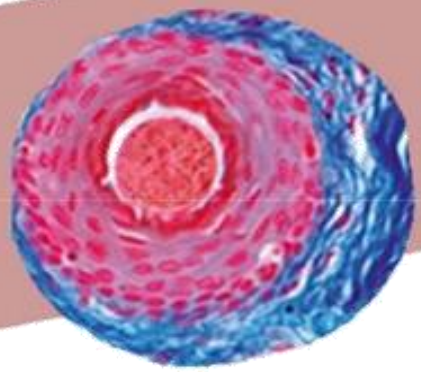
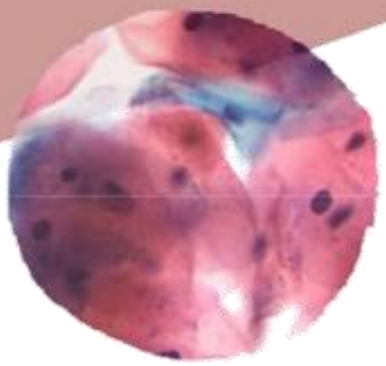
INTRODUCTION TO PATHOLOGY





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Sheet# 14

In this sheet, scar formation is the first topic to be discussed.

Scar Formation

So far, we know that repair may be completed by regeneration process or scarring. So what is a scar? And how is it formed?

Scar is a fibrous tissue, and it is formed by 3 steps; angiogenesis, Migration and proliferation of fibroblasts, and Remodeling.

Steps in Scar Formation

1- Angiogenesis

Angiogenesis is the process of new blood vessel development from existing vessels, primarily venules.

- Angiogenesis vs. neovascularization vs. vasculogenesis

These three concepts are basically used interchangeable. But angiogenesis is the main one; which is used in the contexts of scarring, collateral blood vessels formation" which follows ischemia", and in tumors. Whereas vasculogenesis is used as an embryological concept which explains the formation of new blood vessels. Neovascularization differs from angiogenesis in that angiogenesis is mainly characterized by the protrusion and outgrowth of capillary buds and sprouts from pre-existing blood vessels.

- Why angiogenesis?
  In this step, an infrastructure is being established, which supports the preceding steps, and to allow building scar tissue since scar formation needs certain growth factors coming from blood. So angiogenesis is the first step of scar formation.

- What are the steps of angiogenesis?
  1-Vasodilation occurring in response to NO and **increased permeability** induced by VEGF:

  in this step, a suitable settings are prepared to allow the formation of the new blood vessel from the previously existed one "mainly venule". Vasodilation is induced by NO, which is produced by eNOS enzyme in the endothelial cells. Permeability increase which allows the leakage of growth factors, and it happens under the influence of vascular endothelial growth factor "VEGF".

  2- Separation of pericytes from the abluminal surface:

  Pericytes are supportive cells that surround the blood vessels. These cells are detached in this step; so that the endothelial cells can migrate and proliferate to form the new blood vessel.

3- Endothelial cell migration and proliferation:

Endothelial cells migrate to the injured area. They proliferate to form the primer structure of the new blood vessel. The forming blood vessel has no lumen yet.

4- Remodeling of the migrated endothelial cells into capillary tubes:

Some endothelial cells will die by apoptosis and the newly formed vessel is remodeled into a tube.

5- Recruitment of periendothelial cells; pericytes and smooth muscle cells.

6- Suppression of endothelial proliferation and deposition of basement membrane (ECM).

0:00 – 10:00

- Growth Factors Involved in Angiogenesis

growth factor	function
VEGF	i.e. Vascular epithelial growth factor (the most important one in angiogenesis) -Increase proliferation and migration of endothelial cells -Increase permeability, and NO synthesis (thus indirect vasodilation) -Act by receptors which are stimulated by hypoxia and PDGF and TGFs
FGF	i.e. Fibroblast growth factor -Important for the next steps also -Increase fibrous tissue formation rate; and so increase ECM deposition - Causes proliferation and migration of endothelial cells
Angiopoietins	; Ang1 and Ang2 -Stabilization of newly formed blood vessels by pericytes, smooth muscle cells and deposition of connective tissue -Especially important for ECM production

- Clinical usage of anti-VEGFs

These drugs are used to treat clinical cases associated with increased angiogenesis; such as:

- Tumors and cancers need blood supply; so they are associated with increased angiogenesis. By using anti-VEGFs, those tissues will undergo necrosis and die in response to the ischemia formed by the decreased blood supply.

- Wet macular degeneration: this clinical case is associated with increased angiogenesis in the eye for unknown reasons, resulting with increased intraocular pressure because of the increased permeability by VEGF. This case is related to diabetics and elderly people. A correlation between this case and the prolonged exposure to electronic screens may exist.

2- Migration and proliferation of fibroblasts/ Deposition of connective tissue

The most important component of the deposited ECM in the scar area is the *fibrillary* collagen "types 1, 2, 3, 5"; because fibrillary collagen gives the needed strength to the formed scar. The source of this collagen is the active fibroblasts which migrate to the site of scarring. So, it can be said that this phase is made of 2 steps: (1) migration and proliferation of fibroblasts into the site of injury and (2) deposition of ECM proteins produced by these cells. This process is induced by the following growth factors:

Growth factor	Function
FGF	Mentioned
Transforming growth factor β	Inhibits inflammation and induces fibrosis
Platelet derived growth factor	Least important induces fibrosis
Cytokines	Migration & proliferation of fibroblasts and ECM deposition

- What have we got till now?
- The area of injury is full with newly formed blood vessels, migrated fibroblasts which deposit fibrillary collagen, in addition to some inflammatory cells "which are a good source of growth factors". This microscopic view is called granulation tissue. Granulation tissue is the phase prior to scar tissue.

- Scar vs. granulation tissue:
- With time, collagen amount predominates in the ECM, so fibroblasts get inactived, and the new blood vessels are not needed as previous, so the blood vessels get reduced. This is scar tissue. So we can notice that scar tissue is full with strong fibrillary collagen; whereas granulation tissue is tender and much vascularized.

- Cytokines:
- These proteins have a major influence on inflammation, scar formation and neoplasia.

3- Remodeling:

In this step, the final shape of the scar tissue is terminally controlled, so after the previous step, collagen synthesis decreases. Remodeling is all about balance between collagen deposition and degradation. This balance is achieved by controlling the following points:

1- Collagen synthesis: it is induced by the mentioned growth factors.

2- Collagen degradation: can be done by many enzymes, such as:

Enzyme group	Examples	Notes
Matrix metallo-proteinases (MMPs) - These enzymes are dependent on zinc ions for their activity "metallo"	Interstitial collagenase	Degrades fibrillary collagen
	Gelatinase	degrades amorphous collagen and fibronectin
	Stromelysin	can degrade almost all ECM component except fibrillary collagen
others	Elastase and any enzyme that can degrade proteins	MMP are more specialized in performing this function

MMP are dangerous! They can degrade ECM so they need to be tightly regulated. They are secreted as zymogenes (inactive enzymes) and get activated when needed. GFs and cytokines regulate their secretion and synthesis, and they are inhibited by tissue inhibitors of metalloproteinases "TIMPs".

So the final volume of the scar tissue depends on the balance between mentioned points. The higher the activity of MMPs "degradation", the smaller the scar tissue volume formed. And the higher the activity of collagen synthesis and TIMPs, the larger the scar tissue formed.

20:00 – 30:00

Factors affecting wound healing

There are many factors that can affect the quality of healing; those can be intrinsic or extrinsic, such as:

1- Infections: the most common problem that delays healing; because it increases tissue damage and inflammation.

2- Nutritional deficiency: different deficiencies may alter healing; such as:

deficiency	The resulting problem
Vitamin C	affects lysyl-hydroxylase; alters cross-linking in collagen
Zinc (rare)	Affects MMPs

Protein intake	No enough amino acids for the synthesis of ECM proteins "i.e. collagen" Example: hypoalbuminemia, malnutrition, hypoproteinemia and so on.

3- Steroidal drugs: these inhibit the growth factor TGF β, which decreases fibrosis.

4- Mechanical causes: such as exerting pressure on the wound site "ex. Unsuitable body position after caesarian section".

5- Poor reperfusion: in this case, blood supply is not enough to the injured site, which results with lowered healing quality; such in DM (diabetes mellitus), atherosclerosis and other vascular diseases.

6- Foreign bodies: foreign bodies have to be removed so healing can occur completely. Sutures are foreign bodies, that's why we must remove them after a week (for example). But since they're foreign why do we use them? Because they strengthen the injured tissue (70% of its original strength) thus helping wounds heal better.

7- Cell growth aberrations: if no balanced inhibition controls collagen deposition in scarring site "due to genetic reasons", keloid may result. Sometimes, granulation tissue is formed in high amounts, resulting in proud flesh.

- Do we remove keloids?
- If removed, these keloids may form again; because the surgical operation of its removal causes a new wound, which may not heal properly, and result with new keloid.

Skin wound healing

Depending on the nature and size of the wound, the healing of skin wounds is said to occur by first or second intention.

Healing type	information
first intention "primary union"	- Healing of a clean, uninfected surgical incision approximated by surgical *sutures* - Focal disruption of epithelial basement membrane continuity, so a small scar is formed, with minimal wound contraction - Epithelial regeneration is the principal mechanism of repair

Second intention "secondary union"	- Tissue loss is extensive "examples: large wounds, abscess ,ulceration, or infected wounds " - The repair process is more complex and involves a combination of regeneration and scarring - involves Intense inflammation, Large clot in the wound, abundant granulation tissue, formation of a large scar and more *wound contraction* mediated by myofibroblasts

Steps of first intention healing:

1- Within 24 hours, neutrophils predominate as inflammatory cells, and granulation tissue formation starts. Basal cells at the cut edge of the epidermis begin to show increased mitotic activity. 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.

2- By the third day, macrophages predominate in the site of injury, and granulation tissue increases. Collagen fibers are now evident at the incision margins, but these are vertically oriented and do not bridge the incision. Epidermis gets thickened.

3- By day 5, angiogenesis reaches its peak, and deposited collagen is now enough to bridge the incision. The epidermis recovers its normal thickness, and the surface gets the architectural maturation.

4- During the second week, inflammatory cells decrease in number, and granulation tissue is replaced by scar tissue. Collagen deposition increases.

5- By the end of the first month, the scar consists of a cellular connective tissue, largely devoid of inflammatory cells, covered by an essentially normal epidermis.

Important note:

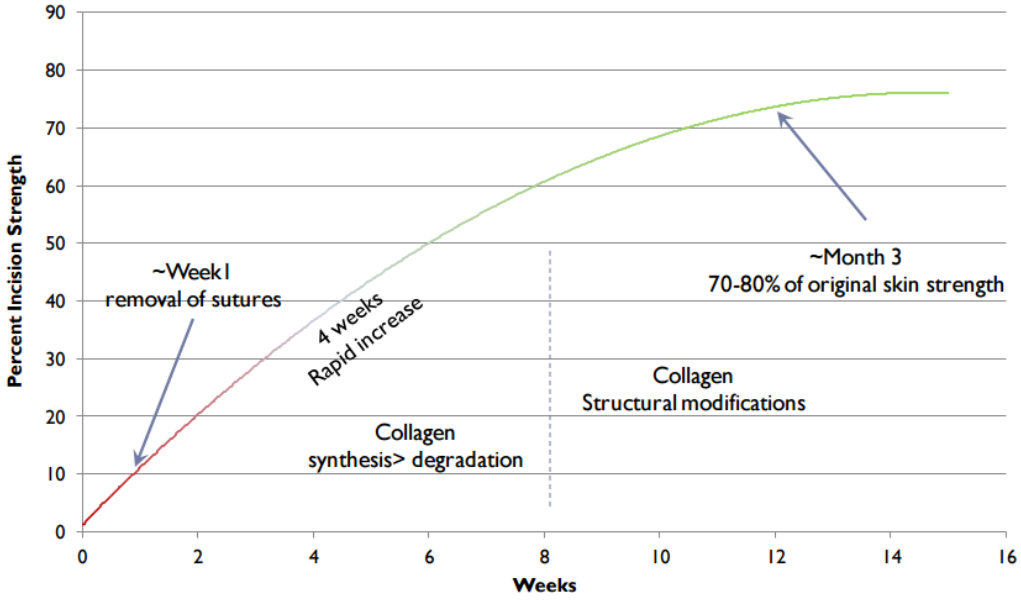
- The dermal appendages (e.g. sebaceous glands, hair follicles) destroyed in the line of the incision are permanently lost.

Wound contraction

Wound contraction is the reason behind observing shrinkage in the formed wounds after time. This process is performed by myofibroblasts; which contain contracting proteins. With this process, large skin defects may be reduced to 5% to 10% of their original size within 6 weeks.

Wound strength

The most important factor for the wounds to heal nicely is the approximation by sutures. Sutures give healing process the needed framework, in addition to giving it strength. Sutured wounds have 70% of normal skin strength due to the sutures. Sutures are not dangerous foreign bodies, but rather they are important for healing as described. But with time, they have to be taken out from the site of injury.



The strength of the sutured wound is 70% that of the normal skin. In the 1st week after sutures removal, wound strength reaches 10% of normal strength. Strength then increases gradually as a result of collagen synthesis exceeding degradation during the first 2 months and by structural modification of collagen. Maximum strength reached equals 70% to 80% of normal strength by the 3rd month. Notice that 100% strength recovery does not happen.

30:00-45:00

END OF REPAIR

"Inflammation and repair course has to give us the wisdom that god did not create us to be unbreakable, but he gave us the ability to repair within ourselves"

Sorry for mistakes