Chapter 2
The Extracellular Matrix

Abstract The extracellular matrix is the ordered macromolecular network, on the surface of which and inside the tissue cells are attached to it and to each other, migrate, proliferate or survive. The matrix is composed of protein–carbohydrate complexes, which, in particular, include the glycoproteins carrying out mainly structural or mainly adhesive functions. The extracellular matrix is not only a mechanical framework but also a regulator of cell behavior. The matrix proteins are bound with the specific cell surface receptors resulting in the cell–matrix adhesion, which exerts effect on cell shapes, migration, proliferation, cell survival, and metabolism.

In multicellular animal organisms, the majority of tissue cells are surrounded by the complex orderly network of interconnected extracellular macromolecules termed the *extracellular matrix*. The matrix consists of secreted complex molecules containing covalently attached protein and carbohydrate moieties; these matrix macromolecules are called protein–carbohydrate complexes. The extracellular matrix also includes highly specialized structures, such as cartilage, tendons, basement membranes, and also (with secondary deposition of calcium phosphate crystals) bones and teeth.

The matrix macromolecules are produced and secreted by fibroblasts in connective tissue, chondroblasts in cartilage, osteoblasts in bone, histiocytes (macrophages in connective tissue), mast cells, epithelial cells in parenchymal organs, muscle cells, and endothelial cells of blood vessels. Molecular composition of the matrix is also influenced by white blood cells, which can migrate from blood vessel into the matrix in response to the specific stimuli.

The molecular composition of the extracellular matrix includes several classes of the protein–carbohydrate complexes. The carbohydrate component content in these complexes may vary from less than 10% to more than 95%.

(a) *Proteoglycans* are composed of the proteins (called core proteins) covalently attached to long nonbranched chains of polysaccharides, *glycosaminoglycans*. The polysaccharide content is more than 95% in the proteoglycans.

Y.A. Rovensky, *Adhesive Interactions in Normal and Transformed Cells*,
DOI 10.1007/978-1-61779-304-2_2, © Springer Science+Business Media, LLC 2011

Glycosaminoglycans include several families: hyaluronic acid (which is in a free state, not bound to the protein), chondroitin sulfates, dermatan sulfates, keratan sulfates, heparin, and heparan sulfates.

Owing to their high hydrophilia, glycosaminoglycans occupy large volumes in tissues, forming strongly hydrated gels that cause tissue turgor (resilience). The turgor gives the tissue an ability to resist compression forces. For example, an articular cartilage can resist mechanical pressures of a hundred atmospheres.

Proteoglycans can form huge polymeric complexes in the extracellular matrix. Besides providing tissue turgor, proteoglycans can also be connected to other extracellular matrix proteins forming complex structures, e.g., basement membranes.

Proteoglycans, such as heparan sulfate proteoglycans, are able to bind to and interact with a variety of proteins, including growth factors, some extracellular matrix components, and other molecules. Heparan sulfate proteoglycans can be involved in intracellular signaling as cell surface receptors or coreceptors for multiple ligands to modulate the distinct signal transduction pathways [1–4]. For instance, *syndecans*, which are members of the heparan sulfate proteoglycan family, act as coreceptors for growth factors in conjunction with cell surface integrin receptors and are involved in the regulation of cell–extracellular matrix adhesion and migration [5–9].

(b) *Glycoproteins and proteoglycans* consist of proteins with attached oligosaccharides. Glycoproteins and proteoglycans are similar in their structures and differ only in their carbohydrate content, which is significantly lower in glycoproteins (less than 10%, in comparison with 10–50% in proteoglycans).

In contrast to proteoglycans, the carbohydrate component in glycoproteins is represented by short branched oligosaccharides, often with sialic acid at their ends.

The most important glycoproteins of the extracellular matrix are represented by proteins of two functional types:

- Collagen and elastin proteins that are mainly structural.
- Fibronectin and laminin proteins that are mainly adhesive.

Collagens are the main proteins of the extracellular matrix. They account for 25% of total protein content in a human organism. Unlike proteoglycans, collagens provide resistance to the mechanical stretching of a tissue, whereas proteoglycans oppose to its compression. Collagens are secreted by the cells of connective tissue, such as fibroblasts, osteoblasts, chondroblasts, and many other cells [10, 11].

To date, at least 29 types of collagen (they are collagen isoforms) are known. All collagen molecules contain a stiff triple helix structure: three polypeptide chains (named α-chains) are twisted up to the regular helix forming a collagen molecule. Many collagen types also have noncollagenous domains that do not form triple helices. The carbohydrate component in collagens is represented by monosaccharides and disaccharides.

Collagens types I–III are the main collagens of connective tissues; type I collagen accounts for 90% of total collagen content in a human organism. After their secretion,

molecules of collagen types I–III self-assemble into orderly polymers called collagen fibrils. The fibrils are further assembled to fibers of several micrometers (μm) in thickness called *collagen fibers*.

Type IV collagen is a main component of basement membranes that also contain type VII collagen and some other collagen types.

Types V, IX, and XII collagens provide connections of the collagen fibers with other proteins of the extracellular matrix.

Elastin, unlike collagen, does not form the stiff triple helix. An elastin molecule consists of flexible polypeptide chains and has an ability to be reversibly unrolled under the action of mechanical stretching forces. Like collagen, elastin molecules are secreted into the extracellular space, where they are connected with each other to form fibers and sheets. The elastic fibers are coated by microfibrils of 10–20 nanometers (nm) in diameter. The microfibrils contain glycoproteins called *fibrillins* [12] that are members of the fibronectin family. These microfibrils obviously play an important role in the formation of elastin fibers.

There is a striking difference between the mechanical characteristics of the stiff, nontensile collagen fibers and the rubber-like network of elastic fibers. The ability of elastic fibers to be stretched allows the tissues to restore their shapes after mechanical influences.

Fibronectin. The extracellular matrix contains several adhesive noncollagenous proteins. Their characteristic features are the domains able to specifically bind with the cell surface receptors. The necessary component of these domains is the amino acid sequence arginine-glycine-aspartic acid (RGD).

Fibronectin is one of the adhesive glycoproteins providing the attachment of cells to the extracellular matrix. Fibronectin is secreted by various types of cells, including fibroblasts and epithelial cells. There are at least 20 different fibronectin isoforms in humans. Secreted fibronectin molecules assemble into fibrils in the matrix. The fibronectin fibrillogenesis is initiated by the cell surface integrin receptors [13, 14]. Some part of fibronectin in form of fibrils is connected with the cell surfaces. Fibronectin in soluble state is found in blood and other biological fluids.

Fibronectin has several domains, which can specifically bind to the cells and also to other matrix molecules, such as collagens (the strongest binding being with type III collagen) and heparin.

Laminins (at least 15 isoforms identified so far) are cross-shaped trimeric adhesive glycoproteins that have different domains to specifically bind to cells, type IV collagen, nidogens, and some glycosaminoglycans. Laminins, just as type IV collagen and fibronectin, are components of basement membranes.

Laminins mediate the attachment of parenchymal cells to type IV collagen thereby providing the interaction between cells and basement membranes.

Other extracellular matrix glycoproteins are *nidogens, tenascins, and fibulins*.

Nidogens (*entactins*) bind to both laminin and type IV collagen forming the additional connection between laminins and collagen.

Tenascin family of proteins (tenascin-C, -X, -R, and -W) can bind fibronectin. However, unlike fibronectin, tenascins have both cell adhesive and antiadhesive functions depending on the cell type. These different functions are mediated by different tenascin domains; the number of these domains in a tenascin molecule varies because of alternative splicing [15, 16].

Fibulins can interact with many matrix components, such as some basement membrane proteins, fibronectin, fibrillin, and proteoglycans, to form supramolecular structures within the matrix [17].

The extracellular matrix is not only a mechanical framework that stabilizes a tissue structure. The matrix plays a much more active and complex role in the regulation of cell behavior, influencing the shape, migration, proliferation, survival, and metabolism of cells, which are involved in adhesive interactions with the matrix [18–20].

Migrations of cells during embryogenesis or in regeneration processes depend on the extracellular matrix.

The matrix molecules are involved in acute and chronic inflammation in tissues and also in such widespread human diseases as rheumatoid arthritis, osteoarthritis, asthma, and others [21–26]. The collagen diseases (collagenosis) are caused by genetic disturbances in the expression and regulation of extracellular matrix molecules. For instance, mutations in the genes encoding types I, III, or V collagen cause heritable connective tissues disorders, mutations in the gene encoding type VI collagen result in congenital muscular dystrophy or myopathies, and mutations in the genes encoding types II, IX, and XI collagen cause skeletal dysplasias [27–29].

The problem of cancer cell invasion and metastasis is closely related to the extracellular matrix.

Adhesive interactions of tissue cells with the extracellular matrix include the following:

1. Spreading of cells on the extracellular matrix.
2. Active displacement of cells (cell migration).
3. Cell responses to the chemical heterogeneity of the extracellular matrix.
4. Cell responses to the geometric configuration of the extracellular matrix.

All these adhesive interactions are accomplished by means of two base cellular functions: formation of the *pseudopodia* and formation of the special *adhesive structures*, which ensure the attachment of cells to the extracellular matrix.

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http://www.springer.com/978-1-61779-303-5

Adhesive Interactions in Normal and Transformed Cells
Rovensky, Y.A.
2011, XX, 225 p., Hardcover
ISBN: 978-1-61779-303-5
A product of Humana Press