MOLECULAR MECHANISMS OF THE REGULATORY ACTION OF HIGH-DENSITY LIPOPROTEINS ON THE ENDOTHELIAL FUNCTION

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Endothelial dysfunction underlies the pathogenesis of many diseases, primarily cardiovascular diseases. Epidemiological studies have shown an inverse dependence between the plasma level of high-density lipoproteins (HDL) and cardiovascular diseases. The results of experimental studies indicate that the antiatherogenic effect of HDL is associated not only with their participation in the reverse transport of excess cholesterol, but also with their regulatory effect on the functions of cells of various organs and tissues, including endothelial cells. The purpose of this review is to consider recent data on the participation of plasma receptors and related intracellular signaling pathways in the mechanism of protective effect of HDL on endothelial cell functions. Understanding the mechanisms of cell function regulation under the influence of HDL is an important step for the development of new ways of pharmacological correction of impaired endothelial functions and creation of effective endothelial protection drugs.

Key words: high density lipoproteins; apolipoprotein A-I; signaling pathways; endothelial dysfunction

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INTRODUCTION

Endothelial dysfunction is common to all cardiovascular diseases (CVD). It is characterized by a shift in the actions of the endothelium towards a proinflammatory state, prothrombotic properties and decreased vasorelaxation. [1]. Epidemiological studies have shown an inverse relationship between CVD and the level of high-density lipoprotein (HDL) in the blood plasma [2, 3]. The results of experimental studies indicate that the antiatherogenic effect of HDL is associated not only with their participation in the reverse cholesterol transport, but also with their regulatory effect on the functions of cells of various organs and tissues [4]. The mechanism of the regulatory action of HDL is associated with the presence of a protein component, apolipoprotein A-I (apoA-I), on the surface of the lipoprotein particle [5]. We have previously shown that apoA-I is involved in the regulation of protein and DNA biosynthesis in the liver and red bone marrow cells [6]; it stimulates the secretion of insulin and matrix metalloproteinases by the islets of Langerhans of the pancreas [7], activates proliferation of monocytic progenitor cells (monoblasts, promonocytes) and granulocytic (myeloblasts, promyelocytes) lineage, as well as bone marrow stromal cells [8].

Convincing evidence now exists that HDL exhibit several potential vasoprotective effects on the endothelium: they induce endothelial nitric oxide synthase (eNOS), increase production of nitric oxide (NO), suppress synthesis of endothelial adhesion molecules, and prevent migration of leukocytes and monocytes/macrophages through the vascular wall. In addition, HDL reduce production of reactive oxygen species (ROS) and prevent apoptosis; they also stimulate proliferation and migration of endothelial cells, required for the vascular bed remodeling in accordance with tissue needs [9, 10].

It should be noted that many pathological conditions, such as metabolic syndrome, diabetes mellitus, ischemic heart disease (IHD) etc., are accompanied by changes in the structure and

Abbreviations used: Akt – protein kinase B; AMPK – 5′AMP-activated protein kinase; ABCG1 – ATP-binding cassette transporter G1; BAD – a protein with a proapoptotic effect; BAEC – bovine aortic endothelial cells; Bcl-xl – antiapoptotic protein; CAMK – calcium/calmodulin-dependent protein kinase; COX-2 – cyclooxygenase 2; eNOS – endothelial NO synthase; EPC – endothelial progenitor cells; FAK – focal adhesion kinase; ICAM-1 – type 1 intercellular adhesion molecules; IHD – ischemic heart disease; IL-6 – interleukin-6; HIF-1α – hypoxia-inducible factor 1α; HAEC – human aortic endothelial cells; HBMEC – human brain microvascular endothelial cells; HDL – high density lipoproteins; HUAEC – human umbilical artery endothelial cells; HUVEC – human umbilical vein endothelial cells; LKB1 – liver serine/threonine kinase B1; LY294002 – selective inhibitor of the PI3K/Akt pathway; MAPK – mitogen-activated protein kinase; MMP9 – matrix metalloprotease 9; NO – nitric oxide; NF-κB – nuclear factor kappa B; P2Y – purinergic receptors; PGI_2 – prostacyclin; PDZK1 – adapter protein; PI3K – phosphatidylinositol 3-kinase; PLA_2 – phospholipase A_2; Rac1 – a protein from the GTPase superfamily, belonging to the "small" G proteins; ROS – reactive oxygen species; S1P – sphingosine-1-phosphate; S1PR – S1P receptors; SR-BI – "scavenger" receptor class B type I; Src – non-receptor tyrosine kinase; Smad2/3 – protein, transcriptional modulator of TGFβ; TGFβ – transforming growth factor β; TLR2 – toll-like receptors 2; TNF-α – tumor necrosis factor-α; VCAM-1 – vascular endothelial adhesion molecules type 1; VEGF – vascular endothelial growth factor; VEGFR – VEGF receptor.

chemical composition of HDL, leading to the formation of so-called dysfunctional HDL, which lose their antiatherogenic properties [11] and a protective effect on the endothelium [10–13]. On the contrary, an increase in physical activity and a significant decrease in excess body weight improve the HDL ability to activate eNOS and NO production, which has a beneficial effect on the state of endothelium-dependent vasodilation [14]. Increasing the apoA-I level by administering reconstructed HDL or mimetic peptides into the body has a positive effect on the state of the endothelium and regression of the atherosclerotic plaque [15, 16].

The aim of this review is to provide a modern understanding of the participation of proteins of the plasma membrane of endothelial cells and associated intracellular signaling pathways in the mechanism of the protective effect of HDL on the endothelial cell functions.

1. SR-BI-RECEPTORS

Scavenger receptor class B type I (SR-BI) is a widely expressed multiligand transmembrane glycoprotein of 82 kDa consisting of 509 amino acid residues. SR-BI binds various ligands, including native and oxidized LDL, VLDL, Lp(a), modified serum proteins, lipid vesicles containing negatively charged phospholipids, apoptotic cells, and viruses such as hepatitis C and SARS-CoV-2 [17].

SR-BI has been identified as a high-affinity HDL receptor that mediates the selective uptake of HDL cholesterol esters into hepatocytes. Although the expression level of SR-BI in endothelial cells is relatively low compared to hepatocytes and tissue macrophages, recent evidence suggests an important function of the endothelial receptor SR-BI [18, 19]. In endothelial cells, the receptor is found on the apical and basolateral sides of the membrane and consists of two cytoplasmic domains and a large, highly glycosylated extracellular domain responsible for interaction with ligands. Cholesterol esters are the main substrate for endothelial SR-BI, but the receptor also promotes transport of non-esterified cholesterol, phospholipids, and triglycerides [4, 19]. Transport of HDL by SR-BI is possible only for mature particles, but not for free apoA-I [10, 18]. Modification of HDL by myeloperoxidase results in high-affinity but non-productive binding of HDL to SR-BI, impairing cholesterol uptake and efflux [9]. Deletion of the SR-BI gene in mice leads to an abnormal lipid profile and the development of severe atherosclerosis [19]. Overexpression of SR-BI in endothelial cells reduced susceptibility to atherosclerosis in C57BL/6 mice fed a high-cholesterol diet. At the same time, inhibition of the development of atherosclerosis correlated with an increase in the level of HDL cholesterol and a decrease in the level of total cholesterol [18].

In endothelial cells, HDL binding to SR-BI not only leads to transendothelial lipid transport [10, 19] but also triggers several intracellular signaling events. This requires the adapter protein PDZ with four domains, one of which, PDZK1, interacts with the C-terminal cytoplasmic domain of SR-BI [20]. The adapter protein stabilizes SR-BI on the plasma membrane of the endothelial cell by interacting with the receptor amino acid residues Ala-Lys-Leu. Figure 1 shows a scheme of the activation of intracellular signaling pathways in an endothelial cell during the HDL interaction with the SR-B1 receptor.

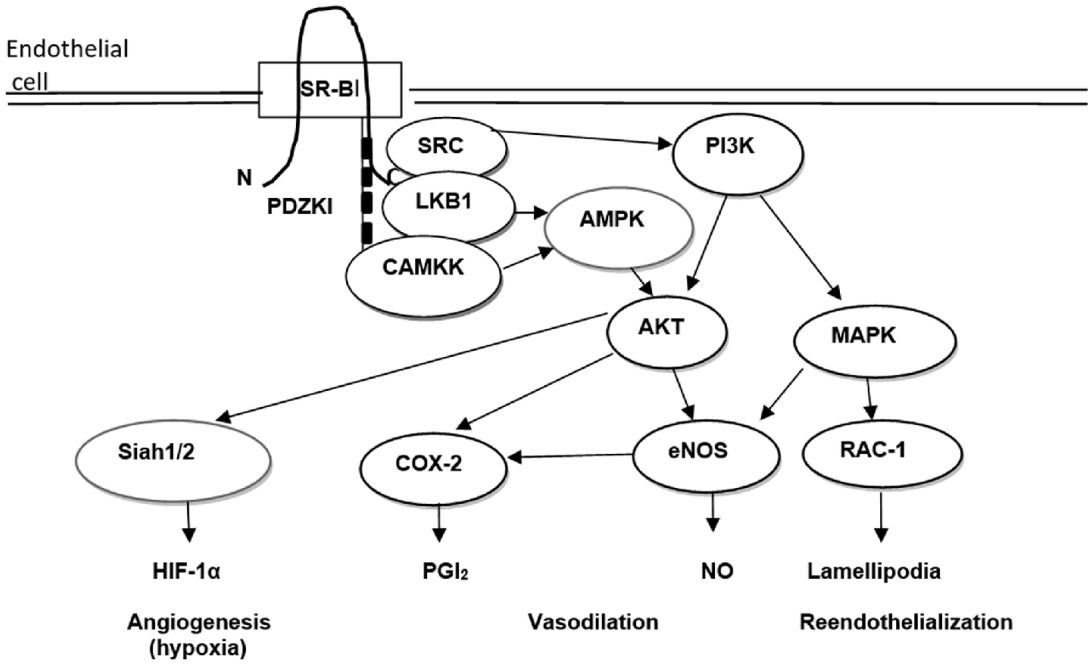

Figure 1. Activation of intracellular signaling pathways during HDL interaction with the SR-B1 receptor (adapted from [4]). Explanations are given in the text.

SR-BI and PDZK1 promote phosphorylation of non-receptor tyrosine kinase (Src) and AMP-activated protein kinase (AMPK). Activation of Src causes subsequent phosphorylation of phosphatidylinositol 3-kinase (PI3K), which in turn causes parallel activation of serine/threonine protein kinase B (Akt) and mitogen-activated protein kinase (MAPK)/Erk1/2 with subsequent stimulation of eNOS synthesis, production of nitric oxide (NO), and vascular relaxation. Serine/threonine protein kinase B activates eNOS by phosphorylating the enzyme at Ser1179 [20]. It has been suggested that MAPK stimulation is necessary to increase the eNOS enzymatic activity [4].

The Akt/MAPK signaling pathways were partially suppressed by knockdown of SR-B1 or PDZK1 by using small interfering RNA (siRNA), while induction of SR-BI by HMG-CoA reductase inhibitors (statins) increased eNOS activation [21]. Inhibition of Akt phosphorylation and eNOS activation was observed in endothelial cells preincubated with wortmannin (a nonspecific covalent inhibitor of PI3K) or LY294002 (a selective inhibitor of the PI3K/Akt signaling pathway). The use of inactive protein kinase B (AktAAA) effectively inhibited HDL-induced eNOS phosphorylation [22]. Antibodies to SR-BI blocked eNOS activation [23].

In addition, it was found that signal transduction from HDL to kinases required cholesterol influx mediated by the C-terminal transmembrane domain of SR-BI. The SR-BI receptor and eNOS are located in cholesterol-rich caveolae containing various signaling molecules, including MAPK [23]. Changes in cholesterol concentration induced by methyl-β-cyclodextrin (a synthetic cholesterol scavenger) activated MAPK and caused comparable activation of eNOS [23].

Phosphorylation of MAPK is necessary for subsequent stimulation of the GTPase activity of small G protein (Rac1), which promotes the rearrangement of the actin cytoskeleton, induces migration of carotid endothelial cells and formation of lamellipodia (Fig. 1), promoting their re-endothelialization after perivascular electrical injury [22]. In bovine aortic endothelial cells (BAEC), HDL increased Rac1 activity, which stimulated endothelial cell migration and lamellipodia formation. The PD 98059 inhibitor, which blocks the MEK/ERK pathway, inhibited endothelial cell migration by 84%, and PP2 (an inhibitor of Src family kinases) by 72%. HDL-induced Rac1 activation in the presence of PD98059 decreased by 82% [9, 22].

Activation of Akt by HDL increased expression of cyclooxygenase-2 (COX-2), involved in synthesis of prostacyclin (PGI_2), a known vasoactive endothelial mediator and a powerful factor that prevents platelet aggregation. Different HDL_2 and HDL_3 subtypes had a dose-dependent effect on PGI_2 production by endothelial cells. Knockdown of SR-B1 receptors also significantly reduced PGI_2 release [24].

Thus, SR-BI receptors not only participate in the transendothelial transport of HDL [10, 19], but also contribute to the regulation of the functional activity of endothelial cells: they stimulate eNOS synthesis, production of NO, PGI_2, cause relaxation of the vascular wall, prevent platelet aggregation, activate migration of endothelial cells, increase lamellipodia formation and, as a consequence, wound repair.

2. THE SPHINGOSINE-1-PHOSPHATE SIGNALING SYSTEM

Sphingosine 1-phosphate (S1P) is a bioactive lysosphingolipid produced in cell membranes by phosphorylation of sphingomyelin by sphingosine kinase 1 and sphingosine kinase 2. S1P is secreted by cells of the hematopoietic origin. In plasma, the concentration of S1P ranges from 0.5 μM to 1.2 μM; moreover, most of S1P is transported in HDL (≈65%), and the rest is transported with albumin [25, 26]. The poor solubility of S1P in plasma determines ultimate need of its association with protein molecules for transport into the blood, lymph and access to receptors. S1P is carried by HDL (HDL-S1P), a minor subfraction containing apolipoprotein M (apoM). ApoM is a member of the lipocalin family (a group of transport proteins) with a characteristic secondary structure containing eight antiparallel peptide sequences. Based on its β-sheet structure, a cylinder is formed containing a hydrophobic pocket where S1P is located [25]. An unusual property of apoM is that its signal peptide is not cleaved during secretion, but is used by the mature protein to attach to the phospholipid surface of HDL [27].

The vascular effects of HDL-S1P depend on the expression of S1P receptors (S1PR). Endothelial cells express S1PR1, S1PR2 and S1PR3, which are coupled to G proteins [10, 28]. The G proteins are heterotrimeric protein complexes including the G_α subunit and the $G_\beta G_\gamma$ subunit dimer. After S1P binding to the G protein, its G_α subunit undergoes a conformational change and dissociates from the $G_\beta G_\gamma$ dimer. The dissociated G_α subunit activates several downstream signaling pathways. It has been found that endothelial S1PRs are mainly functionally coupled to inhibitory type G proteins ($G_{i/o}$) [29]. S1P receptors regulate a wide range of cytoprotective functions, including cell motility, cell proliferation and survival, cytoskeletal remodeling, and endothelial barrier integrity. Mice with mutations in S1PR or the metabolic enzymes associated with S1P (sphingosine kinase 1,2) exhibit significant embryonic defects in various organs [4, 28]. In normal endothelium S1PR1 is the most expressed receptor; in contrast, dysfunctional endothelium is characterized by a decrease in S1PR1 and increased expression of S1PR2 [26, 30]. The number of S1PR2 increased in rats with diabetic retinopathy [31].

Activation of S1PR2 in various experimental models increased vascular permeability and induced expression of adhesion molecules [25, 32], triggering pathological angiogenesis, which was absent in S1PR2$^{-/-}$ mice [31]. Pharmacological blockade of S1PR1/3 caused a marked increase in the area of myocardial damage in the experimental model. Administration of the S1P mimetic FTY720 [33] or S1P-enriched HDL reduced the size of myocardial infarction [26, 34].

It is suggested that apoM plays a role in facilitating HDL-S1P transport, but not in activating signaling pathways. The signaling activity of HDL is mainly dependent on its ability to transport, retain and present S1P. Intracellular G protein-mediated S1PR1 signaling inhibits adenylate cyclase and activates the PI3K, Akt and ERK1/2 pathways [28]. Figure 2 schematically shows the effect of HDL-S1P on signaling pathways in endothelial cells through S1PR1/3.

The interaction of HDL-S1P with S1PR exerted a potent vasodilator effect in the isolated aorta of wild-type mice [4]. Addition of S1P (10 nM) to BAEC increased Akt phosphorylation and caused a 4-fold increase in eNOS activity. Phosphorylation of eNOS occurred at Ser1179. The extent of eNOS activation by S1P was comparable to classical eNOS agonists including bradykinin, VEGF (vascular endothelial growth factor), and others. S1P-induced activation of both Akt and eNOS was inhibited by pertussis toxin (PTX, an inhibitor of $G_{i/o}$ proteins), wortmannin (a specific inhibitor of PI3K), and BAPTA (an intracellular calcium chelator) [35].

Experiments performed using S1P1 receptor knockdown have shown that Akt phosphorylation and endothelium-dependent vasodilation by HDL-S1P (Fig. 2) occurred through activation of S1PR1/3 [10, 35]. Fenofibrate treatment of LDL receptor knockout mice not only increased plasma HDL-S1P, but also S1PR1/3 expression, Akt and eNOS activity in the abdominal aorta endothelium [36].

Kimura et al. [37] have shown that activation of S1P receptors in human umbilical vein endothelial cells (HUVEC) stimulates AMPK, which regulates eNOS activity and NO synthesis through Akt (Fig. 2).

HDL-S1P signal transduction through S1PR1/3 regulates activation of the nuclear transcription factor NF-κB, playing a key role in the signaling cascade induced by TNF-α in endothelial cells (Fig. 2). In HUVEC cells, formation of the antiinflammatory signaling complex S1PR1-β-arrestin 2 on the cell surface resulted in attenuation of NF-κB activation by proinflammatory cytokines. The association between S1PR1 and β-arrestin 2 correlated with the antiinflammatory activity of HDL-S1P [38] and was critical for the inhibition of inflammatory responses [26, 39]. The mechanism of the antiinflammatory action of HDL-S1P partially

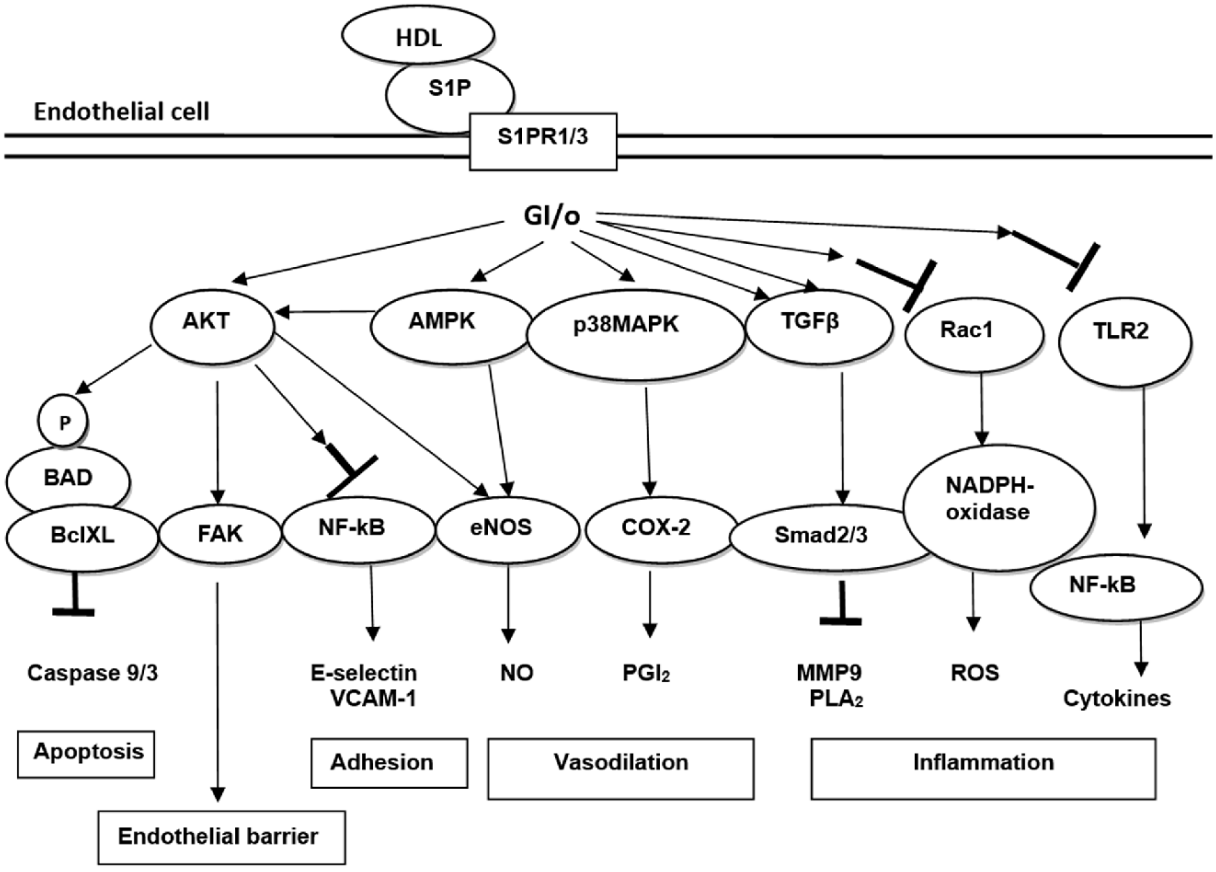

Figure 2. Schematic representation of the HDL-S1P-mediated signaling in an endothelial cell (adapted from [4]). Explanations are given in the text.

depends on the formation of the S1PR1 with β-arrestin 2 complex, which negatively regulates NF-κB through direct binding to the inhibitor of the nuclear factor NF-κB (IκB) [26].

Recombinant human apoM containing S1P had antiinflammatory effects in human aortic endothelial cells (HAEC) and human brain microvascular endothelial cells (HBMEC) exposed to TNF-α, while the content of E-selectin and VCAM-1 in the cell membrane reduced. In addition, apoM-S1P significantly inhibited the passage of FITC-dextran (70 kDa) through the endothelial barrier, thus indicating a decrease in cell membrane permeability. The effects were blocked by the S1P1 antagonist W146, while the specific S1P1 agonist SEW2871 had the opposite effect [25, 39].

HDL containing S1P increase proliferation and survival of HUVEC endothelial cells. This effect is suppressed by knockdown of S1PR1/3, PTX, or by ERK inhibitors. In addition, ERK kinase has been shown to play an important role in the cytoprotective effect of S1P-HDL [20, 37]. The N17Ras mutant protein completely blocked ERK activation and proliferation induced by reconstituted or native HDL-S1P [4, 29, 37]. The HDL-S1P/G proteins/ERK signaling pathway also stimulated proliferation of human placental endothelial cells [40].

Using HUVEC cells, it was shown that HDL isolated from the blood plasma of IHD patients contained 4–5 times less S1P than HDL from healthy people (45.06±6.74 pmol/mg HDL protein versus 273.78±15,01 pmol/mg; $p<0.05$) and they were ineffective in activating intracellular signaling cascades. On the other hand, in Chinese hamster ovary cells overexpressing the human S1PR1 receptor, HDL (from healthy people and IHD patients) caused pronounced activation of signaling pathways involving ERK1/2 and Akt; addition of a specific S1PR1 antagonist (W146) completely abolished this activation [41]. In apoM-deficient mice, administration of S1P-enriched HDL completely restored signaling through ERK1/2 [26].

HDL-S1P regulates vascular wall permeability [28, 42]. In genetically modified mice (apoM$^{-/-}$), with a decrease in the blood level of S1P, plasma exudation into extravascular tissues increased [43]. Using this model an increase in the permeability of the blood-brain barrier for small molecules (fluorescent albumin, 45 kDa) was also demonstrated [44]. ApoM deficiency disrupts the endothelial barrier in the lungs and brown adipose tissue of mice [44, 45]. It is suggested that S1P signaling increases endothelial barrier function by stabilizing cell-cell contacts. In addition, NO, an inhibitor of myosin activity, promotes cell contractility suppression. A detailed mechanism is considered by Wilkerson et al. [46].

S1P has been shown to protect the glycocalyx, a glycoprotein-rich layer that lines the apical surface of blood vessels [28]. It is believed that glycocalyx damage in the area of endothelial inflammation is a key step in the formation of atheroma. In this regard, the development of therapeutic approaches aimed at preserving it will help to reduce CVD and chronic renal failure [47, 48].

HDL prevented TNF-α-induced apoptosis of HUVEC endothelial cells through reducing the induction of caspase 3, a component of all primary apoptotic pathways. HDL-S1P, activating Akt, caused phosphorylation of the Akt target — BAD (a proapoptotic protein) thus promoting detachment of Bcl-xL (an antiapoptotic protein) and suppression of apoptosis (Fig. 2) [4, 20, 49]. Dysfunctional HDL from the blood of patients with stable IHD or acute coronary syndrome, containing increased amounts of apoC-III, caused a potent activation of apoptosis in endothelial and vascular smooth muscle cells [4].

It is known, that endothelial cells have the ability to proliferate and migrate; this is important for neovascularization and maintenance of the vascular wall integrity. Increased angiogenesis is a favorable sign for the restoration of ischemic tissues during myocardial infarction, ischemic stroke, peripheral occlusive arterial disease, etc. In contrast to LDL, impairing angiogenesis, HDL can stimulate it [10]. HDL dose-dependently increased proliferation of HUVEC cells by 2–5 times compared to the control group [39]. Stimulation of angiogenesis in HUVEC cells HDL involves S1PR3 activation and increased expression and phosphorylation of VEGF receptor 2 (VEGFR2), the main receptor for VEGF mediating angiogenesis in endothelial cells. Blockade of VEGFR2 activation by the inhibitor SU1498 almost completely suppressed the proangiogenic properties of HDL. Moreover, the S1PR3 inhibitor suramin prevented VEGFR2 expression and related endothelial cell proliferation and migration, whereas the S1PR1 agonist CYM-5442 and the S1PR2 inhibitor JTE-013 had no effect. Gene expression analysis in HUVEC and HUAEC cells revealed a significant correlation between VEGFR2 and S1P3 expression. It is likely that S1PR3 and VEGFR2 form a signaling complex that increases ERK1/2 phosphorylation, leading to increased endothelial cell proliferation, migration, and formation of vascular-like endothelial tubes [39]. Using genetic models with the functions of S1PR2 and S1PR3 switched off, alone or in combination with S1PR1, the development of vascular abnormalities, increased growth and metastasis of tumors was demonstrated [28].

HDL glycation in type 2 diabetes mellitus reduced its ability to increase COX-2 expression and prostacyclin release in endothelial cells. Addition of S1P to glycated HDL restored its ability to induce COX-2 in endothelial cells. The process of regulation of COX-2 expression includes phosphorylation of the ERK/MAPK signaling pathway (Fig. 2) and phosphorylation of the nuclear transcription factor CREB [41].

Endothelial progenitor cells (EPC) play a critical role in endothelial repair through proliferation, migration, and differentiation into endothelial cells. SEW2871 (selective S1PR1 agonist) or CYM5541 (selective S1PR3 agonist) have been shown to promote proliferation and reduce apoptosis of EPC. In addition, S1P increased VEGF secretion from EPC, while selective inhibition of S1PR1/3 or PI3K decreased VEGF expression and secretion [50].

Thus, HDL-S1P, through activation of S1PR1/3, stimulates several signaling pathways; this results in increased vasodilation, endothelial cell survival, mobilization of EPC from the bone marrow, induction of VEGF synthesis, and blockade of vascular inflammation and apoptosis (Fig. 2).

3. ATP BINDING CASSETTE TRANSPORTER G1 (ABCG1)

High expression of ABCG1 receptors was detected in endothelial cells. These receptors consist of six transmembrane domains and their functioning requires formation of dimeric forms. ABCG1, unlike ABCA1, does not interact directly with lipid acceptors (HDL, LDL, phospholipid vesicles, and cyclodextrin). However, they can serve as a triggering element of the intracellular cascade of second messengers, having a significant impact on signaling processes occurring in the neighborhood [4]. It has been shown that ABCG1 interacts with the structural component of caveolae, the caveolin protein, containing in adipocytes, endothelial cells, and fibroblasts. Caveolin-1 is an integral protein. Its NH_2 and COOH ends are faced into the cell, and the hydrophobic region of the molecule is inserted into the membrane. Caveolins, interacting with signaling molecules, modulate their activity and, in most cases, act as an inhibitor [51]. The interaction of the eNOS enzyme with the cholesterol-binding protein caveolin suppressed its catalytic activity. An increase in cholesterol in the lung endothelial cells of mice fed a high-cholesterol diet increased the interaction between caveolin-1 and eNOS, which impaired NO release. HDL reversed eNOS inhibition in endothelial cells but had no effect in caveolin-1-deficient mice. Stimulation of the efflux of cholesterol and oxysterols through the endothelial receptor ABCG1 is accompanied by a decrease in the interaction of caveolin-1 and eNOS with subsequent phosphorylation of eNOS and vasodilation [52, 53]. It is believed that these changes also have an antiinflammatory effect in the vascular wall [54, 55].

4. ENDOTHELIAL LIPASE

Unlike other members of the triglyceride lipase family with phospholipase activity, endothelial lipase, is expressed and secreted by endothelial cells and then binds to heparan sulfate proteoglycans covering their luminal surface [9]. Endothelial lipase bound to HDL with high affinity hydrolyzes phospholipids to form free fatty acids and lysophospholipids. HDL remodeling initiated by endothelial lipase not only reduces particle size, but also improves their vasoprotective functions, and the increase in the antioxidant capacity of HDL occurs independently of paraoxonase 1 [53, 56].

Cultivation of endothelial cells in the presence of the proinflammatory cytokine interleukin-6 (IL-6) leads to increased expression of endothelial lipase and increased binding and transport of ^{125}I-HDL [57]. A similar effect was found when cells were transfected with endothelial lipase. During specific transport of HDL through endothelial cells, lipase reduces the HDL particle size. In contrast, inhibition of the enzyme with tetrahydrolipstatin (a common lipase inhibitor) blocked the inducing effect of IL-6 on the binding and transport of these particles [57]. It is important to note that the observed effects were not due to changes in the expression of SR-BI and ABCG1.

HDL particles modified by endothelial lipase reduce the content of free cholesterol in endothelial cell membranes, promote eNOS interaction with caveolae, increase phosphorylation of Akt and eNOS, and also cause relaxation of the aorta precontracted by norepinephrine. Aortic relaxation was completely suppressed when eNOS was inhibited with L-NNA [53].

In endothelial lipase gene knockout mice, HDL-induced angiogenesis was markedly reduced compared to wild-type mice. Similar events occur in BAEC cells when endothelial lipase activity is inhibited by siRNA [58].

5. APOA-1/ECTOPIC DOMAIN F1-ATPASES

Until recently, it was believed that the expression of mitochondrial ATP synthase was strictly limited to the inner mitochondrial membrane. F_1F_0-ATP synthase is an enzymatic complex (~600 kDa) consisting of two main components F1, F0; using the energy of an electrochemical transmembrane proton gradient it synthesizes ATP. F_1F_0-ATP synthase is the final enzyme of the oxidative phosphorylation pathway involved in ATP synthesis [59].

It was surprising to find some components of the catalytic portion of F_1-ATP synthase (with the outward-facing F1 domain) on the surface of the membranes of some cells, including hepatocytes, adipocytes, and endothelial cells. Subsequently, the discovered enzyme was named ecto-F_1-ATPase, which catalytically works in the opposite direction to that described in mitochondria. The binding of apoA-I to ecto-F_1-ATPase stimulates the hydrolysis of extracellular ATP to ADP and phosphate, while the enzyme cannot synthesize ATP [60].

Under pathological conditions such as inflammation, hypoxia, and vascular damage, large amounts of glycolytically produced ATP can be released locally into the circulation from erythrocytes, platelets, endothelial cells [61, 62]. ADP formed during hydrolysis binds to ADP-sensitive purinergic (nucleotide) receptors (the purinergic receptor P2Y) (Fig. 3). Depending on the cell type, different P2Ys are activated thus leading to the activation of different intracellular events [55, 63].

Studies performed on hepatocytes have shown that the ecto-F_1-ATPase β-chain is a high-affinity receptor for the lipid-free form of apoA-I, and its activity is associated with the P2Y13 receptor, which is necessary for the subsequent endocytosis of whole HDL particles and hepatobiliary efflux of cholesterol [1, 64].

In contrast to hepatocytes, endothelial cells predominantly express P2Y1 and, to a lesser extent, P2Y12 receptors [1, 60]. P2Y1 receptor activation by ADP (Fig. 3) leads to stimulation of the PI3K/Akt signaling pathway, which promotes cell proliferation [55], inhibits apoptosis [1, 65], and increases vasodilation [61].

It was previously shown that in endothelial cells, apoA-1/ecto-F_1-ATPase, through activation of P2Y12 receptors, stimulated internalization of lipid-depleted HDL and apoA-1, allowing them to reach the subendothelial space of the arteries [63].

In human and mouse aortic endothelial cells (MAEC), physiological concentrations of apoA-I increase eNOS activity and NO production (Fig. 3). Ecto-F_1-ATPase receptors bind 60–70% of lipid-free apoA-I [65]; this activates P2Y1 receptors and leads to phosphorylation of eNOS Ser1177, NO synthesis, followed by vasodilation of isolated mouse aorta. In addition, apoA-I suppressed vasoconstriction caused by thromboxane A2 receptor agonist (an eicosanoid that can constrict blood vessels) and increased femoral artery blood flow in mice. These effects were attenuated by inhibitors of eNOS, ecto-F_1-ATPase, and P2Y1 receptor [1]. Ecto-F_1-ATPase is the only receptor involved in NO-dependent vascular relaxation induced by lipid-free apoA-I. It is known that human pre-β1-HDL is mainly represented by lipid-free apoA-I and constitutes 5–10% (50–200 μg/ml) of the total concentration of apoA-I in the plasma of healthy people [1]. It is suggested that the apoA-1/ecto-F_1-ATPase/P2Y1 signaling pathway (prior to NO synthesis) is mediated by activation of the downstream PI3Kβ/Akt pathway [1, 61].

Activation of ecto-F_1-ATPase in endothelial cells induced by apoA-I is accompanied by stimulation of cell proliferation and inhibition of apoptosis [66]. In HUVEC endothelial cells expressing high levels of P2Y1, ecto-F1-ATPase activation by apoA-I triggered a signaling mechanism leading to phosphorylation and activation of PI3Kβ/Akt, which increased endothelial cell proliferation and survival (Fig. 3). ApoA-1 (100 μg/ml) increased Akt phosphorylation at its activation sites, Thr308 and Ser473, by 40-fold [55]. It was found that a selective ecto-F_1-ATPase inhibitor (H49K) sharply reduced (~93%) Akt phosphorylation, similar results were obtained with oligomycin (another enzyme inhibitor) and the P2Y1 purinergic receptor antagonist MRS2179. Silencing of P2Y1 gene expression inhibited Akt phosphorylation induced by apoA-1 and completely blocked cell proliferation [55].

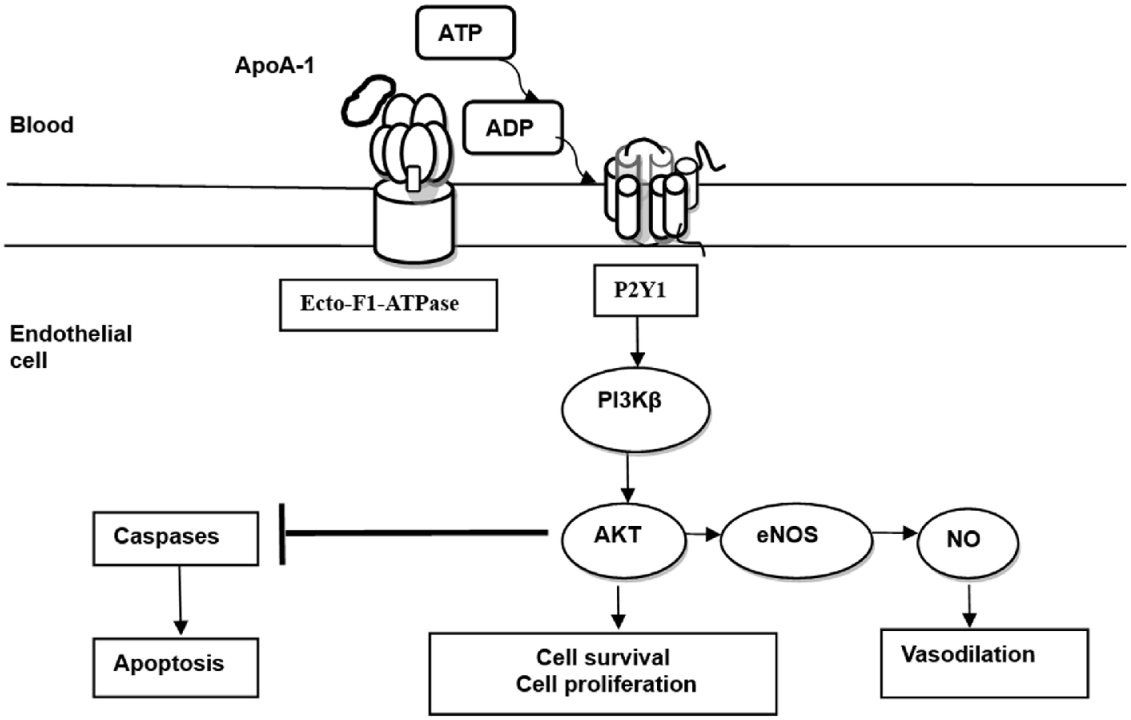

Figure 3. Schematic representation of apoA-1/ecto-F_1-ATPase/P2Y1-mediated signaling in an endothelial cell.

It was previously reported that human EPC treated with apoA-I also expressed ecto-F_1-ATPase. ApoA-I mimetic peptides increased the number and functionality (proliferation, migration and formation of vascular tubes) of mouse and human EPC [67]. In the presence of angiogenic stimuli, EPC can be mobilized from the bone marrow into the blood and then recruited to damaged endothelium, where they differentiate into mature endothelial cells. ApoA-I significantly increased EPC proliferation by 14.5% and angiogenesis by 31%; these effects completely disappeared in the presence of ecto-F_1-ATPase inhibitors [66].

The study by Cabou et al. [1] performed using human blood vessels has shown that apoA-I increased endothelial NO-dependent vasodilation *ex vivo* and increased arterial blood flow *in vivo* in wild-type mice via the ecto-F1-ATPase/P2Y1 pathway. In addition, the increase in femoral arterial blood flow *in vivo* was inhibited by the P2Y1 receptor antagonist MRS2179 [1].

CONCLUSIONS

The mechanism of the regulatory effect of HDL on endothelial cells involves plasma membrane proteins (SR-BI, S1PR, ABCG1, endothelial lipase, ecto-F_1-ATPase); HDL interaction with these proteins activates intracellular signaling pathways. Figure 4 shows the main functions of endothelial cells, which are activated in response to HDL/apoA-I binding to these proteins. The HDL binding to receptors not only leads to transendothelial transport of these particles, but also triggers various signaling cascades associated with important vasoprotective effects. HDL supports endothelium-dependent vasorelaxation, suppresses the synthesis of endothelial adhesion molecules, regulates migration of leukocytes and monocytes/macrophages through the vascular wall, inhibits ROS production, prevents apoptosis, supports angiogenesis and reendothelialization (Fig. 4).

Activation of the above mentioned pathways represents a promising approach for the development of endothelial protective agents, as has already been demonstrated in patients with degenerative brain diseases. The drugs fingolimod (FTY720), ozanimod and siponimod, which have been successfully used in the treatment of multiple sclerosis since 2010, increase the differentiation and survival of neurons [29, 68]. The main molecular mechanism of action of these drugs is their binding to the receptors of the biologically active lysophospholipid S1P [69]. Retinal proliferative diseases (diabetic retinopathy) are treated by means of S1P neutralizing antibodies, decreasing retinal neovascularization [28, 70].

It should be noted that the functions of endothelial cells can also be influenced by other HDL proteins. For example, significant correlations have been found between the antiapoptotic activity and the content of clusterin in HDL [10, 71]. In patients with myocardial infarction, the content of clusterin in HDL was significantly reduced [49]. Its deficiency leads to ineffective stimulation of PI3K/Akt and a subsequent decrease in the expression of the antiapoptotic factor Bcl-xL [49]. In a model of myocardial infarction, it was shown that coronary reperfusion with clusterin reduced the infarct area by 75% [26]. Another HDL protein that influences signaling pathways in endothelial cells is annexin (lipokartin) [72], which inhibits the expression of cell adhesion molecules [73]. It has been shown that microRNAs associated with HDL can also influence angiogenesis, vascular inflammation, vascular tone, and barrier functions of endothelial cells [74].

Understanding the mechanisms of regulation of cell functions by HDL is an important step for the development of new methods for pharmacological correction of endothelial dysfunction and the creation of effective endothelial protective agents under conditions of insufficient HDL production or high levels of modified HDL in the blood.

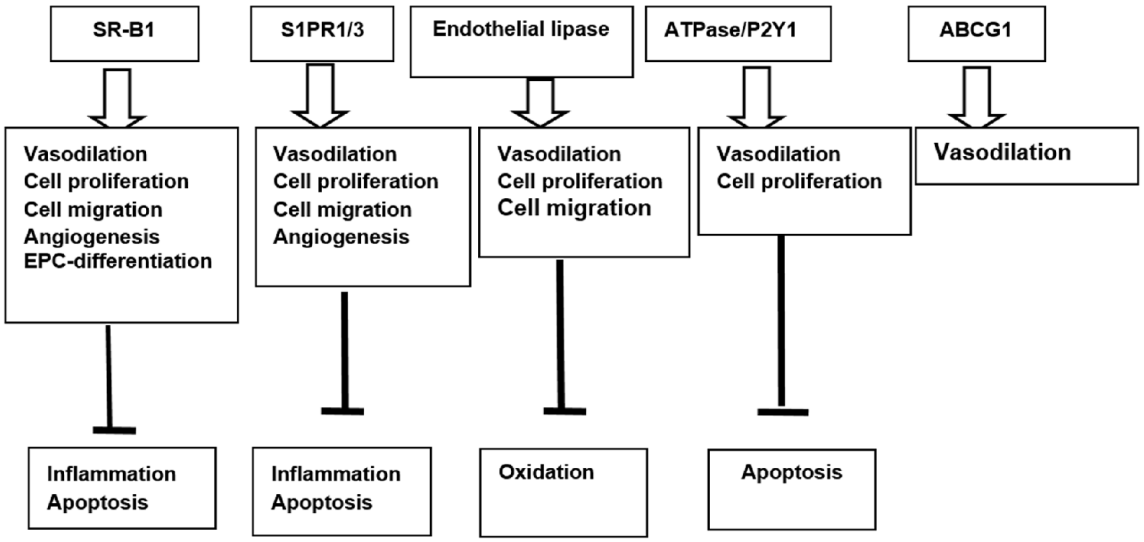

Figure 4. Scheme of the vasoprotective effect of HDL on endothelial cells (adapted from [10]).

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COMPLIANCE WITH ETHICAL STANDARDS

This article does not contain any research involving humans or the use of animals as objects.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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МОЛЕКУЛЯРНЫЕ МЕХАНИЗМЫ РЕГУЛЯТОРНОГО ДЕЙСТВИЯ ЛИПОПРОТЕИНОВ ВЫСОКОЙ ПЛОТНОСТИ НА ФУНКЦИИ ЭНДОТЕЛИЯ

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Дисфункция эндотелия лежит в основе патогенеза многих заболеваний, прежде всего сердечно-сосудистых. Эпидемиологическими исследованиями показана обратная зависимость между уровнем в плазме крови липопротеинов высокой плотности (ЛПВП) и сердечно-сосудистыми заболеваниями. Результаты экспериментальных исследований свидетельствуют о том, что антиатерогенное действие ЛПВП связано не только с их участием в обратном транспорте избытка холестерина, но и с их регуляторным влиянием на функции клеток различных органов и тканей, в том числе эндотелиальных клеток. Цель настоящего обзора — представить новые данные об участии плазматических рецепторов и связанных с ними внутриклеточных сигнальных путей в механизме защитного действия ЛПВП на функции эндотелиальных клеток. Понимание механизмов регуляции функций клеток под влиянием ЛПВП является важным этапом для разработки новых способов фармакологической коррекции дисфункции эндотелия и создания эффективных эндотелиопротекторных средств.

Полный текст статьи на русском языке доступен на сайте журнала (http://pbmc.ibmc.msk.ru).

Ключевые слова: липопротеины высокой плотности; аполипопротеин A-I; сигнальные пути; эндотелий; дисфункция

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