THE EXTRACELLULAR MATRIX

The extracellular matrix (ECM) is a complex network composed of macromolecules produced and secreted by cells. It is located in the extracellular space and plays an important role in the structural and functional support of tissues. It is essential for biological processes such as development, tissue repair, and cell communication. This matrix is composed of various proteins and polysaccharides that are locally secreted and assembled in an organized meshwork associated with the surfaces of the cells that produce them.

The extracellular matrix is made up of three major types of macromolecules:

- large fibrous proteins: collagen and elastin,
- glycoproteins that allow adhesion between the different molecules of the ECM and between the ECM and the cells: fibronectin and laminin,
- polysaccharide chains of the glycosaminoglycan (GAG) family, generally covalently linked to proteins to form proteoglycans (PG).

The organization of the ECM is specific to each tissue. Variations in the proportions of these three types of molecules lead to different tissue morphologies. The macromolecules that constitute the ECM are produced locally by the cells within the matrix.

In epithelial tissues, the cells are arranged in layers and rest on a thin and dense ECM called the **basal lamina**.

The extracellular matrix is in constant renewal, resulting from the balance between the synthesis of its components and their degradation by specialized enzymes. This degradation is a normal process that ensures matrix turnover and also occurs during several physiological processes. The disruption of this balance leads to pathologies, either through matrix accumulation (as in fibrosis) or destruction (as in osteoarthritis). There is an adaptive remodeling of the matrix depending on the needs of the tissues. Matrix metalloproteinases (MMPs) are a family of enzymes highly involved in this adaptive remodeling. MMPs are scarcely present in healthy tissues but are highly expressed during repair or pathological processes.

Interactions between cells and the extracellular matrix are mediated by specific transmembrane receptors, the SAMs (Substrate Adhesion Molecules), which include integrins. These interactions are involved in cell adhesion to the matrix but also allow the exchange of information between the cells and the extracellular matrix.

Integrins are the main receptors used by animal cells to bind to the extracellular matrix. They are transmembrane proteins located between the extracellular matrix and the cytoskeleton, generally connecting to actin. Integrin molecules are heterodimers, and the binding of their ligand is associated with important conformational changes. This creates a coupling between the interactions with the ECM and those with the intracellular cytoskeleton, allowing integrins to transmit signals in both directions across the plasma membrane.

II- COMPONENTS OF THE EXTRACELLULAR MATRIX

1- Fibrous proteins

A- Collagens

Collagens constitute a family of fibrous glycoproteins found exclusively in extracellular matrices. They are present throughout the animal kingdom and are characterized

by their high resistance to tensile forces. Collagens are polymers of an elementary molecule synthesized by fibroblasts in the form of a precursor, procollagen. At the time of secretion, extracellular peptidases convert it into tropocollagen. Tropocollagen is a glycoprotein formed by the helical winding of three α-polypeptide chains that carry carbohydrate residues (glucose and galactose). When associated together, tropocollagen molecules allow collagen to be classified either as fibrillar collagen (such as collagens I, II, III: protofibrils → fibrils → fibers → bundles), or as non-fibrillar or reticular collagen (such as collagen IV which forms two-dimensional networks in all basal laminae). Within the different components of the ECM, collagen molecules provide an insoluble framework responsible for many of the mechanical properties of the matrix.

B- Elastin

Elastin is the main protein component of elastic fibers. These elastic fibers are interwoven with collagen fibrils in certain tissues and provide elasticity, thereby preventing tearing. They are abundant in the ECM of tissues subjected to significant variations in size and shape, such as the skin, blood vessels, and lungs.
Elastin is a hydrophobic protein, non-glycosylated, and rich in proline and glycine.

2- Adhesive glycoproteins

A- Fibronectin

Fibronectin is composed of two chains, each containing 2,446 amino acids, linked together by two disulfide bonds near their C-terminal end. Each chain consists of distinct domains specialized in binding to different matrix macromolecules or to cells.
Fibronectin ensures cell adhesion to the matrix through its binding sites to integrins (the binding site is constituted by the RGD sequence [Arginine-Glycine-Aspartate]), to collagen, and to proteoglycans.

3- Polysaccharide chains

A- Glycosaminoglycans

Glycosaminoglycans (GAGs) are unbranched polysaccharide chains composed of repeating disaccharide units. They are called GAGs because one of the two sugars of the repeating disaccharide (N-acetylglucosamine or N-acetylgalactosamine) is always an amino sugar, which is generally sulfated. The second sugar is often a uronic acid (glucuronic or iduronic acid). Because most of their sugars contain either a sulfate or a carboxyl group, GAGs carry a strong negative charge.

These negative charges attract positively charged ions that have a strong osmotic effect, bringing large amounts of water into the matrix. GAGs form a highly hydrated gel that fills most of the extracellular space and enables the ECM to resist compressive forces.
Five major groups of GAGs are distinguished according to the sugar they contain, the type of linkage between the sugars and the number of sulfate substituents:
a/ chondroitin sulfates
b/ dermatan sulfates
c/ keratan sulfates
d/ heparan sulfates
e/ hyaluronic acid

Only hyaluronic acid exists freely in the matrix; all other GAGs are covalently linked to proteins to form proteoglycans.

B- Proteoglycans

The extracellular matrix contains large amounts of proteoglycans. Proteoglycans are composed of a central protein core to which long, unbranched glycosaminoglycan (GAG) chains are attached.

III- BASAL LAMINA

One of the best-defined extracellular matrices is the basal lamina, a thick layer of 50 to 200 nm that surrounds muscle and adipose cells, is located beneath epithelial tissues, and is also found under the inner endothelial layer of blood vessels.

The composition of the mature basal lamina varies from one tissue to another and even from one region to another within the same lamina. It generally includes glycoproteins (laminin), type IV collagen, entactin, as well as proteoglycans (perlecan).

A- Laminin

Classical laminin (laminin-1) is a trimeric glycoprotein characteristic of basal laminae. It is formed by three long polypeptide chains (α, β, and γ) held together by disulfide bonds and arranged into a cross-like structure.

Cells that rest on a basal lamina such as epithelial, endothelial, muscle, or nerve cells (Schwann cells) synthesize this protein.

It contains binding sites mainly for type IV collagen, cells, and proteoglycans.

This multi-adhesive protein forms a fibrous network with collagen IV and binds to the extracellular domain of an intramembrane protein: integrin.

Type IV collagen and laminin form the structural framework of the basal lamina.

B- Type IV collagen

Type IV collagen is the second essential component of the mature basal lamina. Collagen IV exists in all basal laminae and is specific to them. This molecule is a triple helix formed by three protein chains.

C- Nidogen

Nidogen is a monomeric protein that stabilizes the framework of the basal lamina by forming bridging interactions between type IV collagen and laminin.
The complex (type IV collagen – laminin – nidogen) has the ability to bind to perlecan.

D- Perlecan

Perlecan contains three heparan sulfate chains attached to a protein core. This molecule is present in all cells that synthesize a basal lamina (epithelial cells, muscle cells, etc.). It binds to other perlecan molecules and to many components of the extracellular matrix as well as to cell surface molecules.

IV- FUNCTIONS

The extracellular matrix plays an essential role in the formation, maintenance, and remodeling of tissue architecture. It provides structure and anchorage for cells.

Collagen fibers ensure resistance to tensile forces and also contribute to the organization of the matrix.

Fibronectin contributes to the organization of the extracellular matrix and helps cells attach to it.

GAG chains provide mechanical support to tissues (gel structure) while allowing the easy diffusion of water, ions, nutrients, hormones, growth factors, and other intercellular signaling molecules. GAGs also enable the matrix to resist compressive forces.

The extracellular matrix is involved in major cellular functions: cell differentiation, cell migration, proliferation, and cell survival. Studies in cell culture show that many cells do not proliferate unless they are attached to an extracellular matrix. For some cell types, including epithelial, endothelial, and muscle cells, even cell survival depends on this attachment. Cells that lose contact with the extracellular matrix undergo programmed cell death or apoptosis.

This dependence of cell growth, proliferation, and survival on anchorage to a substrate is called anchorage dependence.

Basal laminae provide mechanical support for attached cells and generate signals responsible for cell survival. They serve as a substrate for cell migration; they separate contiguous tissues within an organ and prevent the passage of macromolecules. Basal laminae also act as a protective barrier that prevents tissues from invasion by wandering cancer cells.

V- PATHOLOGY OF THE EXTRACELLULAR MATRIX

1- Genetic diseases

A/ Hereditary diseases affecting collagen synthesis

These rare diseases can affect different steps of collagen biosynthesis and are linked to abnormalities in the genes encoding collagen chains or to deficiencies in certain enzymes involved in collagen maturation.

Example: Ehlers–Danlos syndromes constitute a heterogeneous group of connective tissue disorders that manifest as skin fragility, hyperextensibility of the skin, and abnormally flexible joints.

2- Acquired diseases

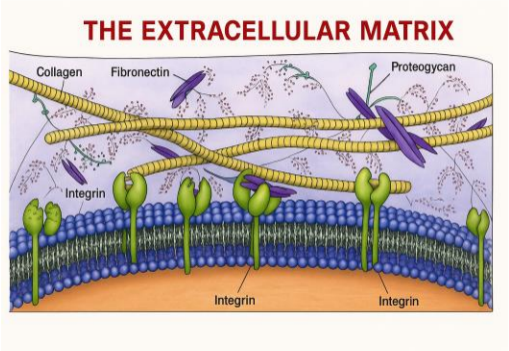
A/ Scurvy

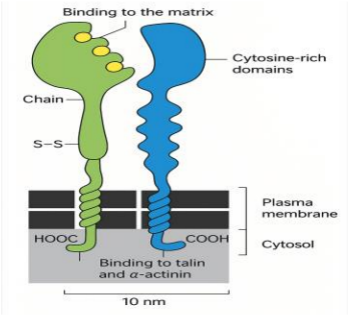
Scurvy is caused by a deficiency in ascorbic acid (vitamin C), which is a cofactor in collagen synthesis. This deficiency decreases the activity of prolyl hydroxylase, resulting in reduced hydroxylation of proline residues, and thus decreased stability of procollagen molecules, which are degraded inside the cell. This post-translational defect in collagen synthesis results in tissue fragility, particularly loosening of the teeth due to weakening of the ligaments that anchor them to the jaws, as well as impaired wound healing.

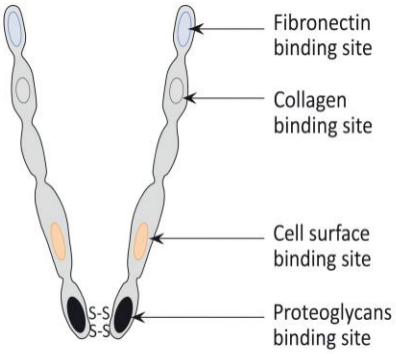
B/ Fibrosis

Fibrosis is characterized by an increase, within a tissue, of the components of the extracellular matrix. It is due to excessive stimulation of matrix component synthesis in response to a local inflammatory reaction. It is often responsible for functional impairment of the affected organ (respiratory failure, kidney failure, liver failure).

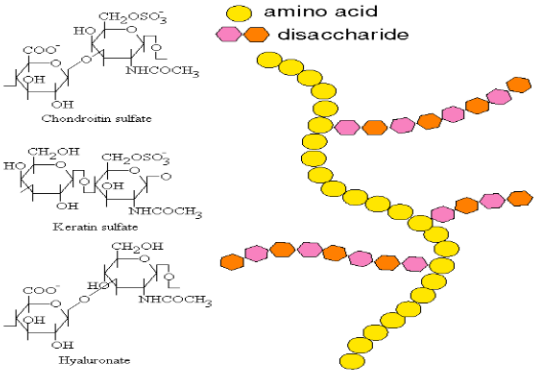
INTEGRIN



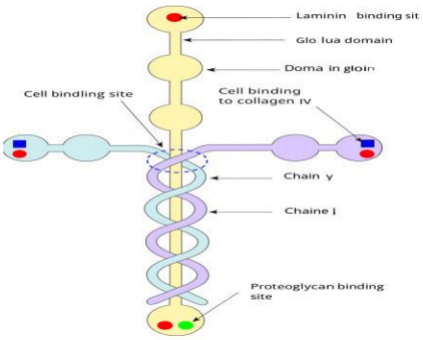




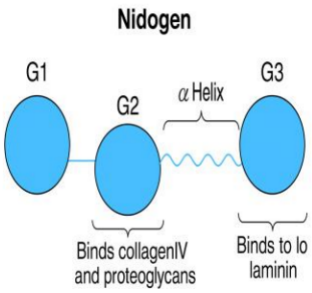
Structure of a fibronectin dimer



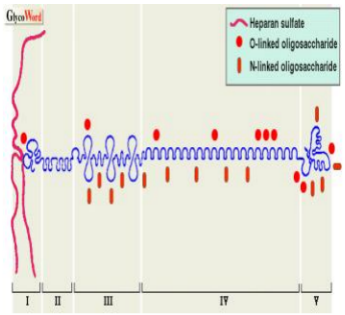
Proteoglycans



Structure of the laminin



Structure of the nidogen



Structure of the perlecan