Chapter 10
ExtraCellular Matrix (ECM)

10.1. Functions of the ExtraCellular Matrix (ECM)

1. It provides Structural support and
2. Exert Influences on cell extensibility, cell shape and movement and development of specialized cell characteristics.

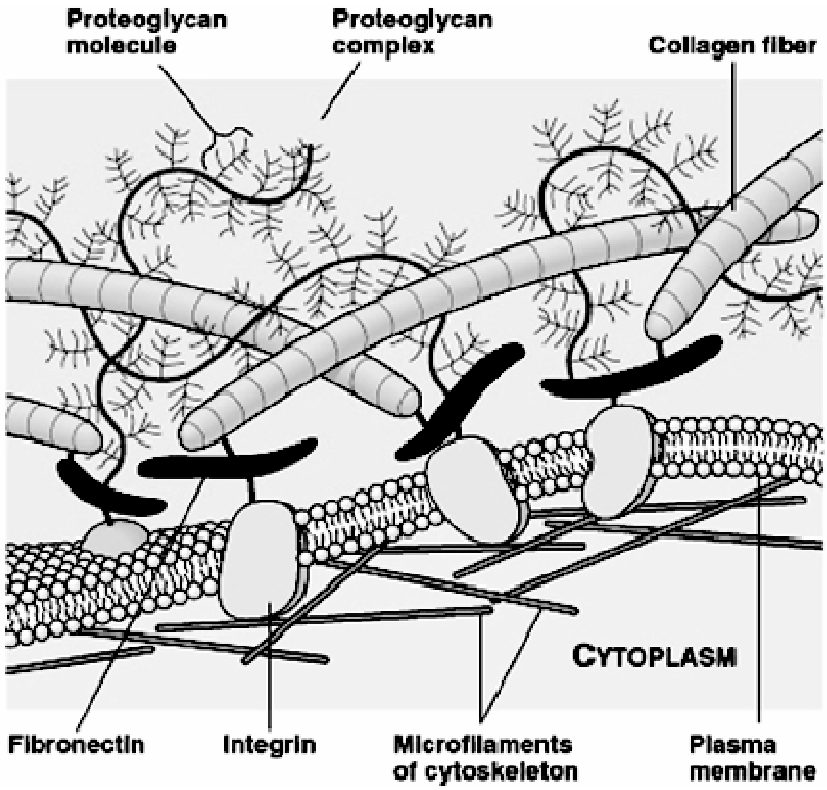

Fig.10.1. Elements of Extra-Cellular Matrix

10.2. Classes of ECM Molecules

(a) Structural Proteins

1. These are collagens and **elastin**
2. They give ECM strength and flexibility
3. **Proteoglycans** are **protein-polysaccharide complexes**. These provide the gelatinous matrix, in which the structural proteins are embedded.

(b) Adhesive Glycoproteins

1. **fibronectins** and **laminins**
2. Function to attach cells to the matrix

(c) Collagens

Collagens are a large family of closely related proteins. They are the most abundant component of the ECM. In a typical vertebrate body, as much as 25-30% of proteins are collagens. Collagens give tissues the strength to maintain their form. All collagens are **triple-helices** of **polypeptides**, called α chains.

(d) Assembly of Collagen Fibers

In **fibroblast ER lumens** three α chains assemble to form a triple helix, called **procollagen**. Then an enzyme, **procollagen peptidase**, remove the amino acid sequences from the N- and C- terminal ends, allowing the formation of **mature collagen molecules** (a triple helix). These assemble into **Collagen Fibrils**, which in turn assemble laterally into **Collagen Fibers**. **Collagen fibers** have a **striated appearance** due to a regular, but staggered arrangement of the collagen molecules in the collagen fibrils. The 25+ different α chains assemble to form at least 25 different collagen molecules. Types I, II, and III are the most common, with type I making up 90% of human collagen.

(e) Elastic Fibers

Elastic fibers provide tissues with flexibility, whereas the collagen fibers provide strength. It is the ratio between elastic and collagen fibers that gives tissues their needed balance of flexibility and strength. Flexibility is important in organs such as: lungs, blood vessels, skin and intestines. Elastic fibers are made from ECM proteins called **elastins**, and are elastic (return to original form after being stretched. As people age the collagen fibers become more cross-linked and loose flexibility and elastic fibers are lost from tissues such as skin. This leads to less flexible joints and bones, and skin develops wrinkles and is less elastic.

10.3. Proteoglycans

Proteoglycans provide a hydrated gelatinous matrix, in which the structural proteins are enmeshed. **Proteoglycans (mucoproteins)** consist of a single protein molecule, to which are attached a large number of **glycosaminoglycans** (**GAGs**) **(mucopolysaccharides)**. GAGs are long polysaccharide chains made from two monosaccharides or monosaccharide derivatives in a strict alternating fashion. The average length is 800 monosaccharides. The three most common disaccharides are **chondroitin sulfate, keratan sulfate**, & **hyaluronate**. The large number of **carboxyls** and **sulfates** attract **water molecules** and **cations.**

Proteoglycans consists of a single core protein (10 to 500 kDa (kilodaltons)) with 1 to 200 GAGs attached to it. This forms molecules ranging from 250 to 3,000 kDa. Up to 95% of these molecules are carbohydrate. **Proteoglycans** are attached directly to **collagen** fibers to form the **fiber/network** of the **ECM.** Because **proteoglycans** can hold up to 50 times there weight in water, the ECM is resistant to compression and is able to regain its shape quickly.

Hyaluronate can also exist as a free molecule made from hundreds to thousands of disaccharide units. Functions of these molecules include lubrication of joints and to aid migration of cells. Hyaluronate is found on the surfaces of migrating cells, but when they reach their destinations it is removed. Hyaluronate attaches to cells by a surface protein, **CD44**. Some cancel cells express a variant of CD44, which would allow them to migrate and thereby be invasive.

10.4. Adhesive Glycoproteins

Adhesive glycoproteins function to attach cells to the matrix, frequently by way of a family of **transmembrane** receptor proteins called **integrins**. **Fibronectins** and **laminins** are the most **common adhesive glycoproteins**. The most common **adhesive glycoproteins** are the **fibronectins**, which are a family of closely related proteins found in the ECM throughout the animal kingdom.

The **fibronectin molecule** consists of two polypeptide subunits joined by two disulfide bonds near their carboxyl ends. Each polypeptide subunit is made of about 2500 amino acids and is folded into a series of rod-like domains, connected by flexible sections. Fibronectin **domains** bind specifically to macromolecules in the ECM and on cell surfaces. These macromolecules include: collagens I, II, & IV, heparin, fibrin (a blood clotting protein), and cell surface receptors. Fibronectin acts as a bridging molecule, attaching cells to the ECM.

The neural crest cells form in embryos when the neural tube closes; these cells are left between the ectoderm and neural tube. The cells of the neural crest play a vital role in the development by migrating to a variety of locations where they form numerous structures. Some of the structures formed by the neural crest cells are as follows: chromatophores, most of the visceral skeleton, the papillae of teeth, ganglia of the Autonomic Nervous System, some cranial nerve ganglia, Schwann cells, meninges and spinal ganglia. The pathways these cell follow are rich in fibronectin, which serves to guide their paths. The **intracellular cytoskeleton** aligns with the **extracellular fibronectin** network. Many **cancer cell types** cannot synthesize fibronectin, so they detach from the ECM and loose their normal form. Introduction of fibronectin reverses these effects.

10.5. Laminins

B. **Laminins** are found mainly in the **basal lamina** & function to bind **cells** to the **basal lamina**.

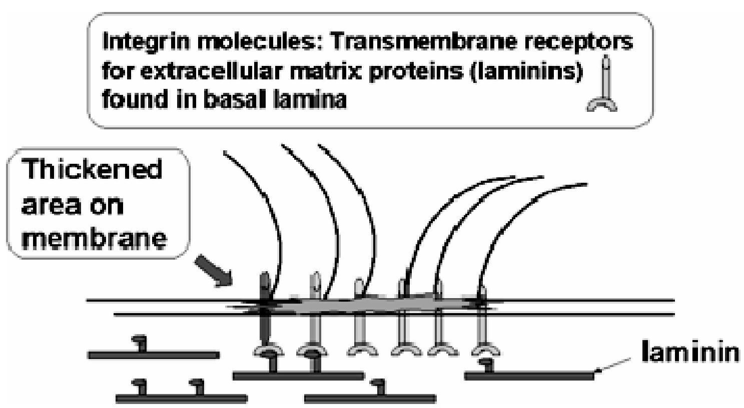

Fig.10.2. Position of Laminins in the Basal Lamina

The **basal lamina** (basement membrane) is a 50 nm thick sheet to which epithelial cells attach. Therefore, it separates epithelium from connective tissue. The basal lamina provides **structural support** and provides a **permeability barrier**. The basal lamina prevents **migration** of **most cells**. It does allow **passage** <u>of</u> **leucocytes**. Some **cancer cells** have increased ability to bind to the basal lamina, which may allow them to cross the basal lamina and aid in their **metastasis** (spread to other tissues).

The **laminin** molecule is made from variations of three polypeptides, **α** (alpha), **ß** (beta), and τ (gamma), which are partially wound together in the shape of a cross. The polypeptide are bound together with disulfide bonds. Within this 850 kDa molecule there are functional domains for the binding of various molecules, including: collagen IV, heparin, heparan sulfate, entactin, and for laminin receptors on the surface of cells.

10.6. Integrins

C. **Integrins** are a large family of transmembrane proteins that integrate the cytoskeleton and the ECM, because they bind to ECM proteins (such as laminin, fibronectin, and collagen) and on the inside of the cell they bind to specific cytoskeleton molecules.

1. Integrins are made from two transmembrane polypeptide subunits, **α** and **ß**, which exist in multiple forms. The α subunit is 110-140 kDa (kilodaltons) and the ß subunit is 85-91 kDa.
2. By way of integrins, the influence between the cellular cytoskeleton arrangement and the orientation of ECM component can be reciprocal.
3. In both embryos and adults, integrins are essential for cell movement and cell attachment.

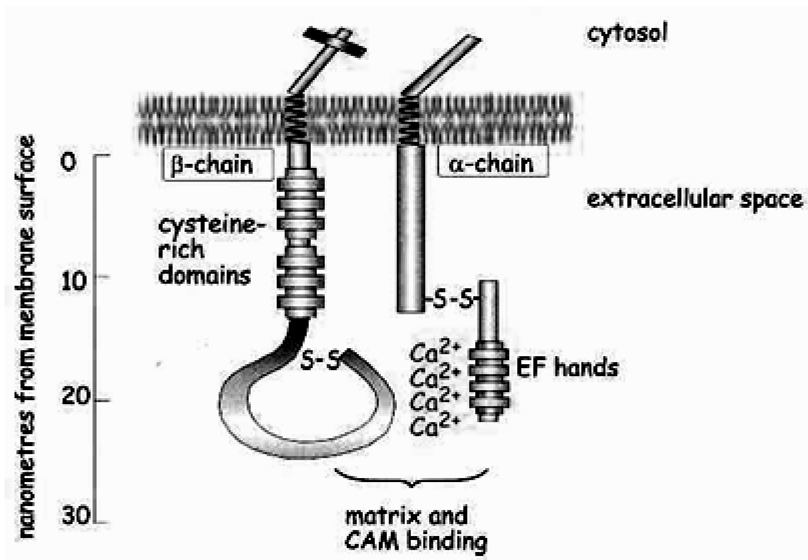

Fig.10.3. Structure of Integrins

10.7. Integrins and Cancer

Even in the presence of growth factors, most **normal cells** must attach to a substratum in order to proliferate. This is called **anchorage-dependent growth**. **Cancer cells** can **proliferate even if not attached** to an ECM component. They no longer require the signal that would be passed to them from the ECM. For **normal cells** to attain anchorage-dependent growth, the integrins form clusters, which then activate several **kinases** (including **focal adhesion kinase,** (FAK) & **integrin-linked kinase**, (ILK)). **Cancer cells** have activated FAK, even when they are not attached.