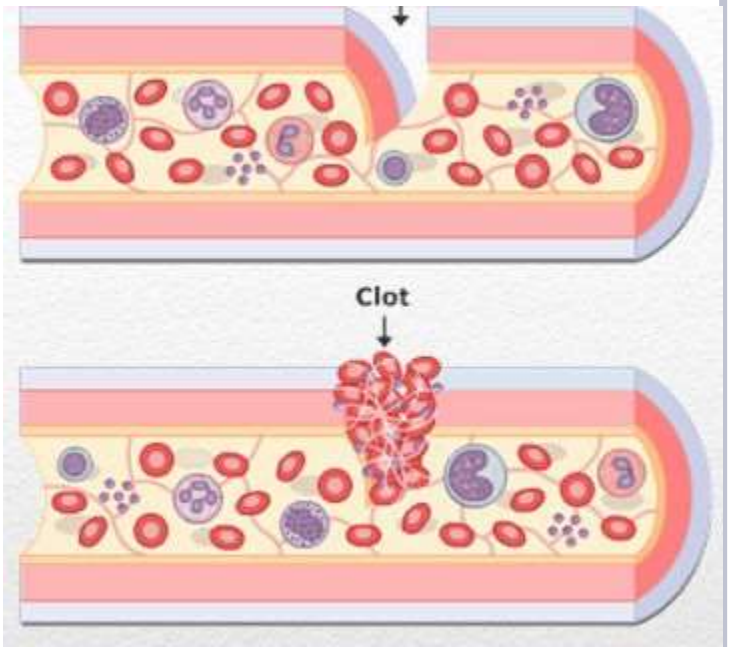
Remnants of injured tissue	Vascular Endothelial cells	Fibroblasts
Attempt to restore normal tissue	Creates blood vessels for nutrition during repair	Forms scar For defects which cannot regenerate

Deposition of **connective tissue (SCAR)**

Steps in Scar Formation

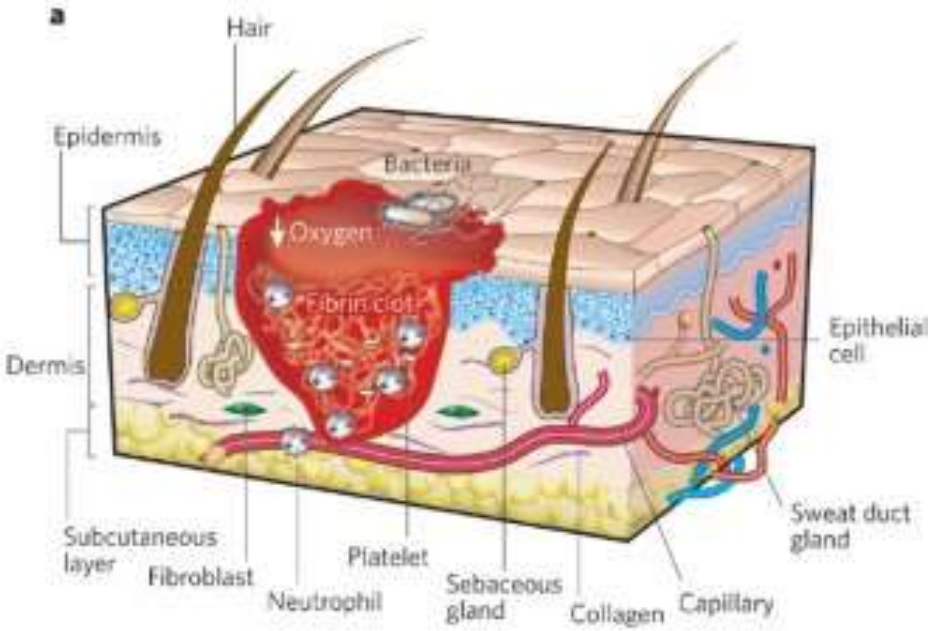
- 1. Within minutes after injury, a hemostatic plug comprised of platelets is formed:

- stops bleeding .
- provides a scaffold for infiltrating inflammatory cells.



- 2.Inflammation:

- Include acute and chronic inflammatory responses.
  - The inflammatory cells aimed to:
    - eliminate the offending agents
    - clear the debris



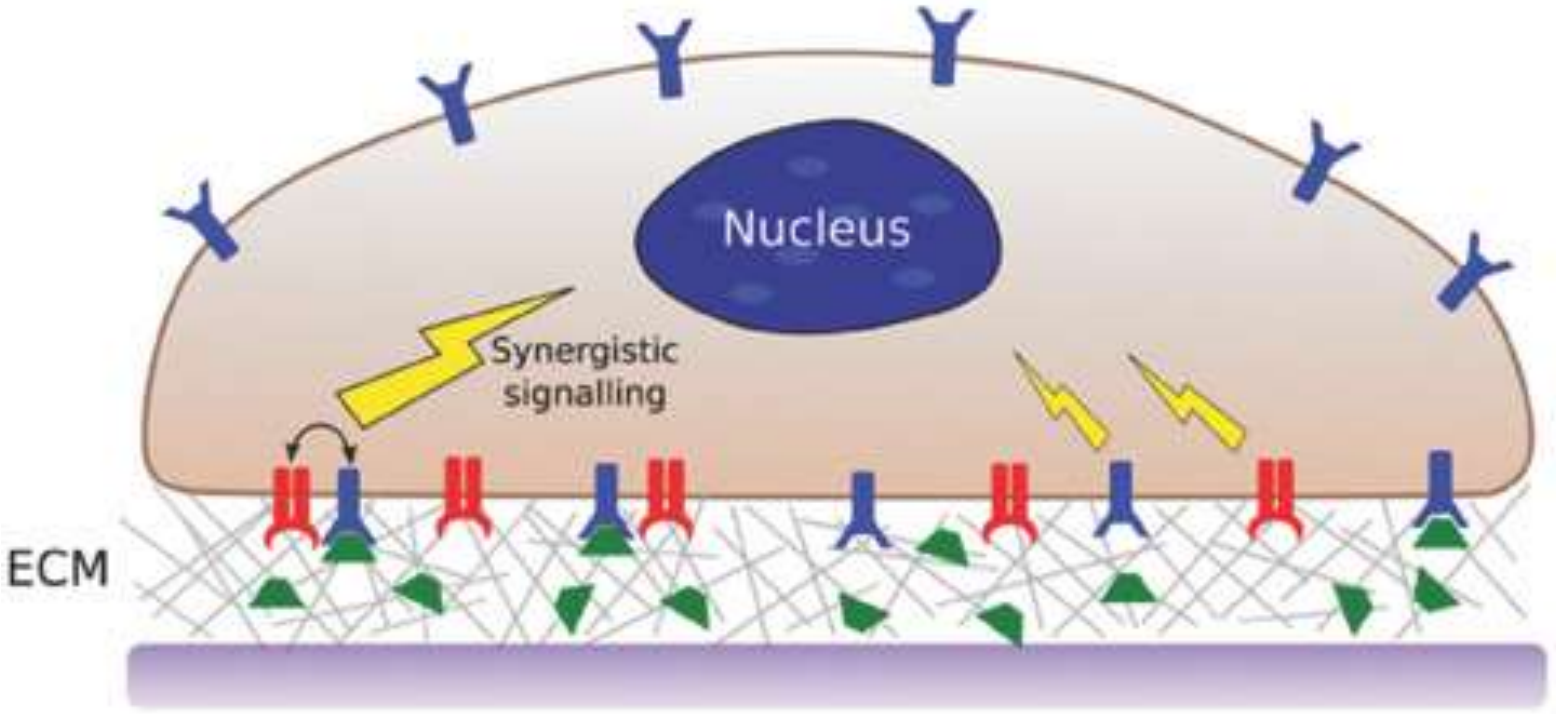
- Macrophages are the central cellular players in the repair process:

- M1 macrophages :
- clear microbes and necrotic tissue and promote inflammation .
- M2 macrophages:
- produce growth factors that stimulate the proliferation of many cell types in the next stage of repair.

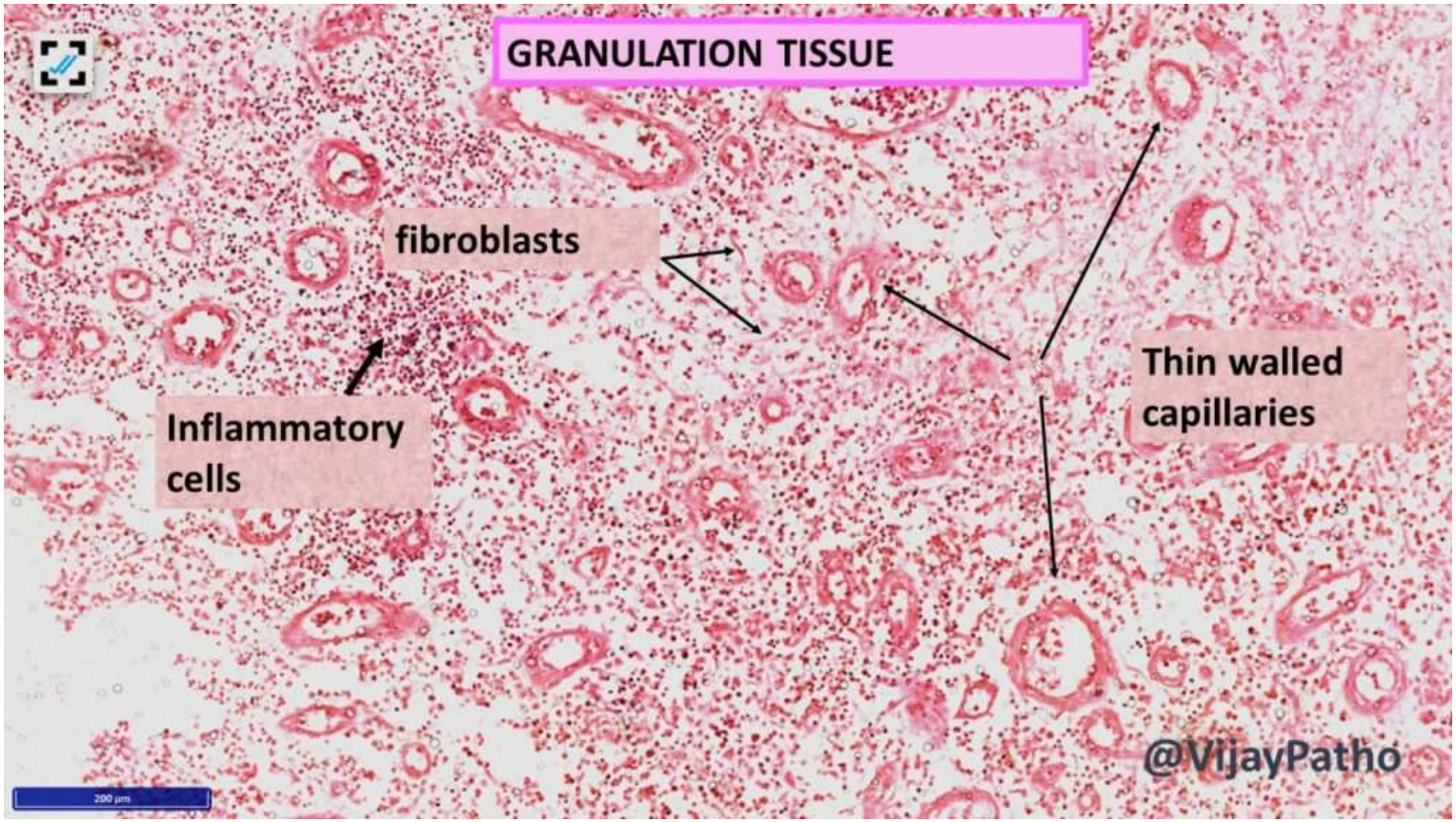
- 3.Cell proliferation.
- In the next stage, which takes up to 10 days, several cell types migrate to close the now-clean wound, including :

- Epithelial cells: migrate over the wound to cover it.
- Endothelial and other vascular cells: proliferate to form new blood vessels, a process known as angiogenesis
- Fibroblasts: proliferate and migrate into the site of injury and lay down collagen fibers that form the scar.

- Cell proliferation is driven by signals provided by growth factors and from the extracellular matrix.

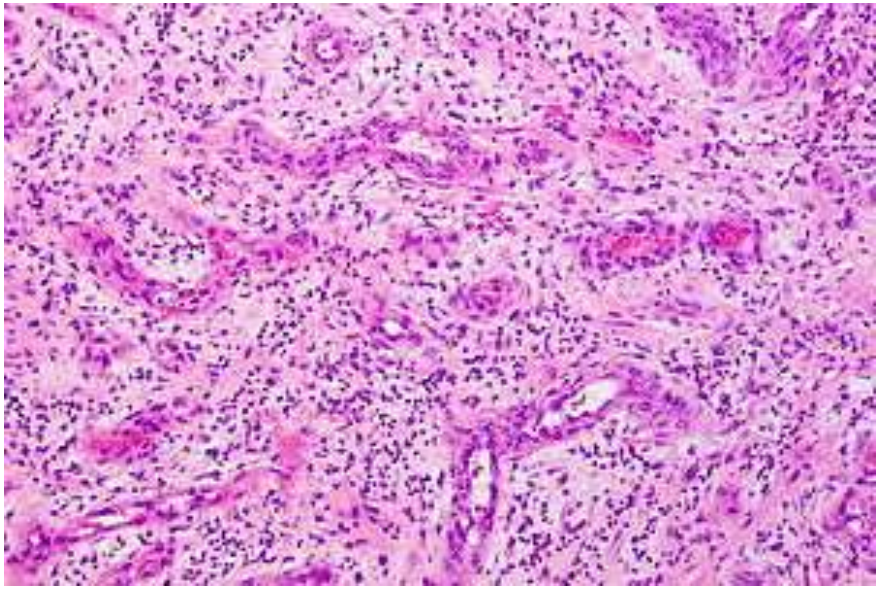


- The combination of proliferating fibroblasts, loose connective tissue, new blood vessels and scattered chronic inflammatory cells, forms a **granulation tissue.**



Granulation tissue.

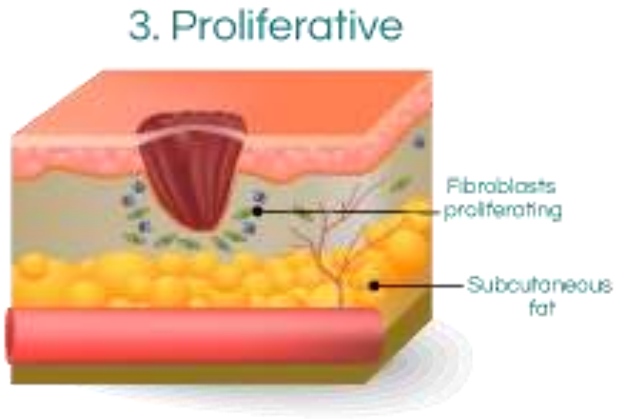
pink, soft, granular gross appearance, such as that seen beneath the scab of a skin wound.

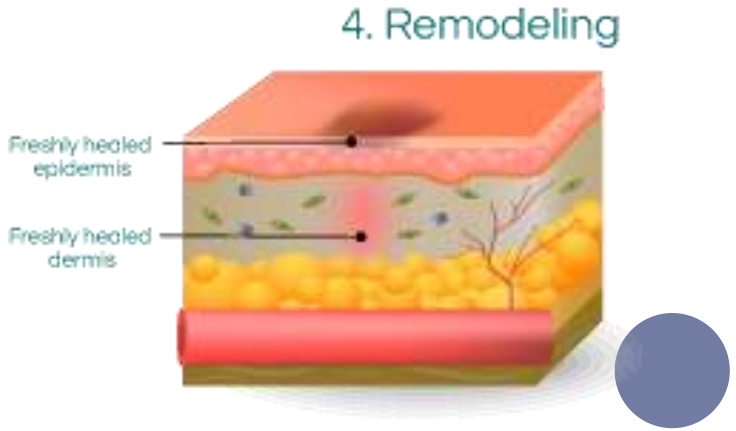


proliferating fibroblasts, loose connective tissue, new blood vessels and scattered chronic inflammatory cells

4. Remodeling.

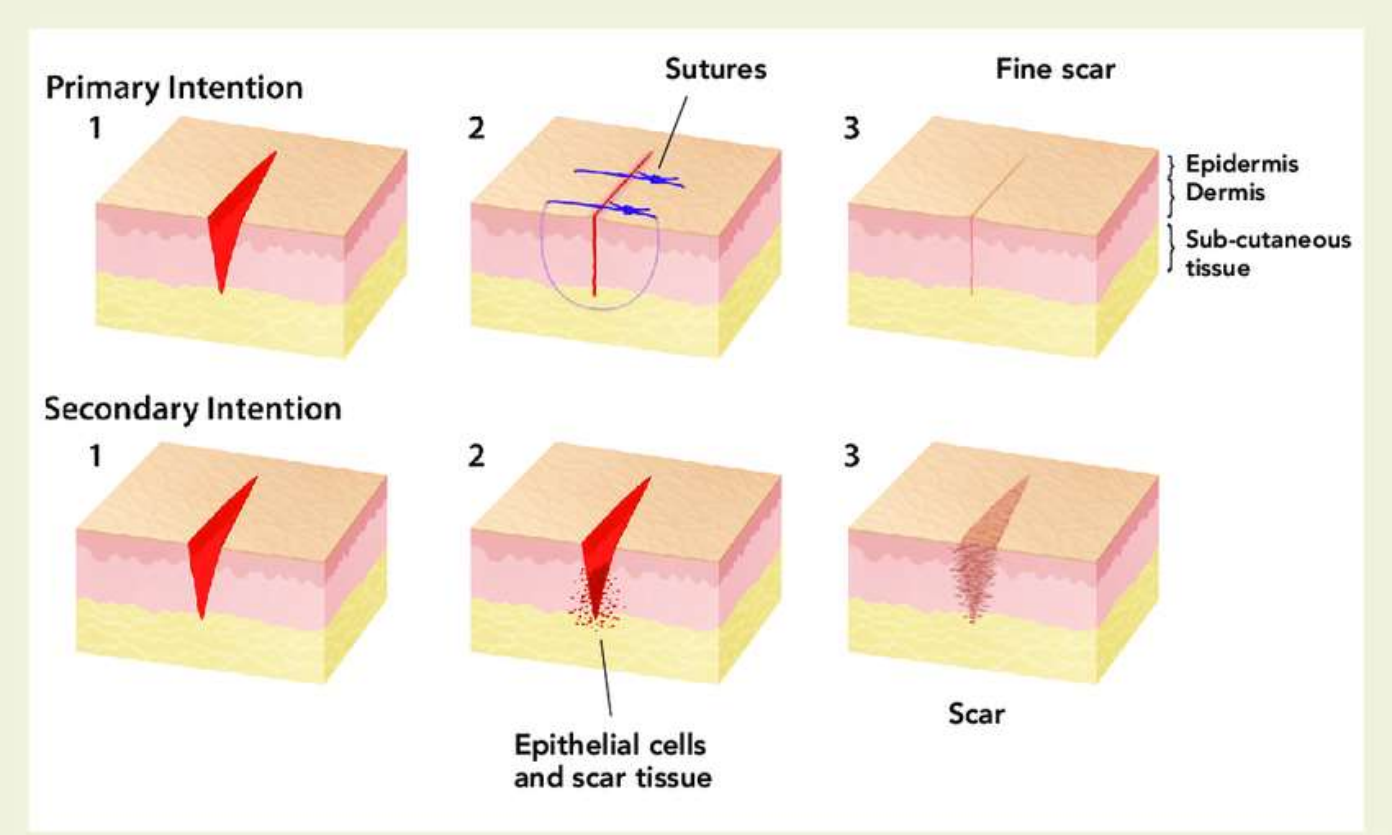
- The connective tissue that has been deposited by fibroblasts is reorganized to produce the stable fibrous scar.
- This process begins 2 to 3 weeks after injury and may continue for months or years





- Healing of skin wounds can be classified into healing by :

- first intention (primary union).
- second intention (secondary union).



Angiogenesis

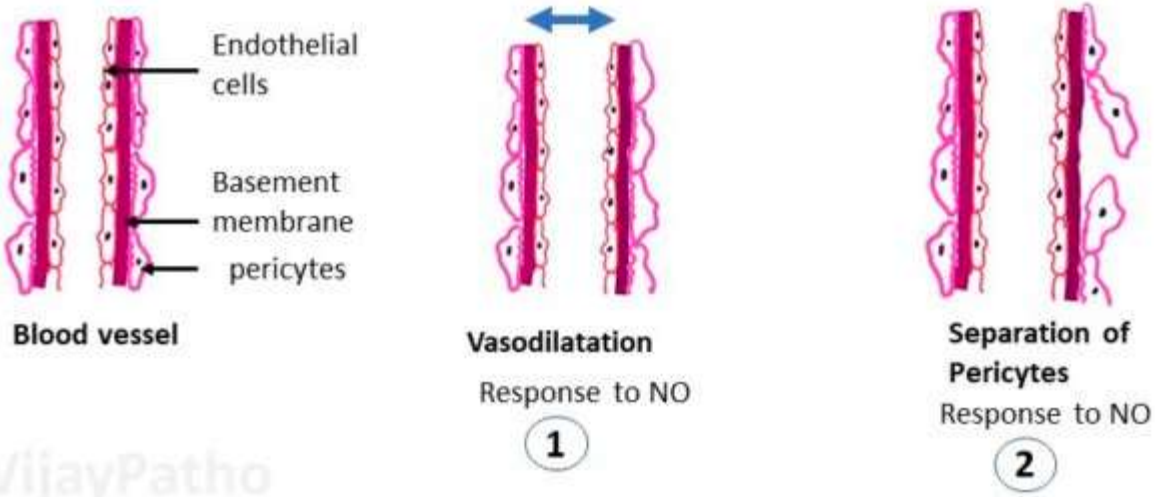
- Angiogenesis is the process of new blood vessel development from existing vessels.

- It is critical in:
  - healing at sites of injury.
  - development of collateral circulations at sites of ischemia.
  - allowing tumors to increase in size

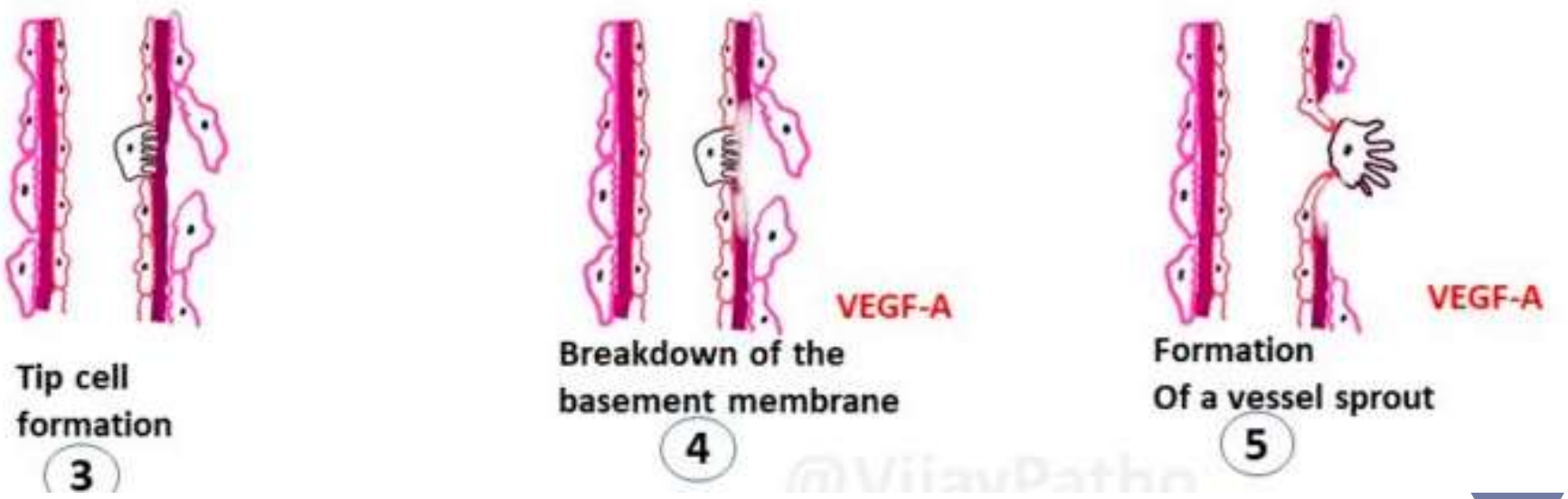
- Angiogenesis involves sprouting of new vessels from existing ones, and consists of the following steps:

- Vasodilation in response to NO and increased permeability induced by VEGF .

- Separation of pericytes from the abluminal surface



- Migration of endothelial cells toward the area of tissue injury.
- Proliferation of endothelial cells just behind the leading front (“tip”) of migrating cells.
- breakdown of the basement membrane to allow formation of a vessel sprout .



- 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

Fusion of tip cells

9

Remodeling into capillary tubes

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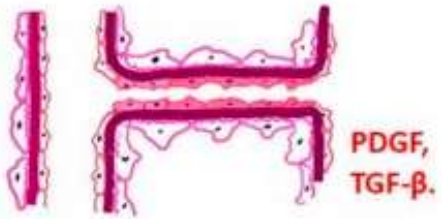

Recruitment of periendothelial cells/pericytes and basement membrane deposition

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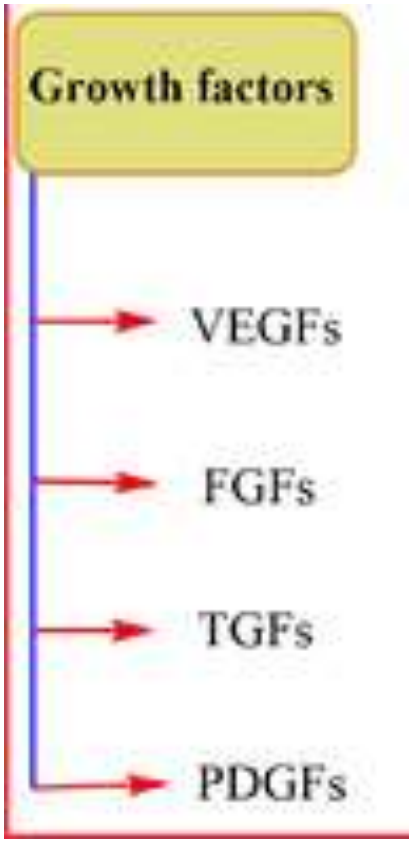
The process of angiogenesis involves several signaling pathways, cell–cell interactions, ECM proteins, and tissue enzymes:

1.Growth factors:



- stimulates both migration and proliferation of endothelial cells
- proliferation of endothelial cells.
- suppresses endothelial proliferation and migration.
- recruits smooth muscle cells

❖So PDGF and TGF-B participate in the stabilization process

- 2.Notch signaling.
- regulates the sprouting and branching of new vessels .

- 3.ECM proteins:
- participate in the process of vessel sprouting in angiogenesis, through interactions with integrin receptors .
- Enzymes in the ECM, notably the matrix metalloproteinases (MMPs), degrade the ECM to permit remodeling and extension of the vascular tube.