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Review

Transcriptional regulatory networks in lipid metabolism control ABCA1 expression

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Abstract

The ATP-binding cassette transporters, ABCA1 and ABCG1, are major players in mediating cellular efflux of phospholipids and cholesterol to apoA-I containing lipoproteins including preβ-HDL and αHDL and thereby exert important antiatherogenic properties. Although the exact mechanisms how ABC transporters mediate lipid transport are not completely resolved, recent evidence from several laboratories including ours suggests that vesicular transport processes involving different interactive proteins like β2-syntrophin, α1-syntrophin, Lin7, and cdc42 are critically involved in cellular lipid homeostasis controlled by ABCA1 and ABCG1. Besides sterols and fatty acids as known physiological modulators of the LXR/RXR and SREBP pathways, a growing list of natural and synthetic substances and metabolic regulators such as retinoids, PPAR-ligands, hormones, cytokines, and drugs are particularly effective in modulating ABCA1 and ABCG1 gene expression. Although ABCA1 protein amounts are regulated at the level of stability, the majority of potent activating and repressing mechanisms on ABCA1 function directly act on the ABCA1 gene promoter. Among the inducing factors, liver-X-receptors (LXR), retinoic acid receptors (RAR) and peroxisome proliferator-activated receptors (PPARs) along with their coactivators provide an amplification loop for ABCA1 and ABCG1 expression. The ABCA1 promoter is further stimulated by the ubiquitous factor Sp1 and the hypoxia-induced factor 1 (HIF1), which bind to GC-boxes and the E-box, respectively. Shutdown of ABCA1 expression in the absence of sterols or in certain tissues is mediated by corepressor complexes involving unliganded LXR, sterol-regulatory element binding protein 2 (SREBP2), Sp3, and the SCAN-domain protein ZNF202, which also impacts nuclear receptor signaling. Thus, a highly sophisticated transcriptional network controls the balanced expression of ABCA1.

Keywords: ABCA1; ABCG1; Lipid transport; Nuclear receptor; Sterol regulatory element binding protein; Oxysterols; Retinoid; ZNF202

Abbreviations: $A_{2A}R$, adenosine A_{2A} receptor; ABC, ATP-binding cassette; ACAT1, acyl-CoA:cholesterol acyltransferase 1; AP, adapter protein; apo, apolipoprotein; ARL7, ADR-ribosylation factor-like 7; ARNT, arylhydrocarbon receptor nuclear translocator; ATRA, all-trans retinoic acid; CETP, cholesterylester transfer protein; CFTR, cystic fibrosis transmembrane conductance regulator; DMHCA, *N*,*N*-dimethyl-3β-hydroxycholenamide; DR4, direct repeat separated by four nucleotides; ER, estrogen receptor; GGPP, geranylgeranyl pyrophosphate; HAC, histone acetylase; HDAC, histone deacetylase; HDL, high-density lipoprotein; HIF, hypoxia-inducible factor; HP-1, heterochromatin 1; IFN, interferon; IL, interleukin; KRAB, Krüppel associated box; LDL, low-density lipoprotein; LPS, lipopolysaccharide; LXR, liver-X-receptor; PGC, PPARγ coactivator; PKA, protein kinase A; PPAR, peroxisome proliferator activated receptor; RA, retinoic acid; RAR, retinoic acid receptor; RIP140, receptor interacting protein 140; RXR, retinoid-X-receptor; SDP1, SCAN domain protein 1; SMRT, silencing mediator of retinoic acid and thyroid hormone receptors; SRC, steroid receptor coactivator; SREBP, sterol regulatory element binding protein; SUR, sulfonylurea receptor; T3, thyroid hormone; TNF, tumor necrosis factors; TXNIP, thioredoxin-interacting protein; USF, upstream stimulatory factor

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1. Introduction

It is now generally accepted that atherosclerosis is a chronic inflammatory disease, triggered by several factors associated with constituents of the metabolic syndrome including dyslipidemia, hypertension, diabetes, hyperhomocysteinemia, infections, and environmental factors such as smoking and nutrition [1]. High LDL-cholesterol, low HDL-cholesterol, and increased triglyceride levels significantly contribute to the accumulation of lipids in atherosclerotic lesions by promoting excessive uptake of cholesterol-rich modified low-density lipoprotein particles. Enzymatically modified LDL (E-LDL) and oxidized LDL (Ox-LDL), which are formed in the circulation and in the subendothelial space, are internalized via phagocytosis and clathrin coated-pit-mediated endocytosis and promote macrophage foam formation [2,3]. Lipid loaded and activated macrophage foam cells can significantly contribute to the maintenance and progression of atherogenesis by producing nitric oxide, reactive oxygen species, inflammatory lipids, growth factors, and proinflammatory cytokines including interleukin 1 (IL-1), IL-6, interferonγ (IFNγ), and tumor necrosis factorα (TNFα) [4]. Foam cell homeostasis is regulated by a rheostat model of receptor-mediated lipid influx, intracellular synthesis, and storage in lipid droplets and vesicles, and export via the reverse cholesterol transport pathway [5]. Lipid efflux involves high-density lipoproteins, apolipoprotein A-I (apoA-I) apolipoprotein E (apoE), and lipid-regulated ABC transporters, especially ABCA1 and ABCG1 [6,7]. The importance of these pathways in total body lipid homeostasis has been highlighted by the identification of monogenetic diseases in ABC transporters such as ABCA1 (familial HDL deficiency) [8–10] and ABCG5/ABCG8 (β-Sitosterolemia) [11,12] and in molecules of associated pathways including NPC1 and NPC2/HE1 (Niemann–Pick Type C) [13,14].

Despite the lack of profound knowledge how ABC transporters function to transport lipids, significant progress has been made in characterizing regulatory factors controlling the expression of lipid-sensitive ABC transporters [6,7]. The present review summarizes current aspects of transcriptional regulatory networks in lipid metabolism which control gene expression of ABCA1 and ABCG1, with a special emphasis on metabolic factors and tissue-selective mechanisms relevant for the development of atherosclerosis and other diseases of the metabolic syndrome.

2. Cellular lipid efflux pathways

Cellular cholesterol and phospholipid efflux in macrophages is facilitated by at least three different mechanisms besides passive diffusion processes between membranes (Fig. 1). One major pathway depends on the presence of lipophilic acceptor particles containing apoA-I and involves the Golgi compartment as well as ABCA1 function. Likewise, ABCA1-deficiency in mice and humans causes impaired vesicular traffic from the Golgi to the plasma membrane, characterized by structural and functional abnormalities of the trans-Golgi compartment [15,16]. Furthermore, a significant basal lipid efflux occurs in the absence of lipoprotein acceptors in cholesterol-loaded macrophages and this second mechanism is also operative in monocytes from patients with familial HDL deficiency, thus it is independent of ABCA1 and it is not affected by disturbances of phospholipid and cholesterol release from the trans-Golgi network in ABCA1 deficiency. This pathway may involve other ABC transporter proteins, such as MDR1, ABCG1, and ABCG4 [17,18]. A third mechanism of cholesterol efflux in peripheral cells involves the mitochondrial generation of 27-hydroxycholesterol and 24(S),25-epoxycholesterol [19]. The formation of these oxysterols constitutes a significant mechanism by which macrophages can eliminate an excess of cholesterol via direct secretion independent of lipophilic acceptor particles [20]. Interestingly, 24-hydroxycholesterol, which is to a larger extend formed in the brain is involved in several neurological disorders including vascular dementia and Alzheimer's disease [21,22], indicating that lipid homeostasis is also a critical factor for peripheral vascular disorders.

3. Functions of ABCA1 and ABCG1

The physiological functions of lipid-sensitive ABC transporters in specialized cells are mainly based on their distinct tissue-specific" expression, their interactions with specific partners, cellular localization, and functional characteristics. ABCA1 and ABCG1 are broadly expressed with high levels in macrophages, liver cells, intestinal cells, adrenal gland, endothelial cells, and in placental trophoblasts [23,24]. Other lipid-sensitive ABC transporters display a very restricted pattern, thus, the expression of ABCA3 is confined mostly to the lung [25] and ABCG5/ABCG8 are exclusively expressed in liver and gut [26]. ABCA1 and ABCG1 are tightly regulated at the expression level by the intracellular cholesterol content [17,23] and several alternative transcripts have been described, partially causing different protein isoforms [27,28]. ABCA1 localizes to the plasma membrane and to intracellular sites, where it facilitates lipid transport to external acceptors or internalized apoA-I. ABCA-1 is not associated with classical Triton X-100 rafts [29], but partially resides in Lubrol WX-resistant membrane microdomains, from where the majority of apoA-I-mediated cholesterol and phospholipid extraction occurs [30].

Diverse protein kinases triggered by apoA-I influence the expression level and activity state of ABCA1. The calpain-mediated proteolytic degradation of ABCA1 is mainly regulated by PKA-dependent phosphorylation of the PEST sequence [31,32], whereas the catalytic activity of the