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REVIEWS

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Role of the ABC Transporters A1 and G1, Key Reverse Cholesterol Transport Proteins, in Atherosclerosis

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Abstract—Atherosclerosis is one of the most common causes of death worldwide. Epidemiology studies firmly established an inverse relationship between atherogenesis and distorted lipid metabolism, in particular, higher levels of total cholesterol, an accumulation of CH-laden macrophages (foam cells), and lower plasma levels of antiatherogenic high density lipoprotein (HDL). It is believed that the reverse cholesterol transport, a process that removes excess cholesterol from peripheral tissues/cells including macrophages to circulating HDL, is one of the main mechanisms responsible for anti-atherogenic properties of HDL. The key proteins of reverse cholesterol transport—ATP-binding cassette transporters A1 (ABCA1) and G1 (ABCG1)—mediate the cholesterol efflux from macrophages and prevent their transformation into foam cells. This review focuses on the role of ABC transporters A1 and G1 in the pathogenesis of atherosclerosis.

Keywords: atherosclerosis, reverse cholesterol transport, ABCA1, ABCG1

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INTRODUCTION

Atherosclerosis and its complications, such as coronary heart disease (CHD), ischemic stroke, and others, are a major cause of adult mortality in many countries. Atherosclerosis is currently thought to be a multifactorial disease, which results from the interaction of enviromental and genetic factors. The key triggering events for atherogenesis are cholesterol (cholesterol)-laden machrophages, intracellular lipids and the extracellular matrix accumulation in the cell wall, while circulating high density lipoprotein (HDL) plays antiatherogenic role [1]. An accumulation of cholesterol esters in the reticuloendothelial system in Tangier disease patients, which lack HDL, indicate that HDL play a crucial role in removing cholesterol from peripheral tissues [2]. Reverse cholesterol transport (RCT) from tissues to the liver is thought to be a major mechanism responsible for the antiatherogenic properties of HDL. Regulating the efficiency of cholesterol elimination from macrophages of the vascular wall (the intima) may help to protect the cardiovascular system against atherosclerosis. Thus, RCT activation can be considered as an effective therapeutic strategy aimed at reducing risk of atherosclerosis [3]. A key role in RCT is played by the ATP-binding cassette (ABC) transporters A1 (ABCA1) and G1 (ABCG1), which form HDL particles and substantially affect total cholesterol and HDL metabolism in the body and the development of atherosclerosis. Dysfunction of ABCA1 and ABCG1 or a decrease in *ABCA1* and *ABCG1* gene expression accelerates atherogenesis and leads to early-onset atherosclerosis [3]. Thus, regulation ABCA1 and ABCG1-dependent cholesterol efflux and the efficiency of RCT and, consequently, atherogenesis may provide a promising strategy of antiatherogenic therapy.

CHOLESTEROL HOMEOSTASIS AND REVERSE CHOLESTEROL TRANSPORT

Homeostasis of HC is maintained by balancing cholesterol synthesis in the cell, exogenous cholesterol intake, and cholesterol efflux from the cell to HDL. Macrophages do not synthesize cholesterol, as the majority of other cells, but they are capable of accumulating cholesterol in adverse conditions and are thereby converted to foam cells; the conversion is thought to be a key step in the formation of atherosclerotic plaques in vascular walls. Therefore, modulating cholesterol elimination predominantly regulates the cholesterol content in macrophages. cholesterol transport from the cell is a main process that reduces the cholesterol content in macrophages and leads to atherosclerotic plaque regression [4]. The majority of peripheral cells and tissues are incapable of cholesterol

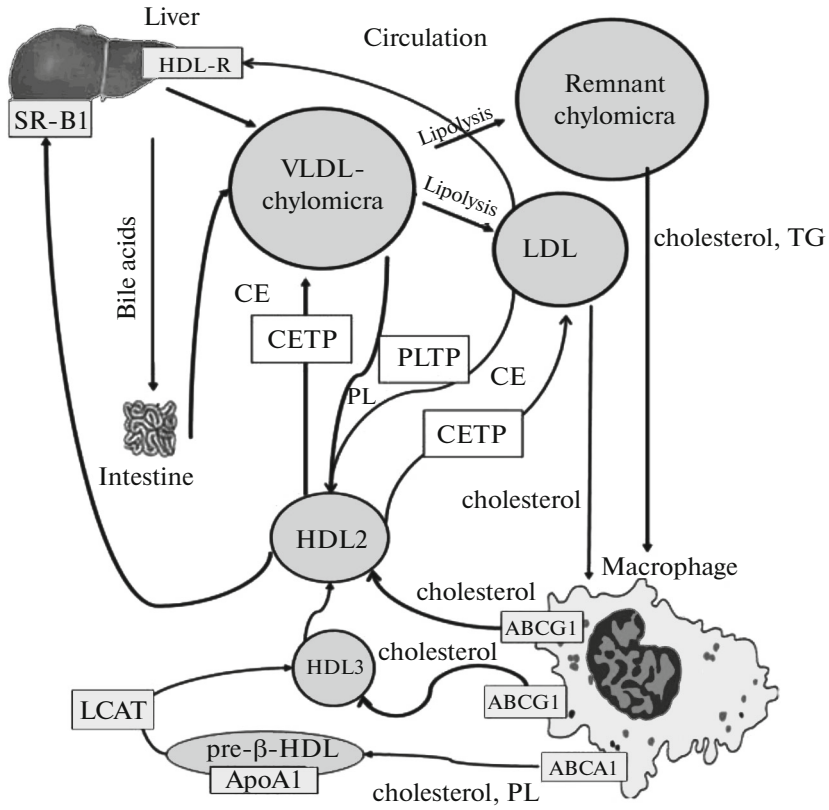

Fig. 1. Cholesterol elimination from peripheral cells and the lipid transport system of the blood. SR-B1, scavenger receptor class B1; PLTP, phospholipid transfer protein; CETP, cholesterol ester transfer protein; HDL, high density lipoprotein; LCAT, lecithin–cholesterol acyltransferase; TG, triglycerides; PL, phospholipid; cholesterol, free cholesterol; CE, cholesterol ester.

catabolism. Cholesterol is removed from cells by transferring free cholesterol to extracellular acceptors and HDL acts as one of them. ABCA1 and ABCG1 mediate the interaction of free HC with apolipoprotein A1 (ApoA1) and mature HDL particles, respectively, to sustain a predominant pathway of RHT from peripheral cells [5, 6].

Maintaining cholesterol homeostasis is a complex process that includes cholesterol synthesis in the liver, cholesterol adsorption in the intestine, cholesterol transport to peripheral tissues, RCT from peripheral tissues to the liver and cholesterol excretion from the body with bile acids. ABCA1 and ABCG1 play a leading role in LDH biogenesis and cholesterol removal from peripheral tissues [7, 8].

An inverse relationship between the concentration of HDL-associated cholesterol in the blood plasma and the development of atherosclerosis has been observed in numerous clinical and epidemiological studies [9]. Independent evidence for the antiatherogenic function of HDL is provided by the fact that the risk for atherosclerosis is substantially higher in patients with familial hypoalphalipoproteinemia, which is characterized by significantly lower HDL levels [10, 11]. Hypercholesterolemia is thought to be a risk factor for atherosclerosis and is often accompanied by HDL metabolic defects, such as lower ApoA1 and lower HDL-cholesterol concentrations in the blood plasma [12, 13]. According to current understanding, the most important HDL function that is responsible for their antiatherogenic properties are participation HDL in RCT and [9]. RCT is a complex process (Fig. 1).

The first RCT step consists in removing excess free cholesterol from lipid-laden cells and is of immense importance for preventing cholesterol accumulation in peripheral tissues. ABCA1 specifically interacts with ApoA1, which is a major structural protein of HDL, to produce immature pre-β-HDL [14]. Pre-β-HDL is then transformed into α-HDL by lecithin–HC acyltransferase (LCAT) [14]. Furthering α-HDL saturation with cholesterol involves ABCG1 [15]. cholesterol is accepted predominantly by the densest and smallest HDL particles, which belong to HDL3 subfraction. With cholesterol saturation and esterification, HDL3 particles gradually increase in size and are transformed to particles of HDL2 subfraction [14]. HDL2 particles enter the liver through specific apolipoprotein receptors [14].

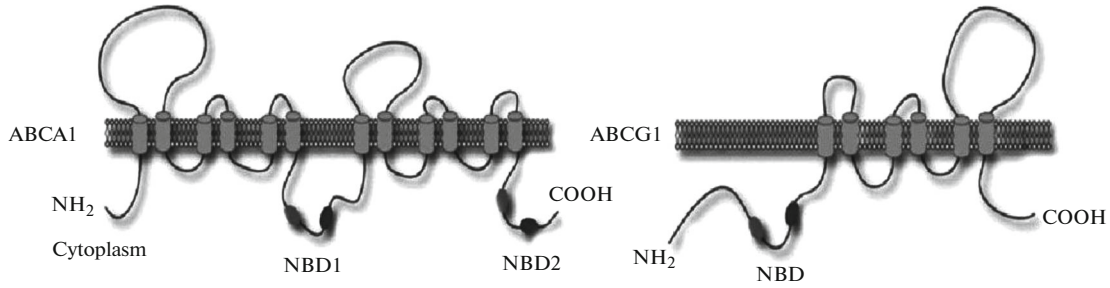

Fig. 2. Schemes of the ABCA1 and ABCG1 transporters.

Distorted RCT from intimal macrophages is critical for atherosclerotic plaque development, leading to macrophage transformation into foam cells and subsequent lipid accumulation in the vascular wall [15]. The ABCG1 mRNA was detected in postmortem human atherosclerotic plaques, indicating that ABCG1 is possibly involved in removing cholesterol from plaques and may trigger the onset and progression of atherosclerosis [17]. Substantial amounts of the *ABCA1* and *ABCG1* mRNAs are found in the arterial intima in patients withvatherosclerosis [16], implicating ABCA1 and ABCG1 in removing cholesterol from atherosclerotic plaques, in particular, at the step of initiation atherosclerosis development.

ANTIATHEROGENIC ROLE OF ATP-BINDING CASSETTE TRANSPORTERS A1 AND G1

The human genome carries 49 ABC genes of the superfamily of ATP-binding cassette (ABC) transporter that bind ATP and use the energy to drive the transport of various molecules across membranes [17]. ABC transporters contain one or two highly conserved hydrophilic cytoplasmic nucleotide binding domains (NBD), and two sets of transmembrane (TM) domains, typically containing six membrane-spanning α-helices (Fig. 2).

The ABCA1 protein consists of 2201 amino acids with two transmembrane domains composed of six transmembrane helices and two NBD. Depending on the isoform, ABCG1 consists of 678 or 666 amino acids. The ABCG1 structure includes one transmembrane domain and one NBD. Because two transmembrane domains and two ATP hydrolysis domains are necessary for an active ABC transporter, ABCG1 is thought to function as a homodimer.

The *ABCA1* gene is located on chromosome 9, in locus 9q31. Its open reading frame consists of 6783 bp and has 50 exons. ABCA1 was initially cloned in 1994 as a homolog of *Saccharomyces cerevisiae CED-7* [18]. The molecular mechanisms sustaining the ABCA1 function in HDL biogenesis remained unclear until 1999, when ABCA1 mutations were found to cause a severe autosomal recessive disorder known as Tangier disease [2]. Almost total lack of HDL (<5% of the normal level) and ApoA1 (<1% of the normal level) is observed in the blood plasma, cholesterol esters dramatically accumulate in the reticuloendothelial system, and early atherosclerotic damage to vessels occurs in Tangier disease. Low ApoA1 levels in the blood plasma are seen because ApoA1 is rapidly catabolized, being incapable to interact with functionally inactive ABCA1. More than 70 mutations in *ABCA1* gene were identified in people with low HDL levels, and more than half of them are missense mutations [2]. Furthermore, the HDL level decreases to 45% in homozygous mutation carriers [19]. A decrease in HDL in heterozygous carriers of *ABCA1* mutations is accompanied by lower cholesterol efflux from the cell, a higher CHD incidence and a higher arterial wall thickness. Approximately 10% of people with low HDL levels are heterozygous carriers of *ABCA1* mutations [19].

The mammalian ABCG1 protein was first described as a homolog of the *Drosophila melanogaster* white protein, which regulates the uptake of tryptophan and guanine [20]. The *ABCG1* gene is located on chromosome 21 in locus q22.3. There is still no data on hereditary disorders associated with genetic variants of *ABCG1*, however, it has been shown that substantial decreases in *ABCG1* expression and ABCG1 function are potentially capable of promoting the generation of lipid-laden macrophages and accelerating atherogenesis in type 2 diabetes mellitus [21].

An important role which ABCA1 and ABCG1 play in eliminating cholesterol from macrophages was demonstrated in transgenic animal models. For instance, ABCA1 performs a key function in HDL biogenesis in liver cells, and its activity determines the antiatherogenic HDL level in the blood plasma [14]. RCT is slow in *ABCA1* knockout mice, like in Tangier disease patients, thus determining an extremely low HDL level in the blood plasma and a higher content of lipid-laden macrophages [22]. An increase in atherosclerosis development and a 50% decrease in cholesterol transport into the liver and bile were observed in ABCA1-deficient mice [19]. It should also be noted that cholesterol transport from macrophages is inversely associated with the development of atherosclerosis regardless of the HDL levels [23]. When bone

marrow is grafted from *ABCA1* knockout mice, a block of ABCA1 synthesis in macrophages increases atherosclerotic damage to vessels without affecting the plasma HDL-cholesterol level [24]. A substantial decrease in RCT in vivo was revealed in an analysis of ABCA1-deficient macrophages [25]. *ABCG1* knockout mice display mass lipid deposition in vascular wall macrophages and liver cells without changes in lipid levels in the blood plasma [26]. Thus, ABCG1 does not substantially affect the HDL level, but possibly plays a primary role in removing cholesterol and its derivatives from macrophages. ABCG1 activity additionally prevents the cell from accumulating the cytotoxic oxidized cholesterol derivatives 7-keto-cholesterol and 7β-hydroxy-HC [27, 28]. An accumulation of 7-keto-HC and 7β-hydroxy-HC distinguishes mature and progressing plaques from early formation atherosclerotic lesions [22]. A combined *ABCA1/ABCG1* knockout leads to a far higher rate of HC accumulation in the arterial wall and earlier onset of atherosclerosis as compared with a knockout in either gene alone in mice [28].

Apart from the role in preventing the generation of foam cells, a role in anti-inflammatory reactions may contribute to antiatherogenic activity of ABCA1 and ABCG1 [29]. A hypothesis was advanced that sustaining RCT from macrophages is an essential component of the anti-inflammatory potential of HDL. Macrophages of *ABCA1*$^{-/-}$ *ABCG1*$^{-/-}$ double-knockout mice are characterized by activation of the TLR–NF-kB signaling cascade and higher secretion of anti-inflammatory cytokines (the tumor necrosis factor (TNF-α) and interleukins (IL)-6, -1β, and -12p70) and chemokines (macrophage inflammatory proteins (MIP-1α and MIP-2) and monocyte chemoattractant protein 1 (MCP-1)), which may facilitate a progression of atherosclerosis [29]. The IL-10 secretion level in ABCA1$^{+/+}$ macrophages is higher than in ABCA1$^{-/-}$ macrophages, pointing again to a role of ABCA1 in inflammatory reactions [30]. ABCA1 was shown to promote macrophage secretion of the anti-inflammatory cytokine IL-10, while a decrease in ABCA1 or ABCG1 might explain why inflammation increases during atherosclerosis development, facilitating and accelerating this process [29]. There is data that implicates ABCG1 in NO synthase processing in endothelial cells and this ABCG1 activity is also possible to classify as atheroprotective [31].

The above findings make it possible to assume that dysfunction of ABCA1 and ABCG1 or downregulation of their genes accelerates atherogenesis and leads to early-onset atherosclerosis [32]. However, while many studies were performed in transgenic animals, the role of *ABCA1* and *ABCG1* in human atherosclerosis development is still poorly documented.

EXPRESSION OF THE ABCA1 AND ABCG1 GENES AND REGULATION OF THE ABCA1 AND ABCG1 PROTEIN LEVELS

The *ABCA1* gene is expressed in all tissues but the highest level of *ABCA1* mRNA is observed in the liver, the brain, and macrophages, while the ABCG1 mRNA is expressed to the highest extent in the spleen, lung, and thymus. *ABCA1* and *ABCG1* transcription can be activated by the LXRα/LXRβ transcription factors, which form heterodimers with RXR, and are possibly triggered by overloading cell with cholesterol [33]. Oxidized cholesterol derivatives, which are a major form of cholesterol accumulating in the cell, serve as ligands of the LXRα and LXRβ factors. LXR/RXR heterodimers bind to the LXRE elements (DR4 repeats) in the regulatory regions of *ABCA1* and *ABCG1* to induce their expression. In addition, their expression can be regulated via interactions with other transcription factors, such as Sp1/3, upstream stimulatory factor 1/2 (USF), hepatocyte nuclear factor 1a (HNF-1a), cAMP, and a zinc finger protein 202 (ZNF202) protein group [34].

Owing to recent interest in microRNA-dependent mechanisms of gene expression regulation, microRNAs involved in regulating lipid metabolism genes were identified [35]. A binding of microRNA-128-2 to the 3'-untranslated region of the *ABCA1* and *ABCG1* mRNAs was shown to negatively regulate expression of their genes [35].

An epigenetic regulation was shown for *ABCA1* expression [36]. Methylation of a certain region in the *ABCA1* promoter negatively correlates with the HDL level and is associated with higher risk of coronary insufficiency [36]. Epigenetic modification affects ABCG1 expression as well. For instance, the *ABCG1* promoter is hypermethylated in 90.5% of CHD patients and only 29.6% of people without clinical signs of cardiovascular disorders [37]. The epigenetic control of gene expression regulation is of immense importance for determining hereditary predisposition and, compared with structural gene polymorphisms, may play a greater role in mediating the effects of environmental risk factors in the pathogenesis of multifactorial diseases, including atherosclerosis [38]. Thus, *ABCG1* promoter hypermethylation, which is associated with lower *ABCG1* expression, may provide a marker and a genetic predictor of CHD. The extent of methylation of the *ABCA1* and *ABCG1* promoters was additionally associated with changes in the plasma lipid spectrum, and variations of *ABCA1* and *ABCG1* expression were found to contribute to interindividual differences in total cholesterol and HDL-cholesterol [36, 37].

Variations in gene expression substantially contribute to the development of atherosclerosis according to epidemiological studies [39, 40]. Microarray studies showed that *ABCA1* and *ABCG1* expression in the peripheral blood is decreased in CHD and cardiovas-

cular risk-modulating disorders, such as diabetes mellitus and hypertension [22, 41, 42]. The most promising approach is *ABCA1* and *ABCG1* expression profiling in macrophages derived via monocyte differentiation in the presence of M-CSF; these cells provide an adequate model to study the pathological processes that take place during atherogenesis in vivo [43]. A macrophage population is heterogeneous, while M-CSF treatment makes it possible to obtain macrophages that express the proatherogenic phenotype and occur predominantly in atherosclerotic plaques [44].

For instance, the *ABCA1* mRNA content in M-CSF-generated macrophages from atherosclerosis patients was found to be higher than in cells from a control group [45, 46]. It is important to note that statins and other hypolipidemic drugs were not administered to the patients examined in the study, and this circumstance allowed an adequate analysis of the association between the *ABCA1* and *ABCG1* mRNA levels and atherosclerosis. However, a decrease in *ABCA1* expression was observed in circulating monocytes of patients with CHD and myocardial infarction occurring at an early age (less than 40 years) [42]. The result is possibly explained by simvastatin administration to all patients involved in the study [42] because simvastatin, like other statins, is known to downregulate *ABCA1* and *ABCG1* expression in human monocytes [47, 48]. On the other hand, there is evidence that the *ABCA1* expression level in atheromatous plaques is higher than in normal arteries [49] and arteries varying in extent of atherosclerotic damage [50]. An increase in *ABCA1* mRNA level in atherosclerosis was similarly observed when patients with aneurysms of the carotid artery or abdominal aorta were compared with control subjects having no signs of atherosclerosis [51].

Data that the *ABCG1* mRNA and ABCG1 protein levels are lower in macrophages from atherosclerosis patients shows the association between the presence of mature atherosclerotic plaques and lower ABCG1 activity [52]. Because a decrease in ABCG1 activity was earlier shown to be correlated with a decrease in HC efflux [21], the above data indicate that cholesterol elimination from the vascular wall is possibly distorted in atherosclerosis. The *ABCG1* mRNA content in monocytes was tested for correlation with the severity of atherosclerotic damage and proved to be lower in monocytes from patients with arterial occlusion in various parts of the cardiovascular system than in monocytes from patients without occlusion or control subjects [52]. It should be noted that the plaque size depends on the rate of lipid accumulation in the arterial wall, but does not always correlate with the disease duration. In fact, the severity of atherosclerotic damage was not found to correlate with the disease duration. The finding indicates that the *ABCG1* expression level possibly affects the atherosclerotic plaque formation rate.

Note that only scarce data are available for the posttranslational regulation of the ABCA1 and ABCG1 protein levels. The half-life of either protein is no more than 1 hour. A decrease in ABCA1 in macrophages was observed in atherosclerosis, while ABCA1 expression was elevated [45]. Yet the level of a mRNA does not always predict the content of the corresponding protein in the cell. For instance, the heart and kidney are characterized by the highest levels of the *ABCA1* mRNA and have the lowest contents of the ABCA1 protein in mice [52]. There are data that ABCA1 protein levels in human atherosclerotic arteries are substantially lower than in intact arteries, while *ABCA1* mRNA levels are higher [49], and that the ABCA1 levels are decreased in spite of the higher *ABCA1* expression level in atherosclerotic arteries compared with healthy arteries [50]. The data indicate that HC elimination from macrophages is possibly distorted in atherosclerosis [45, 46]. Discordance between the *ABCA1* mRNA and ABCA1 protein levels in macrophages and arterial tissues suggests a complex posttranslational regulation for ABCA1 activity in vivo [53]. Studies in vitro support the idea that a regulation of ABCA1 degradation is a main mechanism involved in the posttranslational regulation of ABCA1. Degradation of ABCA1 decreases in rate upon its interaction with ApoA1 and is stimulated by unsaturated fatty acids [54]. It is thought that the posttranslational regulation of the ABCA1 protein level may proceed in a manner independent of the *ABCA1* expression level.

Given that genetic factors substantially contribute to atherosclerosis and that the rate of RCT from the vascular wall is determined by the ApoA1 and HDL concentrations in the blood plasma and, on the other hand, cholesterol elimination from intimal monocytes and macrophages, it is possible to assume that changes in *ABCA1* and *ABCG1* expression levels and the contents of the corresponding proteins as key RCT mediators affect the RCT rate in the vascular wall in atherosclerosis. Studying the mechanisms that regulate *ABCA1* and *ABCG1* expression and contribute to the posttranslational regulation of the two transporters holds promise for developing new pharmacological approaches to therapy for atherosclerosis.

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