12

Pathology

Doctor 2017 | Medicine | JU

◉ Sheet ○ Slides

DONE BY

Ibrahim Awaisheh

CONTRIBUTED IN THE SCIENTIFIC CORRECTION

...

CONTRIBUTED IN THE GRAMMATICAL CORRECTION

...

DOCTOR

Mousa Al-Abbadi

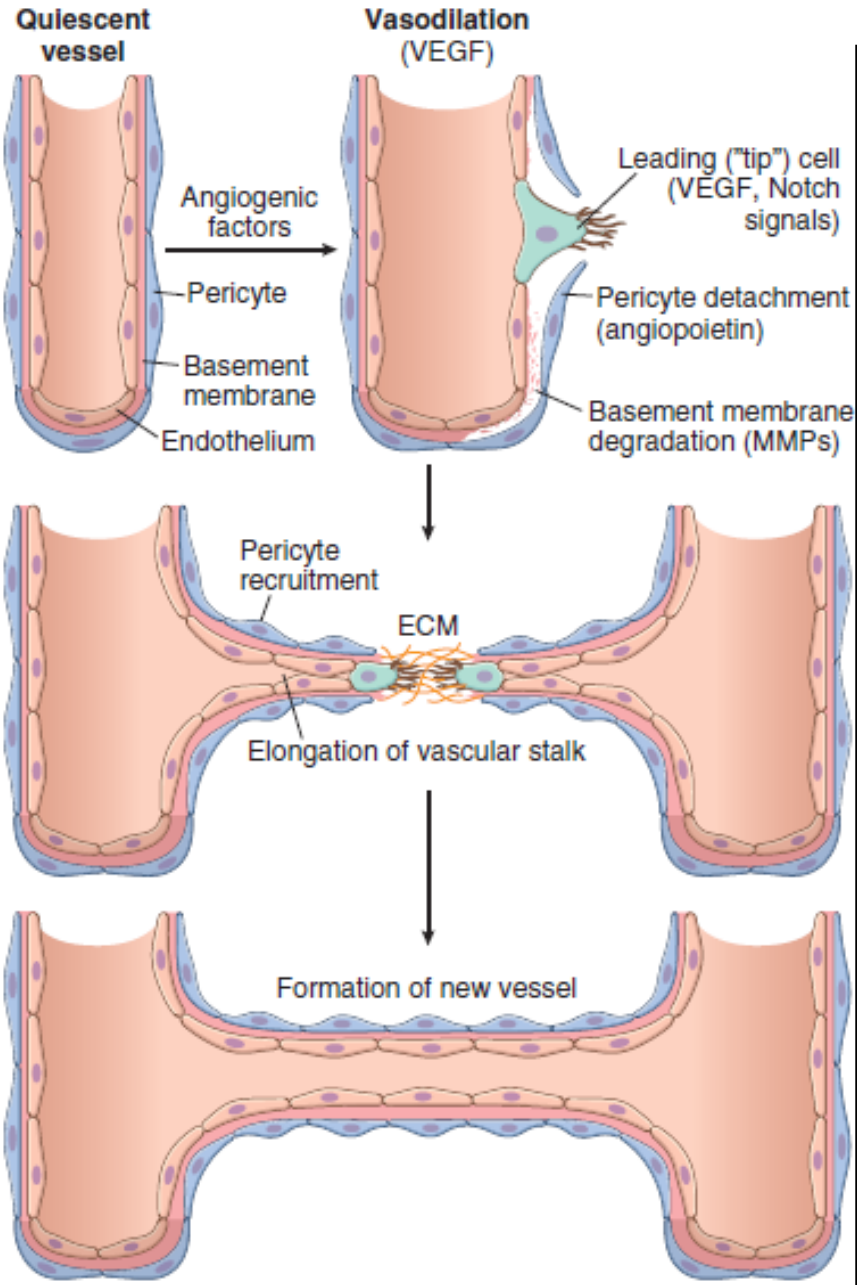

Fig. 3.25 Angiogenesis. In tissue repair, angiogenesis occurs mainly by the sprouting of new vessels. The steps in the process, and the major signals involved, are illustrated. The newly formed vessel joins up with other vessels (not shown) to form the new vascular bed.

Angiogenesis steps:

1. **Separation of pericytes under the influence of angiopoietin.**
2. **Breakdown of the basement membrane** to allow formation of a vessel sprout **by MMPs. The basement mem. mainly consists of collagen IV and laminin** which are broken down by collagen IV-ase and lamininase (specific names for 2 of the MMPs, which are discussed more in detail later).
3. **One cell becomes the leading ("tip") cell under the influence of VEGF and other notching mediators** and develops cytoplasmic (ameboid) processes by restructuring its cytoskeleton.
4. Migration of endothelial cells toward the area of tissue injury.
5. Proliferation of endothelial cells just behind the leading front ("tip") of migrating cells.
6. Recruitment of periendothelial cells (pericytes for small capillaries) to form the mature vessel.
7. Suppression of endothelial proliferation and migration and deposition of the basement membrane by TGF-β.

**Memorise the steps in bold but pls do not dismiss the other steps from ur attention for a clearer understanding of the process.*

C) Activation of Fibroblasts and Deposition of Matrix:

The laying down of connective tissue occurs in two steps:

1. **Migration** (similar to WBC recruitment in inflammation) **and proliferation** of fibroblasts *at* the site of repair (fibroblast activation upon stimulation by growth factors).
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 inflammatory cells, particularly (M2) macrophages that infiltrate sites of injury (from the book).*

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 actin and have increased contractile activity and serve to close the wound by pulling its margins toward the centre (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.

***TGF-β* is the most important cytokine for the synthesis ECM proteins.** It is produced by most of the cells in granulation tissue, including **M2 macrophages**.

With time there will be maturation and changes in the protein structure to increase the tensile strength of the ECM.

D) Remodelling 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) Degradation of collagen by **Matrix Metalloproteinases** (MMPs, so called because they are dependent on metal ions -e.g., zinc- for their enzymatic activity). They include enzymes specific for degrading fibrous collagen, proteoglycans, laminin, fibronectin, and amorphous collagen. MMP activity is balanced by their inhibitors →**(TIMPs**: Tissue Inhibitors of Metalloproteinases). **Thus, a balance of MMPs and TIMPs regulates the size and nature of the scar**.

**Any errors or imbalance in these steps → abnormal repair (discussed in the next sheet).*

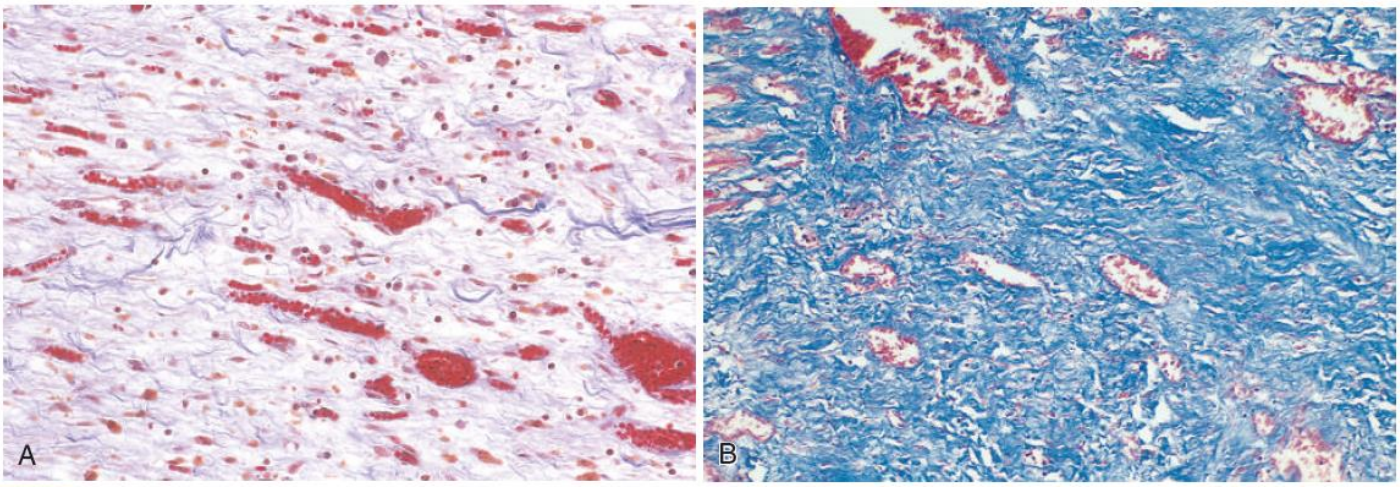

Fig. 3.26 (A) Granulation tissue showing numerous blood vessels, edema, and a loose extracellular matrix containing occasional inflammatory cells. Collagen is stained blue by the trichrome stain; minimal mature collagen can be seen at this point. (B) Trichrome stain of mature scar, showing dense collagen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

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

This is young (early) 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)*

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

**During the lecture, the Dr. explained that 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).*

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).

GOOD LUCK