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MORPHOFUNCTIONAL CHARACTERISTICS OF ENDOTHELIAL CELLS IN CORONARY ATHEROSCLEROSIS

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Abstract - Atherosclerosis represents a complex disease which encompasses all the components of the vascular wall. Nevertheless, according to all known theories of the pathogenesis of atherosclerosis, the key role in this process belongs to the endothelial cells, i.e. the changes that they are subjected to especially during the initial stage of the lesion. In this review we have attempted, according to the results of our continuous research and numerous data from available modern literature, to show the cytohistological characteristics of endothelial cells, as well as the changes they are subjected to in all stages of atherosclerosis. In the first part we have reviewed the ultrastructure, function and pathology of the endothelium, subcellular organization of the endothelial cells, their specific characteristics, micro compartments and intercellular junctions. In the second part we have described the morphological and functional changes of endothelial cells during atherosclerosis. Special attention is given to the role of endothelial cells in the development of the initial stage of lesion: endothelial dysfunction, factors that cause the increased expression of adhesion molecules in endothelial cells and mechanisms that cause leukocytes to migrate through the endothelial layer to subendothelial connective tissue in the early stage of atherosclerosis.

Key words: Endothelial cell, cellular adhesion molecules, atherosclerosis

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INTRODUCTION

The vascular wall is composed of three main constituents, the endothelium, smooth muscle tissue and connective tissue that are interconnected with complex mechanisms into an active, highly integrated organ. The quantity and distribution of these tissues are influenced by mechanical factors, especially blood pressure and metabolic factors that reflect the local needs of a tissue.

The endothelium coats the internal surface of the heart and all blood vessels. It consists of a layer of flat endothelial cells and a basement membrane. Thanks to its position, it represents a highly selective barrier between the blood and the tissues of antithrombotic nature, because it has the ability to inhibit platelet adhesion and thrombocyte formation (Williams et al., 1989). This multifunctional organ regulates the blood coagulation processes, permeability and vascular tone, lipid metabolism,

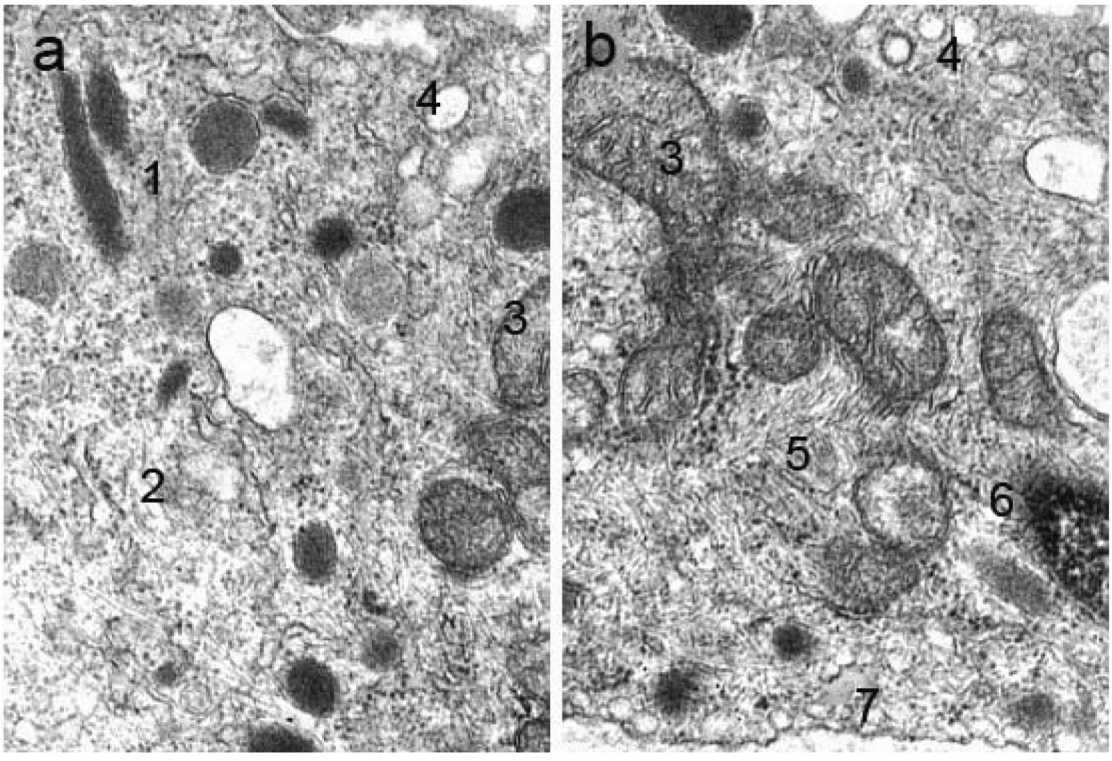

Fig. 1. Ultrastructural characteristics of endothelial cell (TEM x 45.000). 1. Weibel-Palade bodies; 2. rough endoplasmic reticulum; 3. mitochondria; 4. plasmalemmal vesicles; 5. cytoskeletal structures; 6. nucleus; 7. internal elastic lamina.

inflammatory and immunologic processes, as well as processes of atherogenesis and angiogenesis (Lippert and Pabst, 1985; Fawcett, 1986). It possesses a membranal angiotensin-converting enzyme (ACE) that generates angiotensin II. The endothelium secretes prostacyclins, cytokines, von Willebrand factor (vWF), thrombomodulin, tissue plasminogen activator (tPA), platelet-activating factor (PAF), cell adhesion molecules (CAMs), vasoactive substances, proteoglycans, free radicals and matrix metalloproteinases (MMPs) (Gartner and Hiatt, 1997).

One of the most important roles of the endothelium is the regulation of vascular tone. In this process, the endothelium secretes vasodilator and vasoconstrictor mediators between which are in balance under normal conditions. Endothelium-Derived Relaxing Factor (EDRF) or nitric oxide (NO) represents one of the most important vasodilatatory substances, while another important relaxing factor is prostacyclin (PGI2). NO primarily significant plays an important role in the regulation of blood pressure and blood flow. This free radical has a suppressive effect on the migration and proliferation of smooth muscle cells, leukocyte adhesion on the surface of endothelial cells, activation and platelet aggregation and apoptosis. Therefore, dysfunction of the endothelium which is reflected by a reduced synthesis or secretion of NO, leads to hypertension, atherosclerosis, congestive heart disease and the acute coronary syndrome. Endothelin-1 (ET-1) is the most important vasoconstrictor substance. In addition to causing strong vasoconstriction, including coronary blood vessels, in endothelial dysfunction it promotes the proliferation of smooth muscle cells in the neointima and thereby stimulates atherosclerosis and restenosis (Bult et al., 1988; Gallagher, 1997).

Characteristics of a endothelial cell

Endothelial cells are polygonal in shape, extremely thin, with the longer axis oriented in the direction of the flow of blood or lymph. Their shape varies depending on local hemodynamic effects. Normal, laminar blood flow promotes the expression of anti-inflammatory, antiproliferative, antiapoptotic and antioxidative endothelial genes, while altered arterial hemodynamics promote the onset and progression of atherosclerosis, restenosis and intimal hyperplasia in vein grafts (Adachi et al., 1997). The most characteristic organelles are Weibel-Palade bodies (WPBs), oval granules containing vWF which are involved in platelet adhesion to subendothelial layer of damaged blood vessels (Fig. 1). Besides the endothelium, vWF is located in the subendothelium, plasma, megakaryocytes and platelets (Ruggeri, 1997). Under normal conditions, endothelial cells maintain circulating platelets in an inactive state through NO and prostacyclin. But in places where the blood vessel is damaged, platelets adhere to the exposed subendothelium through the interaction of platelet receptors with collagen, vWF and fibronectin in the subendothelium. An important feature of endothelial cells is their polarization (asymmetry), which manifests itself through differently organized apical, lateral and basal parts (reviewed in: Lačković et al., 2000; Lačković et al., 2001a; Lačković et al., 2001b).

The apical luminal surface of endothelial cells is smooth and offers minimal resistance to blood flow (Varagic et al., 2000). It has a well-developed glycocalyx-limiting permeability of the endothelial cells, leukocyte adhesion and their emigration; it affects the processes of angiogenesis and modulates the endothelial cell metabolic status (reviewed in: Vukovic et al., 2006). Also, it functions as a sensor of power surges of the blood regulating NO production. It has been shown that oxidized low-density lipoprotein (OxLDL) induces its degradation.

In the apical section of the endothelium of the coronary arteries and other major blood vessels, plasmalemmal vesicles (caveolae), chlathrin pits and vesicles are present. Caveolae are numerous (up to 10,000 in the cell), hydrophobic plasmalemmal invaginations of endothelial cells. They participate in the process of passage of substances (albumin, insulin, native and modified LDL for which they have CD36 scavenger receptors) from the blood into the tissues, in signal transduction, atherosclerosis, lipid metabolism, vascular permeability and angiogenesis. Caveolae contain endothelial NO synthase (eNOS) whose removal in the process of atherosclerosis can induce OxLDL and thus lead to a decrease of NO production. In caveolae there is a receptor for vascular endothelial growth factor (VEGF) which induces the accumulation of caveolae and fenestrations. Chlathrin pits and vesicles participate in receptor endocytosis through which the endothelial cells import hormones, growth factors, LDL cholesterol, antibodies, coagulation proteins, enzymes and certain metabolites. In addition to endocytosis, endothelial cells possess the ability of transcytosis by which the greatest amount of plasma proteins (albumin) passes through the endothelium.

The lateral compartment of endothelial cells is characterized by the presence of intercellular junctions that regulate the permeability of endothelial cells, cohesion between them, extravasation and infiltration of leukocytes, the processes of angiogenesis and vasculogenesis, spreading waves of depolarization, the transfer of nutrients and maintenance of the polarization of endothelial cells (Wada et al., 2003). Between adjacent endothelial cells occludent, adherent and communicative junctions are differentiated. Occludent junctions are points where two adherent plasmalemmas of endothelial cells are closely connected by integral transmembrane proteins called occludins and claudins. Damage to this barrier leads to increased endothelial permeability.

Adherent junctions provide the mechanical stability of cells and their cohesive functioning. They have a fundamental role in the regulation of endothelial permeability. Through adhesion proteins, cadherins, they connect the cytoskeletal structure of adherent cells. For endothelial cells vascular endothelial cadherin (VE-cadherin) is specific and is involved in the transendothelial migration of leukocytes and tumor

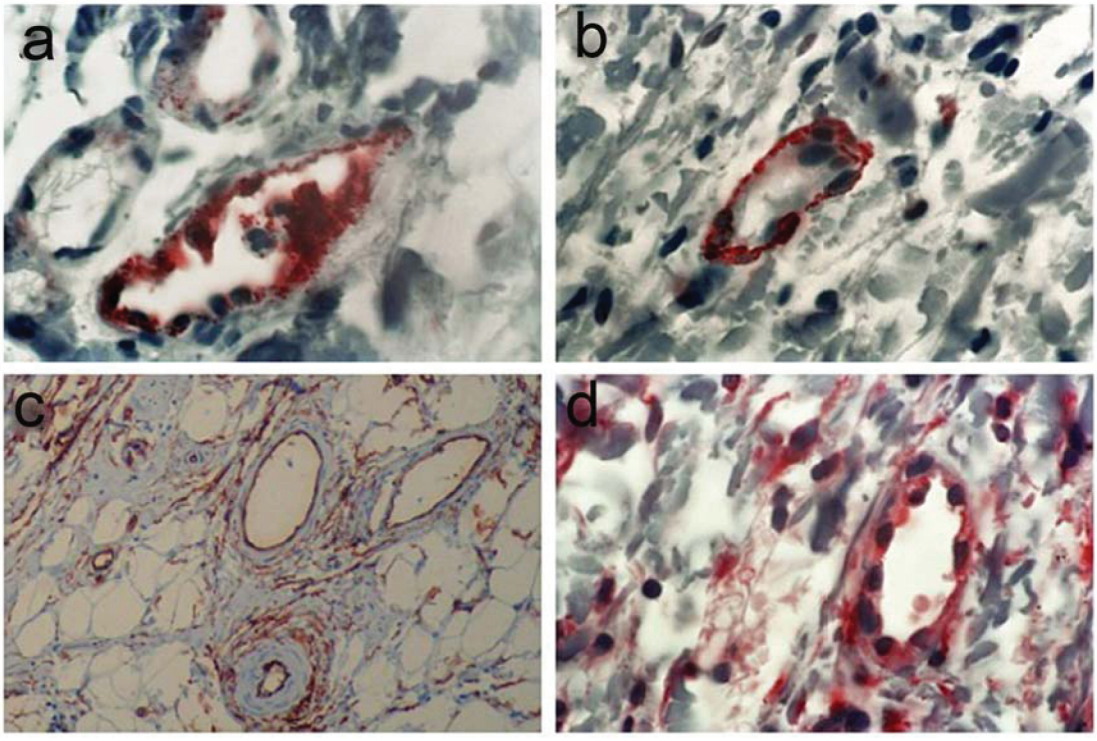

Fig. 2. Immunohistochemical characteristics of the endothelial layer (x 256). Endothelial immunoreactivity of: a) von Willebrand factor; b) CD31; c) CD34; d) vimentin.

cells together with platelet endothelial cell adhesion molecule 1 (PECAM-1). The adhesion of leukocytes to an endothelial cell induces the degradation of the adherent junction, which causes an increase in the permeability of the endothelial cells and an increased migration of leukocytes. It was also found that by blocking the adhesive function, PECAM-1 leads to the inhibition of transmigration of leukocytes. In atherosclerosis, under the influence of OxLDL and inflammatory cytokines, the expression of CAMs on the surface of endothelial cells comes about, which promotes the adhesion, rolling and transendothelial migration of leukocytes (Fig. 2).

Communicating (gap) junctions allow direct communication between cells through connexons which are responsible for the transfer low molecular weight nutrients, the spread of intracellular signals and waves of depolarization, by which the metabolic and functional integration of the two cells is established (Reese et al., 2002).

The basal compartment is characterized by myoendothelial junctions that provide metabolic and functional integration of endothelial and smooth muscle cells, as well as focal adhesions (FAS) by performing the transmission of biochemical, mechanical and inflammatory signals from the ECM to the inside of the cell and vice versa.

The endothelium in atherosclerosis
Activation of the endothelium

According to existing theories about the pathogenesis of atherosclerosis, the main change in the vascular wall which is characteristic for the initial stage, is endothelial dysfunction, i.e., the activation of the endothelial cells as a specific response of the endothelium to the effects of harmful agents. The acute response of the endothelium results in inflammation, coagulation disorders and vasomotor changes (reviewed in: Vukovic, 2003, 2006). The release of inflammatory media-

tors that have been deposited in WPBs represents a rapid response of endothelial cells (Gimbrone, 1995; Risa, 1998).

One of the most important consequences of endothelial activation is manifested by decreased production or complete absence of NO and thereby loss of its antiatherogenic, antiproliferative and vasodilatory effects (reviewed in: Lačković and Bumbaširević, 2000; Lačković et al., 2010). This results in increased intracellular oxidative stress, which is the strongest stimulus for endothelial cell dysfunction. Along with this process, an increased production of ET-1 comes about which, indue to its mitogenic effect, stimulates the proliferation of smooth muscle cells in the intima which leads to thickening in the artery wall (Pearson, 1991, Mehta and Malik, 2006).

During the activation of endothelial cells changes in coagulation are observed. Due to the increased expression of tissue factor, thrombomodulin expression decrease or increased release of tissue plasminogen in the endothelium, modulation of phenotype of endothelial cells from anticoagulant to procoagulant occurs (Cunningham and Gotlieb, 2005; Ruggeri, 1997).

Besides the alteration in tone and coagulation, endothelial activation includes the expression of adhesion proteins (P-selectin, integrins) that promote the adhesion of leukocytes to the surface of endothelial cells, and their infiltration into the subendothelial connective tissue (Lačković et al., 2001; Lačković et al., 2007). This results in the release of free radicals, proteases and elastases leading to cell damage (Ruggeri, 1997).

Expression of adhesion molecules in atherosclerosis

Shortly after the initiation of hypercholesterolemia, leukocytes (initially monocytes and T cells) adhere to the endothelium and actively migrate by diapedesis as well as through the endothelial cells, into the intimal subendothelium (Inoue, 1994; Rauterberg and Jaeger, 1992). In the intimal subendothelium, monocytes begin to accumulate lipids and transform into foam cells. In the process of adhesion of monocytes and T lymphocytes, the adhesion molecules expressed on the endothelial cells have a key role due to the presence of OxLDL in the intimal subendothelium (reviewed in: Vukovic, 2003, 2006). Adhesion molecules promote the adhesion of leukocytes and their migration into subendothelium, initial and advanced stages of atherosclerosis (Goodenough and Paul, 2003; Kreis and Vale, 1993).

Different types of adhesion molecules are involved in this process. These include integrins – members of the immunoglobulin superfamily such as intercellular adhesion molecules 1 and 2 (ICAM-1 and ICAM-2), vascular cell adhesion molecule 1 (VCAM-1), PECAM-1 and E-, P- and L-selectin. The integrins play a role in the adhesion of leukocytes to endothelium, while selectins allow their "rolling" on the surface of the endothelium, until the leukocytes receive the signal for migration into subendothelium (reviewed in: Lačkovic et al., 2001; Vukovic, 2003, 2006). A third group of proteins assumes the role of signaling molecules in this process; these are the chemokines that are synthesized by endothelial cells in response to atherogenic stimuli (Rauterberg and Jaeger, 1992; Timpe and Dziadek, 1986, Holbrook and Smith, 1993).

Increased expression of VCAM-1 is characteristic of the initial phase of atherosclerosis. The molecules interact with specific integrins, very late antigen 4 (VLA-4) which is expressed only on monocytes, and T lymphocytes (Li et al., 1993, Libby et al., 2002). As a result, in the initial stage of atherosclerosis, monocytes and T lymphocytes adhere to the endothelium at a significantly higher percentage than other types of leukocytes (reviewed in: Vukovic et al., 2006, Vukovic, 2006). On the other hand, ICAM-1 adhesion allows many different types of leukocytes, thanks to the interaction with CD11a (LFA-1) and CD11b (Mac-1) integrins on their membranes, and its expression is characteristic of endothelial cells in the later stages of development of atherosclerotic lesions (Bazzoni and Dejana, 2004, Goodenough and Paul, 2003).

E-selectin is a typical representative of this group of adhesion molecules. Its name comes from the finding that it is specifically expressed only endothelial cells. Its increased expression is characteristic of the advanced stage of lesions. As this molecule interacts with Sialyl-Lewis X ligand on the membrane of granulocytes and T memory lymphocytes, in advanced lesions this type of leukocyte adheres to the endothelium at a significantly higher percentage compared to other types of leukocytes (Bazzoni and Dejana, 2004, Goodenough and Paul, 2003). P-selectin is expressed primarily on platelets, but endothelial cells above the atherosclerotic lesions also express it. This molecule interacts with P-selectin glycoprotein ligand 1 (PSGL-1) on monocytes, lymphocytes and neutrophils. It plays an important role in the "rolling" of leukocytes on the endothelium over lesions (Inoue, 1989; Hristov et al., 2003; reviewed in: Lačković and Vukovic 2006). L-selectin is expressed on leukocytes and interacts with the PSGL-1 ligand on monocytes, lymphocytes and neutrophils, but also with the mucosal addressin vascular cell adhesion molecule 1 (Madcom-1) which is expressed on endothelial cells, fibroblasts and melanoma cells (Inoue, 1994; Rauterberg and Jaeger, 1992).

It was determined and established that in the human endothelium above the atherosclerotic plaques at sites of infiltration of monocytes, there was a significant increase in ICAM-1 and P-selectin (Rauterberg and Jaeger, 1992). These findings suggest that the accumulation of monocytes which were later to transform into macrophages, is largely dependent on the synergistic action of ICAM-1 and P-selectin on the endothelium (Mehta et al., 1995).

Many factors, either individual or in combination, can induce the expression of endothelial adhesion molecules in atherosclerosis (reviewed in: Lačković et al., 2001). These include OxLDL, inflammatory cytokines, as well as the biomechanical strengths of the blood currents that cause the remodeling of the vessel wall in atherosclerosis. It has been shown in tissue culture that treatment of endothelial cells with oxidized LDL causes an increased expression of P-selectin, ICAM-1 and VCAM-1 (Mehta et al., 1995; see review Vukovic et al., 2010). Cytokines, including interleukin 1 (IL-1) and tumor necrosis factor α (TNF-α), increase the infiltration of leukocytes through the adhesion molecules (Kreis and Vale, 1993). As regards the biomechanical stimuli, it was shown that blood pressure can directly and indirectly contribute to the increased expression of adhesion molecules. a It is established that the regulation of ICAM-1 is directly affected by power surges of the blood, i.e., that the expression of adhesion proteins is increased in systemic hypertension (Gimbrone, 1995). In addition, hypertension also indirectly affects the expression of adhesion molecules. Under the influence of invasive blood pressure in conditions of hypertension there is a primary compensatory dilatation of the vascular wall, and a proliferation of smooth muscle cells, their migration into the subendothelium, increased synthetic activity and production of large amounts of proteoglycan "ready to connect" LDL, which allows its oxidation and represents one of the strongest signals for the expression of adhesion molecules (Goldstein et al., 1979; reviewed in: Vukovic 2003, 2006).

Migration of leukocytes through the endothelium

When they adhere to the endothelium, leukocytes must receive a signal to pass through the endothelial layer and into the deeper layers of the wall. Two specific processes, integrin-mediated adhesion and selectins mediating "rolling" allow the leukocytes to receive "signals" to enter the vascular wall and the migrate. Migration of leukocytes to the vascular wall takes place as diapedesis between endothelial cells and through the cells by transendothelial migration. The rolling of leukocytes and their migration to the vascular wall are crucial steps in the development of inflammatory reactions in the vascular wall during atherosclerosis (reviewed in: Vukovic et al., 2008; Tanaskovic, 2010). Today's concept of direct migration of adherent leukocytes includes, as was previously mentioned, the activation of chemokines. In the initial phase of the lesion, selective adhesion of monocytes and T cells to the surface of the endothelium and synthesis of specific chemokines in endothelial cells occur. During this phase of

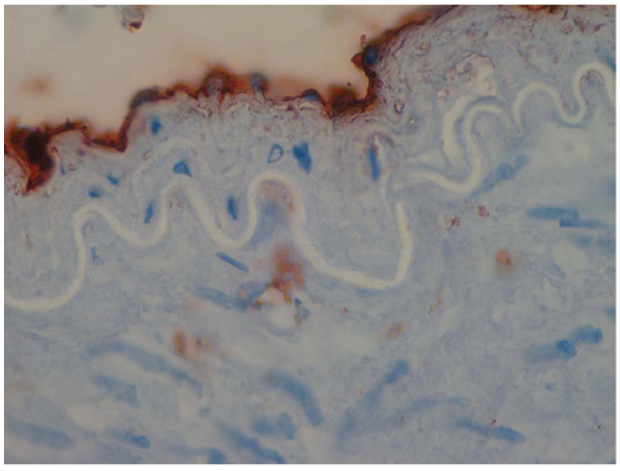

Fig. 3. Morphologically preserved endothelial layer at early stage of coronary atherosclerosis. Immunohistochemical staining of CD34, x 256.

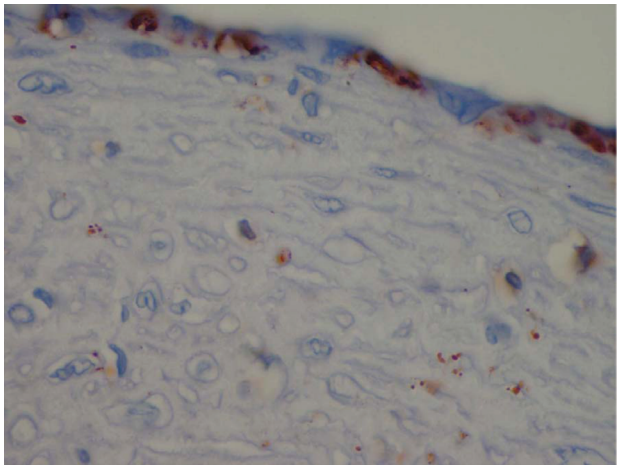

Fig. 4. Focal demaged endothelial layer at preatheroma stage (intermediate lesion type III). Immunohistochemical staining of vimentin, x 256.

the lesion, the chemokine monocyte chemoattractant protein 1 (MCP-1) is produced in the endothelium in response to oxLDL and other stimuli (Jones, 2002; reviewed in: Tanaskovic, 2010). MCP-1 directly initiates chemotaxis and migration of monocytes in the subendothelium. In the stage of initial lesion, the endothelial cells, as well as populations of intimal smooth muscle cells, synthesize macrophage colony-stimulating factor (M-CSF) which also promotes the chemotaxis of monocytes; their adhesion and differentiation into macrophages; regulation of the proliferation of macrophages and other cell types; and is also involved in the inflammatory-fibroproliferative response of the wall during advanced stages of atherosclerosis (Katsudo and Kaji, 2003, reviewed in: Tanaskovic, 2010).

During the initial phase of the lesion, endothelial cells synthesize the chemokines that enhance T lymphocyte accumulation in the plaque. Endothelial cells synthesize three lymphocyte-selective chemokines: interferon-inducible protein 10 (IP-10), interferon-inducible T cell alpha chemoattractant (I-TAC), and monokine induced by interferon-γ (MIG). Interferon-γ which is present in atherosclerotic lesion induces genes that encode a family of T cell chemoattractants, i.e. the chemokines, and consequently promotes the accumulation of T cells in the lesion (Merrilees et al., 2001; reviewed in: Vukovic et al., 2008).

OxLDL also stimulates endothelial cells to synthesize other growth factors such as the granulocyte colony-stimulating factor (G-CSF) and granulocyte-macrophage colony-stimulating factor (GM-CSF). These cytokines are involved in the differentiation, proliferation, migration and metabolism of macrophages/granulocytes, and also affect the migration and proliferation of endothelial cells (Riessen et al., 1994; Schönherr et al., 1993).

Cytohistological endothelial changes in the developmental stages of atherosclerosis

Results of some recent studies of atherosclerotic lesions have shown that in the stage of initial lesion (early lesions type I) there are no visible morphological changes in the structure of the vascular wall (Fig. 3) (Vukovic, 2003). In the initial stage of the lesion, the continuity of the endothelium is preserved; the basement membrane is well differentiated and present in the entire length. On the surface of the endothelium, individual adherent monocytes and T lymphocytes are present, which indirectly indicates the expression of adhesion molecules. In the intimal subendothelium, the individual foam cells and T cells

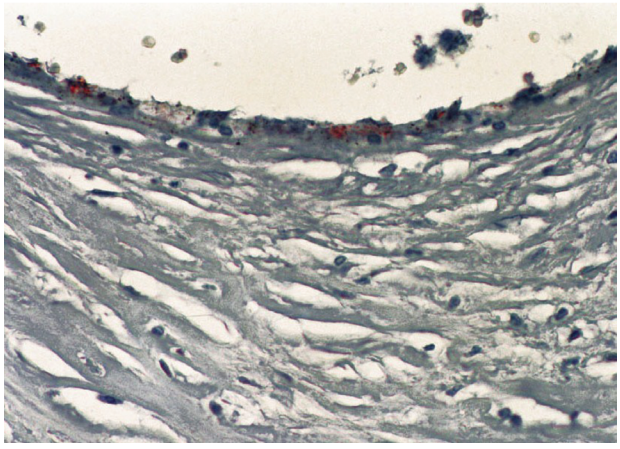

Fig. 5. Endothelium over a fibrous plaque shows complete denudation followed by focal adhesion of endothelial progenitor cells (reendothelization). Immunohistochemical staining of CD34, x 128.

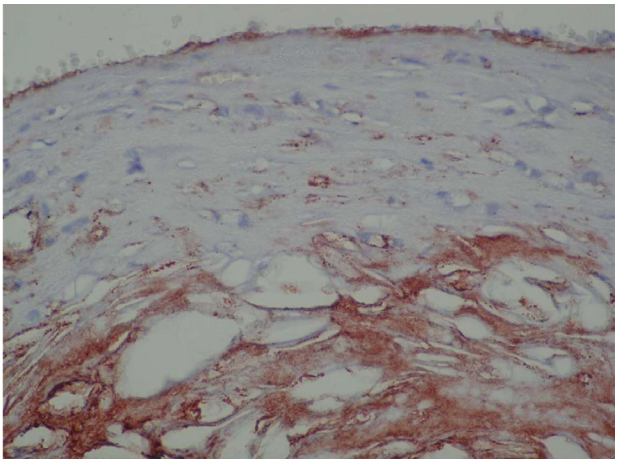

Fig. 6. Endothelium over a fibroatheroma. Immunohistochemical staining of vimentin, x 32.

are present. In the initial phase of the lesion, adherent monocytes are the main precursors of foam cells (Vukovic, 2006; Vukovic et al., 2010). In the stage of fatty streak (early lesions type II), while the endothelium is still preserved morphologically it is functionally defective. On the surface of the endothelium in histological preparations of arteries, with the staging of lesions and in the initial phase of the lesion, the presence of adjacent T cells and monocytes is observed. This is an indirect indicator of the functional impairment of the endothelium, i.e., expression of adhesion molecules (Vukovic et al., 2008a). The endothelial basement membrane is intact. In the intimal subendothelium, besides the increased number of cells compared to the previous stage, an increasing amount of very sulfated mucins (proteoglycan) has been observed with the alcian blue-PAS technique at low pH values (Vukovic et al., 2008 b; Tanaskovic et al., 2010). During further development of the lesion, the stage of preatheroma (intermediate lesion type III) shows focal endothelial damage, while the basement membrane is intact (Fig. 4). In the intimal subendothelium there is a slightly smaller amount of proteoglycans in the stage of fatty streak (Vukovic et al., 2008; Tanaskovic et al., 2010).

In advanced stages of the lesion, the endothelium exhibits distinct morphological damage (Fig. 5, 6) (Vukovic et al., 2007 a). In the stage of atheroma (later lesion type IV), the endothelium over the lesion is discontinuous, focally exhibiting an immunohistochemical reaction to vWF and CD31. At sites where the endothelial layer is preserved, adhesion of neutrophils are observed. It appears thickest in the region of the atheroma, so it focally, eccentrically narrows the lumen. The basement membrane is discontinuous. In the intimal subendothelium, a large lipid core dominates with cholesterol crystals in the cracks (Vukovic 2003; Vukovic et al., 2007). In the stage of fibroatheroma (late lesion type V), the endothelium is also discontinuous (Fig. 6). At sites where the endothelial cells are present, vWF and CD31 are expressed (common features), and focally in some sites above the fibroatheroma, the CD34 (Vukovic 2003; Tanaskovic et al., 2010 a). The basement membrane is fragmented. Eccentric fibrous thickening dominates in the intimal subendothelium of fibroatheroma. At this area a broad fibrous cap and small lipid core, or vulnerable plaque, which contains a soft, lipid core and a collagen rich, sclerotic, fibrous tissue that stabilizes it can be observed (Fig. 5) (Vukovic, 2006, Tanaskovic, 2010).

Endothelial response to vWF and CD31, observed in the initial and also in the later stages of atherosclerosis at those sites where there the endothelium is present, represents the common feature of endothelial cells (Katsudo and Kaji, 2003; Cybulsky

and Gimbrone, 1991; Hristov et al., 2003). However, there is an interesting finding of CD34-immunoreactive endothelium over advanced atherosclerotic intimal changes. Although vascular endothelial cells can express CD34, expression of this antigen in the endothelium can be seen only in advanced lesions (Vukovic, 2006).

Endothelial expression of CD34 can serve as a marker of reendothelization over advanced atherosclerotic plaques (Vukovic, 2003; Tanaskovic et al., 2010 b). Recent studies have showed that the peripheral blood of an adult organism contains a unique subtype of circulating cells produced in the bone marrow that have properties similar to embryonic angioblasts. These cells have the ability to proliferate and differentiate into mature endothelial cells (Christ et al., 2003). They show immunoreactivity to a number of markers that are specific to endothelial phenotype, such as CD31, CD34, CD146, VE-cadherin, vWF, vimentin, NO synthase, and E-selectin (after stimulation). Release of endothelial precursors from the bone marrow is a very complex process regulated by growth factors, enzymes, ligands and surface receptors. It was shown that after platelet microangiopathy and endothelial balloon angioplasty, progenitor cells are involved in the repair of damaged endothelium (Vukovic, 2006).

It is known that damage to endothelial cells is one of the key moments in the pathogenesis of atherosclerosis, and after endothelial damage, rapid reendothelization prevents the formation of neointima (Werner et al., 2003). Reendothelization that activates circulating endothelial progenitor cells originating from the bone marrow is a "defense mechanism" of the vascular wall with an aim to preserve its structure (Hristov et al., 2003, Tanaskovic et al., 2010). However, the number of circulating endothelial precursor CD34-immunoreactive cells (and their total number in the bone marrow) was significantly reduced in patients with coronary disease; all risk factors, primarily hypertension, affect this reduction. In addition, in coronary disease there is a functional impairment of the ability to respond to the migration of circulating endothelial cells which prevents reendothelization in the early stages (that would prevent or reduce the level of development of atherosclerotic lesions) and is manifestedinsufficient in the later stages of atherosclerosis (Vasa et al., 2001). Endothelial expression of CD34 results in the adhesion of leukocytes that characterizes the later stages of atherosclerosis since CD34 has the function of an endothelial ligand for binding L-selectin (CD62) to the membranes of leukocytes (Hristov et al., 2003; Dianzani and Franzoi, 1995; Schlossman, 1995; Tanaskovic, 2010).

CONCLUSION

The endothelium in the early stages of atherosclerotic lesions is morphologically preserved, but functionally defective. Dysfunction of endothelial cells in the initial stage and at the early stages of atherosclerosis has a crucial role in the pathogenesis of this disease. OxLDL stimulates an increased expression of adhesion molecules on endothelial cells which causes the adhesion of leukocytes and production of cytokines-chemokines in endothelial cells promoting the migration of leukocytes (in the initial phase monocytes and T lymphocytes) in the subendothelial layer, and the synthesis of growth factors that influence the differentiation, modification and the proliferation of different cell populations in the lesion. Besides OxLDL, mediators secreted by macrophages also influence the dysfunction of endothelial cells by promoting the expression of platelet-activating factor, tissue factor and plasminogen activators and inhibitors, which cause the transformation of the nonadhesive and anticoagulant surface of endothelial procoagulant and adhesion. In this way, the dysfunction and damage of endothelial cells initiate a vicious circle of events in which a large number of associated factors promote further development of atherosclerosis.

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