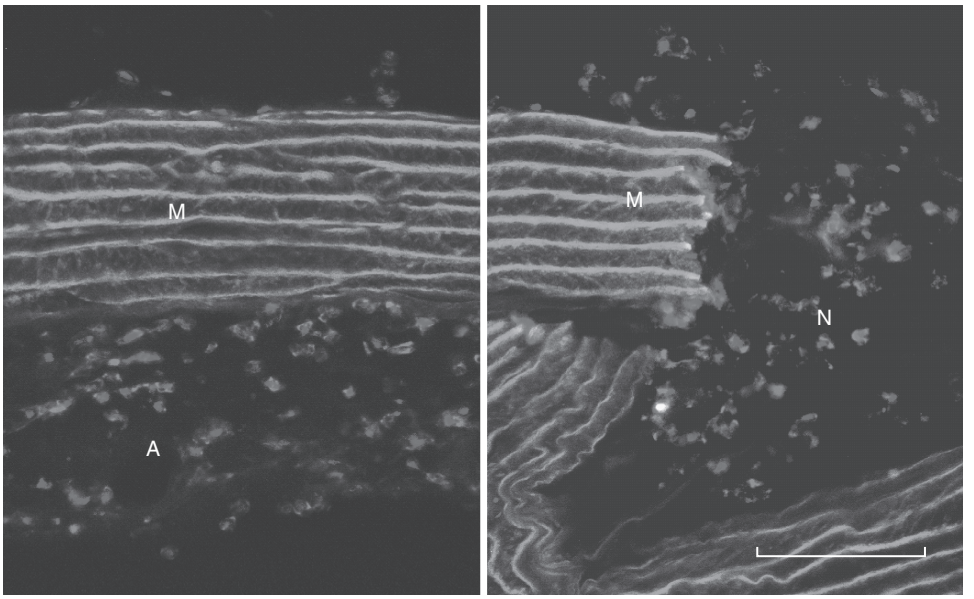
4

EXTRACELLULAR MATRIX



Transverse fluorescent micrographs showing the distribution of CD 11b/c-positive leukocytes in the media and adventitia of matrix-based aortic substitutes. The density of leukocytes in the elastic lamina-containing media was significantly lower than that in the collagen-containing adventitia. Note that leukocytes did not migrate into the gaps between the elastic laminae at the end of the aortic matrix substitutes (right). Red: antibody-labeled CD 11 b/c. Green: elastic laminae. Blue: Hoechst 33258-labeled cell nuclei. M, media. A, adventitia. N, neointima. Scale: 100 μm. (Reprinted from Liu SQ et al: *J Biolo Chem* 280:39294–301, 2005 with permission from the American Society for Biochemistry and Molecular Biology). See color insert.

Bioregenerative Engineering: Principles and Applications, by Shu Q. Liu

The *extracellular matrix* is the noncellular structure found in the extracellular space. This structure is composed of collagen fibers, elastic fibers or laminae, and proteoglycans. All components of extracellular matrix are produced and released by cells residing in the same tissue. Extracellular matrix plays critical roles in several aspects: (1) constituting a matrix framework that supports and organizes cells, tissues, and organs; (2) contributing to the morphogenesis and shape formation of tissues and organs; (3) providing mechanical strength to and protecting tissues and organs from injury; and (4) participating in the regulation of cell adhesion, proliferation, migration, and apoptosis. These aspects are outlined in this chapter.

The extracellular matrix can be used as biological materials for the regeneration of lost tissues and organs. Compared with synthetic polymer materials, extracellular matrix components are naturally occurring polymeric materials that are nontoxic and compatible to host cells and tissues and participate in the maintenance and regulation of cellular functions as described above. In particular, the collagen matrix has been used to construct scaffolds in experimental models for the reconstruction of a variety of tissues, such as the liver, pancreas, bones, and blood vessels. Since collagen matrix promotes cell adhesion, proliferation, and migration, collagen-based scaffolds enhance the regeneration of impaired tissues and organs. As other polymeric materials, extracellular matrix can be engineered and fabricated into various shapes and forms as desired. Thus, extracellular matrix components are preferred materials for the repair, regeneration, and engineering of malfunctioned tissues and organs.

COLLAGEN MATRIX

Composition and Formation of Collagen Matrix [4.1]

The *collagen matrix* is the most abundant type of extracellular matrix that is found primarily in connective tissues, such as the subcutaneous tissue, bone, and the adventitia of tubular organs, including blood vessels, airways, esophagus, stomach, and intestines. In mammalian tissues, there exist more than 20 types of collagen matrix, classified as collagen types I, II, III, and so on. Among these types of collagen, types I, II, III, IV, V, IX, XI, and XII are commonly found in connective tissue. Each type of collagen matrix is formed with one or more types of collagen molecule. A typical collagen molecule is a helical fibrillar structure composed of three peptide chains, termed α *chains*. A large number of collagen genes have been identified; each encodes a distinct collagen α chain. Combinations of various α chains give rise to different types of collagen fibril. Table 4.1 lists 22 types of representative collagen peptide chains.

Collagens are synthesized first as procollagen molecules in the cytoplasm of several cell types, including fibroblast, osteoblast, smooth muscle cell, and endothelial cell. Procollagen molecules are released to the extracellular space, cleaved by proteinases to remove procollagen peptides, and self-assembled into various forms of matrix structure. Collagen types I, II, III, V, and XI are organized into filamentous structures, known as *collagen fibrils*, with a diameter of ~10–100 nm. These fibrils usually form larger collagen bundles as found in the subcutaneous tissue and the adventitia of tubular organs. Collagen types I and V are often found in the bone, skin, cornea, tendon, ligament, and internal organs, such as the lung, liver, pancreas, and kidney. Mutation of the collagen type I genes causes several disorders, including osteogenesis imperfecta, idiopathic osteoporosis, and

TABLE 4.1. Characteristics of Selected Collagen Molecules*

Proteins	Alternative Names	Amino Acids	Molecular Weight (kDa)	Expression	Functions
Collagen type I α1	COL1A1, collagen α1 chain	1464	139	Bone, cartilage, connective tissue, skin, cornea, tendon, ligament, internal organs	Constituting the collagen matrix
Collagen type I α2	COL1A2, collagen I α2 polypeptide	1366	129	Bone, cartilage, connective tissue, skin, cornea, tendon, ligament, internal organs	Constituting the collagen matrix
Collagen type II α1	COL2A1, chondrocalcin, collagen type XI α3 (COL11A3), cartilage collagen	1487	142	Cartilage, notochord, intervertebral disks, vitreous humor of the eye	Constituting the collagen matrix
Collagen type III α1	COL3A1	1466	139	Connective tissues, skin, lung, blood vessels	Constituting the collagen matrix
Collagen type IV α1	COL4A1, collagen of basement membrane, α1 chain	1669	161	Brain, heart, blood vessel, liver, pancreas, kidney, placenta, eye	Constituting basal lamina or basement membrane
Collagen type IV α2	COL4A2, collagen of basement membrane α2 chain	1712	167	Brain, heart, blood vessel, liver, pancreas, kidney, placenta, eye	Constituting the basal lamina or basement membrane
Collagen type V α1	COL5A1	1838	184	Ubiquitous	Present in tissues containing type I collagen, regulating the assembly of type I collagen fibers
Collagen type V α2	COL5A2	1496	145	Bone, skin, cornea, tendon, ligament, lung, liver, pancreas, kidney	Constituting the extracellular matrix and regulating the assembly of type I collagen fibers

Collagen type VI α1	COL6A1	1028	109	Ubiquitous	Constituting the extracellular matrix and regulating the integrity of tissues
Collagen type VII α1	COL7A1	2944	295	Skin, mouth	Found near the basement membrane of stratified squamous epithelia, forming fibrils that contribute to anchoring of epithelia to underlying stroma
Collagen type VIII α1	Endothelial collagen	744	73	Endothelial cells, skin, kidney, cornea, leukocytes	Constituting the extracellular matrix, a major component of the basement membrane of corneal endothelium
Collagen type IX α1	COL9A1, cartilage specific short collagen	921	92	Cartilage, ear, eye (usually found in tissues containing type II collagen)	Constituting the collagen matrix
Collagen type X α1	COL10A1	680	66	Cartilage	Constituting the cartilage matrix
Collagen type XI α1	COL11A1	1818	183	Cartilage, cornea	Constituting the extracellular matrix
Collagen type XII α1	COL12A1	3063	333	Skin, bone	Often found in association with type I collagen and regulating the interaction of collagen I fibrils with other matrix components
Collagen type XIII α1	COL13A1	717	70	Eye, placenta	Containing a transmembrane domain, often localized to the cell membrane, and possibly regulating cell–cell interaction and angiogenesis

TABLE 4.1. *Continued*

Proteins	Alternative Names	Amino Acids	Molecular Weight (kDa)	Expression	Functions
Collagen type XIV α1	COL14A1, undulin	1796	194	Heart, blood vessels, brain, skeletal muscle, liver, uterus, tendon, skin	Constituting the matrix of connective tissues (note that this type of collagen is often associated with mature collagen fibrils)
Collagen type XV α1	COL15A1	1388	142	Ubiquitous	Often found near basal lamina or basement membrane and regulating interaction of basal lamina with underlying connective tissue
Collagen type XVI α1	COL16A1	1603	158	Skin, cartilage, skeletal muscle, placenta	Often found in association with collagen type I and II fibrils, regulating the integrity and organization of collagen matrix
Collagen type XVII	COL17A1	1497	180	Skin, cornea, intestine, esophagus, testis, spleen	A transmembrane protein that regulates the adhesion of epithelial cells to underlying basal lamina
Collagen type XVIII α1	COL18A1	1516	154	Brain, heart, blood vessel, liver, pancreas, kidney, intestine, ovary, skeletal muscle	Constituting the collagen matrix and generating endostatin, an antiangiogenic protein, by proteolytic cleavage of the *C*-terminal fragment of the molecule
Collagen type XIX α1	COL19A1	1143	115	Skin	Function remains to be determined

*Based on bibliography 4.1.

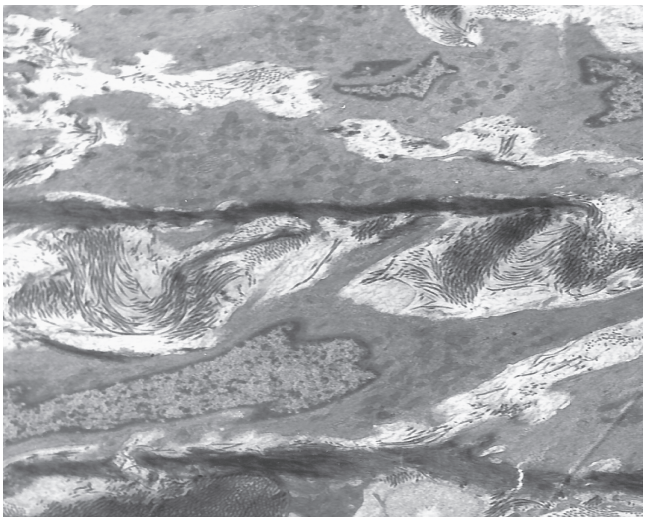


Figure 4.1. Electron micrograph showing collagen fibrils in the wall of a rat mesenteric artery. Scale bar: 1 μm.

atypical Marfan syndrome. Collagen types II and XI are found in the cartilage, notochord, and intervertebral disks. Collagen type III is found in blood vessels (Fig. 4.1), skin, and internal organs. These collagen fibrous structures play critical roles in the support and protection of cells and in the regulation of cellular functions, such as cell adhesion, proliferation, and migration. Collagen types IX and XII are molecules that link other types of collagen fibrils and are known as *fibril-associated collagens*. These types are found in the cartilage, tendon, and ligament. In contrast to the filamentous collagen molecules, collagen type IV participates in the construction of a membrane-like structure, known as the basal lamina or basement membrane, which underlies epithelial and endothelial cells (note that other components of a basal lamina include laminin, entactin, perlecan, nidogen, and heparan sulfate proteoglycans; see Fig. 4.2). Additional types of collagen are listed in Table 4.1.

Function of Collagen Matrix [4.2]

The collagen matrix plays several roles in a mammalian tissue or organ. The collagen matrix serves as a structural material that supports cells, helps organize cells into various forms of tissues and organs, and protects cells from mechanical injury. In addition, the collagen matrix participates in the regulation of cellular activities such as cell survival, adhesion, proliferation, and migration. Collagen molecules can directly interact with cells via the cell membrane collagen receptors, or indirectly via the mediation of *fibronectin*, a matrix component that binds collagen molecules at one side and cell membrane matrix receptors, known as *integrins*, at the other side. The binding of collagen and fibronectin molecules to the matrix receptors initiate the activation of intracellular signaling pathways that stimulate or activate mitogenic processes, including cell adhesion, survival, proliferation, and migration.

Given the structural and functional features, collagen matrix has long been used for constructing drug delivery devices and scaffolds for tissue regeneration. Collagen matrix

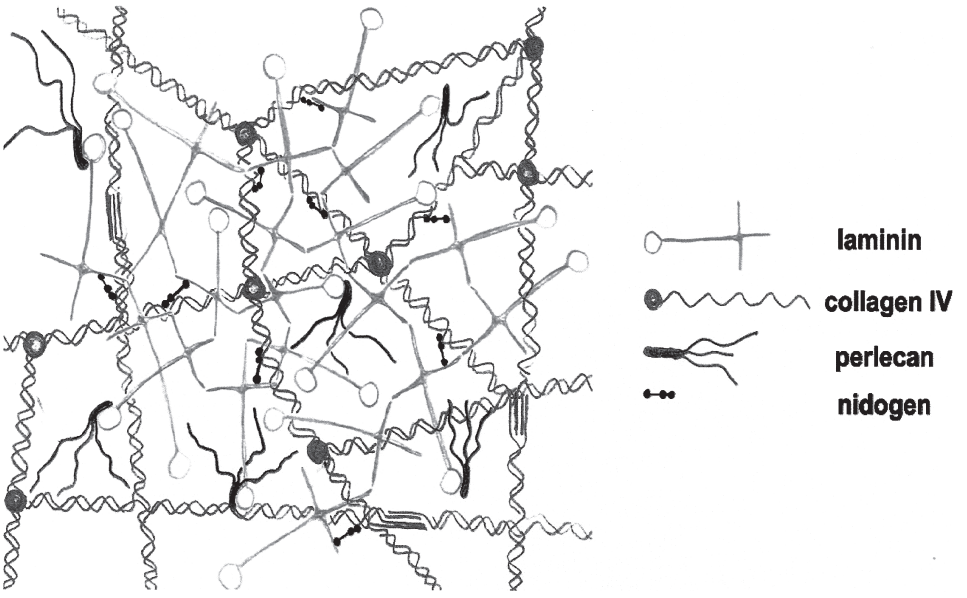


Figure 4.2. Schematic representation of endothelial cell basement membrane. Major components of endothelial cell basement membrane include laminin 8 and 10 isoforms, collagen type IV, and nidogen 1 and 2. (Reprinted from Hallmann R et al: *Physiol Rev* 85:979–1000, 2005 with permission from the American Physiological Society.)

has been used for constructing tissue scaffolds in several forms: collagen gel, collagen mesh, composite structures with other types of extracellular matrix molecules such as elastic fibers and proteoglycans, and decellularized natural collagen matrix scaffolds. The constructed structures can be used for various purposes of regenerative medicine. Collagen gels and meshes are suitable for drug delivery, whereas the cell-free natural collagen matrix can be used as scaffolds or grafts for the repair or regeneration of various tissues and organs, such as blood vessels, airways, intestines, stomach, and bladder.

To prepare collagen gels, natural collagen-containing tissues can be collected and degraded (note that collagen fibers are insoluble), and soluble collagen molecules can be extracted. Collagen molecules can be crosslinked into a gel structure with appropriate pH, temperature, and ionic strength. A therapeutic substance can be blended with the collagen molecules during gele formation. The collagen gel can be implanted or injected into a target tissue, and the therapeutic substance can be released at the rate of collagen gel degradation. In addition, collagen gel can be mixed with selected cells and used to deliver cells into a target tissue to replace malfunctioned cells. The delivered cells can be integrated into and restore the function of the target tissue. Sponge-like collagen matrix can be prepared in vitro and used as a framework for tissue regeneration and as a scaffold for repairing traumatized tissues.

Whereas a native collagen matrix is mechanical tough and strong, an in vitro crosslinked collagen gel exhibits low mechanical strength. Several methods have been developed and used to strengthen collagen gels. One method is to treat collagen gels with glutaraldehyde, which induces collagen crosslink and increases the strength of collagen gels. However, glutaraldehyde is toxic to cells and significantly influences cellular activi-

ties and functions. Another method is to facilitate collagen crosslink by introducing glycation. This method enhances the strength of collagen gels without significantly compromising the cell functions.

Native collagen matrix is a suitable material for the construction of tissue scaffolds. Such a material maintains the natural biological and mechanical characteristics and exhibits superior biocompatibility compared to in vitro crossliked collagen gels or matrix. To prepare a native collagen matrix, mammalian tissue specimens can be collected from selected structures, such as the submucosa of intestines, the adventitia of blood vessels, and the subcutaneous tissue. Cells in these specimens can be removed by various enzymatic and hydrolytic methods. Such treatments eliminate the cellular immunogenicity of allogenic tissues (note that extracellular matrix molecules exhibit little immunogenicity). The resulting cell-free collagen matrix can be tailored into a scaffold with a desired form and used for tissue repair or regeneration.

ELASTIC FIBERS AND LAMINAE

Composition and Structure of Elastic Laminae [4.3]

Elastic fibers and laminae are major extracellular matrix components found in mammalian tissues and organs. Elastic fibers are present in the lung, connective tissue, the submucosa of intestines, and the wall of veins, whereas elastic laminae are found primarily in the media of large and medium arteries (Fig. 4.3). Elastic fibers and laminae are composed of several proteins, including elastin, microfibrils, and microfibril-associated proteins. Elastin is the most abundant protein in elastic fibers and laminae. In this section, arterial elastic laminae are used as an example to describe the composition, structure, and function of elastin-based extracellular matrix.

Elastic laminae (see Table 4.2) are concentrically organized layers composed of tightly organized elastic fibers. These elastic fibers are composed of microfibrils and amorphous elastin and are arranged predominantly in the circumferential direction of arteries. Elastin

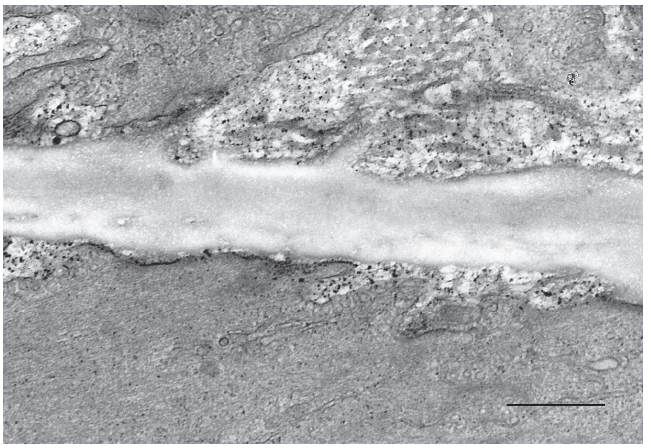


Figure 4.3. Electron micrograph of elastic laminae in the wall of a rat pulmonary artery. Scale bar: 1 μm.

TABLE 4.2. Characteristics of Selected Molecules Constituting the Elastic Laminae*

Proteins	Alternative Names	Amino Acids	Molecular Weight (kDa)	Expression	Functions
Tropoelastin	ELN	757	66	Blood vessels, skin, lung, kidney, cartilage	Constituting elastin, a major component of elastic fibers and laminae
Fibrillin 1	FBN1	2871	312	Blood vessels, skin, lung, kidney, cartilage	A constitutive component of microfibrils, which are organized into scaffolds for deposition of elastin and assembly of elastic fibers, and also a component of nonelastic matrix, causing Marfan syndrome when mutated
Fibrillin 2	FBN2	2911	314	Blood vessel	Same as fibrillin 1
Fibrillin 3	FBN3	2809	300	Skin, lung, kidney, skeletal muscle	Same as fibrillin 1
Microfibril-associated glycoprotein	MAGP, microfibril-associated protein 2	183	21	Skin, lung, kidney, skeletal muscle	Regulating the assembly and stability of microfibrils and elastic fibers

*Based on bibliography 4.3.

is the most abundant protein found in large arteries and contributes to approximately half the dry mass of the arterial wall. Mature elastin is a highly insoluble and hydrophobic protein, and is formed by the crosslinking of the 72-kDa elastin precursor, known as *tropoelastin*. In mammals, approximately 75% of tropoelastin is composed of four amino acids, including glycine, valine, alanine, and proline. Tropoelastin is produced by several cell types, including the smooth muscle cell (SMC) and endothelial cell (EC), and is released into the extracellular space where crosslinking and elastin formation take place. A mature elastin molecule contains two types of domain: the hydrophobic and crosslinking domains. The hydrophobic domains are rich in nonpolar amino acids, including glycine, valine, proline, and alanine, which are often arranged in repeats of three to six amino acid peptides, such as GVGVP, GGVP, and GVGVAP. The crosslinking domains are rich in alanine and lysine; the latter is subject to enzymatic crosslinking by lysyl oxidase. The lysine-containing crosslinking domains appear to be well conserved through evolution, whereas the hydrophobic domains display considerable variability. The structural conservation in the cross-linking domains renders elastin a highly inert and nonimmunogenic protein.

In the extracellular space, tropoelastin molecules are aligned and assembled into elastin based on a nonelastin microfibril mesh. Microfibrils are filaments of 8–16 nm in diameter and are composed of glycoproteins known as *fibrillins* and several microfibril-associated glycoproteins (MAGPs), including MAGP1 and MAGP2. It is thought that microfibrils are established prior to elastin assembly, providing a scaffold for the deposition, alignment, and crosslinking of tropoelastin. The MAGPs have been proposed to mediate the interaction of microfibrils with tropoelastin. One possible role of the MAGPs is to bind to the *C*-terminus of tropoelastin and stabilize tropoelastin prior to enzymatic crosslinking. The *C*-terminus of tropoelastin is critical to the formation of elastin. The lack of the *C*-terminus reduces the assembly of elastic laminae.

Following organized deposition to and alignment along the microfibrils, tropoelastin molecules are crosslinked into elastin via enzymatic reactions mediated by lysyl oxidase. This enzyme catalyzes oxidative deamination of the lysine residues, converting lysine to allysine (α-amino adipic δ-semialdehyde). Most lysine residues in tropoelastin are involved in such an enzymatic reaction. Lysine and allysine residues are then condensed spontaneously, resulting in the formation of elastin-specific crosslinks known as *desmosines* and *isodesmosines*. These crosslinks play a critical role in the assembly of elastin fibers. Since desmosines and isodesmosines are very stable in structure, elastic fibers are considered one of the toughest materials found in mammalian systems.

In addition to lysyl oxidase, elastin assembly may be regulated by other factors. For instance, negatively charged extracellular glycosaminoglycans may interact with the positively charged lysine residues of tropoelastin to promote elastin assembly. Conversely, glycosaminoglycans containing galactose derivatives, such as dermatan and chondroitin sulfate, have been linked to impaired elastogenesis, promoting the degradation of elastic fibers. The overexpression of a chondroitin sulfate-deficient proteoglycan known as *versican* (variant V3) increased tropoelastin expression and elastic fiber formation in vitro, and resulted in elastic lamina formation in balloon-injured carotid arteries in vivo. Another protein, latent transforming growth factor β-binding protein 2 (LTBP2), is coexpressed with tropoelastin and may contribute to elastic fiber formation. These examples demonstrate that various reactions are possible for the formation of elastic fibers and laminae, due to the participation of different extracellular components, although the regulatory mechanisms of elastin assembly remain to be clarified.

In mammals, arteries contain concentric elastic laminae with circumferentially aligned elastic fibers, whereas veins consist of a network of elastic fiber bundles aligned predominantly in the axial direction of the vessel. When observed by optical and electron microscopy, elastic laminae or fibers appear amorphous under physiological conditions. Historically, it has been thought that elastic laminae and fibers are stable structures that undergo little turnover and remodeling through the lifespan. However, recent studies have demonstrated that mechanical stretch in hypoxia-induced pulmonary hypertension can induce swelling and reorganization of elastic laminae within several hours. These observations suggest that elastic laminae and fibers may undergo dynamic remodeling in response to environmental stimuli.

Function of Elastic Fibers and Laminae [4.4]

Large arteries are composed of multiple layers of elastic laminae. These laminae have long been known to contribute to the structural stability, mechanical strength, and elasticity of the arterial wall. Arteries are subject to extensive mechanical stress induced by arterial blood pressure. Without the support of the elastic laminae, vascular cells may be overstretched under arterial blood pressure. The mechanical stretch may induce structural change in or degradation of elastic fibers or laminae. The degradation of elastic laminae has long been considered a major factor for reducing the strength of the arterial wall and inducing arterial aneurysms. The importance of the elastic laminae has been demonstrated in experimental arterial reconstruction with vein grafts. Veins have only loosely organized elastic fibers instead of elastic laminae, although veins and arteries both possess a strong collagen-containing adventitia. When a vein is used as an arterial substitute and exposed to arterial blood pressure, about 60% of endothelial cells and SMCs die within 12 h of implantation due to mechanical stretch. The lack of multilayer elastic laminae reduces the strength of the vein graft wall, contributing to the injury and death of vascualr cells. Thus, elastic laminae are a critical structure for the stability and mechanical strength of the arterial wall.

In addition to structural support, elastic laminae contribute to the elasticity of arteries. The recoil of the arterial wall is a critical mechanism for the continuation of bloodflow during diastole when cardiac ejection is ceased. The unique amino acid organization and crosslinking patterns of elastin are commonly regarded as important determinants for the elasticity of elastic fibers and laminae. Investigations by nuclear magnetic resonance have demonstrated that the backbones of elastin amino acid chains are highly mobile and individual amino acid residues are able to move freely. The crosslinks help organize the tropoelastin peptide chains into a filamentous network, which is an effective structure for the storage of recoiling energy under mechanical stretch. Observations by electron microscopy suggest the presence of ordered filamentous structures in elastic fibers under extensive mechanical stretch (in a range of strain or degree of stretch of ~150–200% with respect to the unstretched state), while amorphous appearance is observed without mechanical stretch. The structure and organization of elastin provide a basis for the elastic properties of elastic fibers.

Elastic laminae have also been shown to serve as a signaling structure and play a role in regulating arterial morphogenesis and pathogenesis. An important contribution of elastic laminae is to confine smooth muscle cells to the arterial media by inhibiting smooth muscle cell proliferation and migration, thus preventing intimal hyperplasia under physiological conditions. In addition, elastic laminae exhibit antiinflammatory effects relative

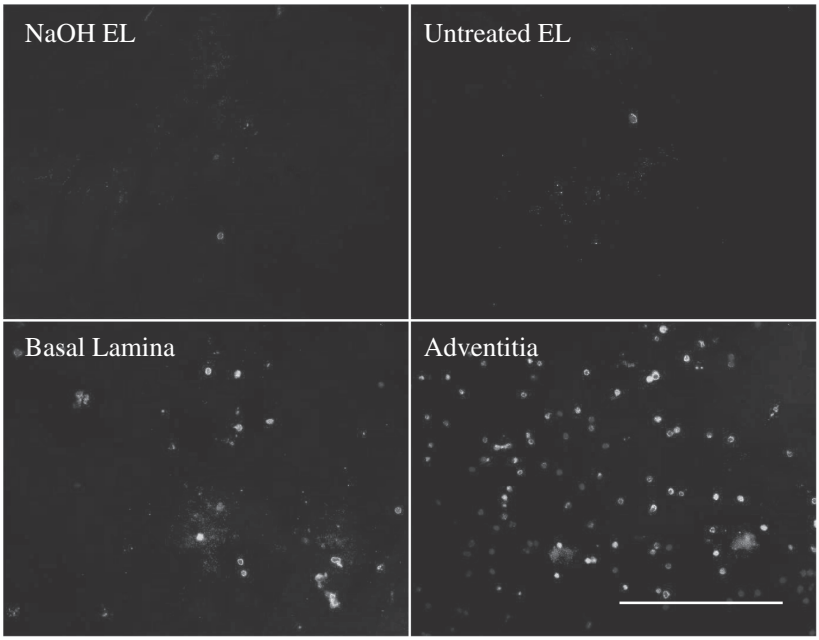


Figure 4.4. En face fluorescent micrographs showing monocytes adhered to NaOH-treated and untreated elastic lamina, basal lamina, and adventitia. EL: elastic lamina. Scale: 100 μm. (Reprinted from Liu SQ et al: *J Biol Chem* 280:39294–301, 2005 with permission from the American Society for Biochemistry and Molecular Biology.)

to collagen matrix. In particular, elastic laminae are capable of inhibiting leukocyte adhesion to and transmigration through the arterial media (Fig. 4.4 and chapter-opening Figure, above). Such inhibitory effects are potentially mediated by an inhibitory receptor known as signal-regulatory protein (SIRP) α. Elastic lamina degradation peptides extracted from arterial specimens bind to and activate SIRP α in monocytes, and induce the recruitment and phosphorylation of a protein tyrosine phosphatase known as SH2 domain-containing protein tyrosine phosphatase (SHP)-1. SHP-1 dephosphorylates mitogenic protein tyrosine kinases (see Chapter 5), resulting in the suppression of monocyte adhesion and activation. These anti-inflammatory effects render elastic laminae a potential material for vascular reconstruction. This issue is discussed in detail in Chapter 15.

PROTEOGLYCANS

Composition and Structure of Proteoglycans [4.5]

Proteoglycan is a complex molecule composed of a core protein and a large number of glycosaminoglycans (GAGs). The core protein is a 10–600-kDa chain-shaped protein. The protein chain can link to GAGs via covalent bonds, forming proteoglycan (Fig. 4.5). A proteoglycan molecule is different in structure and form from a glycoprotein, another type of protein with sugar residues. A proteoglycan is defined as a molecule with long unbranched GAG sidechains and is found primarily in the extracellular space. A glyco-

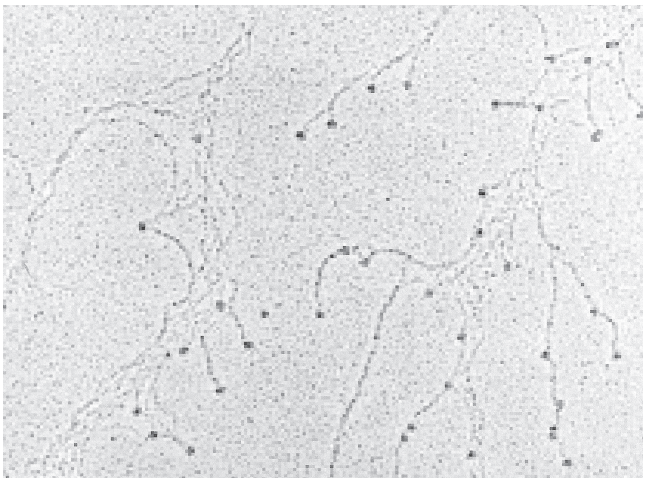


Figure 4.5. Electron micrograph showing interaction of neurocan with hyaluronan. The fiber-like structures are hyaluronan aggregates. Neurocan molecules often interact with the hyaluronan fibers at the end. (Reprinted from Retzler C et al: *J Biol Chem* 271:17107–13, 1996 with permission from the American Society for Biochemistry and Molecular Biology.)

protein usually contains short branched oligosaccharide chains and is found primarily in the cell membrane. Glycoproteins often serve as receptors.

Glycosaminoglycans are polysaccharide chains constituted with repeating disaccharides. Each disaccharide unit is composed of an amino sugar, either an *N*-acetylglucosamine or *N*-acetylgalactosamine. The other molecule is a uronic acid, which is a sugar acid generated by oxidation of the terminal —CH_2OH group of a sugar molecule to a carboxyl (═COOH) group. A large number of disaccharides are sulfated in a GAG molecule. The presence of the carboxyl and sulfate groups renders the GAGs negatively charged. Based on the type and arrangement of the sugar molecules as well as the location and number of sulfate bonds, GAGs can be classified into several groups: chondroitin sulfate and dermatan sulfate, heparin and heparan sulfate, keratan sulfate, and hyaluronic acid.

Chondroitin sulfate and *dermatan sulfate* are GAGs composed of about 60 repeating disaccharide units, each containing a D-glucuronic acid residue and an *N*-acetyl-D-galactosamine residue linked by glycosidic bonds (Fig. 4.6). These GAGs are sulfated at the C4 and C6 locations of the galactosamine residue. Chondroitin sulfate is a GAG with the C4 sulfate bond, whereas dermatan sulfate is a GAG with the C6 sulfate bond. These GAGs are found in cartilage, bone, connective tissue, and blood vessels and serve as ground substance, which supports and protects cells from injury.

Heparin is a highly sulfated GAG composed of repeating disaccharides of D-glucuronic acid and *N*-acetyl-D-glucosamine (Fig. 4.6). *Heparan sulfate* is similar to heparin in structure, but contains fewer *N*- and *O*-sulfate bonds. Heparin and heparan sulfate are generated in hepatocytes and vascular endothelial cells. These GAGs possess potent anticoagulant and antithrombogenic properties. Heparan sulfate is present on the surface of endothelial cells and plays a critical role in the maintenance of blood fluidity.

Keratan sulfate is a GAG consisting of repeating disaccharide units containing D-galactose and *N*-acetyl-D-glucosamine-6-sulfate. This type of GAG is found in the cornea

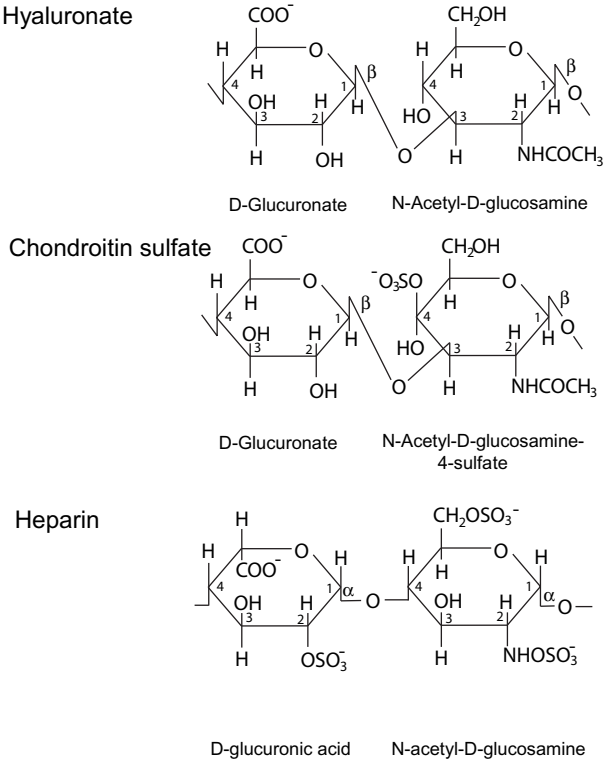


Figure 4.6. Chemical composition of the basic units of hyaluronate, chondroitin sulfate, dermatan sulfate, heparin, and keratan sulfate. Based on bibliography 4.5.

and cartilage. *Hyaluronic acid* is composed of more than 2000 disaccharide units, each containing a D-glucuronic acid and an *N*-acetyl-D-glucosamine residue linked by glycosidic bonds. This GAG is found in the vitreous humor, synovial fluids, cartilage, and blood vessels.

The GAGs described above can form various types of proteoglycan, including aggrecan, β-glycan, decorin, perlecan, syndecans, and versican. *Aggrecan* is a proteoglycan with a molecular weight of ~210 kDa, and is composed of about 130 chondroitin sulfate and keratan sulfate chains. This type of proteoglycan is found primarily in cartilage, forms complexes with hyaluronic acids, and serves as a ground substance in which cells reside. β-*Glycan* is a molecule with a molecular weight of ~36 kDa. It contains a single GAG chain constituted by chondroitin sulfate and dermatan sulfate. β-Glycan is present in extracellular matrix and cell membrane and play a role in mediating the activity of transforming growth factor β.

Decorin is a ~40-kDa proteoglycan with a single chondroitin sulfate and dermatan sulfate GAG chain. It is present in connective tissues and can bind to collagen type I, regulating the organization of the collagen matrix. It also binds to transforming growth factor β and mediates the activity of this growth factor. *Perlecan* is about 500 kDa in molecular weight and is composed of 2–15 heparan sulfate GAG chains. It is found primarily in the basal laminae of various organs and plays a role in the mechanical support of the basal lamina and mediating cellular activities (see next section). *Syndecans* are a

family of proteoglycans, which include four members: syndecan-1, -2, -3, and -4; each member is encoded by a distinct gene. These are cell-associated proteoglycans and their structure and function are discussed in the next section.

Versicans are another family of proteoglycans, including versican-0, -1, -2, -3, and 4. These isoforms are generated by alternative splicing of the mRNA transcript for the versican core protein. A versican proteoglycan contains primarily chondroitin sulfate GAGs. Versicans are found in the extracellular matrix of blood vessels and synthesized by vascular smooth muscle cells. Versicans can bind to growth factors, enzymes, and other extracellular matrix components, and play a critical role in mediating the proliferation and migration of smooth muscle cells. The level of versicans is increased in response to vascular injury, promoting inflammatory reactions, lipid accumulation, mitogenic activity of smooth muscle cells, and intimal hyperplasia. See Table 4.3 for further information on these proteoglycans and additional proteoglycans.

Function of Proteoglycans [4.6]

There are several functions for proteoglycans in general. The most important function of proteoglycans is probably to serve as ground substances that support and protect cells from mechanical injury. Proteoglycans are found primarily in extracellular space and are highly hydrophilic. These molecules are negatively charged and can attract positively charged ions such as Na^+ and K^+. These ions create an osmotic gradient, resulting in the accumulation of water in proteoglycan molecules. Given their hydrophilic nature, these molecules can absorb a large amount of water and form a gel-like structure even at a very low concentration. Such a structure can resist a high level of compressive stress induced by mechanical impacts. The gel-like structure of proteoglycans also helps to organize cells within a tissue and organ.

Proteoglycans play a role in lubricating joint surfaces and preventing blood coagulation. Hyaluronic acids and hyaluronic acid-containing proteoglycans are present in the joint fluid and serve as lubricants, which reduce friction between the joint surfaces. Heparin and heparan sulfate are molecules that prevent blood coagulation and thrombogenesis. These molecules can inhibit the conversion of prothrombin to thrombin, a protease that cleaves soluble fibrinogen and catalyzes the formation of insoluble fibrin. The insoluble fibrin forms a solid meshwork at the site of endothelial injury and stimulates activation and adhesion of leukocytes and platelets. The fibrin meshwork serves as a soil for thrombogenesis and atherogenesis. The inhibition of thrombin formation by heparin or heparan sulfate prevents blood coagulation, thrombogenesis, and atherogenesis.

Proteoglycans are also involved in regulating the activity of signaling molecules. Proteoglycans can form complexes with growth factors, such as fibroblast growth factor and transforming growth factor. Such a process may activate or inhibit the activity of a growth factor, depending on the nature of the proteoglycans and growth factors. For instance, the interaction of fibroblast growth factor with heparan sulfate-containing proteoglycans can promote the activation of the growth factor. In contrast, the binding of transforming growth factor to proteoglycans inhibits the activity of the growth factor.

Proteoglycans participate directly in the regulation of cellular activities and functions. A heparan sulfate proteoglycan molecule found in the basal lamina, known as *perlecan*, has been shown to serve as an inhibitor for vascular smooth muscle cells. At the site of vascular injury, smooth muscle cells are activated to proliferate and migrate from the media to the intima of blood vessels, processes contributing to intimal hyperplasia and

TABLE 4.3. Characteristics of Selected Proteoglycans*

Proteins	Alternative Names	Amino Acids	Molecular Weight (kDa)	Expression	Functions
Versican	Chondroitin sulfate proteoglycan 2, glial hyaluronate-binding protein	3396	373	Blood vessel, liver, lung, uterus, kidney, prostate gland	Regulating cell proliferation and migration
Decorin	Proteoglycan II (PGII), dermatan sulfate proteoglycans II, bone proteoglycan II	359	40	Lung, kidney, skin, skeletal muscle, bone, cartilage, ligament	Constituting the matrix of connective tissues, binding to type I collagen fibrils, regulating matrix assembly, and suppressing tumor cell growth
Perlecan	Heparan sulfate proteoglycan of basement membrane, heparan sulfate proteoglycan 2 (HSPG2)	4393	469	Blood vessel, intestine, cartilage, kidney	Constituting the basement membrane, contributing to stabilization of matrix molecules, regulating glomerular permeability to macromolecules, and regulating cell adhesion
Aggrecan 1	AGC1, chondroitin sulfate proteoglycan core protein 1 (CSPCP1), cartilage-specific proteoglycan core protein 1	2415	250	Cartilage, brain	Constituting the extracellular matrix of cartilage, protecting cartilage from compression injury, and causing skeletal dysplasia and spinal degeneration when mutated

TABLE 4.3. *Continued*

Proteins	Alternative Names	Amino Acids	Molecular Weight (kDa)	Expression	Functions
Biglycan	BGN, proteoglycan I (PG-I), bone/cartilage proteoglycan I, dermatan sulfate proteoglycan I (DSPG-1)	368	42	Bone, cartilage, skin, ligament, brain, lung	Binding to collagen fibrils, regulating both assembly and integrity of extracellular matrix, promoting neuronal survival, and mediating macrophage-related inflammatory reactions
β-Glycan	Transforming growth factor β receptor type 3	849	93	Heart	Found at cell surface and in extracellular matrix, interacting with transforming growth factor, and participating in regulation of cell proliferation and differentiation
Syndecan 2	SYND2, heparan sulfate proteoglycan (HSPG), fibroglycan	201	22	Bone, liver, skin	A transmembrane heparan sulfate proteoglycan; mediating cell binding, proliferation, and migration; regulating cytoskeletal integrity and organization; and mediating HIV transmission to T lymphocytes
Neurocan	Chondroitin sulfate proteoglycan 3	1321	143	Nervous system	A chondroitin sulfate proteoglycan that mediates the adhesion and migration of neural cells
Keratocan	KERA, KTN, keratan sulfate proteoglycan	352	41	Cornea	A keratan sulfate proteoglycan found in cornea and a critical component in corneal transparency

*Based on bibliography 4.5.

atherogenesis. The perlecan molecules in the basal lamina, which resides beneath the endothelium, inhibit the proliferation and migration of smooth muscle cells and thus suppress intimal hyperplasia and atherogenesis.

In general, proteoglycans may regulate the activity of signaling molecules and cells via several approaches: (1) immobilizing signaling molecules and thus confining the molecules to a specified location, (2) blocking or stimulating the activity of signaling molecules via binding interactions, and (3) protecting signaling molecules from enzymatic degradation. Various types of proteoglycan may elect to use different mediating approaches.

While most proteoglycans are present in extracellular space, there exist cell-associated proteoglycans. A typical example is the proteoglycan family of *syndecans*. These proteoglycans are transmembrane receptor type of molecules. Each syndecan molecule is composed of an extracellular domain, a single-span transmembrane domain, and a cytoplasmic domain. The extracellular domain of syndecans contains GAGs, such as chondroitin sulfate and heparan sulfate. The intracellular domain of syndecans interacts with actin filaments. Syndecans are found in fibroblasts and epithelial cells, and serve as receptors for extracellular matrix components, including fibronectin and collagen. These proteoglycan molecules can bind to growth factors, such as fibroblast growth factor, and mediate the interaction of growth factors with their receptors. Such an activity contributes to the regulation of embryonic development, angiogenesis, and tumorigenesis.

Another type of cell-associated proteoglycan is heparan sulfate-containing proteoglycans. In addition to the role in regulating blood coagulation, heparan sulfate proteoglycans can mediate the activity of several signaling pathways involving Wnt, hedgehog, transforming growth factor, and fibroblast growth factor. Such a mediating process is critical to embryonic development and pathogenic remodeling. Furthermore, heparan sulfate proteoglycans are involved in the regulation of tumorigenesis. These molecules may promote tumor growth and metastasis in at least two types of tumor: myeloma and breast cancer. Understanding the role of proteoglycans in regulating signaling processes may lead to the development of new therapeutic approaches for tumors and other pathological disorders.

MATRIX METALLOPROTEINASES

Matrix metalloproteinases (MMPs) are enzymes that induce degradation of extracellular matrix components. There are more than 20 types of MMPs, which are found in mammalian tissues and produced by different cell types. Each type of MMP can target one or more extracellular matrix components, although the activity of MMPs is not highly specific. Almost all MMPs are synthesized in cells as preproenzymes and released as inactive forms known as pro-MMPs. The inactive forms of MMPs can be activated by tissue and plasma proteinases or membrane-type MMPs (MT-MMPs), which cleave pro-MMPs. The production and activation of MMPs are highly regulated processes, which are critical to a number of physiological processes, including embryonic morphogenesis, neurite outgrowth, ovulation, bone growth, angiogenesis, apoptosis, and wound healing. In addition, MMPs are involved in the pathogenesis of a number of disorders, including cancer metastasis, atherosclerosis, skin ulceration, gastric ulcer, corneal ulceration, liver fibrosis, and emphysema. MMPs mediated these physiological and pathological processes via inducing matrix degradation, which promotes two fundamental cellular activities: cell migration and proliferation.

The expression of MMPs can be induced by several types of stimulating factors, such as growth factors, cytokines, phorbol esters, and mechanical stress. In general, factors that mediate inflammatory and growth reactions likely stimulate the expression of MMPs. These growth and inflammatory factors induce activation of cell signaling pathways involving ERK1/2, stress-activated protein kinase (SAPK)/JNK, and p38, resulting in the upregulation of the MMP genes (see Chapter 5 for the signaling pathways). The physiological significance is that MMP-induced matrix degradation, in association with the upregulation of growth factors (e.g., epidermal growth factor and platelet-derived growth factor) and inflammatory cytokines (e.g., tumor necrosis factor α and interleukin-1), facilitates cell migration, an essential process for tissue regeneration in wound healing and leukocyte infiltration in inflammatory reactions. Several factors, such as transforming growth factor β, retinoic acids, glucocorticoids, exert an inhibitory effect on the activity and expression of MMPs. The effects of stimulatory and inhibitory factors are coordinately regulated under physiological and pathological conditions. In a quiescent state, the activity and expression of MMPs are inhibited. The activity and expression of MMPs are usually upregulated in pathological disorders such as mechanical and chemical trauma, atherosclerosis, and carcinogenesis.

Structural Features of MMPs [4.7]

A MMP is composed of several common domains, including a signal peptide domain, a propeptide domain, and a catalytic domain (Fig. 4.7). There are other MMP domains,

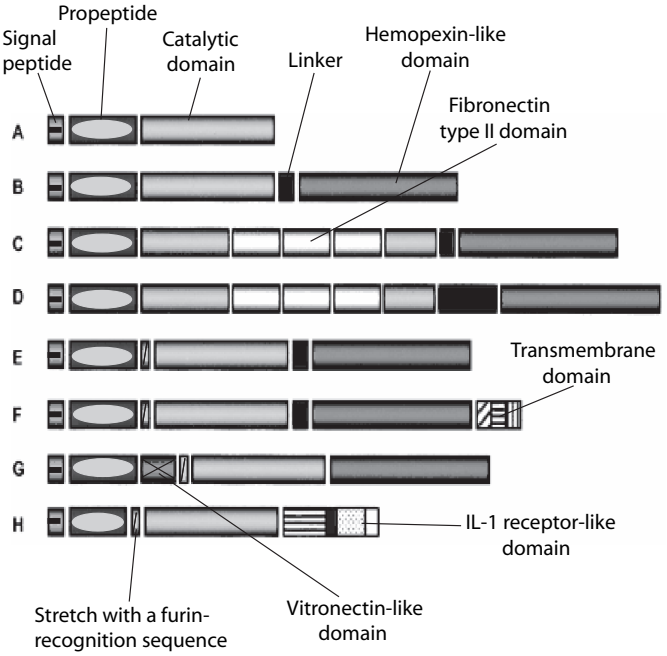


Figure 4.7. Schematic representation of the structure of matrix metalloproteinases (MMPs). (Reprinted from Nagase H, Woessner JF Jr: *J Biol Chem* 274:21491–4, 1999 with permission from the American Society for Biochemistry and Molecular Biology.)

such as hemopexin-like domain, fibronectin type II domain, vitronectin-like domain, furin recognition sequence, linker, and transmembrane-cytoplasmic domain, but these domains are not present in all MMPs. Figure 4.7 shows the common and specific domains for MMPs. There are several structural features that are important for the function of MMPs. The propeptide domain contains a PRCG(V/N)PD sequence, which inhibits the activity of the zinc-dependent catalytic domain of MMPs and renders the enzymes inactive. The removal of the propeptide by an enzyme or chemical compound induces the activation of the MMPs. The catalytic domain can bind to zinc and calcium ions, which are necessary for the stability and activity of MMPs. Several MMPs, including MMP2 and MMP9, contain repeated fibronectin type II-like sequences in the catalytic domain. These sequences mediate the interaction of MMPs with substrate molecules, such as collagen. MMPs that possess a collagenase activity contain a *C*-terminal hemopexin-like domain. This domain is essential for cleaving helical collagen fibrils. The transmembrane domain found in MT-MMPs mediates the integration of the enzymes to the cell membrane.

Activation of MMPs [4.8]

Matrix metalloproteinases (see Table 4.4) are released from cells as inactive pro-MMPs. The inactive forms can be activated by a number of factors, including proteinases, mercurial compounds, reactive-oxygen species, and protein-denaturing reagents, under experimental conditions in vitro. These factors can degrade or remove the propeptide domain, which inhibits the catalytic activity of MMPs. Under physiological conditions in an in vivo system, the propeptide domain of pro-MMPs is cleaved by proteinases, resulting in the activation of MMPs. Plasmin is a typical proteinase that activates pro-MMPs. Furthermore, certain types of pro-MMP, such as pro-MMP2, are activated by a group of MMPs, known as *membrane-type MMPs* (MT-MMPs), which are anchored to the cell membrane. For instance, MT1-MMP can cleave and activate pro-MMP2 on the cell surface. MT-MMP-induced activation of MMP is critical to several biological processes, including angiogenesis, cell migration, and cancer metastasis. In these processes, activated MMPs on the cell surface induce matrix degradation, creating a channel that allows cell migration.

The activity of MMPs can be suppressed by a family of molecules, known as tissue inhibitors of metalloproteinases (TIMPs). This family includes four known members: TIMP1, TIMP2, TIMP3, and TIMP4, with molecular weight ranging from 21 to 30 kDa. TIMPs can inhibit cell migration, tumor cell invasion, and angiogenesis via their negative influence on MMPs. Thus, TIMPs participate in the regulation of the activity of MMPs together with growth factors and cytokines. In addition, TIMPs exert other activities. These activities are dependent on the type of TIMPs and the type of target cells. TIMP1 and TIMP2 have been shown to stimulate cell proliferation and prevent cell apoptosis. However, TIMP2 has also been found to inhibit the proliferation of vascualr endothelial cells and angiogenesis. TIMP3 can induce apoptosis in carcinoma cells and melanoma cells. These diverse activities of TIMPs play important roels in the regulation of not only matrix degradation but also cellular activities.

TABLE 4.4. Characteristics of Selected MMPs*

Proteins	Alternative Names	Amino Acids	Molecular Weight (kDa)	Expression	Functions
MMP1	Fibroblast collagenase, interstitial collagenase	469	54	Connective tissue, bone	An enzyme that degrades collagen types I, II, and III
MMP2	Collagenase type 4, collagenase type 4A, 72-kDa gelatinase, gelatinase A, neutrophil gelatinase	660	74	Connective tissue, skin, bone, blood vessel	An enzyme that degrades type IV collagen and gelatin; also regulates vascularization and inflammatory reactions
MMP3	Stromelysin I, STMY1, STR1, progelatinase, transin, proteoglycanase	477	54	Connective tissue, cartilage, skin, blood vessel	An enzyme that degrades fibronectin, laminin, collagens (types III, IV, IX, and X), and proteoglycans; also plays a role in regulation of wound repair, atherogenesis, and tumor invasion
MMP7	Uterine matrilysin, putative metalloproteinase 1 (PUMP1), Matrin	267	30	Ubiquitous	A proteinase that degrades proteoglycans, fibronectin, elastin and casein; also participates in regulation of wound healing
MMP8	Neutrophil collagenase, collagenase 2	467	52	Leukocytes, bone marrow	A proteinase that degrades collagen types I, II, and III
MMP9	Gelatinase B, 92-kDa gelatinase, collagenase type IV B, 92 KD collagenase type IV, collagenase type V, macrophage gelatinase	707	78	Leukocytes, bone marrow, skin, intestine, liver, kidney, lung, blood vessel	A proteinase that degrades collagen types IV and V, mediates IL8-induced mobilization of hematopoietic progenitor cells from the bone marrow
MMP10	Stromelysin II (STMY2), Transin-2	476	54	Skin, leukocytes, heart, blood vessel, kidney, lung, liver	A proteinase that degrades proteoglycans and fibronectin

MMP11	Stromelysin 3 (STMY3)	488	55	Connective tissue	A proteinase that degrades α1 proteinase inhibitor, fibronectin, laminin
MMP12	Macrophage metalloelastase	470	54	macrophages	A proteinase that degrades elastin and contributes to the development of aneurysm and emphysema
MMP13	Collagenase 3	471	54	Cartilage, skin, blood vessel	A proteinase that degrades collagen types I, II, and III contributes to cartilage turnover and osteoarthritis
MMP14	Membrane type matrix metalloproteinase 1 (MT1 MMP)	582	66	Cartilage, skin, connective tissue	A membrane-type proteinase that activates MMP2 and participates in the regulation of tumor invasion
MMP15	Membrane type matrix metalloproteinase 2 (MT2-MMP)	669	76	Connective tissue	A membrane-type MMP that activates progelatinase A
TIMP1	Metalloproteinase inhibitor 1, fibroblast collagenase inhibitor, collagenase inhibitor, erythroid-potentiating activity	207	23	Bone marrow, connective tissue, bone	A natural inhibitor of the matrix metalloproteinases (MMPs), promoting cell proliferation and preventing cell apoptosis
TIMP2	Metalloproteinase inhibitor 2	220	24	Liver, retina, placenta	Inhibitory MMPs, inhibiting the activity of MMPs and also inhibiting proliferation of endothelial cells and angiogenesis
TIMP3	Metalloproteinase inhibitor 3	211	24	Brain, heart, lung, kidney, liver, pancreas, blood vessel	Inhibitory MMPs
TIMP4	Metalloproteinase inhibitor 4	224	26	Heart, blood vessel, kidney, pancreas, and intestine	Inhibitory matrix metalloproteinases, participating in regulation of platelet aggregation and recruitment

*Based on bibliography 4.7.

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