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Review

ABCA1 and metabolic syndrome; a review of the ABCA1 role in HDL-VLDL production, insulin-glucose homeostasis, inflammation and obesity

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ABSTRACT

ATP-binding cassette transporter A1 (ABCA1) is an integral cell-membrane protein that mediates the rate-limiting step of high density lipoprotein (HDL) biogenesis and suppression of inflammation by triggering a number of signaling pathways via interacting with an apolipoprotein acceptor. The hepatic ABCA1 is involved in regulation of very low density lipoprotein (VLDL) production by affecting the apolipoprotein B trafficking and lipidation of VLDL particles. This protein is involved in protecting the function of pancreatic β-cells and insulin secretion by cholesterol homeostasis. Adipose tissue lipolysis is associated with ABCA1 activity. This transporter is involved in controlling obesity and insulin sensitivity by regulating triglyceride (TG) lipolysis and influencing on adiponectin, visfatin, leptin, and GLUT4 genes expression. The ABCA1 of skeletal muscle cells play a role in increasing the glucose uptake by enhancing the Akt phosphorylation and transferring GLUT4 to the plasma membrane. Abnormal status of ABCA1-regulated phenotypes is observed in metabolic syndrome. This syndrome is associated with the occurrence of many diseases. This review is a summary of the role of ABCA1 in HDL and VLDL production, homeostasis of insulin and glucose, suppression of inflammation and obesity controlling to provide a better insight into the association of this protein with metabolic syndrome.

1. Introduction

Metabolic syndrome (MetS) is a collection of metabolic abnormalities including abdominal obesity, insulin resistance, atherogenic dyslipidemia, chronic low grade inflammation, and high blood pressure that usually cluster together [1,2]. In the next 5–10 years, MetS will increase the risk of developing type 2 diabetes mellitus (T2DM) and cardiovascular disease (CVD) for 5 and 2 folds respectively [3]. People with MetS seem to be prone to other conditions, particularly fatty liver, polycystic ovary syndrome, cholesterol gallstones, asthma, sleep disorders, and some types of cancer [4]. Hereditary factors (genetics, ethnicity and family history) and lifestyle (smoking, medications, overweight, physical inactivity) are involved in its development [5,6].

Severe HDL deficiency has been observed in a rare genetic disorder known as Tangier disease (TD). Homozygous mutations in the ABCA1 gene lead to TD [7]. Hypertriglyceridemia and mild inflammation, similar phenotypes to individuals with MetS are other prominent features of this disease [8]. Accordingly, studies have been conducted to find out the relationship between ABCA1 and the factors mentioned in various diseases [9,10]. In a recent study, the relationship between −565C/T polymorphism as an effective SNP on the ABCA1 gene expression with Hypoalphalipoproteinemia (HA) and the serum lipid profile and inflammatory factors has been investigated, suggesting an increased risk of HA, decreased HDL-C and increased TG, interleukin-6 (IL-6) and C-reactive protein (CRP) levels [11]. In addition, molecular studies revealed a more accurate understanding of ABCA1 and its role in the regulation of these phenotypes.

ABCA1 is a 2261 amino acid integral cell-membrane protein that mediates the rate-limiting step of HDL biogenesis with the transport of cellular excess free cholesterol and phospholipids to an apolipoprotein acceptor [12]. In addition, there is evidence that the

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macrophage ABCA1 has anti-inflammatory activity. The interaction of apoA-I with ABCA1 stimulates signaling cascades that are involved in both the anti-inflammatory and lipid efflux processes mediated by ABCA1 [13]. Recent studies suggest that the hepatic ABCA1 is involved in the VLDL metabolism. Evaluation of ABCA1 silenced mice have shown an increased excretion of TG-rich VLDL1 particles due to a reduction in both apoB trafficking and phosphoinositide-3 kinase (PI3 kinase) activation. These studies provided a new role for liver ABCA1 and a metabolic relationship between the increased TG and decreased HDL levels [14,15]. Meanwhile, new studies investigated the role of ABCA1 in other characteristics of MetS and indicated its association with body weight, decreased insulin secretion and sensitivity, but increased blood glucose levels [12,16,17]. This review is a summary of the cause and mechanism of expression, signaling pathways regulating the actions of ABCA1 and its role in hepatic VLDL production, body weight regulation, secretion and sensitivity of the cells to insulin, homeostasis of blood glucose and the potential that serves as a therapeutic target.

2. Cholesterol and ABCA1 expression

Cholesterol is an essential component of cell membranes and the precursor of all body's steroids, including corticosteroids, sex hormones, bile acids and vitamin D [18,19]. Most of the body's cholesterol is produced by de novo synthesis, and the rest of it provided by the diet [20]. The liver is the key organ of cholesterol metabolism. Intrahepatic cholesterol, absorbed from the gut or de novo synthesized, together with proteins, triglycerides and phospholipids are packaged into VLDL particles. Then, VLDL enters to the bloodstream and it turns to more cholesterol-rich particles, first IDL and then LDL, under the influence of lipoprotein lipase (LPL) and cholesterol ester transfer protein (CETP) [21]. The uptake of LDL into cells is accomplished with two specific and non-specific mechanisms. The specific and non-specific uptake is done with the LDL receptor-dependent endocytosis mechanism and macrophage scavanger receptors, respectively [22]. Non-specific uptake increases by an increase in concentration or a change in the structure of LDL (e.g., oxidized LDL) is occurred, which is associated with atherosclerosis [23]. Although the cholesterol has many benefits; its surplus induces cytotoxicity by various mechanisms which are summarized in Table 1.

Free cholesterol (FC) has different regulatory functions in cells, including: reduction of LDL receptor gene expression and thus reducing LDL uptake [31], prevention of cholesterol synthesis by inhibition of the HMG-CoA reductase gene expression [32], stimulation of acyl-CoA: cholesterol acyltransferase (ACAT) activity and storage of free cholesterol in cholesterol ester form [33], causing the reverse cholesterol transport (RCT) [34]. RCT is a metabolic pathway whereby the excess intracellular cholesterol is transported to the liver through the HDL compartment for elimination [35]. The first and rate-controlling step of this pathway is mediated by ABCA1 [36]. Mutations in ABCA1 gene cause Tangier disease which is characterized by near-zero level of HDL [11]. Lipid-free apolipoproteins exposed to isolated fibroblasts from TD patients were unable to remove cholesterol and phospholipids [37,38]. The targeted destruction of ABCA1 gene in mice leads to accumulation of sterols in a number of tissues [39,40]. The Wisconsin Chicken Hypo Alpha Mutant (WHAM) is an animal model of TD. Similar to human TD patients and ABCA1 knockout mice, severe lipid accumulation was observed especially in their hepatocytes [41]. The study of regulation and tissue expression of ABCA1 showed the presence of a direct repeat response element (DR4) in ABCA1 gene that binds to the liver X and retinoid X receptors (LXR and RXR) [42,43]. Mutation of this site destroys sterol-mediated activation of the promoter [36]. LXR and RXR are activated by binding to oxy sterols and 9-cys retinoic acid, respectively [44]. These ligands can activate the transcription separately or together, but their combined treatment has remarkable synergistic effects [42,45]. Of course, overexpression of LXR-α due to PPARɣ activation was associated with promotion of the ABCA1 expression (Fig. 1) [46].

ABCA1 is highly expressed in the liver cells, macrophages, intestinal and endothelial cells, adrenal gland and placental trophoblast [47].

3. Regulation of ABCA1 functions by signal transduction pathways

Lipid poor apolipoproteins (Apo) A-I that present in circulatory system interacts with ABCA1 [48]. This interaction activates signaling molecules. Each of the signaling molecules triggers a pathway leading to ABCA1-mediated cholesterol efflux and anti-inflammatory activity [49]. They include:

3.1. Janus kinase 2 (JAK2)

The interaction of apoA-I with ABCA1 stimulates autophosphorylation (activation) of JAK2 in a few minutes [50]. Activated JAK2 has two independent effects: I) exacerbation of apoA-I binding activity of ABCA1 that is required for lipid export; II) phosphorylation and activation of signal transducer and activator of transcription 3 (STAT3) in macrophages. The phosphorylated STAT3 migrates to the nucleus and inhibits the expression of inflammatory cytokines IL-6, IL-1β and tumor necrosis factor α (TNF-α) (Fig. 2a) [48].

3.2. Ca^{2+}

The interaction of ApoA-I with ABCA1 induces Ca^{2+} influx into cells. The rise of cytosolic Ca^{2+} leads to calmodulin activation, and then this complex activates calcineurin [49]. The phosphorylation of JAK2 by calcineurin increases the activity of ABCA1 (Fig. 2b) [51].

3.3. Rho family G protein Cdc42

ApoA-I binding to ABCA1 activates Rho family G protein Cdc42. The activated Cdc42 activates PAK-1 and $p54^{JNK}$ [52]. These two proteins, causes the actin polymerization and transfer of vesicles containing cholesterol and phospholipid to ABCA1 by actin phosphorylation (Fig. 2c) [53,54].

Table 1
Potential mechanisms of cytotoxicity induced by free cholesterol.

References	Consequence	Event
[24]	Modify or block the function of the integral membrane proteins	Increased membrane rigidity and loss of its fluidity
[25]	Disruption of signaling process	Disruption in the formation of membrane domain
[26]	Oxidative damage	Promoting the oxysterols production
[27]	Organelle disruption	Crystallization of cholesterol
[28–30]	Cell death	Induction of a series of apoptotic pathways

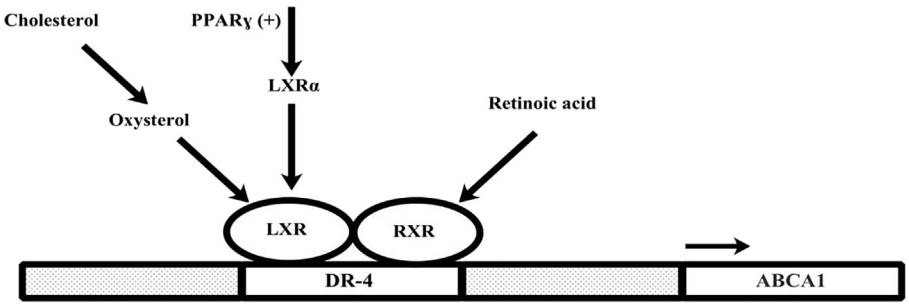

Fig. 1. Regulation of ABCA1 gene expression by oxysterols, retinoic acid and PPARγ activators.

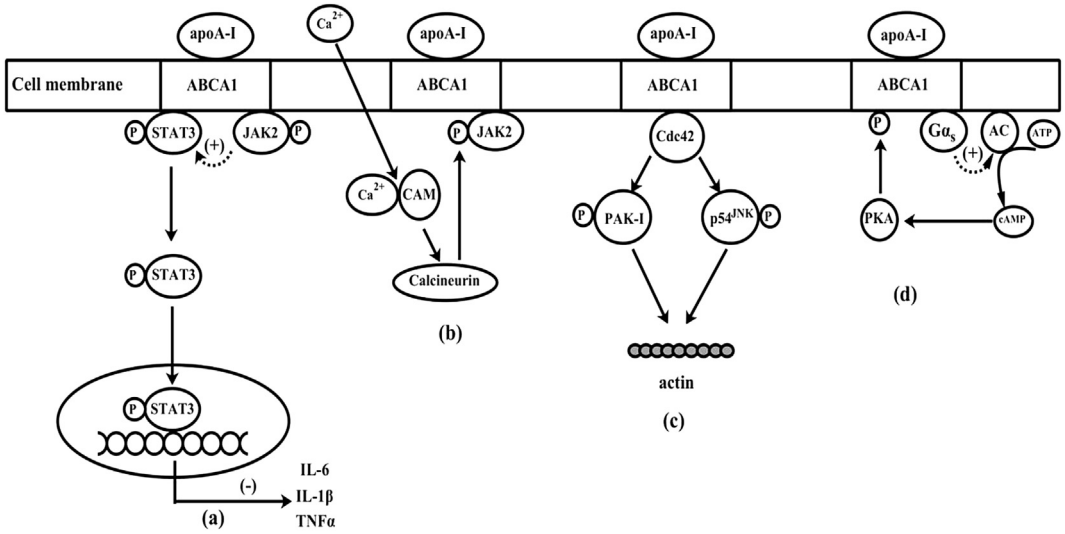

Fig. 2. Regulation of ABCA1 functions by signal transduction pathways.
The interaction of ApoA-I with ABCA1 results in (a) JAK2 phosphorylation and activation. The activated JAK2 increases the ApoA-I binding activity of ABCA1 and suppresses the inflammation by activation of STAT3. (b) Ca^{2+}-influx into the cell and increased JAK2 phosphorylation by exacerbation of the Ca^{2+}-dependent calcineurin pathway. (c) Cdc42 activation followed by PAK-1 and $p54^{JNK}$ phosphorylation and actin polymerization. (d) Gαs/cAMP signaling and subsequently PKA-mediated ABCA1 phosphorylation, leading to ApoA-I lipidation.

3.4. Protein kinase A

The binding of ApoA-I to the coupled ABCA1- $G\alpha_s$ releases the $G\alpha_s$ to activate adenylate cyclase (AC). This activation increases cAMP production, and subsequently the phosphorylation of ABCA1 occurs by mediating of protein kinase A (PKA) leading to apoA-I lipidation (Fig. 2d) [55,56].

4. ABCA1 and VLDL-triglyceride production

Studies of Liu et al. on ABCA1-silenced rat hepatoma cells and hepatocyte-specific ABCA1 knock-out mice (HSKO) revealed delayed apolipoprotein B secretory trafficking and increased VLDL triglyceride (TG) secretion. Based on these results, reducing the apo B trafficking rate gives more opportunity for lipidation of pre-VLDL particles with triglycerides [14].

Another study by Chung et al. on McArdle rat hepatoma cells presented a model that large nascent HDL particles produced by ABCA1 bind to a putative membrane receptor, target of pre-β (Topβ), which activates PI3 kinase, reduces lipid mobilization to VLDL particles and secretes normal sized VLDL particles (VLDL2). Reduction or absence of the ABCA1 activity reduces the production of large nascent HDL particles resulting in less binding to Topβ and lowering of PI3 kinase activation, increased lipid mobilization to VLDL particles, and secretion of large, TG-enriched VLDL1 particles (Fig. 3) [15].

5. ABCA1, insulin-glucose homeostasis and obesity

Increased fasting blood glucose is one of the factors associated with metabolic syndrome [57]. The reason is insulin resistance and reduced insulin secretion [58]. Studies on mice where their β-cell ABCA1 was inactivated showed a significant deficiency in insulin secretion and defective glucose tolerance. An in vitro study on islets isolated from these mice revealed a change in cholesterol homeostasis and insulin secretion deficiency. These results indicated that the cholesterol accumulation causes non-functional β-cell. Therefore, β-cell ABCA1 is involved in insulin secretion by regulating cholesterol homeostasis [12].

The effect of adipocyte ABCA1 on glucose metabolism was studied on adipocyte ABCA1 knockout mice ($ABCA1^{-ad}/ABCA1^{-ad}$). When they fed with high-fat and high-cholesterol diet, they showed an increased TG, cholesterol stored in adipose tissue and a promotion of body weight. An ex vivo study demonstrated decreased lipolysis of TG in $ABCA1^{-ad}/ABCA1^{-ad}$ mice. Investigation of genes expression involving in glucose metabolism, revealed the reduction of adiponectin, visfatin, Glut4, and increased leptin expression following an increase in fat mass, that was associated

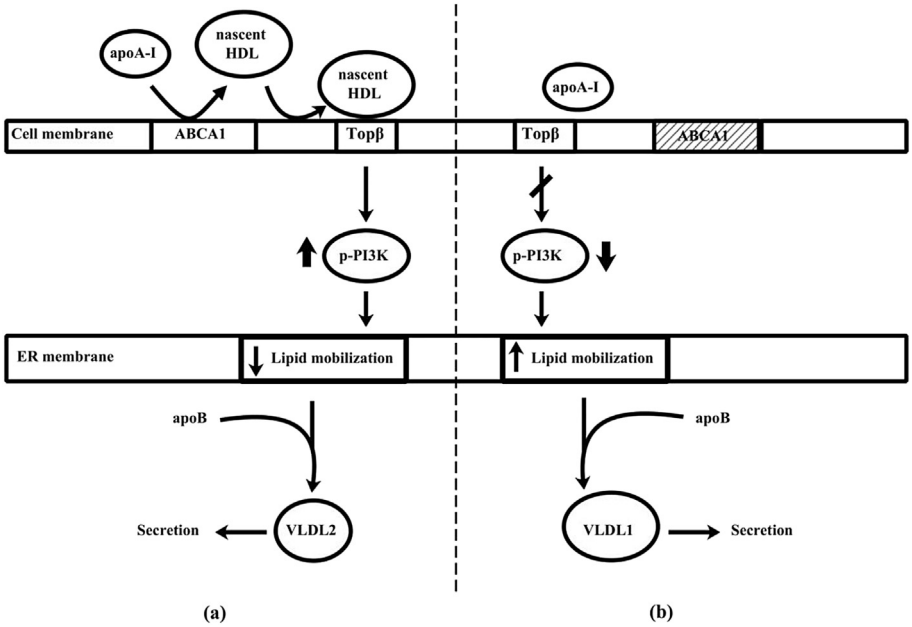

Fig. 3. ABCA1 and VLDL production.
(a) Production of VLDL in the presence of active ABCA1: The nascent HDL particles produced by hepatocyte ABCA1 stimulates the activation of PI3 kinase by binding to the Topβ receptor and results to a decreased lipid mobilization and secretion of normal sized VLDL particle (VLDL2). (b) Production of VLDL in the absence or diminished ABCA1 activity: Lack of formation or reduction of nascent HDL reduces the activation of PI3 kinase due to a reduction of signaling via Topβ, results to an increased lipid mobilization and secretion of large TG-enriched VLDL1 particle.

with insulin resistance and glucose intolerance [16].

Sánchez-Aguilera et al. examined the role of ABCA1 in skeletal muscle glucose uptake. Down regulation of ABCA1 by shABCA1-RFP plasmid indicated a decreased phosphorylation of Akt (Ser^{473}) in skeletal muscle. Accordingly, ABCA1 interferes on the insulin signaling pathways regulation. ABCA1 interacts with the guanine Rho nucleotide exchange factor (RhoGEF) via the PDZ motif. Rho GEF mediates the activation of Rho kinase I. A protein that phosphorylates the insulin receptor substrate 1 (IRS-1) and thus increases the phosphorylation of Akt, transfer of Glut4 to the plasma membrane and skeletal muscle glucose uptake [17]. Effect of ABCA1 disorders on insulin and glucose status are summarized in Table 2.

6. ABCA1 as a therapeutic target

Promotion of expression, Inhibition of degradation and the design of ABCA1 agonist peptides are strategies that have been employed to increase the activity of this protein.

LXR agonist (T0901317) increased the ABCA1 gene expression of mouse intestinal and macrophage cells and enhanced the RCT process [59]. Despite this, the potential problem of LXR agonists is the stimulation of fatty acid synthesis, the incidence of hypertriglyceridemia and fatty liver [60]. PPARγ is a direct stimulant of a scavenger receptor (CD36) gene expression, inducer of ABCA1 by activation of the LXR gene expression and the receptor for thiazolidinediones [61]. Evaluation of PPARγ activators in mice showed a reduction in atherosclerosis [62]. Treatment of cultured macrophage, fibroblast and intestinal cells with a PPARδ agonist (GW501516) as another member of the nuclear receptors family showed the increased ABCA1 mRNA levels and apoA-I-mediated cholesterol efflux without inducing LXR expression [63]. The study of permeable analogues of cAMP had remarkable results, because they stimulated the expression of ABCA1 in macrophages [64].

A number of studies have proven that inhibition of ABCA1 degradation leads to an increase in the HDL biogenesis [49]. The previous studies indicated that spiroquinone, diphenoquinone [65] and calmodulin [66], reduced the calpain activity and resulted in the stability of the ABCA1 protein without affecting ABCA1 mRNA expression. In addition, thiol protease inhibitors increased the levels of ABCA1 protein by reducing the degradation of ABCA1 in THP-1 macrophage-derived foam cells [67].

The design of HDL apolipoproteins mimetic peptides and targeting of ABCA1 has been a fascinating subject for researchers. Of course, only a few of them target ABCA1 with high sensitivity and potency [68–70]. A synthetic peptide based on the C– terminal binding domain of apoE (ATI-5261) stimulates the ABCA1 cholesterol efflux similar to the native apolipoproteins [71]. Studies have shown that this peptide reduces atherosclerosis in mouse models [72].

Table 2
Effect of ABCA1 disorders on insulin and glucose status.

Consequence	Intracellular changes	Cell type
Impaired insulin secretion	• Cholesterol accumulation and defect in cell function	Pancreatic β-cells
Insulin resistance and glucose intolerance	• Cholesterol accumulation, decreased TG lipolysis and increased adipose tissue mass • Decrease of adiponectin, visfatin, and GLUT4 genes expression and increase of leptin expression	Adipocytes
reduction of glucose uptake	• Increased cellular cholesterol content • Disruption of insulin signaling pathway by decreasing Akt phosphorylation and transfer of Glut4 to the plasma membrane	Skeletal muscle cells

7. Conclusion and future directions

ABCA1 mediates the rate-limiting step in HDL biogenesis by interacting with apoA-I and suppression of inflammation in macrophages. ABCA1 has a role in hepatic VLDL production by nascent-HDL synthesis and the effect on apoB trafficking. This protein interferes with glucose homeostasis with the effect on insulin production and insulin cell sensitivity. Adipose tissue lipolysis is involved in the energy supply of this transporter. So, decreased activity of ABCA1 is associated with increased mass of this tissue and obesity.

Abnormalities in the ABCA1 gene and influencing factors of gene to protein process causes the metabolic syndrome phenotypes to progress [11,73]. Understanding these intervening factors and their mechanism of action can be helpful in preventing their interference. Despite the great deal of knowledge about the function of ABCA1 which was achieved to date, it remains a long way to complete the information. Therefore, further studies are required to identify the molecular factors involved in regulating the expression and function of ABCA1. These studies reveal more insight into the role of ABCA1 in health and disease and new therapeutic strategies for the treatment of diseases associated with this protein.

Conflicts of interest

The authors have declared no conflict of interest.

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