PATHOLOGY

◉ Sheets ○ Slides

Number:

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Subject: Repair 2

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Extracellular matrix:

Cells do not swim in vacuum, but surrounded by connective tissue.

- *this connective tissue called **extracellular matrix**, which composed of several protein that assemble into a network surrounds cells*.

❖ It's present in 2 forms:

1. **Interstitial matrix** ; is the connective tissue which surrounds the cells.

   - Sometimes, each cell is surrounded by connective tissue and sometimes group of cell are surrounded by connective tissue.
   -This depends on the organ. For example, in liver every 3 or 4 cells surrounded by elastic fibrous.

2. **basement membrane**; is a highly organized structure present beneath the epithelium cell to support them , for example blood vessel have epithelium and under epithelium there is a basement membrane which is very important for support.

❖ Extracellular functions:

- Mechanical support –the most important- .
- Sequesters water, keep water inside and this important to provide turgor for soft tissue.
- Sequesters minerals, very important to rigidity especially in bone.
- Regulates proliferation, movement and differentiation of cells.
- Reservoir of growth factor.

❖ Component of extracellular matrix:

- *Fibrous* structural proteins, which give support and strength:

Collagen and Elastin.

- Water hydrated gel: important for lubrications.

Proteoglycans and hyaluronon.

- Adhesive glycoproteins , as a glue between cells itself and between cell and ECM.
- Adhesion receptor. (

❖ **Note:** This component present as amorphous gel, but when they convert to basement membrane they became highly organized, so the basement membrane composed of two main protein:

1. Amorphous nonfibrillar type 4 collagen.

2. Laminin.

Let's talk about this component in more details ☺

- **Collagen:**

There is two type of collagen:

1. fibrillar collagen (types 1, 2, 3, and 5) :

-Important for tensile strength.

-Forms a major proportion of connective tissue in healing.

-Composed of triple helix, three chains take strength from the bonds between cross links which need vitamin C for its strength, that's why people who have vitamin C deficiency suffer from problem in healing, scar, bleeding in gum because they don't have enough fibrillar collagen strength.

2. nonfibrillar collagens:

There are three places in our body have nonfibrillar collagen:

Type 4 present in basement membrane.

Type 9 present in intervertebral disks.

Type 7 present in dermal-epidermal junction.

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Elastin :

Important for recoil and returning to a baseline structure after stress, so any structure in our body under stress and need to return to normal size have elastin fibers like lunges , arteries , skin, ligaments ...

Ex: blood vessels are rich in elastin to dilate and constrict.

Proteoglycans and hyaluronic acid:

-They form compressible gel important for lubrication.

-reservoir of growth factors of tissue repair.

Adhesive glycoproteins:

As we mentioned before it's like a glue, involved in cell-to-cell adhesion , the linkage of cells to the ECM.

Include: -fibronectin

-laminin

-integrins

In the previous lecture we start talking about repair and we said the repair happens by :

Regeneration : every things back to normal

Or

Scar formation

So let's talk about scar formation ^_^

❖ Scar formation:

Happens by three steps:

1. Angiogenesis: "infra structure": new blood vessels formation→ we have good support to this scar to consist.
2. Migration and proliferation of fibroblasts and their products "elastin , collagen, and other ECM components ".
3. Remodeling.

Angiogenesis: development of new blood vessels from existing vessels, mainly venules. (from the vessels of the injured area).

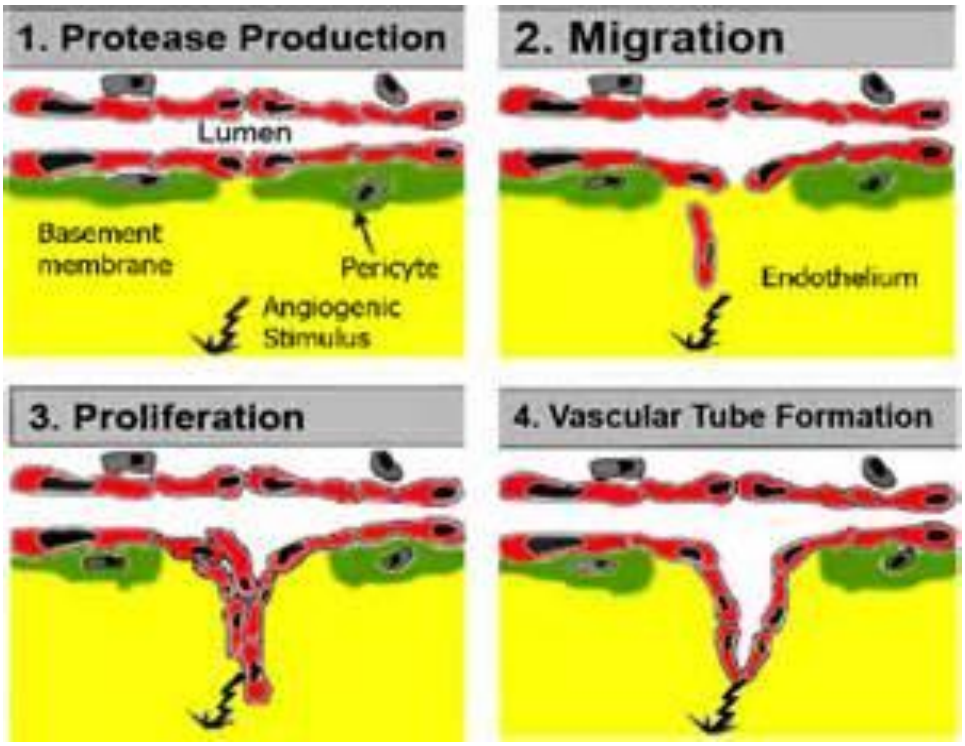
Angiogenesis steps:

- 1. "preparation ", to prepare the vessel by:

vasodilation (due to NO) and increased permeability under (VEGF).

Note: -NO = nitric oxide
-VEGF = vascular endothelial growth factor

- 2. Separate the tissue surrounding the epithelial cells in order to proliferate the endothelial cells don't want anything resist it , so we separate pericytes and smooth muscle cells "supportive cells in capillaries" from abliminal surface.
- 3. endothelial cell migration
- 4. endothelial cell prolifeartion , under the influence of growth factors
- 5. remodeling into capillary tubes, some cell die by apoptosis in order to create lumen.
- 6. recruitment of periendothelial cells: pericytes and smooth muscle cells.
- 7.Supression of endothelial proliferation
- 8. Deposition of basement membrane



❖ **Growth Factor in angiogenesis: three main group:**

1. Vascular Endothelial Growth Factor family (VEGF); stimulates migration and proliferation of endothelial cells.

- When tumors grow, they start angiogenesis because they need blood supply. So if we can't decrease or inhibit angiogenesis in tumor, we can't at least control the growth of that tumor , so nowadays they are trying to find antibodies against VEGF to decrease angiogenesis, thus it deprives the tumor from blood supply, oxygen and nutrition so they might die → the tumor is treated.

2. Epidermal growth factor (EGF).

3. Angiopoietins: ANG1 and ANG2 → especially important for ECM production.

The second step: the scar is formed, how?

By migration and proliferation of fibroblasts into the site of injury, and deposition of ECM proteins produced by these cells.

In the beginning, the scar contain many vessels and many fibroblasts cells and a little collagen, at this stage we called it **granulation tissue**

So granulation tissue is the first step in healing because it's composed of the **angiogenesis** "new blood vessels", the **fibroblasts**, and small amount of collagen fiber and some **inflammatory cells**.

with time, the fibroblasts produce many fibroses and ECM so the fibers increase and the cells decrease that end with scar which is mainly fibrous tissue and very little amount of cells ,also the blood vessels decrease

so the granulation tissue and scar are steps to the same process , the granulation tissue is the first step which consist of cells more than fibers with time cells decrease , vessels decrease and fibers increase then we call it scar and become strong and the main component in the scar is the collagen and mainly fibrillar collagen.

Again all this process depends on GF

Certain GF affect the fibroblast migration and activation:

PDGF = platelet derived growth factor.

TGF BETA = transforming growth factor beta "the most important".

 20:00

The third step: is <u>remodelling of the scar</u>, we don't want the scar to increase, we want it approximately of the same size of the defect.

Remodelling means that there is collagen synthesis (by fibroblast and GF) and collagen degradation (by certain proteins that degrade collagen which they call **MMPs** =matrix metalloproteinases, proteinases mean enzyme degrade protein , metallo mean that they need metals as cofactors, the most important metal used is zinc that why people who suffer from zinc deficiency they might have problem with wound healing.

MMPs types:

1. Interstitial **collagenases** , cleave fibrillar collagen.
2. **Gelatinases** ,degrade amorphous collagen and fibronectin
3. **Stromelysins** ,degrade laminin, fibronectin

This types need to be controlled and regulated by,

*they are present and secreted in inactive form which mean they activated by certain proteins (proteases e.g., plasmin).

*and also they can be inhibited by specific tissue inhibitors of metalloproeinases (TIMPs).

❖ Net effect in the scar depend on:

- Synthesis of fibroblasts
- Degradation by MMPs
- Inhibition of MMPs

❖ **Factor that influence tissue repair:**

1. Infection: the most important cause of delay in healing; because it prolongs inflammation and increase tissue destruction.

2. Nutrition:

A. protein deficiency, leads to deficiency of fibrillar collagen

B. Vitamin C deficiency inhibit collagen synthesis
C. zinc deficiency

3. Steroids: decrease TGF beta

4. Poor perfusion: due to arteriosclerosis and diabetes or to obstructed venous drainage (e.g., in varicose veins).

5. Foreign bodies: such as fragments of steel, glass….

❖ Aberrations of cell growth and ECM production:

1. Keloid: accumulation of very large amounts of collagen forming prominent, raised scars

2. Hyperplastic scar , easier to treat.

3. Proud flesh: nowadays we call it "exuberant granulation tissue" , appear as a fleshy mass sometime need surgical removal.

The end

25:00

As doctor zohlof say: simple and easy, simple and easy :D

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كل التوفيق ^_^