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MODERN VIEW ON THE STRUCTURE OF THE VASCULAR EXTRACELLULAR MATRIX

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SAVREMENI PREGLED STRUKTURE VASKULARNOG EKSTRACELULARNOG MATRIKSA

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ABSTRACT

Endothelium, smooth muscle cells and connective tissue are three basic structural components of the blood vessel wall. They are all finely interconnected and form one active, highly integrated organ. The majority of the connective tissue is located in the sub endothelial layer of the tunica intima, but it is also abundant in the tunica adventitia. Connective tissue is composed primarily of two elements: cells and a matrix which, in turn, is built from ground substance and fibers. Ground substance is an amorphous and viscous fluid containing glycosaminoglycans, proteoglycans and structural glycoproteins that are arranged in a complex manner. Fibers, on the other hand, are the main supportive elements in the connective tissue mainly responsible for its hardness and elasticity. There are three types of protein fibers found within the matrix. Collagen and reticular fibers are built from protein collagen while elastic fibers are composed of protein elastin. Structure and composition of the extracellular matrix plays a crucial role in preservation of the structural and functional characteristics of the blood vessel wall.

Key words: *blood vessels; connective tissue; extracellular matrix.*

SAŽETAK

Vaskularni zid je sastavljen od tri osnovne strukturne komponente, endotela, glatkih mišićnih ćelija i vezivnog tkiva, koje su međusobno povezane složenim mehanizmima u jedan aktivni, visokointegrisani organ. Najveće količine vezivnog tkiva u vaskularnom zidu nalaze se u sastavu ekstracelularnog matriksa subendotela intime. Osim u subendotelu veće količine veziva smeštene su i u adventiciji. Vezivno tkivo grade ćelije i ekstracelularni matriks. U sastavu ekstracelularnog matriksa nalaze se osnovna supstanca i vezivna vlakna. Osnovna supstanca ekstracelularnog matriksa je amorfna želatinozna supstanca, sastavljena iz glikozaminoglikana, proteoglikana i strukturnih glikoproteina koji su u različitim međusobnim interakcijama, što je uslovljeno fiziološkim stanjem tkiva. Vlakna su osnovni mehaničko-potporni elementi odgovorni za čvrstinu i elastičnost vezivnog tkiva. Kolagena i retikularna vlakna sagrađena su iz proteina kolagena, dok su elastična vlakna pretežno sastavljena iz proteina elastina. Struktura i sastav komponenata ekstracelularnog matriksa, kao i njihov međusobni odnos, od suštinskog su značaja za očuvanje morfofunkcionalnih karakteristika vaskularnog zida.

Ključne reči: *krvni sudovi; vezivno tkivo; ekstracelularni matriks.*

INTRODUCTION

Endothelium, smooth muscle cells and connective tissue are three basic structural components of the blood vessel wall. They are all finely interconnected to form one active, highly integrated organ (1-4) (figure 1-3). In the vascular wall the amount of three basic components, as well as their distribution, are under the influence of mechanical factors such as blood pressure and local metabolic needs of the surrounding tissue. The majority of the connective tissue is located in the subendothelial layer of the tunica intima. Endothelial cells are firmly attached to a basement membrane and subendothelial tissue through their cytoskeleton and integrins bonds. These contacts enable the information transfer between connective tissue matrix and integrins on one side and cytoskeleton and nuclei of endothelial cell on the other (5, 6). Hence, the information from "outside" can induce either synthesis or degradation of extracellular matrix proteins, control the degree of integrins expression, transduction of signals that can lead to enhanced growth, motility and proliferation of the endothelial cells, as well as regulation of the inflammation (7-9). Except in the subendothelial layer, significant amount of connective tissue is located in the adventitia. Its basic role is structural support of blood vessel wall and to serve as a mechanical barrier for infective agents. The latter is achieved by the activity of immune cells and phagocytes (1-4).

Organization of the connective tissue in the vascular wall

Connective tissue is composed primarily of two elements: cells and a matrix. Cellular population

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comprises resident cells (such as fibroblasts, mast-cells, adipocytes, pericytes) and migratory cells (plasma-cells, lymphocytes, monocytes and granulocytes) (10-12). The principal cell of the connective tissue is fibroblast because it produces elements of the extracellular matrix and the reticular lamina of the basement membrane as well (9). In adult age, fibroblasts are restricted to the tunica adventitia of the blood vessel, while the subendothelial layer is dominated by smooth muscle cells that are able to produce components of the extracellular matrix (ground substance and fibers) (12-14).

Basement membrane

Basement membrane is a thin layer of extracellular matrix that separates endothelium and subendothelial connective tissue. Its main role is to act as a selective barrier, but this membrane also determines the polarity of the epithelial cells, leads cell migration during embryogenesis and inflammation and has an important function in cellular differentiation and adhesion (14). Structural and functional preservation of this membrane is of great importance when protection of the blood vessel wall against various pathological factors is at stake. On birth, basement membrane is composed of fibronectin and laminin with collagen type IV meshwork (16). In adult organisms entactin, elastin, trombospondin and heparin sulfate (perlecan) are deposited. In the vascular wall specific, Von Willebrand factor is present (15).

Analysis of the basement membrane by electron microscopy reveals two layers dissimilar by origin and structure, basal lamina and reticular lamina (17). Basal lamina is composed of two layers, lamina lucida and lamina densa (15). The former is 50-60 nm thin, transparent, glycoprotein-rich (entactin and laminin) layer located bellow the basal part of the epithelial cells with integrins that binds glycoproteins to cytoskeleton of the endothelial cells (17). Lamina densa is heterogeneous, mesh-like layer located bellow the lucida and is composed of collagen type IV, fibronectin and proteoglycan perlecan. Collagen IV and perlecan are attached to laminin in lamina lucida, while fibronectin has a role in the attachment of the lamina densa to the connective tissue bellow it, through anchoring fibrils. These fibrils, composed largely of type VII collagen, extend from the lamina densa and wrap around the collagen fibers or directly attach to it over anchoring plates thus connecting the collagen fibers to the fibronectin (18, 19). With electron microscopy, lamina densa can be seen as a continuous layer, 80 nm thin (37). All components of the basal lamina are produced by endothelial cells except the fibronectin that can be produced by connective tissue cells as well (20, 21).

Reticular lamina is a layer that connects basal lamina and connective tissues bellow. It is composed of three types of fine collagen fibers (collagen I, III and V) produced by fibroblasts. This mesh-like, argentaffin structure can be easily observed by electron microscopy but for the light microscopy it must be labeled with either immunochemical markers or silver stained (20). Collagen fibers of lamina reticularis are attached to the acid proteoglycans of lamina densa and through them with basement membrane via fibronectin and glycosaminoglycans binds. All these connections enable full integrity and stability of basement membrane (22-24). On light microscopy, carbohydrates and reticular fibers of the basement membrane are routinely stained with PAS (Periodic acid Schiff) and silver stains (figure 2). Better visualization can be achieved with immunochemical markers and electron microscopy (21).

GROUND SUBSTANCE OF THE CONNECTIVE TISSUE OF THE BLOOD VESSEL

Ground substance of the extracellular matrix is amorphous, gel-like structure primarily composed of glycosaminoglycans, proteoglycans and glycoproteins. The components of the ground substance vary depending on the tissue type (25) (figure 2). Glycosaminoglycans (frequently referred to us as GAG, mucopolysaccharides or mucins) are unbranched polysaccharides consisting of a repeating disaccharide unit, often attached to the protein core. Members of the glycosaminoglycan family vary in the type of hexosamine, hexose or hexuronic acid unit they contain. Mucins are mainly of two types: acidic and neutral. Acidic mucins are sub classified in two groups. The first group of acid GAGs contain either sialic acid or sulphate radicals and the second group contain hexosamine or hexuronic acid. Overall, there are seven types of acid GAGs: strongly sulphated (proteoglycans), strongly sulphated epithelial mucins, weakly sulphated epithelial mucins (sulphomucins), atypical sulphated mucins, carboxylated mucins, sulphated sialomucins and hyaluronic acid. Neutral mucins do not contain reactive groups and are consisted of various hexosamines associated with free hexose groups (26, 27).

Proteoglycans are heavily sulphated glycosaminoglycans with protein core. They belong to the acidic GAGs (with hexosamine and glucuronic acid) and are produced by the fibroblasts, mast-cells and smooth muscle cells with synthetic phenotype. The degree of their polymerization determines the viscosity of ground substance. Proteoglycans reacts well with cation dyes at low pH (pH less then 1.0) and are PAS-negative during the standard periodic oxidation. They have a crucial role in the connective tissue matrix organization, cellular adhesion,

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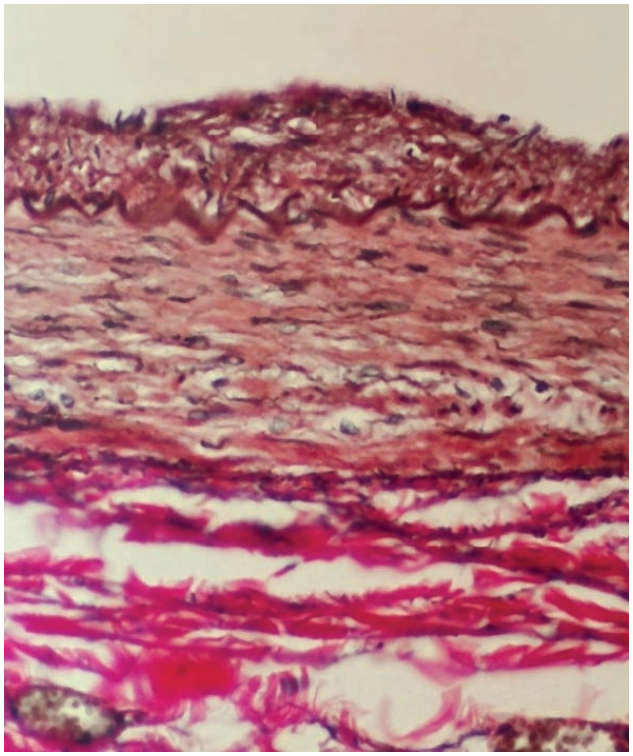

Figure 1. Distribution of the collagen fibers in the wall of the muscular artery (reticulin, x 64).

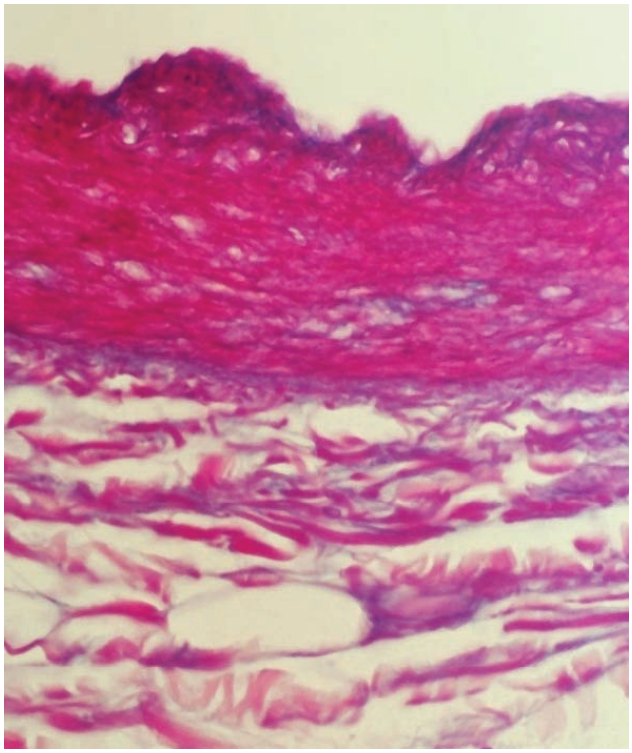

Figure 2. Distribution of the mucopolysaccharides in the wall of the muscular artery (PAS, x 64).

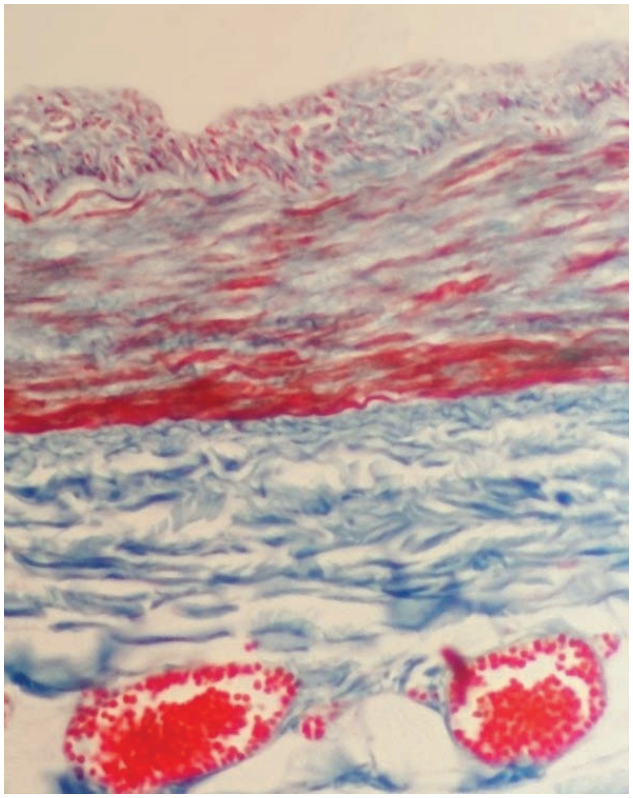

Figure 3. Composition and distribution of the extracellular matrix in the wall of the muscular artery. Red – smooth muscle cells and erythrocytes, blue –collagen fibers, light blue – ground substance (Azzan Heidenhain, x 64).

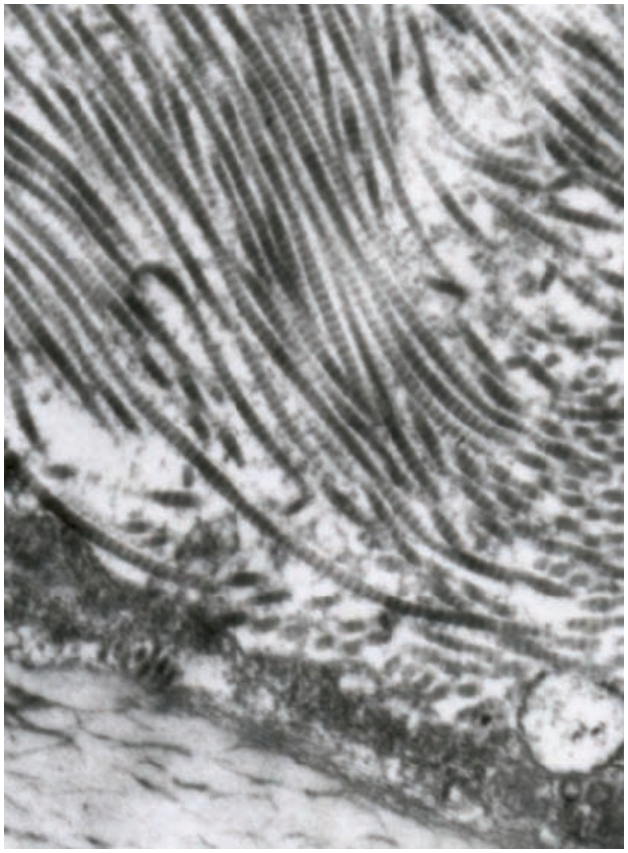

Figure 4. Distribution of the collagen fibers in the extracellular matrix of aorta (TEM, x 32.000).

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migration and proliferation as well as in lipid metabolism, hemostasis and thrombosis (27, 28) (figure 2).

Members of the proteoglycan family are: chondroitin sulphate A (located in cartilage), chondroitin sulphate B (specific for the vascular connective tissue), chondroitin sulphate C (cartilage and dermis), heparin/heparan sulphate (specific for the vascular connective tissue), keratan sulphate (located in the cornea and old cartilage) and chondroitin (located only in cornea) (29).Vascular connective tissue is characterized by the presence of chondroitin sulphate B and heparin/heparan sulphate. Endothelial cells are using these two proteoglycans to synthesize biglycan and perlecan, respectively (30). Recent findings suggest that smooth muscle cells of the vascular wall are able to produce versican, biglycan and decorin (31, 32).

Adhesive glycoproteins are large molecules involved in binding with other cells and/or with the extracellular matrix. They have binding spots for transmembrane proteins, collagen fibers and glycosaminoglycans of the ground substance. Because of their ability to bind cells to the elements of the extracellular matrix, they represent the most important integrative component of the connective tissue. In the vascular wall, especially in the coronary arteries, fibronectin, laminin, entactin, thrombospondin, vitronectin and osteopontin are present (25, 26).

Fibronectin is a large protein with C-terminal disulphide bridges always present in the basement membrane (more precisely basal lamina), external lamina of the smooth muscle cells and in the extracellular matrix. It acts as molecular glue between the cells and connective tissue matrix. Fibronectin is produced by endothelial cells and vascular smooth muscle cells. This protein exists as dimer and because it is an important part of the pericellular fibrous matrix, fibronectin affects growth, differentiation, migration and cell adhesion. Large quantities of this protein can be found in blood stream where it interacts with vascular wall and platelets. Recent reports show that fibronectin affects proliferation, morphology, migration and differentiation of the smooth muscle cells during the atherosclerosis (33).

Laminins are major glycoproteins in the lamina lucida (one of the layers of the basement membrane). They can be found in the external lamina of the smooth muscle cells as well. There are fifteen forms of this protein. Laminins have a large number of binding spots for the elements of the extracellular matrix. Survey of recent reports emphasized their ability to promote contractile phenotype of the smooth muscle cells (34). Entactin is a glycoprotein also found in the lamina lucida of the basement membrane where it binds laminin and collagen type IV (26).

Thrombospondin is adhesive glycoprotein that binds together collagen fibers, fibronectin and heparin in the extracellular matrix. It also has an important role in blood clothing. Thrombospondin 1 is produced by endothelial cells, smooth muscle cells and macrophages. During the atherosclerosis, thrombospondin promotes proliferation and migration of the smooth muscle cells and activate the TGF-β. Recent findings show that thrombospondin-5 is located in the vicinity of the smooth muscle cells and that it promotes their migration during atherosclerosis (35). Vitronectin is also involved in cellular migration through αvβ3 and αvβ3 integrins (36), while osteopontin shows great affinity for collagen and promotes migration of the smooth muscle cells during atherosclerosis. Osteopontin enhances the development of fatty streaks in mice on high cholesterol diet which suggests its role in the plaque formation (37, 38).

CONNECTIVE TISSUE FIBERS IN THE WALL OF THE BLOOD VESSELS

Fibers are major mechanical and supportive elements responsible for the hardness and elasticity of the connective tissue. Collagen and reticular fibers are composed of protein collagen, while elastic fibers are primarily composed of elastin (1-4). Collagen fibers play a major structural role and are the main supportive elements in the connective tissue. Being the most abundant, they represent the main site of resistance to mechanical forces such as stretching and pressing. Collagen molecule comprises three polypeptide chains which form a triple-helical structure and can be produced by fibroblasts, smooth muscle cells with synthetic phenotype as well as the other resident connective tissue cells. Until now, at least 28 types of collagen are identified and the main difference between them is the variation of the α chain. In the human genome, there are 42 different genes that are used for building the different types of the alpha chains. Recombinant DNA technique revealed even more collagen fiber types, but because of unclear alpha chain structure, those have not yet been designated (26). In the vascular wall, thirteen types of collagen fibers are present. They enable structural stability and affect cellular differentiation, adhesion, migration, proliferation and apoptosis. The mentioned processes are mainly controlled by collagens I, III, IV, V, VI and VIII in both, healthy and atherosclerotic, blood vessels (25).

Type I collagen is the most abundant collagen in the extracellular matrix which forms 75 nm thick fibers almost without interfibrillar substance. Specific assembly of its fibrils gives rise to the characteristic striations easily observed by electron microscopy. Type I collagen is usually associated to type III collagen (39). Type II procollagen is known to regulate the diameter of collagen I fibers through copolymer synthesis.

Type III collagen is present only in the tissues containing type I collagen. Collagen III fibers are

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frequently referred to as reticular fibers (40). Electron microscopy reveals stacked fibers surrounded by interfibrillar carbohydrate substance. Reticular fibers are composed of three identical α chains, α1 (III), that are different from the type I collagen chains due to larger amount of hydroxyproline and cysteine (25). Immunoelectron microscopy shows that the 20-25 nm thin fibers are primarily composed of type I collagen and the fibers 30-35 nm thin has additional amount of type III collagen (figure 4). Reticular fibers can also be recognized on paraffin tissue sections by silver impregnation or PAS staining (figure 1, 2). Both these methods are based on staining of particular carbohydrate groups, not the fibers themselves (27). Type III collagen is frequently called fetal collagen, because the fetal connective tissue possesses more of this protein then the adult one in the same spot.

Type IV collagen is the component of the basement membrane. It does not form fibers visible by electron microscopy. This protein is associated with significant amount of carbohydrates, thus, it is intensively stained by PAS technique (41-43) (Figure 2). Type IV collagen forms mesh-like structure found primarily in lamina densa, intertwined with other components. Focal presence of triple-helical non-collagen segments enables the elasticity of this molecule and basement membrane as well (25).

Type V collagen is produced by variety of cells, but small amount originates from the endothelial and smooth muscle cells. After the synthesis, type V collagen stay bound to the cell surface and it is probably involved in cell-to-matrix attachment (44). This molecule is composed of four α chains and can be found in all types of connective tissue, except the hyaline cartilage (25).

Type VI collagen forms thin fibers attached to type III and IV collagen and have a role in cellular adhesions (45). It is composed of three different α chains that form 100 nm long triple helix with globular domains on both ends. Molecule possesses peptide sequences that can be used as a binding spots for the cells (25).

Type VIII collagen forms fibers that are connected to the elastic fibers in the vascular connective tissue (46). It is composed of two different peptide chains and is first isolated from the cell culture of endothelial cells. Structure and tissue distribution of the type VIII collagen is yet to be clarified (39).

Unlike collagen, elastic fibers represent the elements of the connective tissue that enables elasticity of the tissues and organs. Single fiber is composed of central core (amorphous elastin) surrounded by the microfibrils (47, 48). Microfibrils are foundation for the deposition of elastin. They also affect orientation and organization of elastic fibers in the tissue. During the synthesis of the elastic fiber, initially microfibrils are formed and after that, elastin is deposited within microfibrils shaft (25, 27). Young elastic fibers possess more microfibrils, while with age the amount of elastin is increased. This causes loss of elasticity. Elastic fibers are produced by fibroblasts and smooth muscle cell with synthetic phenotype (11, 12). According to the degree of maturity, there are three types of elastic fibers: oxytalan, elaunin and mature fibers (49, 50). Visualization of the elastic fibers can be achieved by many techniques, but *Weigert van Gieson*, *Verhoeff van Gieson* and orcein staining methods are widely used. Elastic fibers are stained intensively, but not selectively. Fine, immature fibers are best stained with PAS because of presence of the carbohydrate glycoproteins bonded to microfibrils (Figure 2). High amount of disulphide cross-bridges are present in the structure of the elastic fibers. After the oxidation during the *Weigert* staining and after the treatment with iodine during the *Verhoeff* reaction, these bridges can be transformed into derivatives of sulfonic acid which are stained intensively. On the other hand, oxytalan fibers can not be stained with orcein and *Verhoeff* reaction in spite of the previous oxidation. These fibers, 17-20 nm thin have periodic striations on every 12-17 nm. Based on their morphology, localization and structural characteristics, one can conclude that oxytalan fibers represent an immature form of elastic fibers, but have an important role in the synthesis of the final adult elastic fibers. On the other hand, elaunin fibers can be stained with orcein, even without previous oxidation, but not with *Verhoeff* reaction. This fact proves that elaunin fibers are more mature form that oxytalan ones (27).

CONCLUSION

The structure and composition of the elements of the extracellular matrix, as well as their relations, are of upmost importance for the preservation of morphological and functional characteristics of the vascular wall. Normally, all structural elements of the vascular wall are connected together via complex bonds forming one active, highly integrated organ. As a consequence to a various pathological stimuli such as hypercholesterolemia, hypertension, diabetes mellitus, biomechanical impact of blood stream, the damage and dysfunction of the endothelium occurs. Along with this, a phenotypic modification of the smooth muscle cells also occurs, e.g. the change from contractile to synthetic phenotype, which leads to the modification of the extracellular matrix composition mainly in the subendothelial layer, but also elsewhere in the vascular wall. All these changes induce the cardiovascular diseases. Having in mind that the change of the composition of the extracellular matrix has a crucial role in vascular wall disease development, researchers focus their attention on possible therapy procedures aimed to preserve the original state of the matrix.

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