**Lec.no.2/ Tissue Repair**

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**Extracellular Matrix (ECM) and Cell-Matrix Interactions**

***The ECM is*** a dynamic ,constantly remodeling macromolecules complex synthesis and secreted locally which assembles into a network in the spaces surrounding cells. It forms a significant proportion of the volume of any tissue.

**The ECM is components of** **three groups of macromolecules:**

1-**Fibrous structural proteins**, such as the collagens and elastin that provide tensile strength & recoil.

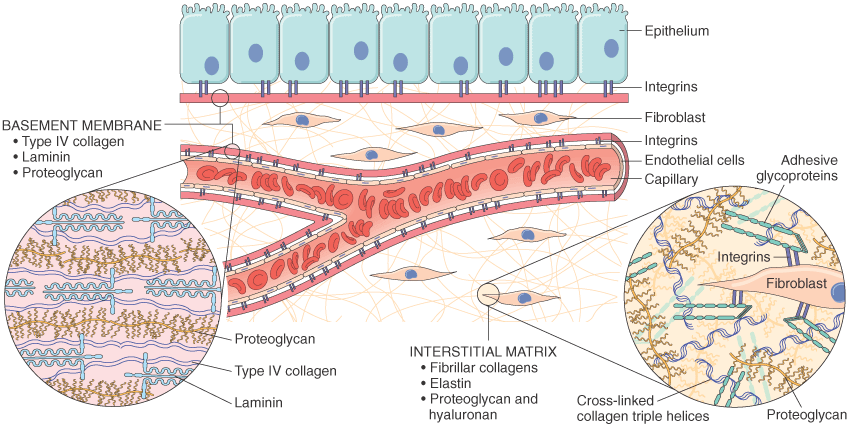
**3-Adhesive glycoproteins** that connect the matrix elements to one another and to cells

**2-Water – hydrated gels** such as proteoglycans and hyaluronic acid that provide resilience and lubrication.

***These molecules occur in two basic forms*** ***of ECM:***

**I-Interstitial matrix** is found in spaces between epithelial, endothelial, and smooth muscle cells and in connective tissue. It consists of fibrillar and nonfibrillar collagen, elastin, fibronectin, proteoglycans, hyaluronan.

**II-Basement membranes** **(BM)** are closely associated with cell surfaces and are produced by overlying epithelium and underlying mesenchymel cells. They consist of a network of amorphous nonfibrillar collagen (mostly type IV), laminin, proteoglycan as see in figure 1.



**figure 1:** **The main** **components of ECM**

**The functions of ECM**

**1-**Mechanical support for cell anchorage and cell migration, and maintenance of cell polarity.

2- Control of cell growth, ECM components can regulate cell proliferation by signaling through cellular receptors of the integrin family.

3-Maintenance of cell differentiation, the type of ECM proteins can affect the degree of differentiation.

4-Scaffolding for tissue renewal.The integrity of the basement membrane or the stroma of the parenchymal cells is critical for the regeneration of the tissues. **The injury to the labile and stable cells are capable of regeneration, and result in tissues restitution of the normal structure only if the ECM is not damaged**.Disruption of these structures lead to collagen deposition and scar formation.

5-Establishment of tissue microenviroments.BM acts as a boundary between epithelium and underlying connective tissue.

6-Storage and presentation of regulatory molecules.Growth factors like FGF is secreted and stored in the ECM in some tissues.This allows rapid distribution of growth factors after local injury or during regeneration.

**The Components of ECM**

**(1) fibrous structural proteins, such as the collagens and elastins.**

**Collagen**

The collagen are fibrous structural proteins that ***confer tensile strength,*** without collagen, human beings would be reduced to a clump of cells, interconnected by a few neurons. The collagens are composed of three polypeptide chains braided into a ropelike triple helix ,***there are 27 different types of collagens*** encoded by 41 genes distributed on at least 14 chromosomes are known. Vitamin C is required for the hydroxylation of procollagen, therefore this requirement explains the inadequate wound healing in scurvy. ***There are two forms of collagens::::***

***1--fibrillar collagens*** as seen in type I, II, III and V, and XI and form a major proportion of the convective tissue in wound healing particularly in scars. The Genetic defects in collagen production cause many inherited syndromes, including various forms of the Ehlers-Danlos syndrome and osteogenesis imperfect.

***2--nonfibrillar (***forms sheets instead of fibrils) and is the main component of the BM( type IV ), or be the component of intervertebral disc (IX),or epidermal-dermal junctions, cartilage (type VII).

**Elastin, Fibrillin and Elastic Fibers**

The ability of these tissues to recoil and return to a baseline structure after physical stress is provided by elastic fibers. This is especially important in the walls of large blood vessels ( which must accommodate recurrent pulsatile flow of blood),as well as in the skin, ligaments ,uterus, and lung require elasticity for their function.

Morphologically, ***elastic fibers differ from collagen by having fewer cross-links . The fibrillin meshwork serves as scaffolding for deposition of elastin and the assembly of elastic fibers.***

Inherited defects in fibrillin synthesis lead to skeleton abnormalities , Marfan syndrome, (weakened of aortic wall) .

**(2) Adhesive Glycoproteins and Adhesion Receptors**

Glycoproteins are structurally different molecules involved in adhesion to the extracellular matrix (ECM) and cell-cell interactions. The adhesive glycoproteins include ***Fibronectin*** (the major component of interstitial ECM ) and ***laminin*** (the major component of BM ).

***The adhesion receptors, also called CAMs (cell adhesion molecules),*** can be classified into four main families: immunoglobulin family CAMs, cadherins, integrins, and selectins..

**Fibronectin**is the major component of interstitial ECM, its producing by a variety of cells , including fibroblasts ,monocytes and endothelium . Fibronectin have specific domains that binds to wide spectrum of ECM components.Tissue Fibronectin forms fibrillar aggregates at wound healing sites.The plasma form binds to fibrin, forming the provisional blood clot that fills the space created by a wound, and serves as a substratum for ECM deposition.

**Laminin** is the most abundant glycoprotein in the basement membrane and has binding domains for both ECM and cell surface receptors and also mediate the attachment of cells to connective tissue substrates.

**(3) Proteoglycans and Hyaluronan**

**Proteoglycans::** these are compounds consisting of a protein bonded to mucopolysaccharide groups, present especially in connective tissue, these have a role in regulating connective tissue structure and permeability, also act as modulators of inflammation, immune response, cell growth and differentiation.

**Hyaluronan (HA)**:: is a huge molecule that consists of many repeats of a simple disaccharide without a protein core , Because of its ability to binds a large amount of water, it forms a viscous hydrated gel that gives connective tissue the ability to resist compression forces and provides resilience and lubrication to many types of connective tissue, particularly for the cartilage in joints.

**Healing by Repair, Scar Formation and Fibrosis**

If tissue injury is severe or chronic, and results in damage of **both parenchymal cells and stromal framework of the tissu**e, healing can not be accomplished be regeneration.In these conditions, the main healing process is done by **depositions of collagen and other ECM components, causing the formation of a scar.**

**Repair by connective tissue deposition include the following basic features::**

* **Inflammation**
* **Angiogenesis**
* **Migration and proliferation of fibroblast**
* **Scar formation**
* **Connective tissue remodeling**

When there is inflammatory reaction caused by the injury contains the damage, removes injured tissue and promotes the deposition of ECM components in the area of injury, at the same time the angiogenesis is stimulated.

If the damage persists ,inflammation becomes chronic, leading to an excess deposition of connective tissue known as **fibrosis**. In most healing processes, a combination of repair and regeneration occurs.

**The relative contributions of repair and regeneration are influenced by:**

1-The proliferative capacity of the cells of the tissue .

2-The integrity ECM.

3-The resolution or chronicity of the injury and inflammation.

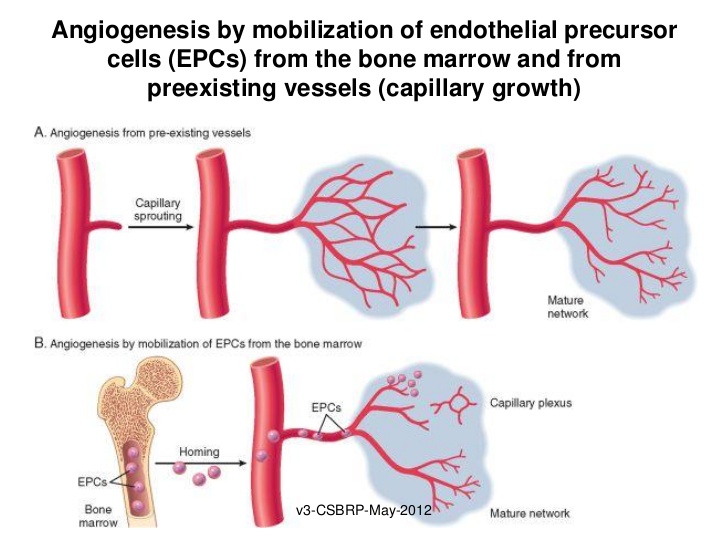
**Angiogenesis**

Angiogenesis is a critical process that affects the physiological reactions (wound healing) and pathological processes (tumor development and metastasis). Angiogenesis occurs in two froms::

**Angiogenesis from preexisting vessels** , in this type of angiogenesis , there is vasodilation and increased vascular permeability of the existing vessels, degradation of ECM and migration of endothelial cells.

**Angiogenesis from endothelial precursor cells (EPCs)**

**EPCs** are mobilized from bone marrow and may migrate to the site of injury or tumor growth , at these sites EPCs differentiate and form a mature network by linking to existing vessels.These cells express some markers of hematopoietic stem cells as well as **vascular endothelial growth factor VEGF.**



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