Diabetes and atherosclerosis. Cellular mechanisms of the pathogenesis. Literature review

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Abstract. The review of the literature analyzes the cellular mechanisms of the pathogenesis of the complication of diabetes mellitus — the accelerated development of atherosclerosis. The mechanisms of metabolic impairment and the genesis of endothelial dysfunction in diabetes mellitus have been analyzed; the role of intercellular junctions of vascular endothelial cells to support vascular integrity and permeability barrier in norm and pathology has been shown. Data on involvement in the pathogenesis of atherosclerosis on the background of diabetes mellitus of vascular smooth muscle cells, macrophages, platelets and erythrocytes are summarized. The role of the nuclear factor NF-κB — regulator of inflammatory reactions in endothelial cells, vascular smooth muscle cells and macrophages is shown.
Keywords: atherosclerosis, diabetes, endothelium, vascular cells, NF-κB.

Diabetes mellitus (DM) is associated with a risk of developing the different complications, including atherosclerosis (AS) — chronic inflammatory lesion of large- and medium-sized arteries [1]. Patients with DM are characterized by a high level of diseases and a large number of atherosclerotic plaques in the coronary vessels as compared with those without DM. Atherosclerotic plaques mainly consist of modified lipids, infiltrated macrophages (MPs), T-cells and smooth muscle cells (SMC) that are accumulated in the arterial wall. Plaques can significantly narrow or close the artery lumen with the formation of coronary arterial stenosis or occlusion. The plaque destruction with the thrombus formation can lead to the acute coronary syndrome development and to a lethal outcome [2, 3].

Mechanism formatting the atherosclerotic plaque

The endothelial dysfunction (ED) is considered a key event initiating atherogenesis in DM and the increase level of low density lipoprotein (LDL) in plasma associated with it. ED leads to a decrease in the level of nitric oxide (NO) and to the expression of adhesion molecules, mediating the adsorption of monocytes, the production of inflammatory cytokines and increased endothelial permeability. Apolipoprotein B-containing lipoproteins penetrate into the vascular wall by diffusion, resulting in the LDL accumulation, interacting with the extracel-

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lular matrix (ECM), retaining LDL in the vascular wall where they can be oxidized with ROS to oxLDL. Then proinflammatory oxLDL lipids can stimulate endothelial cells (EC), strengthening the formation of cell adhesion molecules, chemotactic proteins, growth factors, and suppressing NO production [9]. Monocytes are recruited from the blood into the intima, attracted by chemokines, such as CCL2, which are expressing by the endothelium. In subendothelial space of the intima, they are differentiated into MPs, which then are taken oxLDL in the vascular wall with phagocytosis through the scavenger receptors. This pathway of modified LDL absorption leads to the accumulation of cholesterol droplets in the MP cytoplasm, creating canonical foam cells, typical for early atherosclerotic formations. T-cells, CD4+ Th1-cells in particular, are also mobilized in early foci of vascular lesions and recognize autoantigens, including oxLDL and HSP60. IFNγ, activating MPs, leading to further secretion of cytokines and chemokines is produced by Th1-cells. Continued mobilization of inflammatory cells and the accumulation of modified lipids lead to the formation of necrotic nucleus in the plaque, consisting of dead and dying cells, as well as extracellular cholesterol. As the plaque develops, the SMC are migrated from the median arterial membrane into the intima, where they are divided and secrete ECM, consisting of collagen, elastin, proteoglycans and glycoproteins, which initiates the fibrotic formation covering the inflammatory necrotic nucleus of plaque. Atherosclerotic plaques in DM are characterized by increased calcification, the formation of necrotic nuclei, the presence of receptors for AGE (RAGE), as well as the infiltration MPs and T-cells. There is also an increased number of plaques with ruptures and vascular rearrangements [1]. These features can contribute to the development of more severe AS and increase the frequency of acute side effects in DM.

Cellular mechanisms of atherogenesis

The atherosclerosis development involves the activation, dysfunction and migration of various cells types (including EC, SMC, lymphocytes, monocytes, and MPs) in the arterial intima, leading to a local inflammatory reaction.

Endothelial cells. A great number of regulatory substances such as NO, prostaglandins, angiotensin (AT), endothelin-1 (ET-1) are synthesized by EC, and the formation of adhesion molecules can be stimulated by them for interaction with neutrophils and platelets. Vasodilation and vasoconstriction, hemostasis, inflammation on the vessel surface and within its wall are controlled by these regulators [1, 5]. NO, is an anti-atherogenic agent formed as a result of endothelial nitric oxide synthase (eNOS) activity, and it is one of the key factors of vasodilation and suppression of platelet aggregation. The EC damage and dysfunction is the key events in AS development. Intact endothelium usually inhibits the inflammation and activation of platelets by reducing the formation of the platelet-leukocyte adhesion molecules and their subsequent migration through the vessel wall, as well as inhibition of SMC vessel proliferation and migration [5]. The EC are particularly sensitive to glucose increase and many effects of DM, including insulin resistance (IR) [1].

Metabolism of endothelial cells. It should be taken into account that the EC population from capillaries, large arteries and veins is very heterogeneous [6]. Therefore, EC may differently react on the growth and migration stimuli, and are also characterized by the activity of the specific gene clusters, depending on the vessel type (arteries and veins, macrovessels and microvessels), anatomical location and environment. Most of the energy is provided by glucose in EC, as opposed to cardiomyocytes, and the fatty acids (FA) generate only 5% of adenosine triphosphate (ATP) total amount [7]. It has been suggested that FA oxidation in EC is primarily directed to the nucleotides synthesis *de novo* for DNA replication and EC proliferation. In most cells using glucose, the initial stage, glycolysis, is occured in the mitochondria, the main path to accumulate ATP [8]. However, the ATP supply in EC is relatively independent on the mitochondria oxidative pathway. Under physiological concentrations, 99% of glucose is metabolized by glycolysis pathway, and only 1% enters the Krebs cycle [9]. The dependence of EC on glycolysis has several advantages [10].

1. The glycolysis enzymes are located in the cytoplasm, in close proximity to the cytoskeleton, that facilitates the immediate ATP delivery for the actin reorganization, providing angiogenesis and vesicular secretion.
2. Use of the glycolytic pathway in EC to generate ATP, excess of oxygen and FA for the nutrition of underlying myocytes. Myocytes have a high oxygen demand, considering that FA oxidative phosphorylation is their main substrate for energy production.

3. Although the mitochondrial oxidative pathway produces more ATP per mole of glucose, a similar ATP amount is formed as a result of a high glycolysis rate.
4. In the glycolysis process, not only energy is generated, but also necessary intermediate products needed for cell growth, migration and angiogenesis.
5. An additional advantage of this adaptation is that EC are protected from ROS generation, which could damage them [10].

Glucose necessary for glycolysis enters the cell by the transporters. GLUT1 is the main isoform of the glucose carriers that are present in EC. This uniporter of the plasma membrane promotes the glucose entry into EC from the luminal side and its output through the abluminal membrane. It is necessary to note the uneven distribution of GLUT1 in favor of the ablaminal side, although not in all types of EC [11]. Such distribution leads to the fact that extrusion occurs faster than glucose uptake in EC of microvessels. And this, in turn, allows EC to direct glucose to adjacent myocytes with high metabolic needs. Then glucose in EC is metabolized by the key glycolysis enzymes to pyruvate, 1% from which is metabolized in the tricarboxylic acid cycle (TCA cycle), and the most part converts to lactate [9]. Thus, oxidative pathways in EC generate a minimum quantity of ATP.

Disorders of EC metabolism in Diabetes Mellitus. As was indicated, glucose enters EC mainly through GLUT1, which is considered an insulin-independent carrier and cells do not respond to glucose in DM by increasing the GLUT1 expression, remaining insensitive to hyperglycemia [7]. This position is in doubt, as EC protect themselves from excess of glucose by decreasing GLUT1 expression. However, if a decrease in the carrier amount on the cavity side can be a favorable response, its decrease on the abluminal side will make it difficult to extrude glucose into the myocytes. And this will lead to an increase in the intracellular glucose concentration, the ROS generation and glycolytic inhibition. New data suggest that EC reduce the GLUT1 expression and glucose uptake under the influence of high glucose concentrations (HG). The decrease of glycolytic flow in DM can by explained by these data, together with the fact of the decreased enzymatic activity in glycolytic processes [10]. Stopping of glycolytic flow means that the intermediate products of glycolysis are accumulated and directed to different metabolic pathways. These include the polyol pathway with the sorbitol and fructose formation, hexosamine biosynthesis pathway, which inhibits angiogenesis, methyl glyoxal pathway, protein kinase C activation, and defects of the mitochondria biogenesis and fragmentation [10]. The end result is excessive production of ROS and active forms of nitrogen, the AGE synthesis — mediators of EC dysfunction [10, 12]. The TXNIP system (thioredoxin-interacting protein) is involved in the mechanisms explaining the change in GLUT1 content under hyperglycemia condition [13]. TXNIP, directly binding to GLUT1, causes its endocytosis and subsequent cleavage in lysosomes (acute effect), in addition to decrease in GLUT1 mRNA level (chronic effect) [13]. The TXNIP level is suppressed in many tumors, as cancer cells require the high expression of GLUT1 to maintain the intense glycolysis. It is known that TXNIP is the product of a special glucose-sensitive gene that is induced in the response to HG or the lowering of insulin level [14]. Whether DM is associated with increased TXNIP expression in EC is not yet clear. According to alternative pathway, TXNIP can reversibly bind to thioredoxin-1 (TRX1), which interaction is weakened by ROS, and allows TXNIP to dissociate from oxidized TRX1 following by GLUT1 downregulation [15]. Probably, TXNIP expression and dissociation from TRX1 are enhanced with HG and ROS generation, which increases its availability for interaction with GLUT1. It is also assumed that the exosomes of myocytes, transporting the glucose transporters and enzymes associated with glycolysis in EC, can modulate the endothelial transport of glucose and metabolism [16]. The question whether this process is suppressed in hyperglycemia, is interested as an additional mechanism explaining the changes in the rate of glucose uptake and metabolism in EC in DM. The increase of FA intake is provoked by limit of the glucose utilization in cardiomyocytes, to ensuring adequate production of energy. For this, FA absorption and oxidation are necessary — processes, which are amplified in myocytes in DM, but still not sufficiently studied in EC [7]. The presence of the reserve oxidation potential and the ability to enhance oxidation in high metabolic need or stress conditions showed in EC culture experiments [9]. Under conditions of glycolytic inhibition in DM, it is assumed that increased FA availability may lead to the addi-

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tional oxidation of this substrate. A fact confirming that fatty acid oxidation (FAO) is increasing in EC, raises other questions. It is unclear whether this FAO amplification is directed to ATP formation or the nucleotide synthesis and whether the excess of energy production from FA is associated with undesirable effects in EC. It is known that acetyl-CoA, forming in FAO is used for DNA synthesis and cell proliferation, division in EC [17]. ROS forming as a result of FAO will interfere with the transport of glucose and glycolytic enzymes (GAPDH), which can additionally decrease the glycolysis level under HG conditions [18]. The readiness degree of EC to use the FAO excess is also unknown. The number of mitochondria capable to FAO consists only 2-6% of EC volume in comparison with hepatocytes (28%) or cardiomyocytes (32%). Thus, the excess of FA entering EC can be associated with a gradually weakening effect on the oxidation process and, consequently, this substrate will either migrate through EC or be stored as triglycerides (TG). The latter seems particularly important, taking into account the negative consequences, storage of TG in cells other than adipocytes, in addition to the negative consequences of utilizing the excess of FA. The changes in metabolism and the EC function may result not only in their death, but the death and dysfunction of the underlying myocytes [7].

Intercellular junctions of EC. The unique barrier between the vessel lumen and the vascular wall is formed by EC. Different functions are performed by endothelium, including the control of vascular tone and permeability, the regulation of vascular inflammation, the prevention of thrombosis and maintaining vascular integrity [19, 20]. Maintenance of vascular integrity and barrier of permeability is realized through the system of intercellular junctions between EC [21]. Two major subtypes of intercellular contacts — tight junctions (TJ, or Zona occludens) and adhesive junctions (AJ or Zona adherens) are spread in EC [22]. As a rule, TJ are localized in the apical zone of the intercellular gap. They are responsible for the barrier function, control the transport of the dissolved substances between neighboring cells, and regulate the lateral diffusion of proteins in the plasma membrane [20].

Limited vascular permeability is provided by the barrier function of arterial endothelium under physiological conditions. In vascular pathology, such as AS, the proinflammatory signals activate EC, inducing the expression of adhesion molecules and destabilizing the endothelial barrier. This attracts leukocytes, including T-lymphocytes, monocytes / MPs and enhances their junction with the endothelium. Then the leukocytes penetrate through the endothelial layer and infiltrate the arterial intima [20].

Intercellular junctions between ECs are formed by complicated protein complexes containing transmembrane and cytosol proteins that connect the membrane proteins with the intracellular cytoskeleton [22]. In TJ proteins associated with membranes, are presented by claudins, playing a central role in the regulation of endothelial permeability, by occludins, involved in the TJ sealing and barrier functions and junctional adhesion molecules (JAM). AJ contain only one membrane protein — VE-cadherin (CD144), that is involved in the formation of EC intercellular contacts, required for angiogenesis, maintaining the vascular integrity and barrier function [20].

EC, enveloping the vessel lumen represent the border between blood and extravascular tissues. Nevertheless, the endothelial barrier is permeable for various molecules and even cells. Ions and soluble substances can move through the spaces between EC by paracellular or transcellular mechanisms [20]. Leukocytes migrate through the endothelial layer between the cells. Under the physiological and pathological conditions, transendothelial migration of leukocytes is necessary for the formation of immune response, angiogenesis, vascular remodeling and tissue regeneration [21, 23].

Movement of the VE-cadherin-catenin complex leads to weakening of the barrier function in the endothelium under hypoxia/reoxygenation conditions. An increase of endothelial permeability is suppressed with eNOS excess in cultivated EC. In EC cultures, treatment with hydrogen peroxide stimulates the occludin and cadherin loss in intercellular junctions, which indicates the destabilizing role of oxidative stress and ROS-mediated signaling with respect to the vascular integrity. Vascular permeability can also be regulated by extracellular proteases. Thrombin, initiating a blood clotting cascade by the VE-cadherin cleavage, can disrupt the endothelial barrier integrity. In the VE-cadherin, thrombin cleaves ectodomain followed by the protein proteolysis with participation of γ-secretase and metalloprotease ADAM-10 (A disintegrin and metalloproteinase domain 10) [20]. This mechanism facilitates

the T-cells transmigration through the endothelium. Transendothelial migration of neutrophils and monocytes using the activation of Src/ ERK1/2 signal mechanism is mediated by ADAM-15. However, VE-cadherin is not cleaved by this metalloproteinase. In apolipoprotein E deficiency in mice, the genetic silence of ADAM-15 resulted in decrease of the plaque area by 52% and MPs infiltration into lesions foci by 69% [24]. In inflammatory conditions characteristic for DM, the activation and the accumulation of matrix metalloproteinases (MMP) are noted in the EC intercellular contacts, which suggest their possible participation in eliminating the barrier and facilitating the leukocyte migration to the intima. This mechanism, probably, underlies ED and atherogenesis [24]. In human and mouse atherosclerotic lesions, the JAM-A expression is enhanced, that is induced in the EC by pro-inflammatory cytokines. Enhancing of JAM expression stimulates adhesion of EC, attracts cells of the immune system and promotes the invasion of arterial intima by the leukocytes [25], indicating the JAM pro-atherogenic role.

Endothelial progenitor cells (EPCs). EPCs and vascular endothelial growth factor (VEGF), are important components of the vascular response to hypoxia and trauma, which functions are disturbed in DM.

Vascular injuries and tissues ischemia is trigger of EPCs mediated cytokine release from the bone marrow into the circulation, where they contribute to angiogenesis and restoration of injured endothelial sites. The low levels of ECPs, are as a rule associated with more high incidence of cardiovascular disease (CVD) [1]. Tissue ischemia is considered as the most important stimulus of EPCs release and is realized through the activation of hypoxia-inducible pathways, particularly, the expression of HIF-1 factor (hypoxia inducible factor). HIF-1 is a heterodimer composed of two subunits, which dimerizes in the nucleus under hypoxic conditions, and acts as the transcription factor with cofactor p300. Glycolytic metabolite, methylglyoxal, can modify p300, forming AGE, which inhibits HIF-1-mediated gene transactivation. HIF-1 quantity is also decreased with ROS excess and the reduction of NO level. Decrease in the number of EPCs in DM is the result of their reduced mobilization, proliferation and survival, as well as functional disorders [26, 27].

Smooth muscle cells of blood vessels. SMCs are mainly part of the middle shell (tunica media) of blood vessels and are responsible for their contraction and relaxation, changing their diameter and the internal pressure. The vessels, being in systems of high pressure, contain more SMCs than the vessels in the systems of lower pressure. Vascular contractile function is mainly regulated by the sympathetic nervous system. Vegetative function is changed in DM, leading to abnormal vasodilatation and vasoconstriction in response to the local factors. SMCs penetrate the sites of damaged intima from the medial layer and serve as the collagen source to strengthening the atherosclerotic plaques [1].

Migration SMCs from the medial layer into the intima is associated with the ECM accumulation, stabilizing plaque that reduces the risk of its rupture [5]. In persons with DM, the plaques contain fewer SMCs, that increases the likelihood of rupture and thrombosis. In addition, lipid modifications, marked in diabetic patients, such as glycosylated oxLDL, are contributed to SMCs apoptosis [5]. ROS and AGE products are increased in DM, PI-3-kinase is inhibited, PKC and NF-κB are activated that promotes development of atherogenic phenotype in SMCs [5]. These factors increase the SMCs apoptosis, positively regulate the proatherogenic tissue factor (TF) and inhibit the collagen synthesis, stabilizing the plaque [28]. DM is also associated with MMPs increase cleaving collagen, exacerbating the plaque instability. Therefore, DM not only contributes to AS, but also destabilizes the plaque, provoking the thrombus formation [28]. DM also promotes the up-regulation and increase of ET-1 activity, activating receptors on the SMCs, that leads to a vascular tone increase [29]. Hyperactivation of ET receptors can cause the pathological vasoconstriction. ET-1 is also responsible for the increase of salt concentration and retention of water, activating the renin-angiotensin system and causing SMCs hypertrophy. Formation of other vasoactive substances such as prostanoids and ATII, further increasing vasoconstriction [29].

SMCs in the healthy part of the artery are heterogeneous — their phenotype can vary from a contractile to a dedifferentiated. Contractile or differentiated phenotype, is typical for normal SMCs vessels, and has highly organized cytoskeleton, with expressed F-actin filaments supporting the contractile function, a high level of smooth muscle α-actin and heavy chain of smooth muscle myosin and h1-calponin [30]. In CVD, the reorganization of SMCs cytoskeletal leads to the predominance of synthetic phenotype. Synthetic SMCs are characterized by changes in the distribution of organelles,

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abnormal matrix metabolism, increased proliferation and migration, and expression of specific glycoproteins [31]. Main features of dedifferentiated SMCs are enlarged nuclei, developed Golgi apparatus, and increased number of ribosomes. Changes in SMCs phenotype lead to the activation of receptors, regulating proliferation, migration and survival. Functionally, the dedifferentiation of SMCs changes the ability to divide and migrate due to increased sensitivity to growth factors and mitogens [32]. SMCs of diabetic patients demonstrate a significant increase in the proliferation, adhesion and contact inhibition, associated with the intensification of atheromatous process and restenosis. Intimal hyperplasia is closely linked with synthetic phenotype of SMCs and should be considered in the treatment of AS and restenosis in patients with type 2 DM [33].

HG activates NF-κB that transactivates proinflammatory and proatherosclerotic target genes in SMCs, EC and MPs. Increased activity of NF-κB is also characteristic to SMCs with synthetic phenotype and NF-κB inhibition promotes SMCs apoptosis [31]. NF-κB also regulates proapoptotic reaction of intimal SMC to neurotransmitters such as nerve growth factor [34].

Lipids accumulation additionally stimulates the recruitment of MPs and other inflammatory cells, maintaining condition of vascular inflammation. The latter causes the accumulation of intimal SMCs that exhibit macrophage and increased synthetic activity with deposition of extracellular collagen [31]. Expression in vascular cells Flt-1+ (VEGFR1) and c-Kit+ (mast and stem cells growth factor receptor — SCFR (CD117)) affects the SMC properties. In particular, Flt-1-signaling regulates NF-κB mediated cell survival [35] in accordance with the assumption that SMCs with stem cell phenotype facilitate arterial remodeling [36, 37]. It is supposed that the precursors of blood cells can be involved in plaque stabilization. Circulating and resident cells with the phenotype of stem cells play a different role in the aorta remodeling in patients with type 2 DM [38].

Interferon-regulatory factor 1 (IRF-1) is a molecular mediator of vascular diseases. IRF-1 inhibits the growth of vascular cells in normal glucose concentrations and promotes the SMC division in high ones [39]. It is also shown that the ROS accumulation effects on proliferation activating cyclins/CDK [40]. Hyperglycemia stimulates an increase of intracellular ROS and ERK1/2 activation, mitogen-activated protein kinase, required for SMC growth [41]. HG also stimulates the ECM synthesis and accumulation, that is mediated by the activity of TGF-β and its mediator — connective tissue growth factor (CTGF), controlling vascular fibrosis. HG increases the protein quantity and mRNA of CTGF in SMC, and its inhibition by siRNA suppresses SMC proliferation [42].

AGE accumulation activates NF-κB in many types of cells, in SMCs, in particular. In addition, AGE activate MAPK. The role of AGE and their receptors (RAGE) was studied. RAGE and galectin-3 are connected with the AS progression. SMC proliferation, mediated by galectin-3 and abnormal interaction of AGE-galectin-3, is related to macroangiopathies in patients with type 2 DM [31].

Hyperinsulinemia is an important factor in the plaques formation in patients with type 2 DM. Insulin exerts a mitogenic effect on human aortal SMC, and insulin-like growth factor-1 (IGF-1) activates SMC proliferation through different signaling pathways, including — MAPK that, in turn, enhances the SMC chemotaxis [43]. IGF-1 also affects the SMC survival. IGF-1 with high affinity is binding to IGF-1R receptor, resulting in the activation tyrosine kinase of receptor, inducing a signal mechanisms associated with survival and growth. SMC resistance to insulin in patients with type 2 DM is associated with ATII-mediated vascular disease [44]. Prolonged oxidative stress and the increase in ATII content can result in IR in SMC mediated through ROS activation of insulin receptor substrate-1 (IRS-1). IRS-1 phosphorylation reduces the activity of phosphatidylinositol 3-kinase (PI3K) and inhibits insulin-induced Akt activation [44]. This effect inhibits GLUT4 translocation to the plasma membrane, that reduces the glucose absorption in SMCs. Thus, the insulin-dependent glucose uptake in SMCs is associated with IRS-1/PI3K/Akt cascade, as in other insulin sensitive tissues. ROS formation and ATII production lead to increased SMC proliferation, vascular inflammation and ECM accumulation [31].

Monocytes / MPs. The monocyte activation and their transformation in MPs are key stages of atherosclerotic and inflammatory processes. One of the earliest events in the AS pathogenesis is lipid accumulation in the monocytes by absorption of modified or oxLDL, leading to infiltration of foam cells into the arterial wall. MPs activation

followed by release of smooth muscle regulatory growth factors in diabetic injuries, promotes proliferation of vascular SMC [1, 45]. It is considered that MPs are derived from circulating monocytes have a high degree of heterogeneity. Human monocytes are subdivided into three populations, depending upon the expression of CD14 and CD16 on the cell surface: classical monocytes expressing the high levels of CD14, but not CD16 (CD14++/CD16-), intermediate monocytes, expressing CD14 and CD16 (CD14++/CD16+) and nonclassical monocytes, with very low levels of CD14 and high ones of CD16 (CD14-/CD16+) [46]. These groups have different functions and play both the anti- and proinflammatory roles in various diseases, including AS. CD14++/CD16- and CD14++/CD16+ monocytes remind the subtype of Ly6C+ mouse monocytes, whereas as the CD14+/ CD16++ are close to mouse Ly6C- monocytes. Ly6C+ are inflammatory monocytes and MP precursors, whereas Ly6C- are considered less inflammatory ones [45].

It is known that CC-chemokine ligand 2 (CCL 2), another name — monocyte chemoattractant protein 1 (MCP-1) and its receptor CCR2 play an important role in the MP recruitment and infiltration [47].

One of the main features of MPs is functional diversity, that allows them to respond differently to environmental signals. Two main MP phenotypes are selected: classically activated (M1) and alternatively activated (M2) [48]. Th1-associated cytokines (IFN-γ), and bacterial endotoxins such as lipopolysaccharide (LPS) polarize MPs to M1 phenotype. Activation of M1 MPs leads to increased bactericidal properties, increased secretion of TNF-α, IFN-γ and inducible nitric oxide synthase (iNOS), that enhances adaptive immunity [49]. M2 MPs are more diverse and induce Th2-dependent cytokines — IL-4 and IL-13. M2 MPs are characterized by expression of arginase-1, CD163, receptor of mannose and anti-inflammatory cytokines such as IL-10 [49]. They play a key role in the immune response to parasites, in allergies, in wound healing, and in tissue remodeling. M2 phenotype of MPs is also induced by glucocorticoid hormones, apoptotic cells and immune complexes [50]. MPs with M1 phenotype are predominated in AS and obesity (inflammatory conditions).

An increase in circulating levels of LDL-cholesterol and subsequent oxLDL accumulation in the subendothelial space causes attraction and retention of monocytes and lymphocytes into the arterial wall. In the intima monocytes are differentiated into MPs, that are captured LDL particles and eventually are transformed into foam cells. Through NF-κB activation these cells secrete inflammatory molecules and factors, contributing to further accumulation of modified LDL, the degradation of extracellular matrix and increased inflammation [51]. The AS progression is associated with apoptosis of resident MPs in lipid nuclei of lesion focus. Clearance of apoptotic cells is accomplished by phagocytes, mostly MPs, that recognize and internalize dead cells in the process of efferocytosis [52]. In initial vascular lesions, phagocytes removed the apoptotic cells, preventing the AS development. In chronic lesions, efferocytosis is not sufficient to utilize all the dead cells and the gradual accumulation of debris, forming a necrotic nuclei, causing further inflammation, necrosis and thrombosis [52]. MPs play a crucial role in maintaining an effective efferocytosis, contributing to the resolution of inflammation and preventing the formation of necrotic nuclei in plaque.

Initially AS was considered as Th1-dependent inflammatory process, but now the concept of resident MP heterogeneity within the lesion focus is extended [51]. It was shown that monocytes and MPs are composed of populations of heterogeneous cell adapting their functional phenotype in response to specific microenvironmental signals. These subtypes of MPs and monocytes can be identified based on the expression of surface markers and chemokine receptors by them [53]. The statement that the resident MPs are not able to division is refuted by proliferating MPs detected in mouse lungs. IL-4 induces the division both resident and infiltrated MPs. Furthermore, MPs in earlier AS foci of mice predominantly originate from involved monocytes, while dividing MPs are predominated in formed plaques and are controlled by microenvironment [54].

The increase in oxLDL quantity is associated with high risk of CVD [55]. On experimental model MPs captured oxLDL through scavenger receptors such as CD36, that induces the IL-1β secretion. OxLDL enhanced the formation of proinflammatory cytokines — IL-6, IL-8 and MCP-1 in human peripheral MPs, derived from monocytes by differentiation involving macrophage colony stimulating factor (M-CSF) [56]. MP polarization from M2 to

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M1 phenotype was induced by oxLDL [56]. These data show that the uptake of modified LDL by macrophages in the arterial wall is associated with their differentiation into pro-inflammatory phenotype in formation the atherosclerotic lesions. A high level of LDL-cholesterol and low level of HDL-cholesterol in the blood are considered risk factors of AS development. Now, lot of attention is paid not only to the quantitative level of LDL- and HDL-cholesterol, but also the qualitative functioning of these lipoproteins [57]. In addition to the oxLDL effects, the link between HDL dysfunction due to oxidation and CVD is of particular attention [57]. HDL from patients with type 2 DM had shown a high level of inflammatory index, that was assessed by the activity of LDL-induced monocyte chemotaxis in EC monolayer of human aorta. HDL, obtained from patients with CRF, enhance the expression of IL-1β, TNF-α and IL-6 mRNA in the THP-1 cells and can not suppress the MCP-1-induced MP chemotaxis [58]. Thus, HDL with inflammatory properties can accelerate the AS development. HDL in the norm contributes to anti-inflammatory reactions of MPs, while HDL, modified in pathological conditions, can act as proinflammatory factors [59]. HDL from healthy individuals do not affect the monocytes differentiation into M2 MPs, but inhibit the differentiation to M1 phenotype. It is assumed that HDL with impaired function can cause MP polarization from M2 to M1 phenotype [60].

Another important function of HDL of macrophages is the removal of lipids from cells, particularly, cholesterol [61]. This HDL function is the initial step for reverse transport of cholesterol in the liver tissues as well as to maintain the cholesterol homeostasis in various cells and tissues, such as MPs and the arterial wall. This function and cholesterol transport associated with it is disturbed in CVD [62] and can be used to predict the disease development. Decreased SRB1 (scavenger receptor class B member 1- and ABCG 1 (ATP-binding cassette sub-family G member 1- mediated cholesterol transport in HDL was noted in serum of patients with type 2 DM. It is also shown that the level of inflammatory serum amyloid A inversely correlated with the level of flow SRB1-mediated cholesterol [63]. Cholesterol efflux disorder accelerates the transformation of MPs into foam cells in the foci of atherosclerotic lesions.

Platelets. An increase in platelet aggregation in DM occurs because of an increase in systemic production of isoprostanes, including thromboxane A_2 (TxA_2), increased sensitivity to the platelet activating factors (PAF), such as adrenaline and ADP, and also disorders of PGI_2 and NO formations. DM also causes increased expression of glycoproteins on the platelet surface that enhances platelet aggregation and their interactions with fibrin [1]. Hyperglycemia also activates PKC and generates ROS in platelets, leading to their dysfunction. Many of these pathophysiological changes are probably result from metabolic consequences of IR but increased platelet reactivity was detected in patients with type 1 DM, without IR. Consequently, hyperglycemia is responsible for a change in the platelet reaction, probably due to the AGE action on the surface receptors of cells [64].

Defective platelet function can accelerate the AS development, plaque destabilization and promote atherothrombosis [28]. Glucose transport into platelets occurs independently on insulin. HG provokes oxidative stress in platelets, PKC activation, reduced NO production, that contributes to their aggregation. Platelet adhesion is enhanced in patients with DM due to increased expression of P-selectin on the cell surface [65]. Growth of platelet receptor expression such as the glycoprotein Ib (CD42), that binds to the von Willebrand factor, and IIb/IIIa (integrin) receptors required for platelets interaction with fibrin is also revealed in patients with DM. These receptors mediate the adhesion and aggregation of platelets, causing thrombosis. Regulation of calcium concentration in platelets, important to change cell form, the aggregation ability and thromboxane production, that further contributes to AS was also impaired in patients with DM [5, 29].

Prothrombotic state is characteristic to diabetes, can be characterized by the following factors: an increase in blood clotting, impaired fibrinolysis, ED, platelet hyperreactivity [66]. Platelet dysfunction in diabetic patients is caused by hyperglycemia, insulin deficiency and IR [67]. The platelets contain two types of large granules — α-granules and dense granules. *Alpha*-granules are the most common and contain proteins that are necessary for platelet adhesion, while the function of dense granules is associated with attracting additional platelets in places of vascular injury. Compounds that are secreted in activation of platelets such as catecholamines, serotonin, calcium, ADP and ATP are stored in dense granules [68].

Platelet plasma membrane, whose main component is a phospholipid bilayer comprising cholesterol, glycolipids, and glycoproteins, lies below the outer layer. In contrast to erythrocytes, platelets present these molecules on the surface. Phospholipid organization between the inner and outer membrane leaflets is asymmetrical, that is important for the coagulation regulation. The inner plasma membrane leaflet comprises a great number of negatively charged phospholipids, that keep the platelet surface in uncoagulated condition. Phospholipids promote coagulation by stimulating the activation of blood coagulation factor by transition X into Xa and prothrombin into thrombin, the key steps in the coagulation cascade [68]. Other protein components of resting platelets include markers of platelet activation CD36, CD63, CD9 and GLUT-3. It was found that patients with type 2 DM demonstrate the increased expression of CD31, CD36, Cd49b, CD62P and CD63. It was established that an amplification of platelet activation, aggregation and expression of CD63 and CD62, promotes the AS and thrombosis development in diabetic patients. Platelets in patients with DM are characterized by increased adhesiveness and ability to aggregation. With platelet hyperactivity associated a decrease in membrane fluidity, change in metabolism of platelets (disturbance of calcium and magnesium homeostasis), the increase in a amount of glycoprotein receptors and TxA_2, non-enzymatic glycosylation of surface proteins, ROS generation, the decrease in a quantity of antioxidants, prostacyclin and NO [68].

Coagulation cascade includes both thrombogenesis and fibrinolysis. Coagulation proteins play an important role in both processes. Higher levels of circulating tissue factor (TF), factor VII, thrombin, fibrinogen, tPA (tissue plasminogen activator) and PAI-I (plasminogen activator inhibitor-I) are noted in patients with DM [69]. TF initiates the thrombotic process, ending the thrombin formation, that is required to convert fibrinogen into fibrin. Elevated levels of TF are under control of glucose and insulin in DM. Another mechanism for raising the TF level is associated with the formation of AGE and ROS [68]. TF / FVII complex is formed in a case of plaque rupture. With basic platelets stimulation, this complex activates the different coagulation factors, that lead to thrombin formation [69]. FVII level is also increased in patients with DM and the metabolic syndrome [67]. It is shown that the coagulation activity of FVII has been associated with fatal events in the cardiovascular system, and that is more importantly, increased activity of FVII coagulant is directly correlated with HG in the blood [69]. The thrombin formation is intensified in both types of DM [70]. Hyperglycemia results in increased thrombin generation in diabetic patients, and thrombin production is decreased by treatment with hypoglycemic agents, that proves the prothrombotic nature of hyperglycemia. The high thrombin concentration leads to a change in thrombus structure, since it becomes denser and less permeable making thrombus more resistant to lysis [70]. Fibrinogen, the fibrin precursor, is considered an independent risk factor for CVD and is often used as a surrogate marker. High fibrinogen levels have prognostic value in latent myocardial ischemia, particularly in patients with type 2 DM [71]. It is known that fibrin network structure changes in diabetic patients. The study of the glycemic control effect on fibrin networks structure in patients with type 2 DM using the isolated fibrinogen [72] showed: higher level of fibrinogen glycation among patients with DM and a significant decrease after normalizing glucose content; thrombus permeability and the average pore size was increased in diabetic patients and a correlation between permeability and the HbA1c content was observed; construction of turbidity curves to characterize the polymerization kinetics and thrombus structure showed an turbidity increase in a group of diabetic patients; visco-elastic properties were similar in both groups, but the part of nonelastic component in fibrin clots was lower in patients with DM; a lower rate of clot lysis was revealed in subjects with DM [72].

Another factor stimulating TF synthesis in DM, besides insulin and glucose, is glycation of end products and ROS content. Furthermore, increased thrombin production has a direct effect on the thrombus formation, its structure and stability in diabetic patients. The thrombus becomes more dense and resistant to lysis. Link, binding diabetes and prothrombotic condition and inflammation, is the secretion of cytokine IL-6, which stimulates the fibrinogen production in hepatocytes. Increased fibrinogen formation by hepatocytes is also observed in IR [73].

Erythrocytes. Erythrocytes also play a role in blood coagulation, enhancing coagulation and platelet aggregation [74]. In addition, the erythrocytes are contained in the coronary atherosclerotic plaques. They are also involved in the pathogenesis

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of microvascular complications in DM. Glucose side effects are manifested in the form of erythrocyte membranes remodeling, disorders of oxygen-hemoglobin binding rate, changes in the mechanical characteristics of membranes and the general properties of cells [75]. This is explained by prothrombotic nature of erythrocytes — they increase the blood viscosity and direct the platelets to the vascular wall. Erythrocyte integration into fibrin thrombus influences on its structure and mechanical properties [76]. In patients with DM erythrocytes membrane becomes hard and loses its ability to deform due to the reduction of cholesterol/phospholipids ratio. In this case, the cholesterol amount in the membranes is increased, but the phospholipid concentration is increased four times. The increase of membrane cholesterol contributes to the atherosclerosis plaque instability [68]. Cytoskeletal proteins, in particular, β-spectrin, ankyrin and protein 4.1 (Beatty's protein) are intensively glycosylated. Ion balance disturbances are explained by reduced Na^+/ K^+-ATPase activity, that leads to increase of sodium concentration in serum and inside of erythrocytes and potassium in the blood serum in diabetic patients. The increase of cell sizes and their osmotic fragility is occurred, that contributes to the development of microvascular complications [69]. Elevated levels of fibrinogen and glucagon is common occurrence in uncontrolled DM [77]. Oxidative stress provokes the increase of peroxidation in membrane lipids, which can lead to deviations in their structure and function. Increased levels of malonic dialdehyde (indicator of lipid peroxidation) and decreased levels of glutathione and membrane SH groups are also erythrocytes particularities in DM [68].

Conclusion

Thus, the dysfunction of blood vessel cells in DM is the basis of the AS pathogenesis. First of all it concerns ECs, SMCs and MPs. Hyperglycemia and hyperinsulinemia significantly affect the cell metabolism, provoke an inflammatory process, and disrupt the contractile function of blood vessels and epithelial barrier function, thus accelerating the formation of atherosclerotic plaques (**Fig.**). Understanding the fine mechanisms of cell metabolism disorders and their interactions in DM will help to find new approaches to the prevention and treatment of AS.

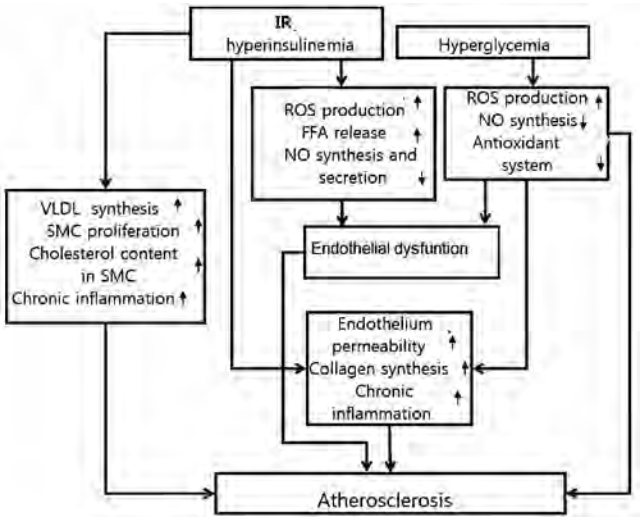

Fig. Role of insulin resistance and hyperglycemia in the pathogenesis of atherosclerosis. Explanations are in text

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Диабет и атеросклероз. Клеточные механизмы патогенеза. Обзор литературы

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Резюме. В обзоре литературы анализируются клеточные механизмы патогенеза осложнения сахарного диабета — ускоренного развития атеросклероза. Проанализированы механизмы нарушения метаболизма и возникновения эндотелиальной дисфункции при диабете, показана роль межклеточных соединений эндотелиальных клеток сосудов в поддержке их целостности и барьера проницаемости в норме и патологии. Обобщены данные относительно участия в патогенезе атеросклероза на фоне сахарного диабета гладкомышечных клеток сосудов, макрофагов, тромбоцитов и эритроцитов. Показана роль ядерного фактора NF-κB — регулятора воспалительных реакций в клетках эндотелия, гладкомышечных клетках сосудов и макрофагах.

Ключевые слова: атеросклероз, диабет, эндотелий, клетки сосудов, NF-κB.

Діабет та атеросклероз. Клітинні механізми патогенезу. Огляд літератури

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Резюме. В огляді літератури аналізуються клітинні механізми патогенезу ускладнення цукрового діабету — прискореного розвитку атеросклерозу. Проаналізовано механізми порушення метаболізму та виникнення ендотеліальної дисфункції на тлі діабету, показано роль міжклітинних сполучень ендотеліальних клітин судин у підтримці їх цілісності та бар'єру проникності в нормі та патології. Узагальнено дані про участь у патогенезі атеросклерозу на тлі цукрового діабету гладеньких м'язів судин, макрофагів, тромбоцитів й еритроцитів. Продемонстровано роль ядерного чинника NF-κB — регулятора запальних реакцій у клітинах ендотелію, гладеньком'язових клітинах судин і макрофагах.

Ключові слова: атеросклероз, діабет, ендотелій, клітини судин, NF-κB.