Doctor 22

PATHOLOGY

Sheet no. 8

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QUICK REVIEW

-Repair (R5) is the last step in inflammation.

-There are two major types of repair and healing

1- healing by first(primary) intention (in cases of the surgical clean wound): is faster, the lost tissue is very small, the amount of granulation tissue produced is very small and the amount of scar tissue which is produced is very small as well,

99.9% of the tissue returns to the pre-inflammatory state cosmetically and functionally in the primary intention.

2- healing by (secondary) intention.

If there is a big amount of lost tissue, the regeneration won't be enough, it requires granulation tissue formation(large scar formation, more obvious cosmetic damage), and sometimes it's big enough up to the point which will interfere with normal functions.

[VERY IMPORTANT NOTE]

Is there granulation tissue formation in the first intention?

Of course, yes, but the amount is very little compared with the second intention. As well as, the scar formation is more in the second intention than in the first intention.

Whether it is first or second healing, it is still repaired, so:

BOTH have SAME steps, but the result is different '', they are:

1.Angiogenesis

2.Activation of fibroblast and deposition of matrix

3.Remodeling of connective tissue

Now, let's ROCK!

ANGIOGENESIS

* inflammation is the response of vascularized to injurious agents.

What have you read recently?

(VASCULARIZED),the inflammatory response needs to be from a vascularized, viable, and alive tissue with enough blood supply for proper steps of healing.So, we need angiogenesis (plays a central role in the process of healing and repair).

angiogenesis (angio: blood vessels + Genesis: creation, formation)

the development of new blood vessels.

- Central role in healing:

Angiogenesis Is a central and critical process for proper healing (R5),an important step in inflammation as well as in neoplasia.

- Requires multiple steps, signaling pathways, growth factors, cell-matrix Interactions (extracellular, extravascular interactions) and enzymes ofremodeling to be able to have a complete angiogenesis.

1→A lot of mediators and growth factors are needed in this process, there are large numbers but the major ones in angiogenesis and reparative process are:

a- VEGF-A: (vascular endothelial growth factor-A (there is multiple ones but the most important is A))

b- FGFS-2 (Fibroblast growth factors family)

C- TGF-B (transforming growth factor beta) one of the most potent fibrogenic or scar-forming mediator.

2→Notch signaling (sprouting):

The initial step which happens in angiogenesis.

Sprouting means التبرعم, a new growing thing that will come from an already existing one.

In angiogenesis, it is defined as a new blood vessel sprouting from pre-existing vessels.

3→ECM proteins (remember there is an important critical interaction between those GF and the ECM proteins), they produced and build up to help lay down the future scar formation.

4→Enzymes for final remodeling:

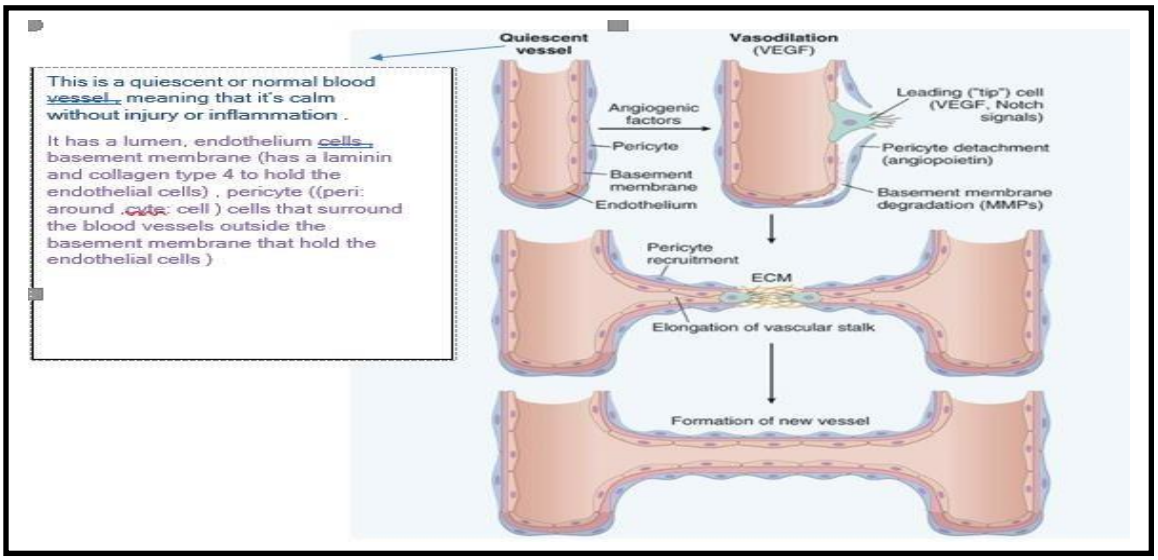
Note: In the final stages of remodeling enzymes are required to cut the extra collagen, and the extra proteins and clean up the mess after the reparative process.

STEPS OF ANGIOGENESIS

Let's revise the main components of blood vessels:

1. **Pericytes: active cells that surround the vessels from the outside.**
2. **Basement membrane: rich with laminin and collagen IV.**
3. **Endothelial cells covering the blood vessel from the inside.**

Look at the figure:



Notch signaling:

1. Starting with pericytes detachment by the GF (angiopoietin), which opens, and detaches the pericytes.

2. Then digesting the basement membrane disrupting its component by MMPs (matrix metalloproteinases) like:

Laminin is disrupted by lamininase, and Collagen by collagen 4ase. To allow endothelial cells to sprout and notch out of the main blood vessels

3. And finally the endothelium becomes naked (it is very active and extends its self outside), facilitating its sprouting By VEGF mainly. seem more differentiated like myocytes.

This will continue on this side and if you have the same changes happing in near capillary or blood vessel the process continues (sprouting) until there is extensive complex interaction between the GFs released from this process and the ECM leading to elongation of vascular stalk(a lot of remodeling process here insure), and this process will continue until the pericyte will attach to the near pericyte on the other blood vessel (the basement membrane and endothelial cells will be connected).

*Granulation tissue: tissue that is rich in BV and matrix.

- When there is any factor or injury stimulates the angiogenic factors: -

Multiply this process five thousand in 1 cm square "for example" you will have a meshwork of newly formed delicate extensive vascularized tissue (granulation tissue). So, this is the base process of the formation of granulation tissue where angiogenesis is an important step for that.

{remember: in wound healing by primary intention the amount of granulation tissue is very little and will switch from this smooth delicate

granulation tissue into a mature scar which is also very small}
The formation of granulation tissue alone is not enough because it's smooth delicate vascularized tissue. So, if you scratch it, it will bleed. So,there must be a second step which is the activation and proliferation of fibroblast.
Those are the basic steps and processes of angiogenesis and multiply this by a thousand or two thousands or five thousands.
This is why whenever you have somebody who has good blood supply, no ischemia, no chronic atherosclerosis, this process takes shorter time than those patients who suffer from ischemic heart disease and atherosclerosis

ACTIVATION OF FIBROBLASTS AND DEPOSITION OF MATRIX:

After angiogenesis, we have to deal with ECM, which is also important for architecture and function.

--Fibroblasts are the main players in this step! (very critical in the formation of reparative of scar tissue at the end)

--fibroblasts originate from mesenchymal cells, and they alter their shapes somehow, most of them become more differentiated to be able to move, so they become myofibroblasts (myo: muscles, indicating differentiation andmovement)

2 STEPS: -

1- Migrations and proliferation of fibroblasts

we need fibroblasts to migrate and proliferate in the tissue in the area of tissue injury so multiple growth factors will stimulate the migration and then the proliferation of fibroblasts. **Then, the activated fibroblast will start:**

2- Deposition of ECM proteins by these cells (activated fibroblasts)

-Mainly it is about ECM protein production

Stimulating and activating each fibroblast (being active metabolically) to produce tissue matrix proteins, predominately collagen to replace the lost tissue (initially, they produce collagen type 3 -which is smooth and not strong enough- and then it will be switched into collagen type 1).

-this phase(activation of fibroblasts and ECM deposition) needs cytokines and GFs: PDGF, FGF-2, *TGF-B*

*PDGF: platelet-derived growth factors

*FGF: fibroblast GF

*TGF-B: the **most potent fibroblast activator**. So, without proper productionof it, there will be no proper repair.

(the major and most important fibrogenic or scar-forming mediator in repair).

-Fibroblasts and myofibroblasts help lay down collagen to close the gap

Fibroblasts sometimes attain muscle functions, becoming like skeletal muscles, and smooth muscles, so they will differentiate into myofibroblasts. (Myofibroblast: is a fibroblast that slightly deviated and became slightly differentiated toward a muscle and have some contractile muscle functions) they always help lay down collagen to close up the gap at the end collagen will be the major protein deposited in the scar formation at the end of repair by granulation tissue formation.

- TGF-ß is the most important

After what happened before, there will be:

REMODELING OF CONNECTIVE TISSUE:

Active process requires multiple chemical mediator of inflammation mainly GF.

-It's needed to make the scar stronger and contract it.

Because the initial scar formation which is composed of young fibroblasts and young matrix usually is not strong enough.
So this is done by :

1• Cross-linking of collagen, to produce stronger collagens.

2• Switching type III to type 1, fibroblast in early phase 2 produces collagen 3 which is weaker than 1.

*So, the result we have is cross-linked collagen and a predominance of collagen type 1 to make the scar tissue stronger enough to hold the architecture and protect the underlying organs.

Degradation of collogen by Matrix Metalloproteinases (MMPs) and balanced by their inhibitors (TIMPs)

*But we still need to remove the extra products of remodeling for example: if there is extra collagen type 3, extra unneeded collagen type 1, or extra matrix proteins.

And this is **done by certain enzymes we call MMP(matrix metalloproteinases)** they are enzymes that will eat up the extra collagen and extra matrix proteins that are not needed, like lamininases, and collagenases,…

*There are other mediators, proteins, and inhibitors that control the MMP because we don't need those MMPs constantly active resulting in digesting the main not excess components of the matrix.
Those inhibitors are called **TIMPs (tissue inhibitors of metalloproteinases)**.
The balance between these is important. (MMP and TIMP)

SOME MICROSCOPIC IMAGES

Granulation tissues appear grossly beefy red.

Under microscope:

young granulation tissue

H&E stain

each one of those is a blood vessel or young capillary very active angiogenetic process

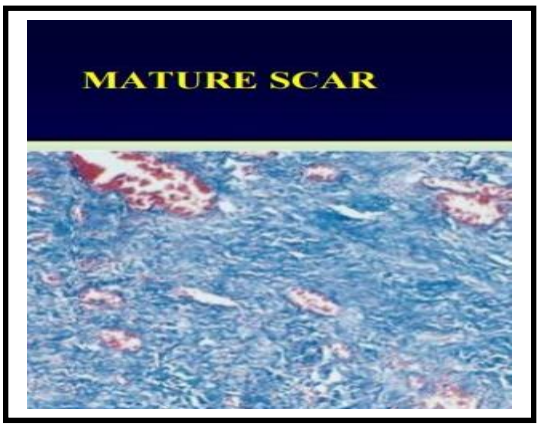
this is not going to be strong enough to withstand any more tissue damage or pressure this granulation tissue should be transformed in the late phases of repair cross-linking type 3 to type 1 collagen to very strong scar tissue

the number of blood vessels is much more

the number of mature scar tissue is very minimal

BVs rich in RBCs giving its red color, surrounded by endothelial cells

White area: young protein matrix, and collagens



Mature scar

trichrome stain (special stain which we use to highlight the scar tissue which is formed collagen type one predominantly and this is the blue color is the amount of scar tissue removed)

full of the **collagen type one** which is strong enough and difficult to separate

less blood vessels

more mature scar tissue

PAST PAPERS:

1. Found in mature scars:

A. cross-linked collagen 1

B. Granulation tissue

C. a lot of thin-walled capillaries

D. collagen 3 only

E. collagen 2 only

2. Secondary repair -compared with initial repair- has:

A. more scar and more tissue injury

B. always associated with tissue granuloma

C. very small tissue lost

D. maintained the function of the repaired tissue

3. In contrast to repair after acute inflammation, repair after chronic inflammation is characterized by:

A. Lesser activity of vascular endothelial growth factor

B. Lesser amount of collagen type 1

C. granulation tissue and scar formation

D. quick and simple with no need for mediators

4-Microscopic examination of granulation tissue and early immature scarformation will show?

A. numerous young capillaries and heavy mixed inflammation cell infiltrate

B. complete re-epithelialization of the surface

C. heavy eosinophilic and mast cell infiltrate

D. Abundant cross-linked collagen type 1 fibers

E. numerous foreign-body type giant cells granulomas

A

A

C

A