ROLE OF EXTRACELLULAR MATRIX IN TISSUE REPAIR

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Composition of Extracellular Matrix (ECM)

- Cells (mesenchymal origin)
- fibroblasts
- smooth muscle cells
- Chondroblasts-
- osteoblasts and epithelial cells
- Organic fibrillar matrix
- Organic non-fibrillar matrix
- Water

Function of ECM

- Provides support and anchorage for cells.
- Regulates and determine cells dynamic behavior :
  - polarity of cells
  - cell differentiation
  - adhesion
  - migration
- Provides mechanical support for tissues and organ architecture
  - growth
  - regenerative and healing processes
  - determination and maintenance of the structure
- Place for active exchange of different metabolites, ions, water.

Structure of ECM collagen

- the main ECM component,
- forms the main fibreselastinproteoglycans-heteropolysacharides structural glycoproteins- fibronectin, laminin

Collagen

- most abundant protein in the body,
- making 25%-35% of all the whole-body proteins.
- Collagen contributes to the stability of tissues and organs.
- It maintains their structural integrity.
- It has great tensile strength.
- The main component of fascia, cartilage, ligaments, tendons, bone and skin.
- Plays an important role in cell differentiation, polarity, movement.
- Plays an important role in tissue and organ development.

Collagen Structure

- Collagen is insoluble glycoprotein (protein + carbohydrate)Collagen polypeptide primary structure:- G – X – A – G – A – A – G – Y – A – G – A – A – G – X – A – G –,G - glycine, X - proline or hydroxyproline, Y – lysin or hydroxylysine, A – amino acidProline and hydroxyproline constitute about 1/6 of the total sequence, provide the stifness of the polypeptide chain.Carbohydrates : glucose, galactose

- Three helical polypeptide units twist to form a triple-helical collagen molecule: a molecular "rope" which has some bending stiffness and does not undergo rotation.
- The tropocollagen molecule has a length of approximately 300 nm and a diameter close to 1.5 nm.In the typical fibrillar collagens, only short terminal portions of the polypeptides (the telopeptides) are not triple helical.

Synthesis

- **Synthesis of a chains of pre-procollagen on ribosomes.**
  Hydroxylation of lysine and proline in rER/Golgi by lysyl-5-hydroxylase and prolyl-4-hydroxylase.Glycosylation: addition of galactose and glucose to some hydroxylysine residues (galactosyl transferase and glycosyl transferase).Assembly of a-chains to form procollagen. Reaction needs the formation of disulphide bonds between registration peptides, at both ends of the prepro- collagen.

- ECM is a non-cellular structure that regulates almost all of the cellular functions.
- ECM is a highly dynamic structural network that continuously undergoes remodeling mediated by several matrix-degrading enzymes during normal and pathological conditions.

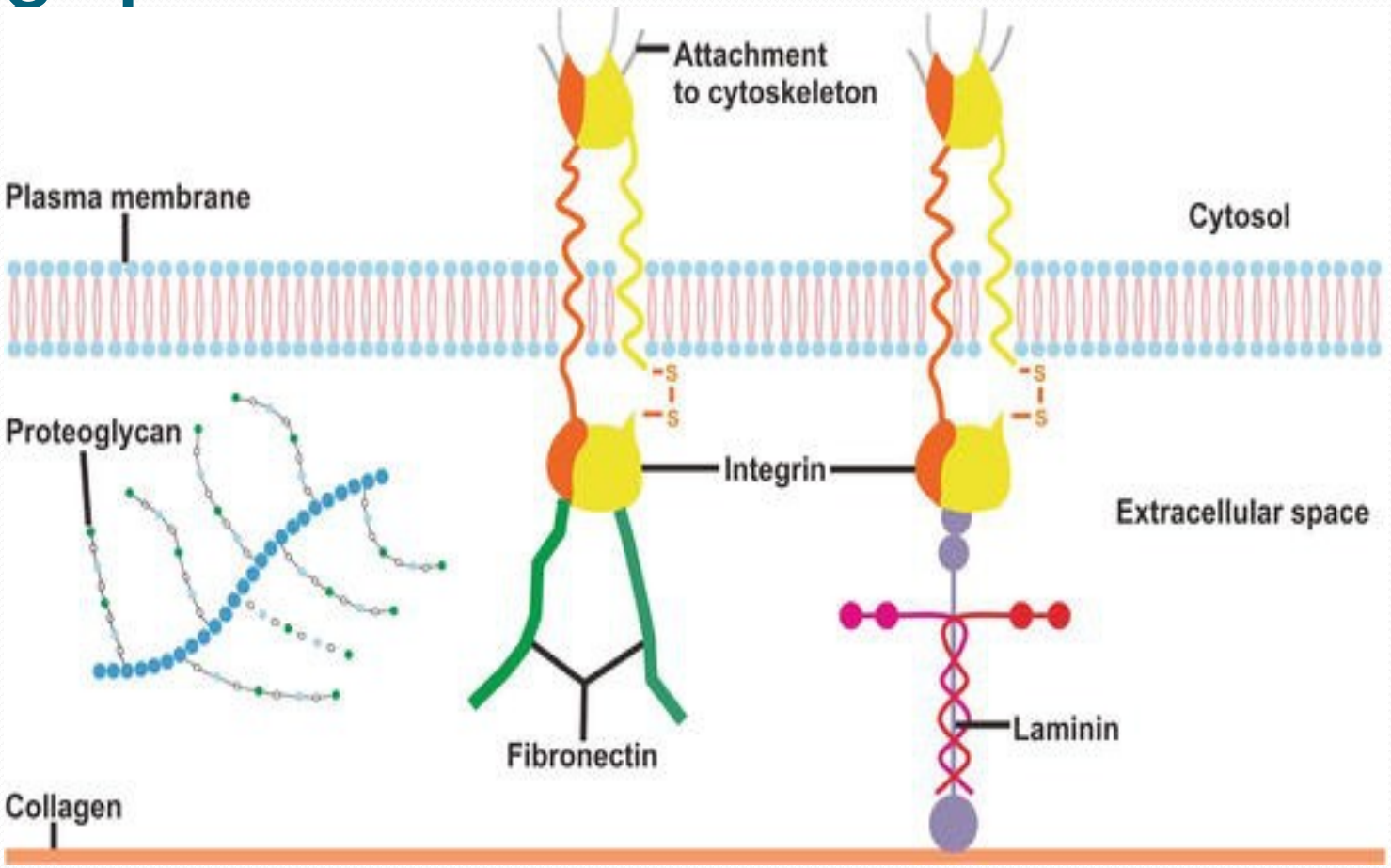
- Deregulation of ECM composition and structure has an association with the development and progression of several physiological and pathologic conditions.

The structure and function of extracellular matrix

- An essential part of the holding capacity of tissues is the extracellular area. The extracellular region is primarily occupied by a complicated network of macromolecules constituent called as extracellular matrix (ECM).

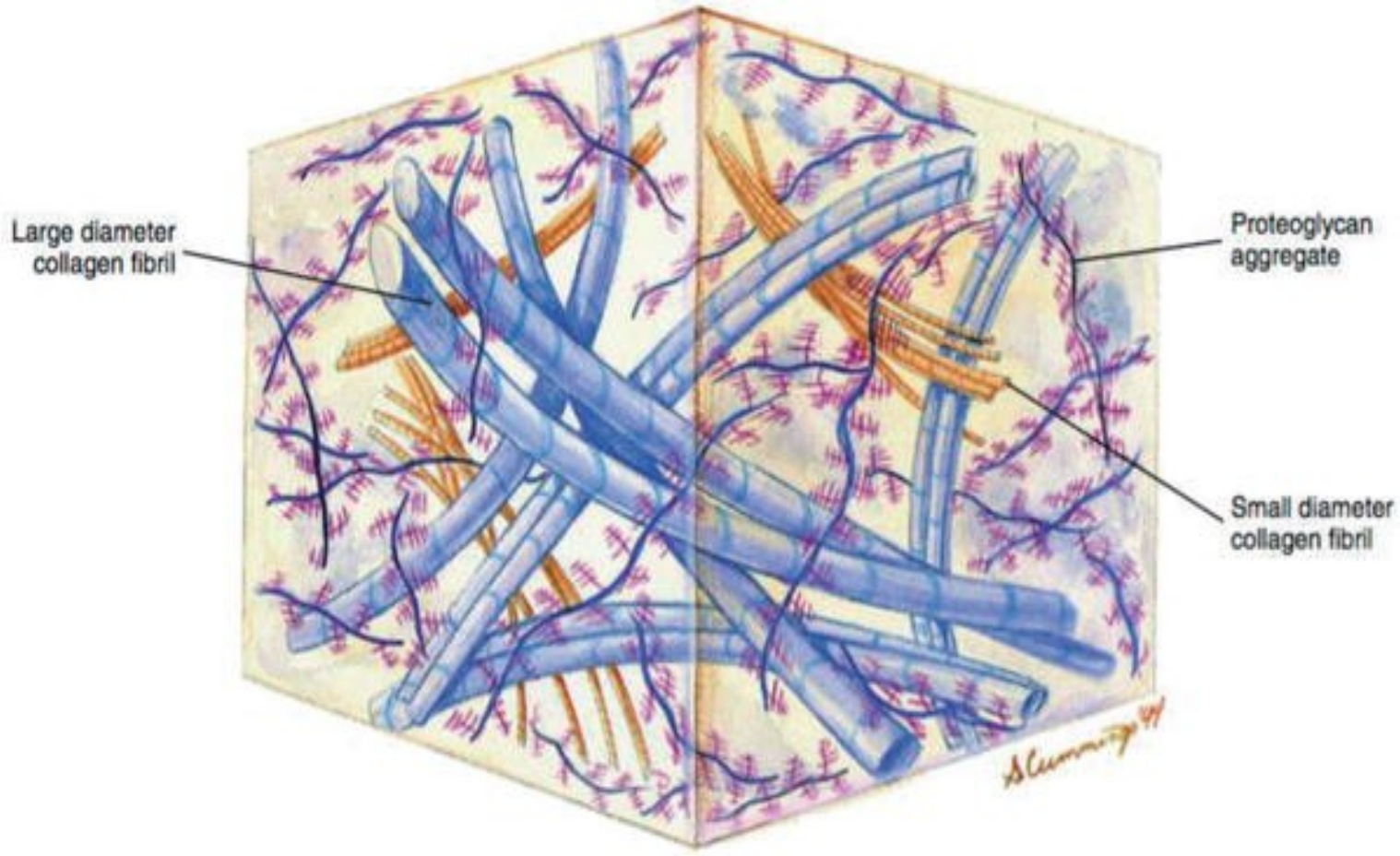
- The composition of ECM is varied, depends on the species and also developing or ground molecules
- Commonly, the ECM is composed of three major classes of biomolecules; there are glycosaminoglycans (GAGs), linked to a protein known as the proteoglycans, and also fibrous proteins, including collagen, elastin, fibronectin, vitronectin, and laminin.

Fig 1


Attachment
to cytoskeleton
Plasma membrane
Cytosol
Proteoglycan
Integrin
Extracellular space
Fibronectin
Laminin
Collagen

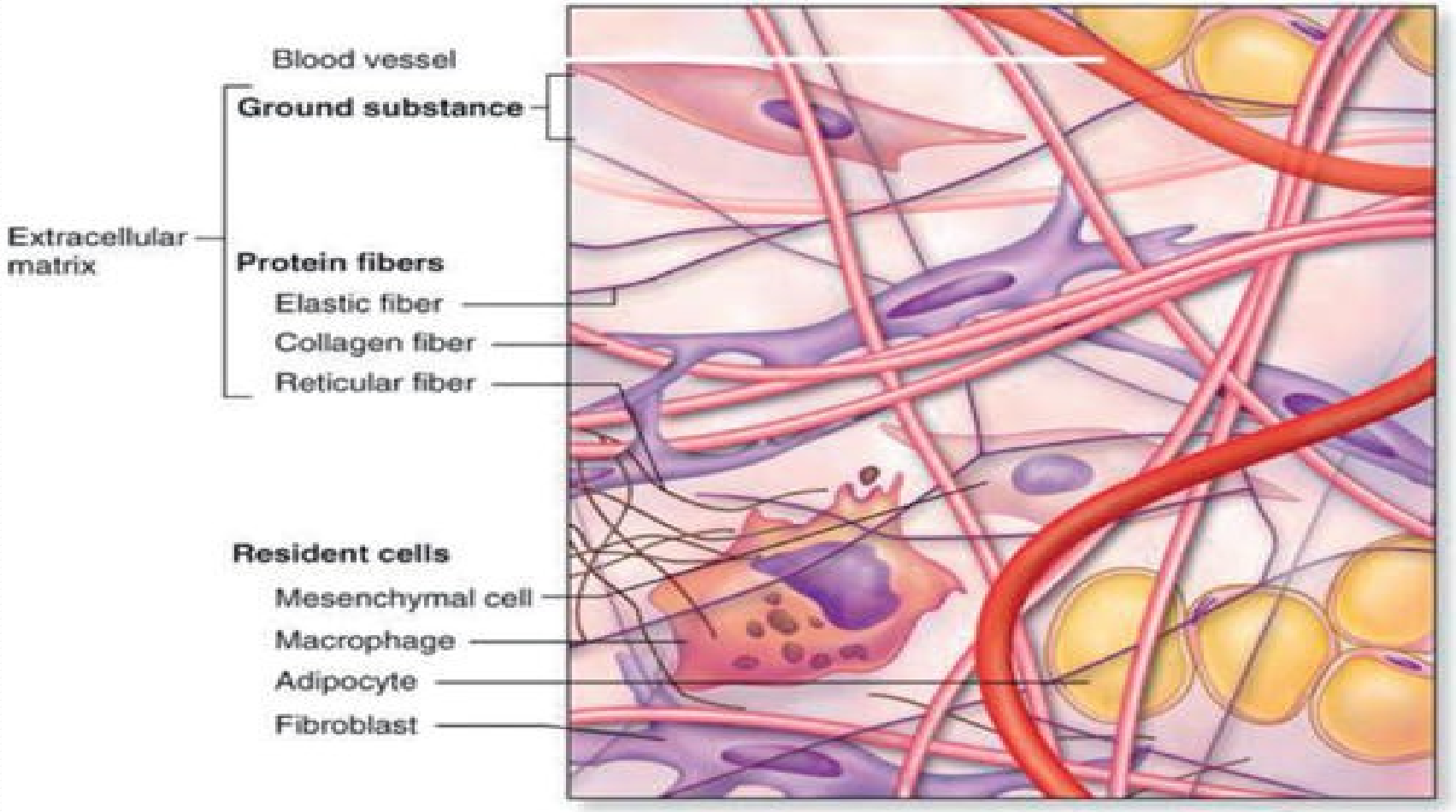
- **Figure 1.**
- The structure of the extracellular matrix. The ECM mainly contained collagen fibers. There are also some glycoproteins as an adhesion molecule, such as integrin family fibronectin and laminin, which conduct cell attachments to the ECM by binding to collagen in the ECM and integrin. The intracellular part of integrin highly associated with the cytoskeleton thus may promote to anchoring the cell. In the end, there are various proteoglycans in the ECM that act as primary proteins and are profoundly modified by the addition of sugars.

Fig 2


Large diameter
collagen fibril
Proteoglycan
aggregate
Small diameter
collagen fibril

- **Figure 2.**
- The extracellular matrix of hyaline cartilage found in abundant collagen fibril and proteoglycan aggregates. The chemical analysis of the ground substance reveals that it contains a few glycoproteins and a high concentration of three types of glycosaminoglycans: hyaluronic acid, chondroitin sulfate, and keratan sulfate. Adapted from Crammer and Bakkum [1].

Fig.3


Blood vessel
Ground substance
Extracellular matrix
Protein fibers
Elastic fiber
Collagen fiber
Reticular fiber
Resident cells
Mesenchymal cell
Macrophage
Adipocyte
Fibroblast

- (Figure 3) is also composed of the matrix of ECM. One of the essential components of connective tissue is fibroblasts and ground substance. Ground substance is a mixing complex between GAGs, proteoglycans, and glycoproteins (mainly laminin and fibronectin). In most connective tissues, the matrix constituents are secreted by fibroblasts, but in several certain specialized types of connective tissues, like cartilage and bone, these components are secreted by chondroblasts and osteoblasts

Fibroblast

- Synthesize and secrete collagen, elastic fibers, reticular fiber, and proteoglycan (among other molecules)
- Support ligaments, tendons, bone, skin, blood vessels, and basement membranes
- distributed Throughout all loose and dense connective tissue
- They are Flat, stellate cells with dark, ovoid, staining nuclei, and one or more nucleoli
- Microscopically may appear to be of different shapes because of the plane of sectioning

Chondroblast

- Synthesize and secrete extracellular matrix of cartilage (collagen, elastic fiber and glycosaminoglycans)
- Support articular cartilage
- Present in hyaline cartilage of articulations and fibrocartilage of intravertebral discs
- Found also in elastic cartilage
- Metabolically active with large vesicular nuclei and prominent nucleoli
- Cytoplasm pale and vacuolated because of high content of lipid and glycogen

Osteoblast

- Synthesize and secrete extracellular matrix of bone
- Present In bone
- Basophilic cytoplasm resulting from presence of a large amount of rough endoplasmic reticulum that produce glycosaminoglycan and glycoprotein

Myofibroblast

- It Synthesize and secrete components of extracellular matrix
- Capable of contractility
- Distributed In blood vessels and skin throughout the body
- It Resemble fibroblast under light microscopy but ultra structurally contain actin filaments for contraction

- In general, all the cells need to attach to the extracellular matrix to grow and multiply. Extracellular matrix provides support and anchorage for the shape of the cells, regulates and determines cells dynamic and behavior including cell survival, cell proliferation, cell polarity, cell differentiation, cell adhesion, and cell migration. Moreover, the ECM, also gives the mechanical support for tissues and is involved in the growth mechanism, regenerative, and healing processes.

- **Glycosaminoglycan (GAGs)**
- GAGs are un branched chains of polysaccharides; GAGs are composed of repeating disaccharide units and are heterogeneous groups in negatively charged polysaccharide chains that are covalently linked to proteins to form proteoglycan molecules.

- **. Collagen**
- Collagen is a major abundant fibrous protein in the extracellular matrix. Collagens, which constitute the primary structural element of the ECM, provide tensile strength, regulate cell adhesion, support chemotaxis and migration, and direct tissue development [4

- **Fibronectin**
- Fibronectin is an extracellular protein that makes cells adhere to the matrix. Fibronectin is considered as a large glycoprotein found in all vertebrates. Fibronectin usually exists as a dimer composed of two nearly identical ~250 kDa subunits linked covalently near the C- terminal by a pair of disulfide bonds at one end side. Fibronectin is a ligand member of the integrin receptor family. Integrins are structurally and functionally related to the cell surface as heterodimeric receptors that link the ECM with the intracellular cytoskeleton.

- **Tissue regeneration**
- Extracellular matrix is the primary factor required in the process of forming a new network and tissue.

- ECM is involved in various mechanisms such as wound healing with or without the involvement of mesenchymal conditioned medium and neuronal regeneration capability associated with pathologic and/or neurodegenerative disease.

- The process of wound healing is strongly influenced by the role of migration and proliferation of fibroblasts in the injury site. Indeed fibroblast is one part of ECM.

- The proliferation of fibroblasts determines the outcome of wound healing. Fibroblasts will produce collagen that will link to the wound, and fibroblasts will also affect the process of re epithelialization that will close the wound.

Thank you