14

Pathology

Doctor 2018 | Medicine | JU

◉ Sheet ○ Slides

Done By

Reham badayneh

Contributed in the Scientific Correction

7ala Aldradka

Contributed in the Grammatical Correction

...

Doctor

Mousa Al-Abbadi

We will continue talking about REAPIR :-

Repair can be achieved by :-

1- Repair by regeneration (already discussed)
2- Repair by scarring

Repair by scarring :-

Scarring happens if the tissue injury is severe or chronic and results in damage to parenchymal cells and epithelial as well as to the connective tissue framework (large amount of tissue is lost) or if non-dividing cells are injured such as : neurons , cardiac muscles , skeletal muscle.

We have said that we have two types of healing (very important concept):-

Healing is affected by several factors including :-

Location of the wound (wound on the tongue , wound on the leg …etc) , age ..etc

Healing by First intention :-

Tissue lost is very small , the gap is very small and it refers to epithelial regeneration with minimal scarring .

Healing by Second intention :-

Referring to larger wound and larger loss of tissue that heal by combination of regeneration and scarring , and repairing by primary intention can't be initiated .

Steps in Scar formation :-

1- Hemostatic plug:-

Very thin scab , mainly composed of platelets and fibrin network , it is very soft it cannot stand with further trauma that's why it has to be changed , it stops

bleeding and provide a scaffold for infiltration of inflammatory cells(macrophages) .

☺ it is formed within minutes for the normal person (normal coagulation ; you are not on anticoagulants , heparin , warfarin …etc) ; normal homeostasis .

2- Inflammation :-

inflammation starts by recruiting the inflammatory cells ; predominantly Macrophages that will be activated in the classic (M1) and the alternative pathway (M2) ; but the alternative pathway functions more now ; because they are the one which decrease the initially inflammatory response and initiate the repair .

☺ During the next 6-48 hours

3- Cell proliferation :- (will be discussed later)

Formation of granulation tissue

Granulation tissue could be recognized by your eye (Macroscopically) Because it has a lot of blood vessels , and it can be seen under the (Microscope)

☺ Up to 10 days

4- Remodeling :-

This granulation tissue is replaced by a stronger, fibratic scar tissue composed predominantly of little number of fibroblasts (activated fibroblasts) + collagen + and fibrous tissue (which has a very strong tensile strength).

☺ 2 to 3 weeks

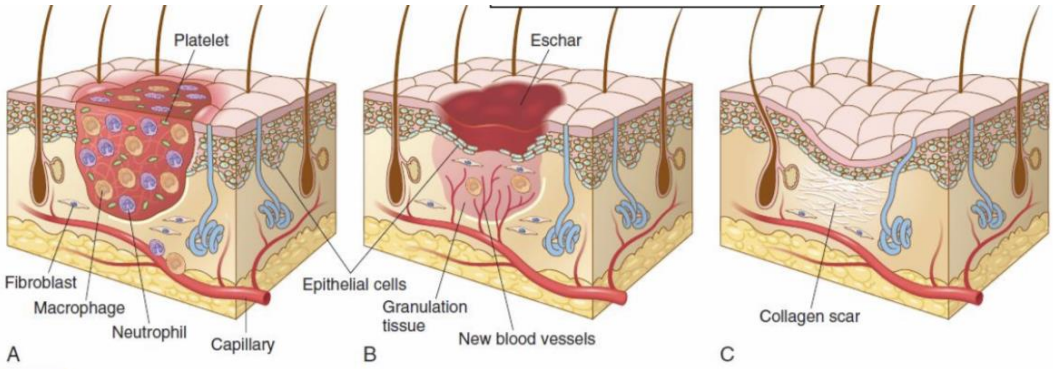
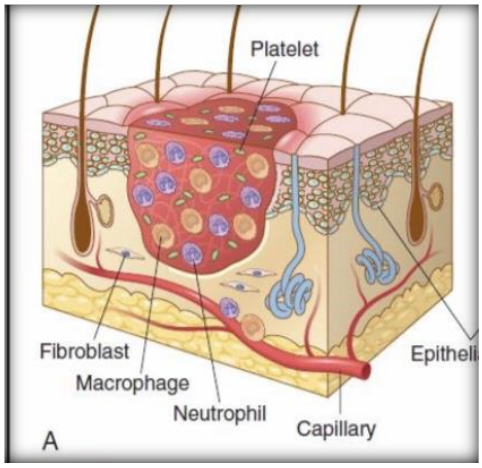


Fig. 3.24 Steps in repair by scar formation: healing of a large wound in the skin. This is an example of healing by second intention. (A) Hemostatic plug and inflammation. (B) Proliferation of epithelial cells; formation of granulation tissue by vessel growth and proliferating fibroblasts. (C) Remodeling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

As we can see in the Figure above :-

The gap is large and it cannot be healed by the first intention and the volume of the tissue lost is big .

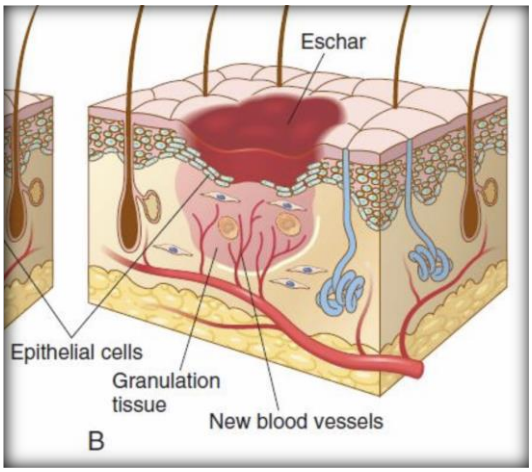
1-Hemostatic plug + Inflammation



2-Cell proliferation

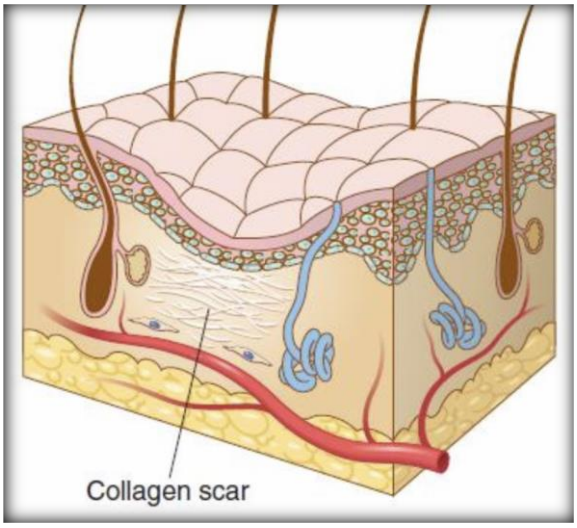
(Formation oF

granular tissue)



Granulation tissue : will start building up from the bottom up ; This requires a good blood supply (so a good blood supply is needed for proper repairing ; this is why if we have a patient who is old , smoker ,

having peripheral vascular disease …etc any wound in the peripheral limbs will take longer to repair since we don't have a good blood supply



3-Remodeling

Now , what are the major steps in healing by secondary intention or by granulation tissue :-

1-Angiogenesis :-

The process of new blood vessels developing from an already existing vessels.

☺ Angiogenesis is critical and it has a central role in healing. And, we really need a good blood supply to that area so that repair be quick and without any complications.

☺ It requires multiple steps: signaling pathways, growth factors, cell-matrix interactions (interaction between the cells, mediators and the extracellular matrix) and enzymes of remodeling

1– GF (Growth Factors) : **VEGF-A** (Vascular Endothelial Growth Factor-A) **FGFs** (Fibroblast Growth Factor) mainly **FGF-2, TGF-ß** (Transforming Growth Factor-ß : it is the most potent fibrogenic and fibroblastic stimulant which is critical in scar formation Central role in recruiting and stimulating the fibroblast proliferation and stimulates their activation ,they lay down ECM proteins , collagen type 1 ending up having a very strong good scar tissue)

2– Notch signaling: sprouting

3– ECM (Extra Cellular Matrix) proteins.

4– Enzymes for final remodeling

* interaction between the mediators and the cells and the extracellular matrix is critical and important _ 20-30 years ago a lot of scientists didn't pay attention to the

extravascular matrix _nowadays it is becoming very important and specially in the developing of cancer .

Steps of angiogenesis :-

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

2-Separation of pericytes from the abluminal surface and breakdown of the basement membrane to allow formation of a vessel sprout

3- Migration of endothelial cells toward the area of tissue injury (the shape of the endothelial cells changes once activated with cytoplasmic extension towards the outside)

{ this step is called sprouting and it is induced by VEGF }

4-Proliferation of endothelial cells just behind the leading front ("tip") of migrating cells

5- Remodeling into capillary tubes

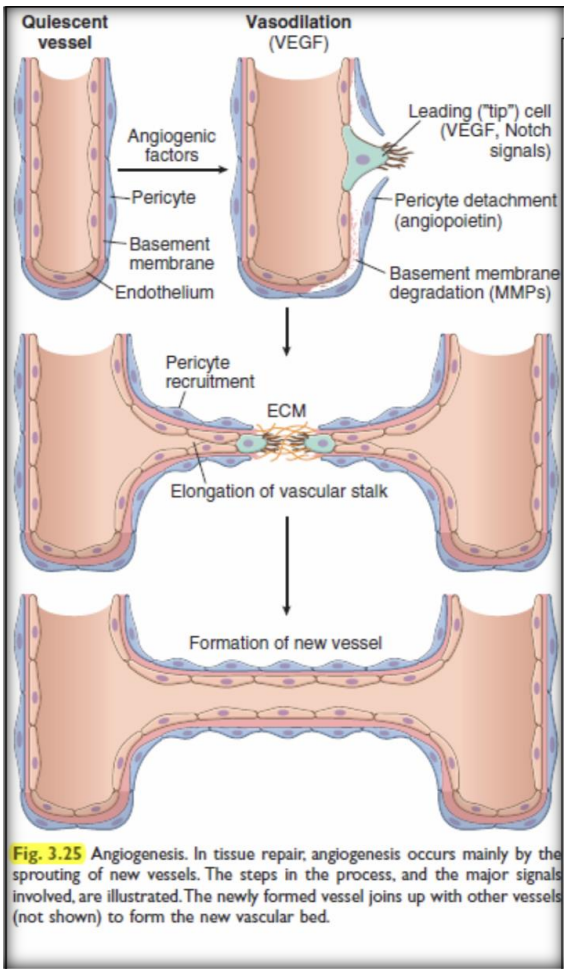


Fig. 3.25 Angiogenesis. In tissue repair, angiogenesis occurs mainly by the sprouting of new vessels. The steps in the process, and the major signals involved, are illustrated. The newly formed vessel joins up with other vessels (not shown) to form the new vascular bed.

6-Recruitment of periendothelial cells (pericytes for small capillaries and smooth muscle cells for larger vessels) to form the mature vessel

7-Suppression of endothelial proliferation and migration and deposition of the basement membrane

NOTE : JUST FOCUS ON THE GENERAL IDEA IN THIS PROCESS ;)

☺ **these steps happens in several other vessels and then they join up forming the vascular bed .**

And this what gives the granulation tissue the beefy-red look !! And that's what we see .

Angiogenesis alone isn't enough – but it is important to stop further bleeding -because if we irritate it bleeds .

2-Activation of fibroblasts and deposition of matrix

We need to switch to a stronger tissue replacing this granulation tissue (beefy-red, full of capillaries). BETTER MATRIX

☺ The laying down of connective tissue occurs in two steps:

1. Migration (similar to WBC recruitment in inflammation), proliferation of fibroblasts at the site of repair and fibroblast activation-they start their internal machinery and protein synthesis of new better ECM.

2. Deposition of ECM proteins produced by these cells.

These processes are orchestrated by locally produced cytokines and growth factors, including **PDGF (Platelet-Derived Growth Factor), **FGF-2**, and **TGF-β** (the most potent fibrogenic mediator/stimulator)* *The major sources of these factors are lymphocytes but they can be produced by neutrophils , local cells and by macrophages (M2) .*

**TGF*- β : the attention to this factor came back 30-20 years ago because they discovered that this factor that sometimes is secreted by tumor cells causing some tumors to be big .

Breast carcinomas are divided into multiple types one of them is called :

* **Schirrous carcinoma**: that means breast cancer where the tumor is really very hard , big and firm . After sectioning of the tumor we see tumor cells but also we see a lot of scar tissue , after proper investigation they concluded that the tumor cells will secrete a lot of TFG- β ; which will recruit fibroblasts and stimulate the formation of scar tissue .So the tumor will look firm , hard and big .

So we have multiple organs where malignancies can occur and they are notorious for secreting TFG- β like breast cancer, pancreatic cancer..etc

But, this actually is considered an obstruct in diagnosis . ☹

Fibroblasts enter the wound from the edges and migrate toward the centre. Some of these cells may differentiate into cells called myofibroblasts, which contain smooth muscle and skeletal muscles actin and have increased contractile activity and serve to close the wound by pulling its margins toward the center (myofibroblasts are more

prevalent in initial stages of scar formation). Activated fibroblasts and myofibroblasts increase their synthetic activity and produce connective tissue proteins, mainly collagen, which is the major component of the fully developed scar.

- **Myofibroblast can cause tumors ☹**
- **We need to strengthen tissue more *by remodeling***

3-Remodeling of Connective Tissue:

• It is needed to make the scar strong and to contract it (by myofibroblasts).

• The major players are enzymes (-ases) and their target is the ECM.

• The major processes occurring are (remember that they all occur almost simultaneously):-

(a) Cross linking of collagen.

(b) Switching type III to the more resilient type I collagen.

(c) we will have extra proteins that have to be degraded (cleaning up) so that the new tissue will look almost like the original tissue, degradation of collagen by Matrix Metalloproteinase (MMPs). They include enzymes specific for degrading fibrous collagen (extra), proteoglycans, laminin, fibronectin, and amorphous collagen. MMP activity is balanced by their inhibitors →(TIMPs: Tissue Inhibitors of Metalloproteinase). Thus, a balance of MMPs and TIMPs regulates the size and nature of the scar.

*Any errors or imbalance in these steps → abnormal repair

Under the microscope :-

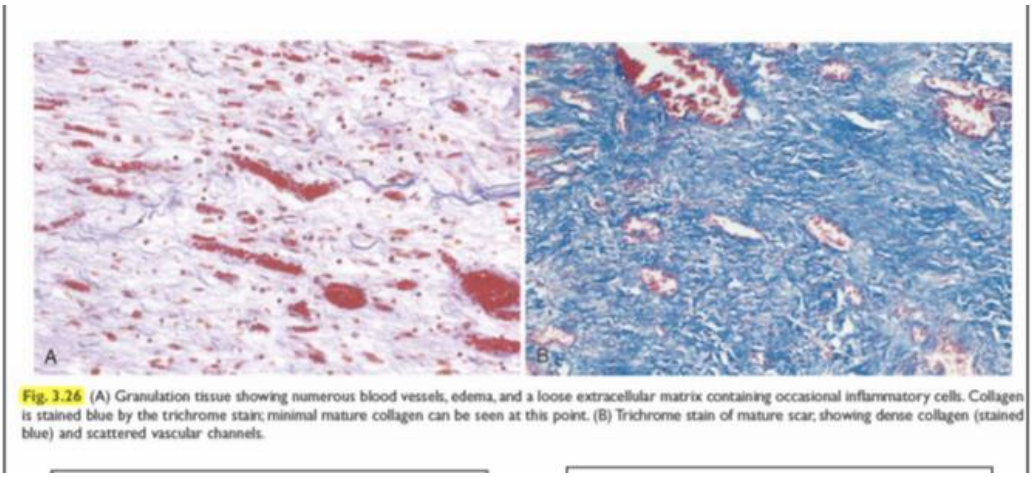


Fig. 3.26 (A) Granulation tissue showing numerous blood vessels, edema, and a loose extracellular matrix containing occasional inflammatory cells. Collagen is stained blue by the trichrome stain; minimal mature collagen can be seen at this point. (B) Trichrome stain of mature scar, showing dense collagen (stained blue) and scattered vascular channels.

A: H&E stain

Granulation tissue showing a lot of thin-walled BVs (capillaries) seen in both cross-section and longitudinally.

Beefy-red look .

Extra-Cellular Matrix looks 'beige' and is loose with minimal collagen.

This is young (early) scar tissue which after couple of days and weeks all this will be transformed to strong scar tissue .

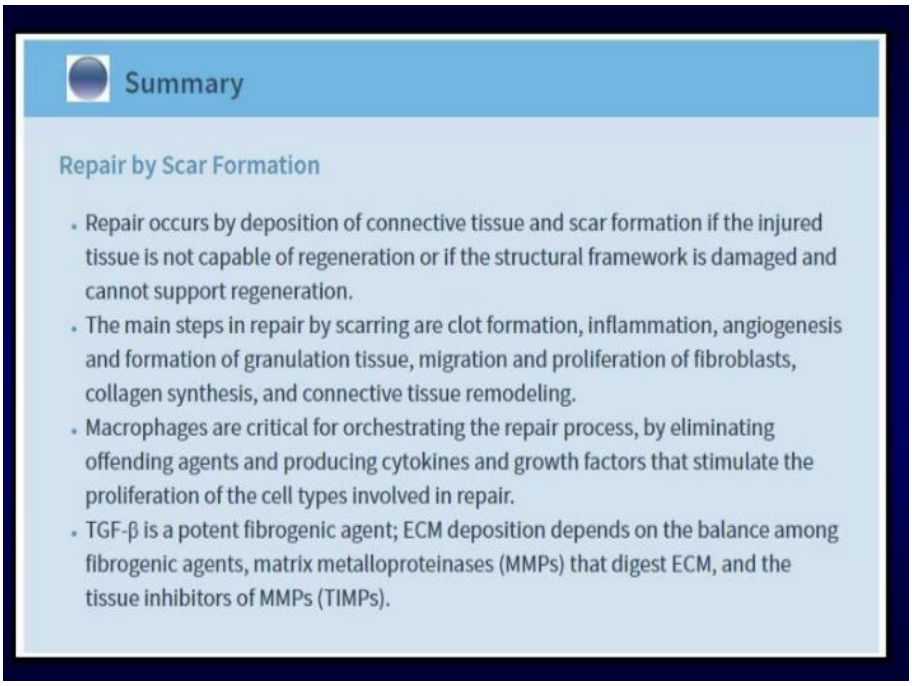
B: Trichrome stain

*Trichrome staining is used to precisely evaluate the amount of mature scar tissue formed (looks pink in H&E stain) , so sometimes we order this stain when it is difficult to recognize scar tissue .

Mature scar tissue showing much less BVs and an abundance of collagen type 1.

A was stained using H&E while B was stained using the trichrome stain, but as shown in the description of the pics above, both samples were treated with trichrome to show the collagen (stained blue).

Too much blue ---------- too much scar tissue



تصرف كما لو أنه من المستحيل أن تفشل !!

cesaretin yoksa hep kaybedersin

İyı şanslar