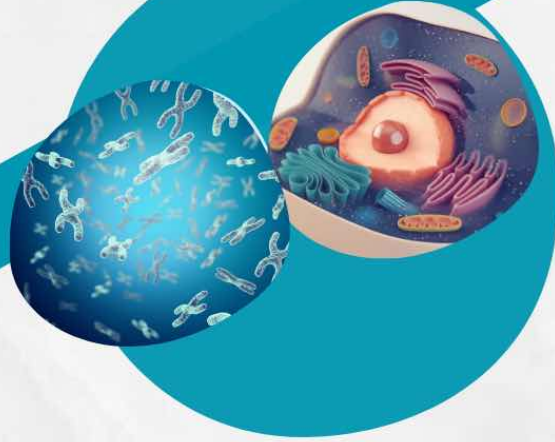


Sheets

# Cell biology



Lecture 7,1



**Writer:** ليان بسام البدور

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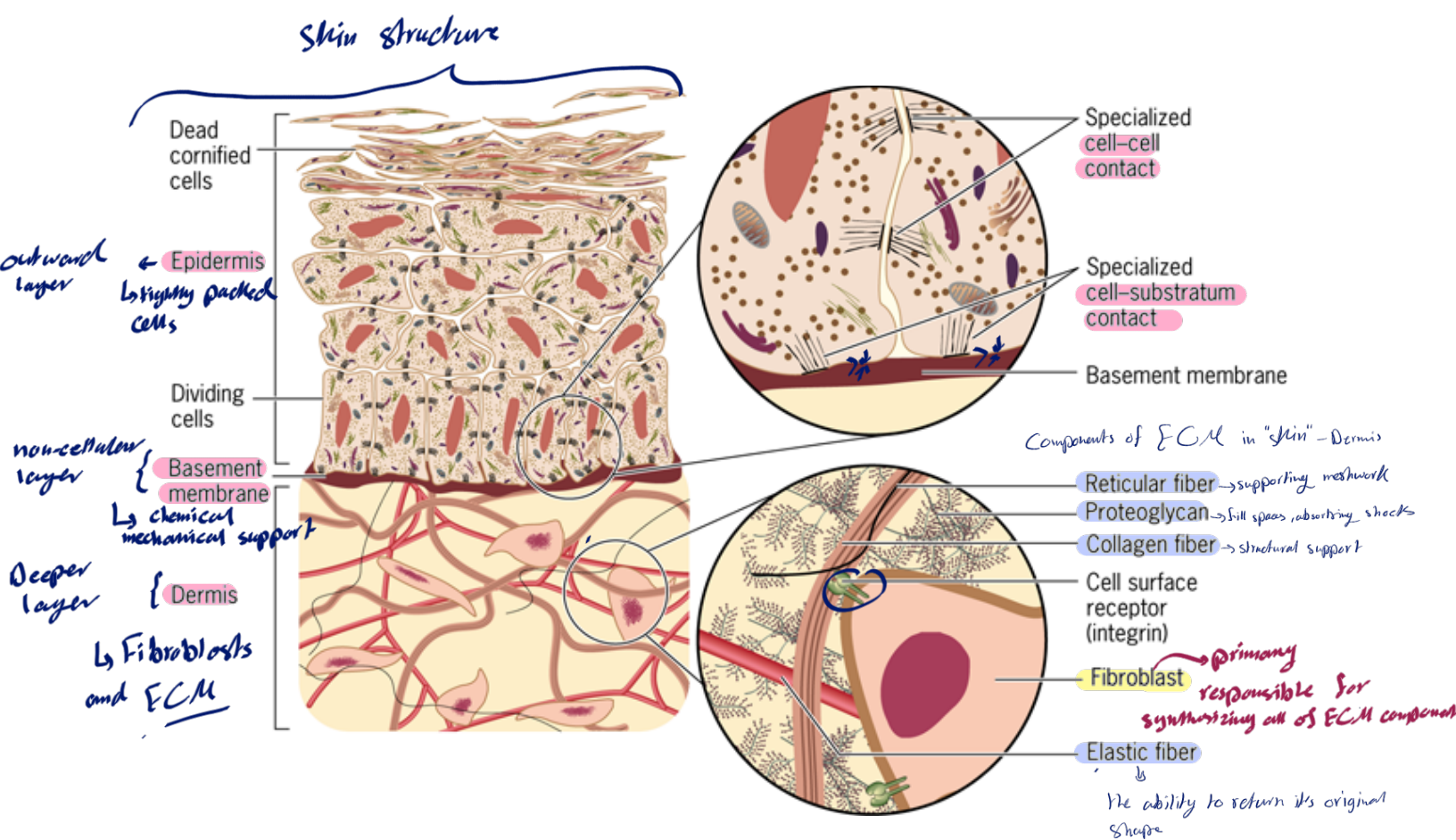
## 7.1 Extracellular Interactions

Although the plasma membrane constitutes the boundary between a living cell and its nonliving environment, materials present outside the plasma membrane play an important role in the life of a cell. Most cells in a multicellular plant or animal are organized into clearly defined tissues in which the component cells maintain a defined relationship with one another and with the extracellular materials that lie between the cells. Even those cells that have no fixed relationship within a solid tissue, such as white blood cells that patrol the body, must interact in highly specific ways with other cells and with extracellular materials with which they come in contact. These interactions regulate such diverse activities as cell migration, cell growth, and cell differentiation, and they determine the three-dimensional organization of tissues and organs that emerges during embryonic development.

We will focus in this chapter on the extracellular environment of cells and the types of interactions in which cells engage. Figure 7.1 shows a diagrammatic section of human skin and provides an overview of several of the subjects to be discussed in the chapter. The outer layer of skin (the epidermis) is a type of epithelial tissue. Like other epithelia, which line the spaces and free surfaces of the body, the epidermis consists largely of closely packed cells attached to one another and to an underlying noncellular layer by specialized contacts (depicted in the top inset of Figure 7.1). These contacts provide a mechanism for cells to adhere to and communicate with one another. In contrast, the deeper layer of the skin (the dermis) is a type of connective tissue. Like other connective tissues, such as those that form a tendon or cartilage, the dermis consists largely of extracellular material, including a variety of distinct fibers that interact in specific ways. A closer look at one of the scattered cells (fibroblasts) of the dermis shows that the outer surface of the plasma membrane contains receptors that mediate interactions between the cell and the components of its environment (depicted in the lower inset of Figure 7.1). These cell-surface receptors interact not only with the external surroundings, but are connected at their internal end to various cytoplasmic proteins. Receptors with this type of dual attachment are well suited to transmitting messages between a cell and its environment.

examples

The role of ECM "in general"



**FIGURE 7.1** An overview of cell organization into tissues and of their interactions with one another and with the extracellular environment. In this schematic diagram of a section through human skin, the cells of the epidermis are seen to adhere to one another by specialized contacts. The basal layer of epidermal cells also adheres to an underlying, noncellular layer (the basement membrane). The dermis consists largely of extracellular elements that interact with each other and with the surfaces of scattered cells (primarily fibroblasts). The cells contain receptors that interact with extracellular materials and transmit signals to the cell interior.

## The Extracellular Matrix

If we begin at the plasma membrane and move outward, we can examine the types of extracellular elements that surround various types of cells. It was noted in Chapter 4 that virtually all integral membrane proteins, as well as certain membrane lipids, bear chains of sugars (oligosaccharides) of variable length that project outward from the plasma membrane (see Figure 4.4a). These carbohydrate projections form part of the **glycocalyx** (or cell coat) on the outer surface of the plasma membrane (Figure 7.2a). This layer is very prominent in some types of cells, such as the epithelial cells that line the mammalian digestive tract and endothelial cells that line blood vessels (Figure 7.2b). The glycocalyx is thought to mediate cell-cell and cell-substratum interactions, provide mechanical protection to cells, serve as a barrier to particles moving toward the plasma membrane, and bind important regulatory factors that act on the cell surface (Figure 7.2c).

*\* To understand properly \**

## Skin Structure

The skin consists of two main layers separated by a basement membrane:

**Epidermis:** The outermost layer, composed of tightly packed cells.

**Basement Membrane:** A thin, non-cellular layer that separates the epidermis from the dermis, serving as both a chemical and mechanical support.

**Dermis:** The deeper layer, characterized by having few cells (such as fibroblasts) and an abundance of Extracellular Matrix (ECM).

*contain receptors*

## The Extracellular Matrix (ECM)

The ECM is the "scaffold" or network in which cells reside, providing tissues with strength and elasticity. It consists of:

1. **Collagen fibers:** Strong proteins that provide structural support and resistance to tension.
2. **Elastic fibers:** These give the skin the ability to return to its original shape after being stretched.
3. **Reticular fibers:** They form a delicate supporting meshwork.
4. **Proteoglycans:** Molecules made of proteins and sugars that act as a "gel" to fill spaces and absorb shocks.
5. **Fibroblasts:** The primary "factory" cells responsible for synthesizing and secreting all the ECM components mentioned above.

## Cellular Interactions

Cells are not isolated; they connect through specific mechanisms (as shown in the magnified circles in the image):

**Specialized cell-cell contact:** Junctions between one cell and another (e.g., the links that hold epidermal cells together to make the skin cohesive).

**Specialized cell-substratum contact:** Connections between a cell and the layer beneath it (e.g., the attachment of epidermal cells to the basement membrane).

**Cell surface receptors (Integrins):** Proteins on the cell membrane that act as "bridges" connecting the cell's interior to the external ECM, transmitting chemical and mechanical signals into the cell.

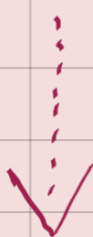
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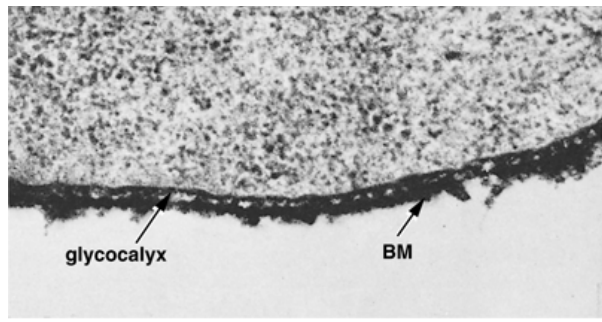
## The Glycocalyx

**Definition:** A coating of sugars (oligosaccharides) attached to membrane proteins and lipids, projecting outward from the cell surface.

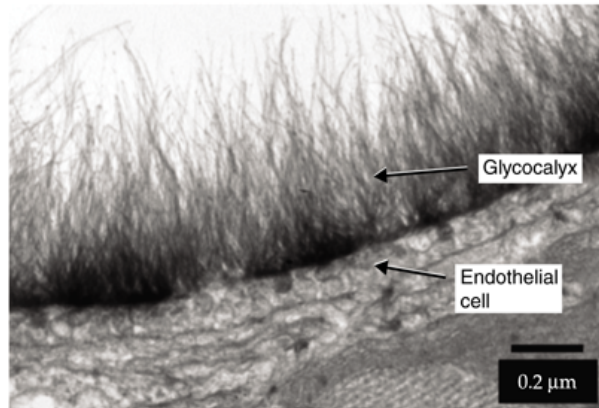
**Importance:**

- A. **Interaction:** Mediates interactions between cells and between a cell and its substratum.
- B. **Protection:** Provides mechanical protection to the plasma membrane.
- C. **Barrier:** Acts as a sieve or barrier, regulating the movement of particles toward the membrane.
- D. **Regulatory Binding:** Binds important regulatory factors (like hormones or growth factors) that act on the cell surface.

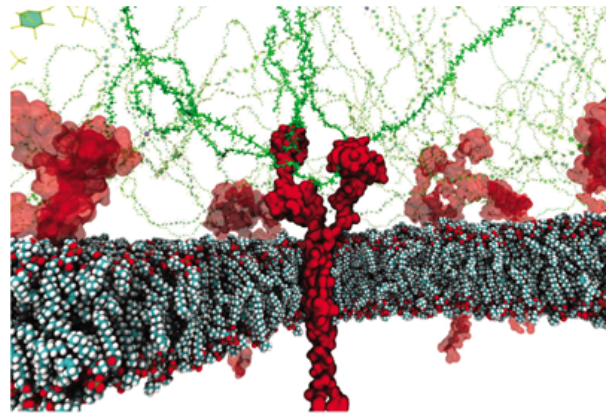




(a)



(b)



(c)

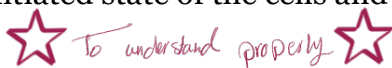
↳ sugar chains "Glycocalyx"

↳ Transmembrane proteins

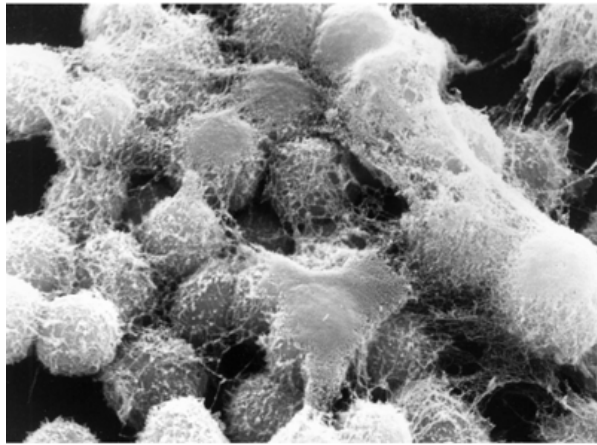
**Source:** (a) From A. Martinez-Palomo, *Int. Rev. Cytol.* 29:64, 1970. ©1970, with permission from Elsevier; (b) By courtesy of B.M. van den Berg, The Einthoven Laboratory for Vascular Medicine, Division of Nephrology, Leiden University Medical Center, Leiden, the Netherlands; (c) Courtesy of Igor Pivkin et al., Università della Svizzera italiana. *Biophys. Journal* 106(1):232–234, 2014, with permission from Elsevier.

**FIGURE 7.2 The glycocalyx.** (a) The basal surface of an ectodermal cell of an early chick embryo. Two distinct structures closely applied to the outer cell surface can be distinguished: an inner glycocalyx (GC) and an outer basement membrane (BM). (b) Electron micrograph of the extensive endothelial glycocalyx in a coronary capillary. (c) Molecular model of the glycocalyx. Sugar chains are shown in green, bound to transmembrane protein in red.

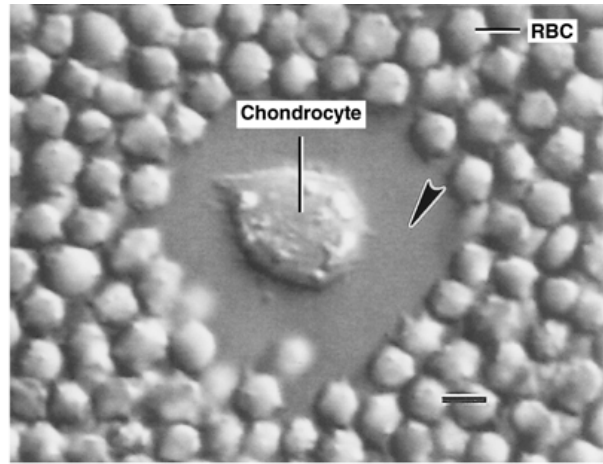
Many types of animal cells produce an **extracellular matrix (ECM)**—an organized network of secreted molecules that provides scaffolding to the cells and tissues it surrounds (**Figure 7.3**). The ECM is more than an inert packing material or a nonspecific glue that holds cells together; it provides physical, biochemical, and mechanical signals that can play key regulatory roles in determining the shape and activities of the cell. For example, enzymatic digestion of the ECM that surrounds cultured cartilage cells or mammary gland epithelial cells causes a marked decrease in the synthetic and secretory activities of the cells. Addition of extracellular matrix materials back to the culture dish can restore the differentiated state of the cells and their ability to manufacture their usual cell products.



While epithelial cells rest on a highly organized basement membrane, other cells—such as **fibroblasts** in connective tissue—are surrounded by a less organized ECM consisting mainly of thread-like fibrils.



(a)



(b)

**Source:** (a) Courtesy Michael Solursh and Gerald Karp; (b) Courtesy of Greta M. Lee, Brian Johnston, Ken Jacobson, and Bruce Caterson.

**FIGURE 7.3** The extracellular matrix (ECM) of cartilage cells. (a) Scanning electron micrograph of a portion of a colony of cartilage cells (chondrocytes) showing the extracellular materials secreted by the cells. (b) The ECM of a single chondrocyte has been made visible by adding a suspension of red blood cells (RBCs). The thickness of the ECM is evident by the clear space (arrowhead) that is not penetrated by the RBCs. The bar represents 10  $\mu\text{m}$ .

الغضائفة

One of the most well-defined extracellular matrices is the **basement membrane** (or basal lamina), a continuous sheet 50 to 200 nm thick that (1) surrounds nerve fibers, muscles, and fat cells; (2) underlies the basal surface of epithelial tissues, such as the epidermis of the skin (Figures 7.1 and 7.4a–b), or the lining of the digestive and respiratory tracts; and (3) underlies the inner endothelial lining of blood vessels. Basement membranes provide mechanical support for the attached cells, generate signals that maintain cell survival, serve as a substratum for cell migration, separate adjacent tissues within an organ, and act as a barrier to the passage of macromolecules. In this latter capacity, basement membranes of the capillaries play an important role in preventing the passage of proteins out of the blood and into the tissues. This is particularly important in the kidney, where the blood is filtered under high pressure through a double-layered basement membrane that separates the capillaries of the glomerulus from the wall of the kidney tubules. Kidney failure in long-term diabetics may result from an abnormal thickening of the basement membranes surrounding the glomeruli. Basement membranes also serve as a barrier to invasion of tissues by cancer cells. The molecular organization of basement membranes is discussed later (see Figure 7.12). Those cells that do not lie on a basement membrane sheet, such as the fibroblasts of a connective tissue, are typically surrounded by a less organized ECM consisting largely of thread-like fibrils (Figure 7.4c).

Just examples  
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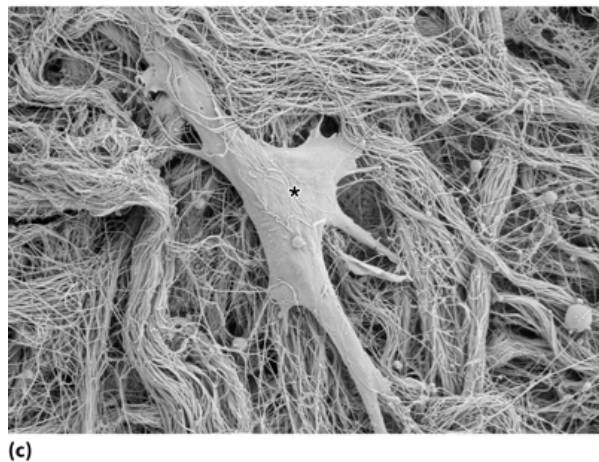
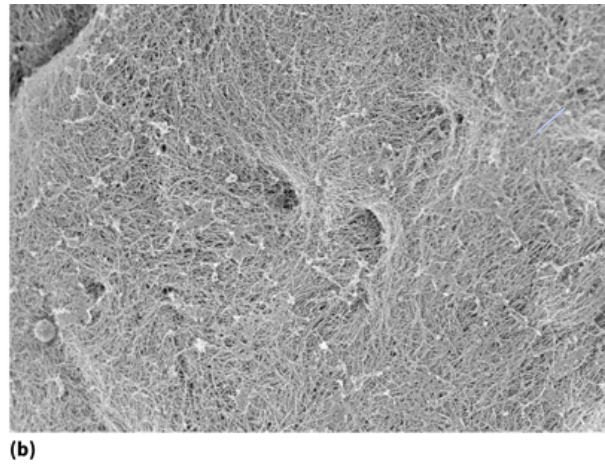
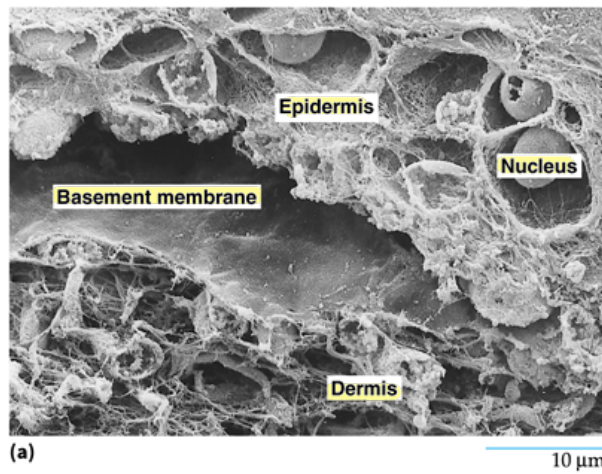
#### The Basement Membrane (Basal Lamina)

##### Description and Location:

It is a continuous, thin sheet ranging from 50 to 200 nm in thickness.

It is found in three primary locations:

- Surrounding nerve fibers, muscles, and fat cells.
- Underlying the basal surface of epithelial tissues (such as the skin/epidermis and the linings of the digestive and respiratory tracts).
- Underlying the inner endothelial lining of blood vessels.

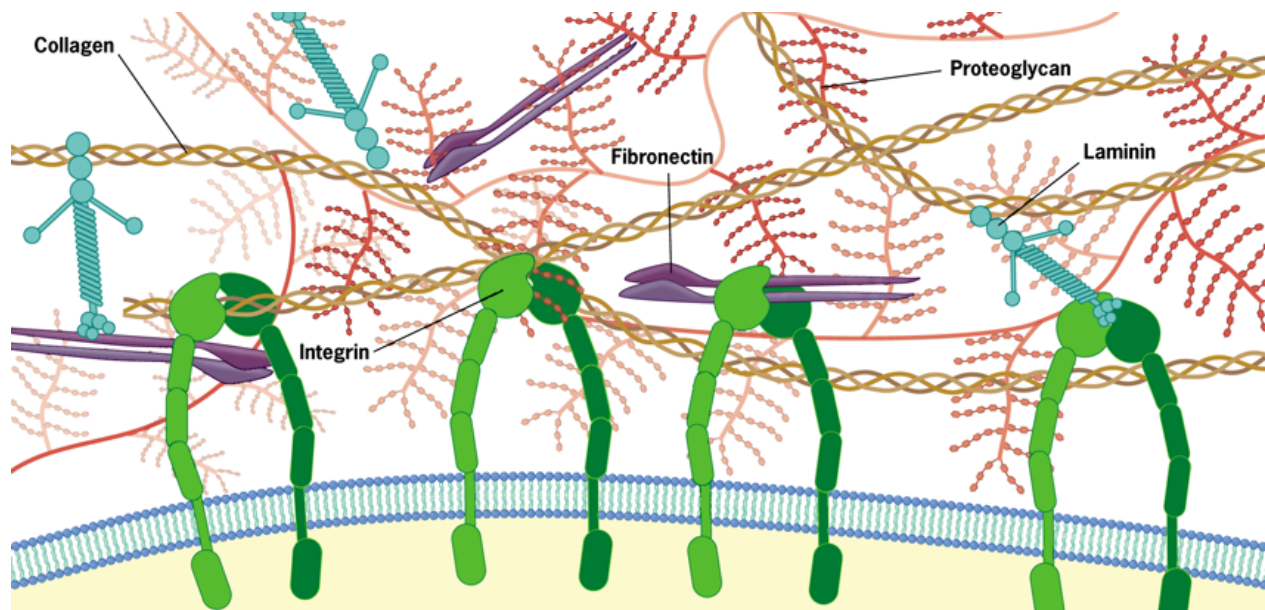


☆ Repeated information ☆

**Source:** (a) Courtesy of Karen Holbrook; (b–c) Reprinted from Stoitzner, P., Pfaller, K. Stössel, H. A Close-Up View of Migrating Langerhans Cells in the Skin. *Journal of Investigative Dermatology* 118: 117–125, 2002, with permission from Elsevier.

**FIGURE 7.4 The basement membrane (basal lamina).** (a) Scanning electron micrograph of human skin. The epidermis has pulled away from part of the basement membrane, which is visible beneath the epidermal cells. (b) The dense network of collagen of the basement membrane is revealed by scanning EM after enzymatic separation of the epidermis. (c) The much looser collagen network of the dermis is visible here, with an adherent fibroblast labeled with an asterisk.

Even though the extracellular matrix may take diverse forms in different tissues and organisms, it tends to be composed of similar macromolecules. Unlike most proteins present inside cells, which are compact, globular molecules, those of the extracellular space are typically extended, fibrous species. These proteins are secreted into the extracellular space where they are capable of self-assembling into an interconnected three-dimensional network, which is depicted in Figure 7.5 and discussed in the following sections. Among their diverse functions, the proteins of the ECM serve as trail markers, scaffolds, girders, wire, and glue. As noted throughout the following discussion, alterations in the amino acid sequence of extracellular proteins can lead to serious disorders.



**FIGURE 7.5** An overview of the macromolecular organization of the extracellular matrix. The proteins and polysaccharides shown in this illustration will be discussed in the following sections. The proteins depicted (fibronectin, collagen, and laminin) contain binding sites for one another, as well as binding sites for receptors (integrins) located at the cell surface. The proteoglycans are huge protein complexes that occupy much of the volume of the extracellular space.

The major components of extracellular matrices include collagens, proteoglycans, and a variety of proteins, such as fibronectin, and laminin. Each of the proteins of the extracellular matrix contains binding sites for one another and for receptors on the cell surface. As a result, these various extracellular materials interact to form an interconnected network that is bound to the cell surface.

## Collagen

**Collagens** comprise a family of fibrous glycoproteins that are present only in extracellular matrices. Collagens are found throughout the animal kingdom and are noted for their high tensile strength, that is, their resistance to pulling forces. It is estimated that a collagen fiber 1 mm in diameter is capable of suspending a weight of 10 kg (22 lb) without breaking. Collagen is the single most abundant protein in the human body—constituting more than 25 percent of all protein—a fact that reflects the widespread occurrence of extracellular materials.

Collagen is produced primarily by fibroblasts, the cells found in various types of connective tissues, but also by smooth muscle cells and epithelial cells. To date, 28 distinct types of human collagen have been identified. Each collagen type is restricted to particular locations within the body, but two or more different types are often present together in the same ECM. Additional functional complexity is provided by mixing several collagen types within the same fiber. These heterotypic fibers are the biological equivalent of a metal alloy. It is likely that different structural and mechanical properties result from different mixtures of collagens in fibers. Although there are many differences among the members of the collagen family, all share at least two important structural features. (1) All collagen molecules are trimers consisting of three polypeptide chains, called  $\alpha$  chains. (2) Along at least part of their length, the three polypeptide chains of a collagen molecule are wound around one another to form a

rod-like triple helix (**Figure 7.6a**). The  $\alpha$  chains of collagen molecules contain large amounts of proline, and many of the proline (and lysine) residues are hydroxylated following synthesis of the polypeptide. The hydroxylated amino acids are important in maintaining the stability of the triple helix by forming hydrogen bonds between component chains. Failure to hydroxylate collagen chains has serious consequences for the structure and function of connective tissues. This is evident from the symptoms of scurvy, a disease that results from a deficiency of vitamin C (ascorbic acid) and is characterized by inflamed gums and tooth loss, poor wound healing, brittle bones, and the weakening of the lining of blood vessels, causing internal bleeding. Ascorbic acid is required as a coenzyme by the enzymes that add hydroxyl groups to the lysine and proline amino acids of collagen.

"Summary"

## 1. What is Collagen?

**Definition:** A family of fibrous glycoproteins found exclusively in extracellular matrices (ECM).

**Abundance:** It is the most abundant protein in the human body, accounting for more than 25% of all proteins.

**Occurrence:** Found throughout the animal kingdom, reflecting its vital role in tissue structure.

## 2. Mechanical Properties (Immense Strength)

Collagen is characterized by very high tensile strength (resistance to pulling forces).

**Example:** A collagen fiber only 1 mm in diameter is capable of suspending a weight of 10 kg without breaking.

## 3. Production and Types

**Sources:** Produced primarily by fibroblasts in connective tissues, as well as by smooth muscle and epithelial cells.

**Diversity:** To date, 28 distinct types of human collagen have been identified.

**Specialization:** While each type is restricted to specific locations, two or more types often coexist within the same ECM to provide functional complexity.

## 4. Molecular Structure

1. **Trimers:** The molecule consists of three polypeptide chains called  $\alpha$  chains.
2. **Triple Helix:** These three chains wind around one another to form a rod-like triple helix.

## 5. Biochemistry and Stability

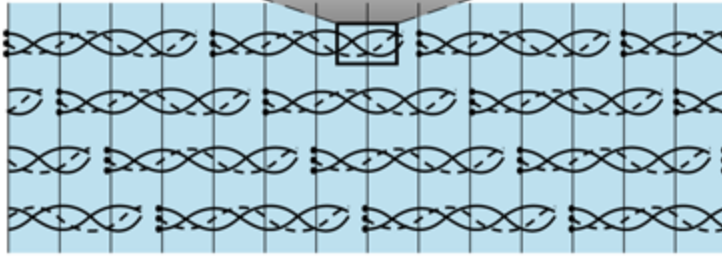
**Amino Acids:** The  $\alpha$  chains contain large amounts of proline and lysine.

**Hydroxylation:** After synthesis, hydroxyl groups (-OH) are added to these amino acids.

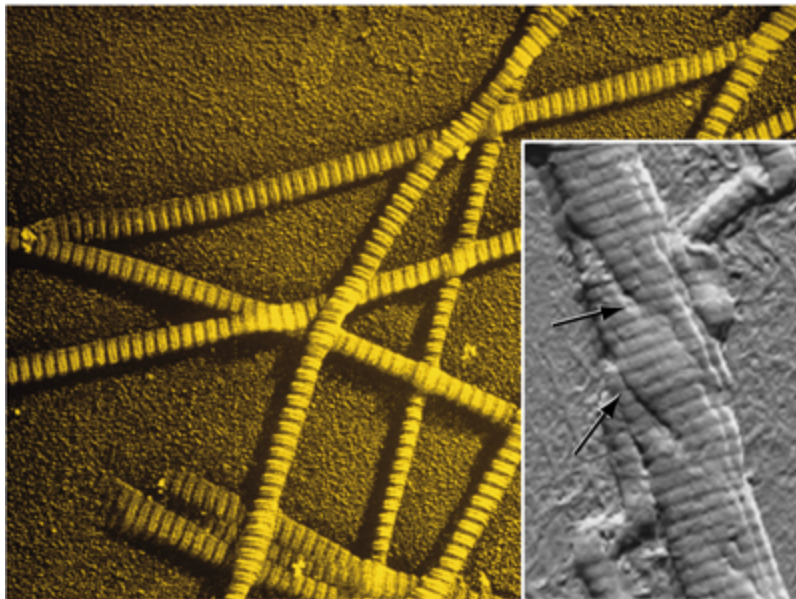
**Importance:** This process is essential for forming hydrogen bonds between the chains, which maintains the stability and strength of the triple helix.



(a)



(b)



(c) 0.3 μm

(d) 250 nm

## 6. Collagen and Scurvy

The text highlights a critical link between collagen and Vitamin C:

**Role of Vitamin C:** It acts as a **coenzyme** for the enzymes responsible for hydroxylating proline and lysine.

**Vitamin C Deficiency:**

Leads to a failure in stabilizing the collagen chains.

**Scurvy Symptoms:** Inflamed gums, tooth loss, poor wound healing, brittle bones, and internal bleeding due to weakened blood vessel linings.

Source: (c) J. Gross/Biozentrum, University of Basel/Science Source; (d) Reprinted From Loren Bozec, et al., *Biophys. J.* 92:71, 2007, with permission from Elsevier.

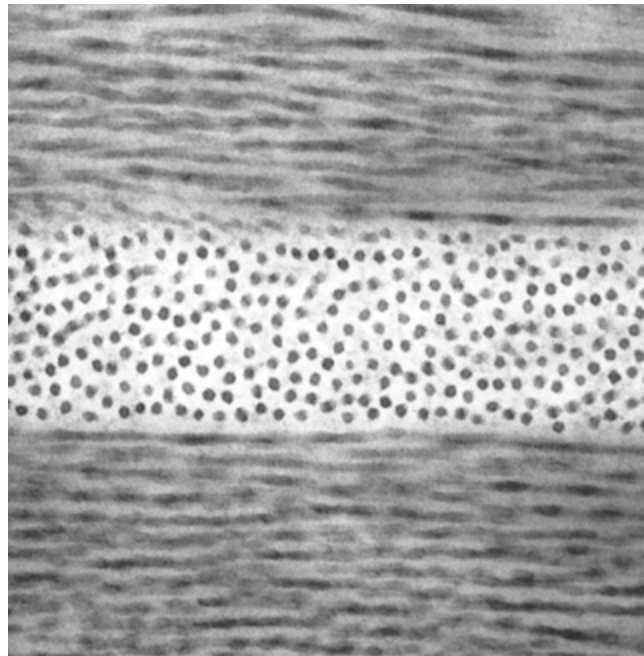
\*Just understand

**FIGURE 7.6 The structure of collagen I.** This figure depicts several levels of organization of a fibrillar collagen. (a) The collagen molecule (or monomer) is a triple helix composed of three helical  $\alpha$  chains. Some types of collagen contain three identical  $\alpha$  chains and thus are homotrimers, while others are heterotrimers containing two or three different chains. Each collagen I molecule is 295 nm in length. (b) Collagen I molecules become aligned in rows in which the molecules in one row are staggered relative to those in the neighboring row. A bundle of collagen I molecules, such as that shown here, forms a collagen fibril. The staggered arrangement of the molecules produces bands (horizontal black lines in the illustration) across the fibril that repeat with a periodicity of 67 nm (which is equal to the length of the gap between molecules plus the overlap). (c) An electron micrograph of human collagen fibrils observed after metal shadowing (see Figure 18.17). The banding pattern of the fibrils is evident. (d) An atomic force micrograph showing the surface of a collagen fibril, which suggests that its subcomponents are twisted spirally around the fibril axis like a rope. The banding pattern remains evident. The arrows point to places where the fibril is slightly unwound, as would occur if you were to twist a rope in the opposite direction it is wound.

A number of the collagens, including types I, II, and III, are described as *fibrillar collagens* because they assemble into rigid, cable-like fibrils, which in turn become packaged into thicker fibers that are typically large enough to be seen in the light microscope. The side-by-side packaging of the rows of collagen I molecules within a collagen fibril is depicted in Figure 7.6b,c. The fibrils are strengthened by covalent cross-links between lysine and hydroxylysine residues on adjacent collagen molecules. This cross-linking process continues through life and may contribute to the decreased elasticity of skin and increased brittleness of bones among the elderly. Recent studies that probe the surface of collagen fibrils suggest that they are composed of strands that are twisted around the axis of the fibril to form a structure that is more like a nanosized rope than a cable (Figure 7.6d).

Among the various components of the ECM, collagen molecules provide the insoluble framework that determines many of the mechanical properties of the matrix. In fact, the properties of a particular tissue can often be correlated with the three-dimensional organization of its collagen molecules. For example, tendons, which connect muscles to bones, must resist tremendous pulling forces during times of muscular contraction. Tendons contain an ECM in which the collagen fibrils are aligned parallel to the long axis of the tendon and thus parallel to the direction of the pulling forces. The cornea is also a remarkable tissue; it must serve as a durable, protective layer at the surface of the eyeball but must also be transparent so that light can pass through the lens to the retina. The thick, middle layer of the cornea is the stroma, which contains relatively short collagen fibrils that are organized into distinct layers. The layered structure of the stroma is similar to that of plywood: the fibrils of each layer are parallel to other fibrils in the layer but nearly perpendicular to the fibrils in the layer on either side (Figure 7.7). This plywood-like structure provides strength to this delicate tissue, while the uniformity of size and ordered packing of the fibrils minimize the scattering of incoming light rays, thereby promoting the tissue's transparency.

In the slide, it's mentioned as a passing example, but understand their role mentioned in lecture



200 nm

**Source:** Reprinted from Nigel J. Fullwood, *Structure* 12:169, 2004, Fig. 1; 2004, with permission from Elsevier.

**FIGURE 7.7** The corneal stroma consists largely of layers of collagen fibrils of uniform diameter and spacing. The molecules of alternate layers are arranged at right angles to one another, resembling the structure of plywood.

Given their abundance and widespread distribution, it is not surprising that abnormalities in fibrillar collagen formation can lead to serious disorders. Burns or traumatic injuries to internal organs can lead to an accumulation of scar tissue, which consists largely of fibrillar collagen. A common condition described as *fibrosis* results from excessive production of collagen-containing connective tissue. Fibrosis occurs most often in the lungs (pulmonary fibrosis) and liver (cirrhosis) where the collagen-containing scar tissue gradually replaces the normal tissue of the organ. Mutations in genes encoding type I collagen can produce *osteogenesis imperfecta*, a potentially lethal condition characterized by extremely fragile bones, thin skin, and weak tendons. Mutations in genes encoding type II collagen alter the properties of cartilage tissue, causing dwarfism and skeletal deformities. Mutations in a number of other collagen genes can lead to a variety of distinct but related defects in collagen matrix structure (called *Ehler-Danlos syndromes*). Persons with one of these syndromes have hyperflexible joints and highly extensible skin.

Not all collagens form fibrils. The distribution of one type of nonfibrillar collagen, type IV, is restricted to basement membranes. Basement membranes are thin, supportive sheets, and the type IV collagen molecules are organized into a network that provides mechanical support and serves as a lattice for the deposition of other extracellular materials (see [Figure 7.12](#)). Unlike type I collagen, which consists of a long, uninterrupted triple helix, the type IV collagen trimer contains nonhelical segments interspersed along the molecule and globular domains at each end. The nonhelical segments make the molecule flexible, while the globular ends serve as sites of interaction between molecules that give the complex its lattice-like character ([Figure 7.8](#)). Mutations in type IV collagen genes have been identified in patients with *Alport syndrome*, an inherited kidney disease in which the glomerular basement

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It discusses  
every class of  
collagen and  
the diseases  
caused by  
abnormalities  
in its structure

membrane (Figure 7.4b) is disrupted.



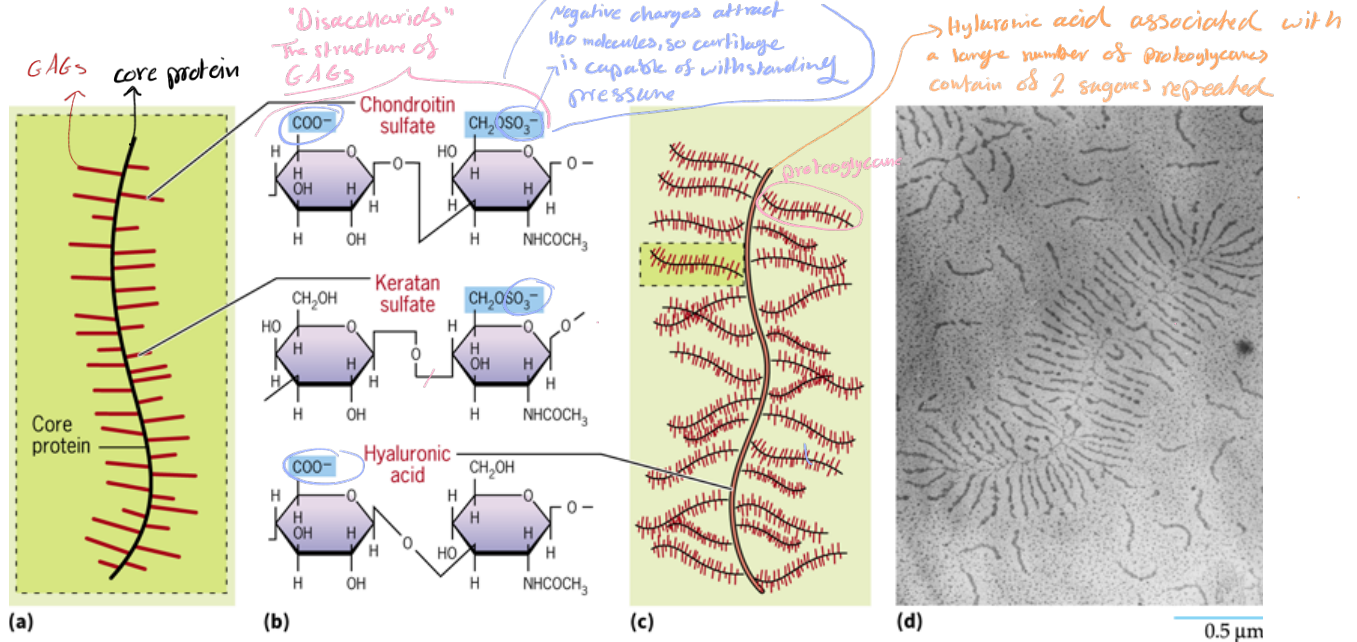
**Source:** ©1987 P D Yurchenco, G C Ruben. Originally published in *The Journal of Cell Biology*  
<https://doi.org/10.1083/jcb.105.6.2559>.

**FIGURE 7.8** The type IV collagen network of the basement membrane. Electron micrograph of a basement membrane from human amniotic tissue that had been extracted with a series of salt solutions to remove noncollagenous materials. The treatment leaves behind an extensive, branching, polygonal network of strands that form an irregular lattice. Evidence indicates that this lattice consists of type IV collagen molecules covalently linked to one another in a complex three-dimensional array. A model of the basement membrane scaffold is shown in Figure 7.12.

→ Just in basement membrane not in Sirtroblast

## Proteoglycans

In addition to collagen, basement membranes and other extracellular matrices typically contain large amounts of a distinctive type of protein-polysaccharide complex called a **proteoglycan**. A proteoglycan (Figure 7.9a) consists of a core protein molecule (shown in black in Figure 7.9a) to which chains of *glycosaminoglycans* (GAGs) are covalently attached (shown in red in the figure). Each glycosaminoglycan chain is composed of a repeating disaccharide; that is, it has the structure -A-B-A-B-, where A and B represent two different sugars. GAGs are highly acidic due to the presence of both sulfate and carboxyl groups attached to the sugar rings (Figure 7.9b). Proteoglycans of the extracellular matrix may be assembled into gigantic complexes by linkage of their core proteins to a molecule of *hyaluronic acid*, a nonsulfated GAG (Figure 7.9c). The microscopic appearance of one of these complexes, which can occupy a volume equivalent to that of a bacterial cell, is shown in Figure 7.9d.



Source: (d) Courtesy Joseph A. Buckwalter.

**FIGURE 7.9** The structure of a cartilage-type proteoglycan complex. (a) Schematic representation of a single proteoglycan consisting of a core protein to which a large number of glycosaminoglycan chains (GAGs, shown in red) are attached. A proteoglycan from cartilage matrix (e.g., aggrecan) may contain about 30 keratan sulfate and 100 chondroitin sulfate chains. Proteoglycans found in basement membranes (e.g., perlecan and agrin) have only a few GAG chains attached to the core protein. (b) The structures of the repeating disaccharides that make up each of the GAGs are shown in this figure. All GAGs bear large numbers of negative charges (indicated by the blue shading). (c) In the cartilage matrix, individual proteoglycans are linked to a nonsulfated GAG, called hyaluronic acid (or hyaluronan), to form a giant complex with a molecular mass of about 3 million daltons. The box indicates one of the proteoglycans of the type shown in part a. (d) Electron micrograph of a proteoglycan complex, comparable to that illustrated in part c, which was isolated from cartilage matrix.

Because of the negative charges borne on the sulfated GAGs, proteoglycans bind huge numbers of cations, which in turn bind large numbers of water molecules. As a result, proteoglycans form a porous, hydrated gel that fills the extracellular space like packing material (Figure 7.5) and resists crushing (compression) forces. This property complements that of the adjacent collagen molecules, which resist pulling forces and provide a scaffold for the proteoglycans. Together, collagens and proteoglycans give cartilage and other extracellular matrices strength and resistance to deformation. The extracellular matrix of bone is also composed of collagen and proteoglycans, but it becomes hardened by impregnation with calcium phosphate salts. Both sulfated and nonsulfated GAGs are taken widely as health supplements with the aim of improving the condition of skin and joints.

In addition to its structural role, proteoglycans are also thought to play an important role in cell-cell signaling. A number of growth factors have been found to bind to proteoglycans, including fibroblast growth factor (FGF) and vascular endothelial growth factor (VEGF). It has been postulated that the ECM may act as a "sink" for growth factors and other signaling molecules, allowing for the formation of a stable signaling gradient.

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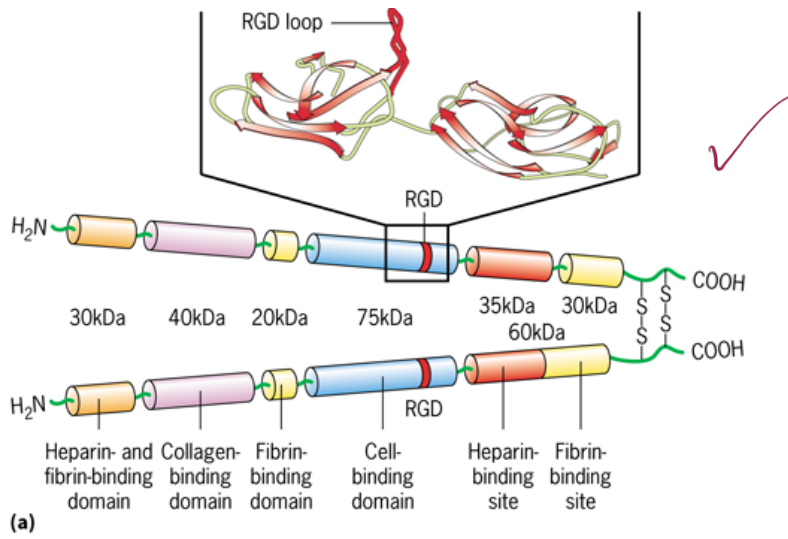
## Fibronectin

The term *matrix* implies a structure made up of a network of interacting components. The term has proven very apt for the extracellular matrix, which contains a number of proteins, that, along with collagen and proteoglycans, interact with one another in highly specific ways (Figure 7.5). *Fibronectin*, like several other proteins discussed in this chapter, consists of a linear array of distinct “building blocks,” or domains, which give each polypeptide a modular construction (Figure 7.10a). Each fibronectin polypeptide is constructed from a sequence of approximately 30 Fn domains, two of which are depicted in the top inset of Figure 7.10a.

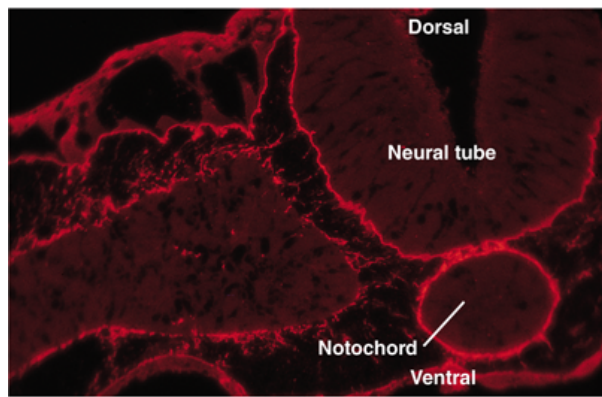
While Fn-type domains were first discovered in fibronectin, they are found as part of many other proteins, ranging from blood clotting factors to membrane receptors (see Figure 7.22). As discussed in Section 2.7, the presence of shared segments among diverse proteins strongly suggests that many present-day genes have arisen during evolution by the fusion of parts of separate ancestral genes. In fibronectin, the 30 or so Fn domains combine to form five or six larger functional units, illustrated by the colored cylinders in Figure 7.10a. Each of the two polypeptide chains that make up a fibronectin molecule contains the following:

1. Binding sites for numerous components of the ECM, such as collagens, proteoglycans, and other fibronectin molecules. These binding sites facilitate interactions that link these diverse molecules into a stable, interconnected network (Figure 7.5). Binding activities of fibronectin molecules are enhanced by mechanical forces that pull on these fibrous proteins and unfold its component modules. Unfolding of these modules exposes binding sites that would otherwise have remained buried.
2. Binding sites for receptors on the cell surface. These binding sites form a stable attachment between the ECM and the cell (Figure 7.5). The importance of a fibronectin-containing substratum for cell attachment is illustrated in Figure 7.10f. The cultured endothelial cell shown in this photo has adopted a shape unlike any it would otherwise have anywhere in the body because it has spread itself over the available surface provided by a square coat of fibronectin.

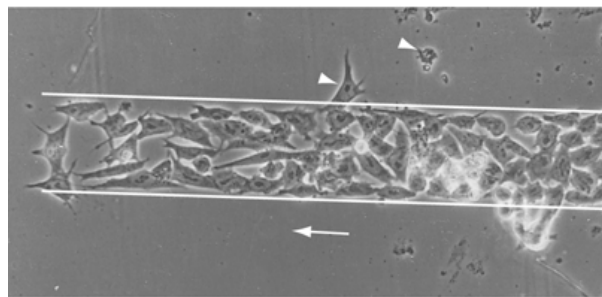
In short: Fibronectin is a "multitasking" protein that binds tissue components together, connects cells to their external environment, and is influenced by physical forces to function more effectively.



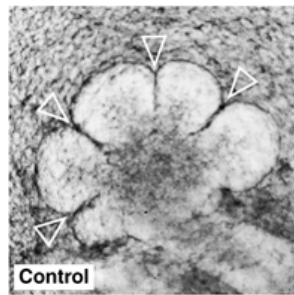
(a)



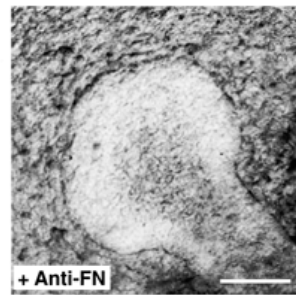
(b)



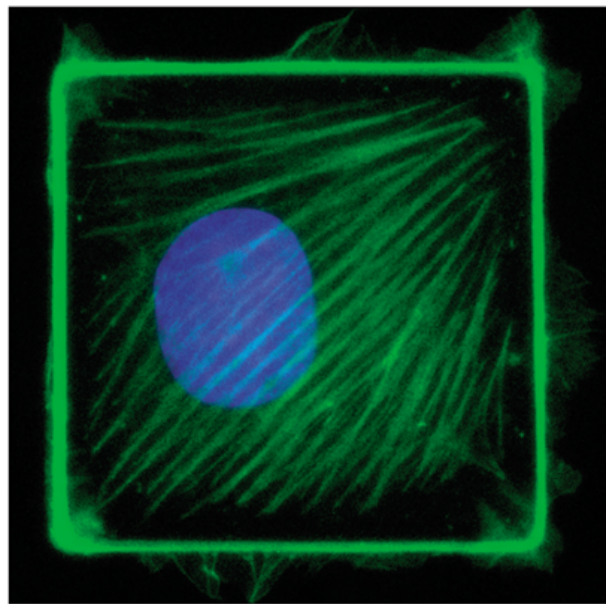
(c)



(d)



(e)



(f)


**Source:** (b) Courtesy James W. Lash; (c) From Giovanni Levi, Jean Loup Duband and Jean Paul Thiery, *Int. Rev. Cytol.* 123: 213, 1990; (d–e) Reprinted by permission from Springer Nature: Takayoshi Sakai et al. *Nature* 423: 876–881, 2003; (f) Reprinted from *Trends Cell Biol.*, vol. 9. From Christopher Chen, Clifford Brangwynne and Donald E. Ingber, “Squaring up to the cell.. shape debate,” p. 283, 1999, with permission of Elsevier.

**FIGURE 7.10** Structure of fibronectin and its importance during embryonic development. (a) A human fibronectin molecule consists of two similar, but nonidentical, polypeptides joined by a pair of disulfide bonds located near the C-termini. Each polypeptide is composed of a linear series of distinct modules, which are organized into several larger functional units, illustrated by the colored cylinders in this figure. Each of these functional units contains one or more binding sites for either a specific component of the ECM or for the surface of cells. Some of these binding activities are indicated by the labels. The cell-binding site of the polypeptide that contains the sequence arg-gly-asp, or RGD, is indicated. As discussed later in the chapter, this sequence binds specifically to a particular class of integral plasma membrane proteins (integrins) that are involved in cell attachment and signal transduction. The inset shows two of the 30 or so repeating Fn modules that comprise the polypeptide; the RGD sequence forms a loop of the polypeptide, protruding from one module. (b) A section through a young chick embryo that has been treated with fluorescent antibodies against fibronectin. Fibronectin is present as fibrils in the basement membranes (dark red sites) that lie beneath the embryonic epithelia and provide a substratum over which cells migrate. (c) In this micrograph, neural crest cells are migrating out from a portion of the developing chick nervous system (beyond the edge of the photo) onto a glass culture dish that contains strips of fibronectin-coated surface alternating with strips of bare glass. The boundary of a fibronectin-coated region is indicated by the white lines. It is evident that the cells remain exclusively on the fibronectin-coated surface. Cells that reach the glass substratum (arrowheads) tend to round up and lose their migratory capabilities. The arrow indicates the direction of migration. (d, e) The role of fibronectin in the formation of the embryonic salivary gland. The micrograph in *d* shows a mouse embryonic salivary gland that has been grown for 10 hours in culture. The gland is seen to be divided into separate buds by a series of clefts (open triangles). The gland shown in *e* has been grown for the same period of time in the presence of an anti-fibronectin antibody, which has completely inhibited cleft formation. Scale bar equals 100  $\mu\text{m}$ . (f) Fluorescence micrograph of an endothelial cell—a type of cell that lines the inner surface of blood vessels. The cell is square because it has spread itself over a tiny square-shaped patch of an adhesive protein called fibronectin that was applied to a culture dish. The cell appears to be mounted in a green frame because it was treated with a green fluorescent antibody that binds to the cytoplasmic protein actin, a component of the cytoskeleton.

The importance of fibronectin and other extracellular proteins is particularly evident during embryonic development. Development is characterized by waves of cell migration during which different cells follow different routes from one part of the embryo to another (**Figure 7.11a**). Migrating cells are guided by proteins, such as fibronectin, that are contained within

## 1. Fibronectin Structure

**Polypeptides:** A human fibronectin molecule consists of two **similar polypeptide chains**.

**Disulfide Bonds:** These two chains are **joined together by disulfide bonds located near the C-termini.** → 

**Modules:** The protein is composed of functional units called "modules," which contain binding sites for either specific components of the Extracellular Matrix (ECM) or the cell surface.

**RGD Sequence:** This is a tripeptide sequence (**arginine-glycine-aspartic acid**) within fibronectin. It is responsible for binding to plasma membrane proteins called **integrins**, which facilitates cell attachment and signal transduction.

*\* Just reading \**

## 2. The Role of Fibronectin in Embryonic Development

The text describes experiments illustrating how the embryo depends on this protein:

**Cell Migration:** In chick embryos, fibronectin acts as a "pathway" for migrating cells (such as neural crest cells). Experiments show that cells move exclusively on fibronectin-coated surfaces; if they reach bare glass, they stop moving and lose their migratory capabilities.

**Organ Formation (Morphogenesis):** In mouse embryonic salivary glands, fibronectin helps form the **clefts** that divide the gland into lobes. When anti-fibronectin antibodies were added to inhibit its function, cleft formation was completely stopped.

## 3. Impact on Cell Shape

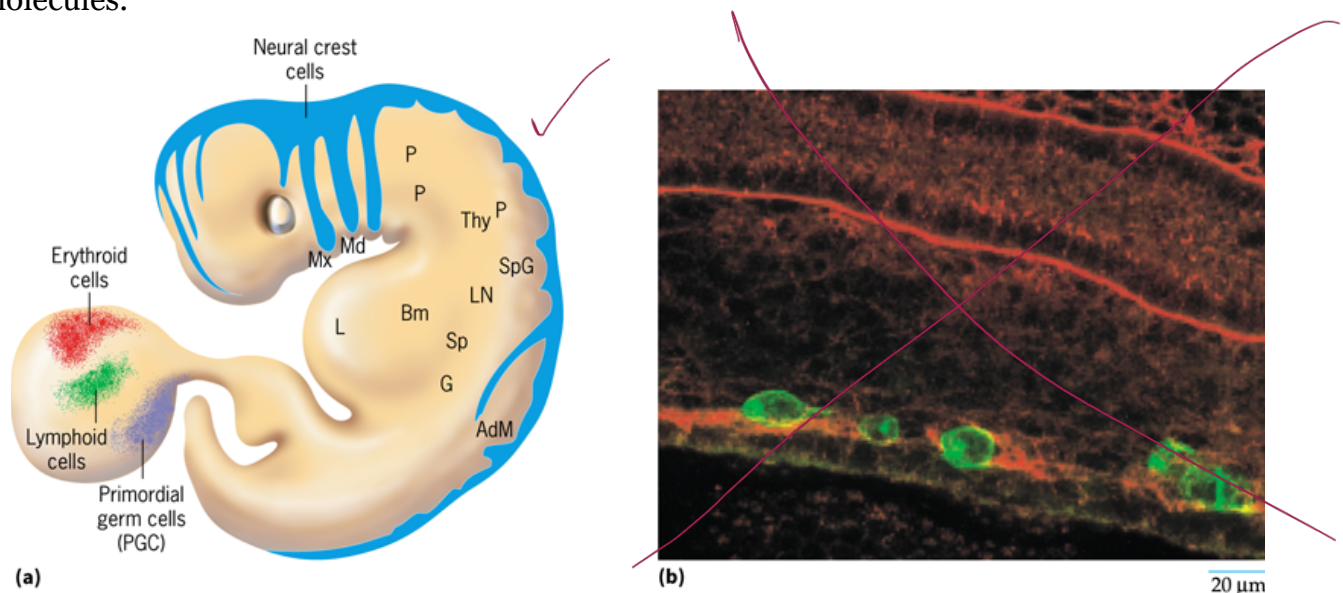
Part(f) indicates that a cell assumes the shape of the surface it adheres to. If a cell is placed on a square-shaped patch of fibronectin, it will spread itself out to become perfectly **square**. This proves that adhesion to the ECM determines the arrangement of the **actin cytoskeleton**.

*In short ---*

Summary of Importance:

1. **Attachment:** It links cells to the ECM via the RGD sequence and integrin proteins.
2. **Guidance:** It serves as a roadmap for migrating cells during embryonic growth.
3. **Morphogenesis:** It contributes to organ formation and defines the physical shape of individual cells.

the molecular landscape through which they pass. For example, the cells of the neural crest, which migrate out of the developing nervous system into virtually all parts of the embryo, traverse pathways rich in fibrils composed of interconnected fibronectin molecules (Figure 7.10b). The ability of these fibronectin pathways to direct neural crest cell migration can be demonstrated on a culture dish as shown in Figure 7.10c. A number of organs of the body, including the salivary gland, kidney, and lung are formed by a process of branching in which the epithelial layer becomes divided by a series of clefts (Figure 7.10d). The importance of fibronectin in the formation of these clefts is illustrated in Figure 7.10e, which shows a salivary gland that has been incubated with antibodies that bind to fibronectin. Cleft formation and branching is entirely abolished as a result of the inactivation of fibronectin molecules.



**Source:** (a) A. A. Moscona & R. E. Hausman, *Cell and Tissue Interactions*, J. W. Lash & M. M. Burger (Eds.), Raven Press, 1977 ISBN: 0890041806; (b) ©1997 Martin J. Garcia-Castro et al. Originally published in *The Journal of Cell Biology* <https://doi.org/10.1083/jcb.138.2.471>.

**FIGURE 7.11** The role of cell migration during embryonic development. (a) A summary of some of the cellular traffic occurring during mammalian development. The most extensive movements are conducted by the neural crest cells (shown in blue), which migrate out of the neural plate in the dorsal midline of the embryo and give rise to all the pigment cells of the skin (P), the sympathetic ganglia (SpG), adrenal medulla (AdM), and the cartilage of the embryonic skull (Mx, Md for maxillary and mandibular arches). The primordial germ cells (PGC) migrate from the yolk sac to the site of gonad (G) formation within the embryo. The progenitors of lymphoid cells are transported to the liver (L), bone marrow (Bm), thymus (Thy), lymph nodes (LN), and spleen (Sp). (Note: The “pathways” shown here connect the original sites of cells with their destinations; they do not accurately depict the actual routes of the cells.) (b) Micrograph of a section of a portion of the hind gut of a 10-day mouse embryo. The primordial germ cells (green) are seen to be migrating along the dorsal mesentery on their way to the developing gonad. The tissue has been stained with antibodies against the protein laminin (red), which is seen to be concentrated in the surface over which the cells are migrating.

## The Role of Fibronectin Protein

Cell migration depends on the molecular environment through which the cells pass. The primary protein here is **fibronectin**, which forms interconnected fibrils that act as pathways for the cells.

**Neural Crest Cells:** These cells migrate from the developing nervous system to various parts of the embryo via pathways rich in fibronectin.

**Organ Formation:** Organs such as the salivary glands, kidneys, and lungs grow through a process called **branching**. Experiments have shown that when fibronectin is inactivated, the branching process stops completely, and these organs do not form properly.

## Key Vocabulary |

**Cell Migration:** هجرة الخلايا

**Molecular Environment:** البيئة الجزيئية

**Interconnected Fibrils:** ألياف مترابطة

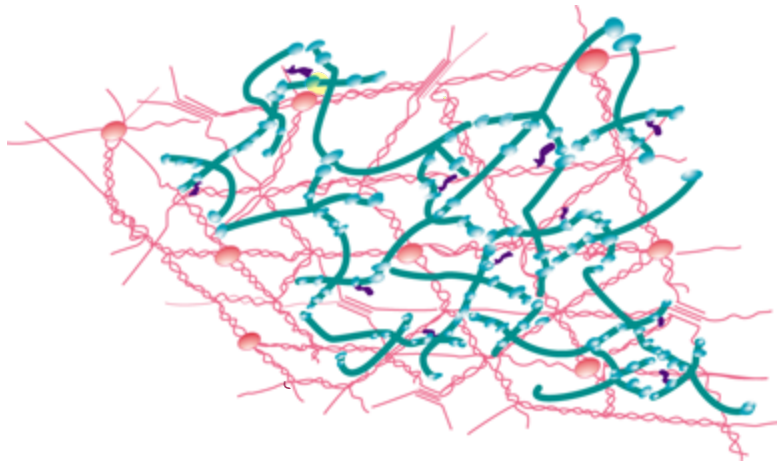
**Neural Crest Cells:** خلايا العرف

## Laminin

جذوة - germ → covalent bond

Laminins are a family of extracellular glycoproteins that consist of three different polypeptide chains linked by disulfide bonds and organized into a molecule resembling a cross with three short arms and one long arm (Figure 7.5). At least 15 different laminins have been identified. Like fibronectin, extracellular laminins can greatly influence a cell's potential for migration, growth, and differentiation. For example, laminins play a critical role in the migration of primordial germ cells (Figure 7.11a). These cells arise in the yolk sac, which is located outside the embryo itself, and then migrate by way of the bloodstream and embryonic tissues to the developing gonad, where they eventually give rise to sperm or eggs. During their migration, the primordial germ cells traverse surfaces that are particularly rich in laminin (Figure 7.11b). Primordial germ cells possess a cell surface protein that adheres strongly to one of the subunits of the laminin molecule. The influence of laminin on nerve outgrowth is shown in Figure 9.42.

In addition to binding tightly to cell-surface receptors, laminins can bind to other laminin molecules, to proteoglycans, and to other components of basement membranes (Figure 7.5). The laminin and type IV collagen molecules of basement membranes are thought to form separate, but interconnected, networks, as depicted in Figure 7.12. These interwoven networks give basement membranes both strength and flexibility. In fact, basement membranes fail to form in mouse embryos that are unable to synthesize laminin, causing the death of the embryo around the time of implantation.



**Source:** Adapted from Rockefeller University Press. Originally published in *The Journal of Cell Biology* 117:1132.

**FIGURE 7.12** A model of the basement membrane scaffold. Basement membranes contain two network-forming molecules, collagen IV (pink), which was illustrated in Figure 7.8, and laminin (green), which is indicated by the thickened cross-shaped molecules. The collagen and laminin networks are connected by entactin molecules (purple).

## Dynamic Properties of the Extracellular Matrix

The micrographs and diagrams presented in the first section of this chapter portray the extracellular matrix (ECM) as a static structure. In actuality, the ECM can exhibit dynamic properties, both in space and time. Spatially, for example, ECM fibrils can be seen to stretch several times their normal length as they are pulled on by cells and contract when tension is relieved. Temporally, the components of an ECM are subject to continual degradation and

# ☆ جدول مهم جداً للتميز بين مكونات الـ ECM ... كل المعلومات

## الأساسية والتي يتكلمنا عنهم ... أرجو قبل الإمتحان

\* مجلس عالٍ

### مقارنة بين مكونات الإكستراسلولر ماتريكس (ECM)

Arabic

المكوّن	الكولاجين (Collagen)	اللامينين (Laminin)	البروتيوجلاكان (Proteoglycan)	الفايبرونيكتين (Fibronectin)
<b>التركيب (Structure)</b>	ثلاث سلاسل ببتيدية (α) ملتفة حلزونيّاً لتكوين ليف ثلاثي ألياف طويلة غير متفرعة	جليكوبروتين على شكل صليب (Cross) مكون من 3 سلاسل: α, β, γ سلسلة طويلة مع 3 أذرع	يتكون من بروتين أساسي مرتبط بسلاسل جليكوزامينوجليكان (GAGs) طويلة غير متفرعة (مثل: هيباران سلفات، كوندرويتين سلفات، كيراتان سلفات)	جليكوبروتين ثنائي (Dimer) مرتبط بروابط ثنائية الكبريت يتكون من وحدات وظيفية متعددة
<b>الخصائص البنيوية التمييزية</b>	• قوة شد عالية جداً • ألياف سمكية (Fibrillar) • مقاوم للتمدد	• غير ليفي (Non-fibrillar) • قدرة على تكوين شبكات • موجود في الصفائح القاعدية	• سلاسل GAGs سالبة الشحنة بشدة • يكون هلاماً ممتائاً (Hydrated gel) • يشغل حجراً كبيراً بسبب الماء المرتبط	• غير ليفي • جزء ثنائي مرن • يحتوي على مواقع ارتباط متعددة
<b>الأهمية</b>	أكثر بروتين وفرة في الجسم يوفر القوة والدعم الميكانيكية للأنسجة	مكون أساسي في الصفائح القاعدية ضروري لتنظيم الخلايا وبنائها	يسمح بترطيب الأنسجة ومقاومة الضغط يساعد في الانتشار والنقل الجزيئي	يربط الخلايا بالمصفوفة يلعب دوراً مهماً في الالتصاق والهجرة الخلوية
<b>الدور</b>	دعم بنيوي ومقاومة الشد يحافظ على سلامة الأنسجة	تكوين الصفائح القاعدية تنظيم تمايز الخلايا، الهجرة، البقاء	مقاومة الانضغاط تنظيم الترشيح والانتشار تخزين عوامل النمو	الالتصاق الخلوي الهجرة الخلوية تنظيم نمو الأنسجة وإصلاحها
<b>الوظيفة</b>	• يعطي الأنسجة قوة شد عالية • يحافظ على الشكل البنيوي • يقاوم التمزق والتمدد	• يربط الخلايا بالصفائح القاعدية • ينظم سلوك الخلايا (التصاق، تمايز، هجرة، بقاء (Survival))	• يمتص الماء ويكون هلاماً مرناً • يسمح بانتشار المغذيات والفضلات • يعمل كمخزن لعوامل النمو والسيوتوكينات	• يربط الخلايا بمكونات الـ ECM الأخرى (الكولاجين، البروتيوجلاكان ...) • مهم في التنام الجروح • يوجه حركة الخلايا
<b>أماكن التواجد الرئيسية</b>	الأدمة، العظام، الغضاريف، الأوتار، الأربطة، جدران الأوعية الدموية، القرنية، الأنسجة الليفيّة	الصفائح القاعدية في جميع الأنسجة (تحت الظهارات، حول العضلات، العصب، الدهن، الشوان)	الغضاريف، العظم، الجلد، القرنية، الأوعية الدموية، الأنسجة الرخوة (في المادة الأساسية)	البلازما، الأنسجة الرخوة، الجروح، حول الخلايا المهاجرة، الصفائح القاعدية، السائل النسيجي
<b>التفاعلات والأرباطات</b>	يرتبط مع نفسه ليكون أليافاً يرتبط مع البروتيوجلاكان والفايبرونيكتين وعوامل أخرى	يرتبط مع الكولاجين نوع IV، البروتيوجلاكان (بيرليكان)، مستقبيلات الخلايا (Integrins)	يرتبط مع الحمض الهيالوروني والبروتينات الرابطة يرتبط مع الكولاجين، اللامينين، الفايبرونيكتين	يرتبط مع الإنتجرينات على سطح الخلايا يرتبط مع الكولاجين، البروتيوجلاكان، الهيباران سلفات، اللامينين
<b>ملاحظات إضافية</b>	يوجد أكثر من 28 نوعاً (I, II, III, IV, V ...)	يوجد عدة نظائر (Isoforms) تختلف حسب نوع النسيج	تنوع كبير في أنواع الـ GAGs يحدد وظيفة البروتيوجلاكان	موجود أيضاً بشكل ذائب في البلازما (المصدر الرئيسي: الكبد)

جميع هذه المكونات تعمل معاً بشكل تكاملي لتكوين بيئة خارج خلوية ديناميكية تدعم البنية، الوظيفة، والتواصل الخلوي.

### Comparison Between Extracellular Matrix (ECM) Components English

Aspect	Fibronectin (Fibronectin)	Proteoglycan (Proteoglycan)	Laminin (Laminin)	Collagen (Collagen)
<b>Structure (Structure)</b>	Dimeric glycoprotein linked by disulfide bonds. Composed of multiple domains and multiple functions.	Consists of a core protein to which one or more GAG (glycosaminoglycan) chains are covalently attached. (Examples: heparan sulfate, chondroitin sulfate, keratan sulfate)	Cross-shaped glycoprotein composed of 3 chains (α, β, γ). A long peptide chain with 3 arms.	Three polypeptide chains (α) twisted into a triple helix. Long, fibrous, non-branched chains.
<b>Distinguishing Features</b>	• Non-fibrous • Dimeric unit • Found at multiple attachment sites	• GAG chains are highly negatively charged • Form a hydrated gel • Greatly bind and retain water	• Non-fibrillar • Forms network-like structures • Present in basal lamina	• Very high tensile strength • Fibrillar fibers • Resistant to stretching
<b>Importance (Importance)</b>	Links cells to the matrix and plays an important role in adhesion, cell migration and wound healing.	Provides tissue hydration and resistance to compression and helps in diffusion and filtration.	A major component of basal lamina essential for the organization and structural integrity of cells.	Most abundant protein in the body. Provides strength and mechanical support to tissues.
<b>Role (Role)</b>	Cell adhesion Cell migration Regulation of tissue growth and repair	Resists compression Regulates signaling and proliferation Stores growth factors	Forms basal lamina Organizes cell polarity, migration and survival	Provides structural support Maintains tissue integrity Wound healing and repair
<b>Function (Function)</b>	• Binds cells to other ECM components (collagen, proteoglycans, ...) • Important in wound healing • Supports cell migration	• Attracts and retains water • Allows diffusion of nutrients and wastes • Stores growth factors and cytokines	• Binds cells to the basal lamina • Regulates cell behavior (adhesion, migration, survival)	• Gives tissues high tensile strength • Maintains the structural shape • Resists stretching and tearing
<b>Main Locations (Main Locations)</b>	Plasma, wound healing, around migrating cells, basal lamina, basal connective tissue.	Cartilage, bone, cornea, skin, blood vessels, loose connective tissue (in the ground substance).	Basal lamina of all tissues (under epithelia, around muscles, nerves, fat, glands, Schwann cells).	Skin, bone, tendons, ligaments, blood vessels, loose connective tissue, cornea, basement membrane.
<b>Interactions and Associations</b>	Binds to cell surface integrins. Binds to collagen, proteoglycans, heparan sulfate, laminin.	Binds to hyaluronic acid and link proteins. Binds to collagen, laminin, fibronectin.	Binds to collagen type IV, proteoglycans (perlecan), and cell surface integrins.	Binds to itself to form fibers. Binds to proteoglycans and fibronectin and other factors.
<b>Additional Notes (Additional Notes)</b>	Exists in a soluble dimeric form in plasma (major source: liver).	Large variety of GAG types determines the function of proteoglycans.	Has several isoforms that differ by tissue type.	More than 28 types (I, II, III, IV, V ...). Type I is the most abundant in the body.

All of these components work together to form a dynamic extracellular environment that supports cell structure, function, and communication.

reconstruction. These processes serve to renew the matrix and to allow it to be remodeled during embryonic development or following tissue injury. Even the calcified matrix of our bones, which we think of as a stable, inert structure, is subject to continual restoration.

The degradation of extracellular materials, along with cell surface proteins, is accomplished largely by a family of zinc-containing enzymes called **matrix metalloproteinases (MMPs)**, which are either secreted into the extracellular space or anchored to the plasma membrane. As a group, MMPs can digest nearly all of the diverse ECM components, although individual family members are limited as to the types of extracellular molecules they can attack. The physiological roles of MMPs are not well understood, but they are thought to be involved in tissue remodeling, embryonic cell migration, wound healing, and the formation of blood vessels. As might be expected from enzymes with the normal function of destroying extracellular materials, the excessive or inappropriate activity of MMPs is likely to cause disease. In fact, MMPs have been implicated in a number of pathological conditions, including arthritis, tooth and gum disease, formation of blood clots and heart attack, and tumor progression. (See the Human Perspective feature on the role of cell adhesion in inflammation and metastasis in [Section 7.4](#).) At least three inherited skeletal disorders have been traced to mutations in MMP genes.

### Review

1. Distinguish among the glycocalyx, a basement membrane, and the extracellular matrix of cartilage tissue.
2. Contrast the roles of collagen and proteoglycans in the extracellular space. How do fibronectin and laminin contribute to embryonic development?
3. List a few of the functions of the extracellular matrix in animal tissues.

## 7.2 Engineering Linkage: Organoids

The idea of growing human organs in a laboratory might sound like the stuff of science fiction. In fact, the engineering of organoids, three-dimensional (3D) cellular structures that resemble organs in both development and organization, has made significant advances in recent years and has numerous promising applications in the lab as well as the clinic.

Several different methods support the growth of 3D cell cultures. Cells are typically derived from stem cells, which can be tissue-specific stem cells from a mature organism (such as stem cells from adult intestinal crypts), embryonic stem cells, or induced pluripotent stem cells. These cells are then grown in a thick, gel-like medium containing a complex mixture of extracellular matrix proteins and other components that encourage cellular growth (the most well known is sold as Matrigel™). Depending on the organ that is being recapitulated, different cocktails of growth factors and additional extracellular matrix components must be added during organoid development. The end result is a small clump of tissue that can often approximate a full-sized organ in different ways.

In recent years, researchers have made progress in developing organoids from a variety of different tissues, including the intestine, stomach, pancreas, optic cup, and brain. How closely these organoids match with the parental tissue varies, but typically organoids can recapitulate many aspects of 3D architecture, tissue development, and cellular differentiation. In the case of intestinal organoids, for example, villus-like epithelia with