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Review

Dancing with the sterols: Critical roles for ABCG1, ABCA1, miRNAs, and nuclear and cell surface receptors in controlling cellular sterol homeostasis☆

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ABSTRACT

ATP binding cassette (ABC) transporters represent a large and diverse family of proteins that transport specific substrates across a membrane. The importance of these transporters is illustrated by the finding that inactivating mutations within 17 different family members are known to lead to specific human diseases. Clinical data from humans and/or studies with mice lacking functional transporters indicate that ABCA1, ABCG1, ABCG4, ABCG5 and ABCG8 are involved in cholesterol and/or phospholipid transport. This review discusses the multiple mechanisms that control cellular sterol homeostasis, including the roles of microRNAs, nuclear and cell surface receptors and ABC transporters, with particular emphasis on recent findings that have provided insights into the role(s) of ABCG1. This article is part of a Special Issue entitled Advances in High Density Lipoprotein Formation and Metabolism: A Tribute to John F. Oram (1945–2010).

1. Introduction

1.1. Cholesterol homeostasis

The control of cellular cholesterol homeostasis is a highly regulated process, consistent with the overall importance of this lipid in normal cellular function. In addition to its role in maintaining membrane fluidity, cholesterol is a precursor for bile acids that function both in lipid absorption and as agonists for various nuclear receptors that include FXR, PXR and VDR [1–3]. Cholesterol is also a precursor for steroid hormones (estrogen, progestins, androgens, glucocorticoids and mineralocorticoids) that activate steroid/nuclear receptors (ER, PR, AR, GR, MR) and for certain oxysterols that function as agonists for LXRα and LXRβ, two additional agonist-activated nuclear receptors [4–6]. Precursors in the cholesterol biosynthetic pathway also play important physiological roles. For example, 7-dehydrocholesterol in the skin is a precursor of vitamin D, desmosterol has been shown to function as an agonist for both LXR nuclear receptors [7] and the 15-carbon isoprenoid, farnesyl diphosphate, is critical for prenylation (farnesylation, geranylgeranylation) of numerous proteins, including many small G proteins [8].

1.2. Genes controlling cholesterol homeostasis

Based on the broad physiological effects of cholesterol and related products, it is not surprising that numerous genes are involved in controlling cellular cholesterol homeostasis (Fig. 1). These genes encode i) receptors, such as the Low Density Lipoprotein Receptor (LDLR), ApoE receptor (ApoER2/LRP8) and scavenger receptors (SR-A, CD36, LOX-1) [9,10], that mediate the cellular uptake of cholesterol-containing lipoproteins, ii) auxiliary proteins such as proprotein convertase subtilisin/kexin type 9 (PCSK9) and the inducible degrader of the LDL receptor (IDOL), that increase degradation of LDLR and related receptors [11–13], iii) SR-B1, a membrane receptor that mediates both the efflux of cellular cholesterol from macrophages to extracellular lipoproteins and the influx of cholesterol ester from HDL to hepatocytes and steroidogenic cells [14], iv) members of the ABC transporter superfamily (ABCA1, ABCG1, ABCG4, ABCG5, ABCG8), that

Abbreviations: ABC, ATP Binding Cassette; AICAR, Aminoimidazole Carboxamide Ribonucleotide; ApoE, Apolipoprotein E; ApoER2, ApoE receptor 2 (LRP8); AR, Androgen Receptor; BAC, Bacterial Artificial Chromosome; CETP, Cholesterol Ester Transfer Protein; eNOS, endothelial Nitric Oxide Synthase; ER, Estrogen Receptor; FXR, Farnesoid X Receptor; GPS2, G protein pathway suppressor; GR, Glucocorticoid Receptor; HDL, High Density Lipoprotein; HETE, Hydroxyeicosatetraenoic acid; HMG-CoA, 3-Hydroxy-3-methyl-glutaryl-CoA; ICAM-1, Inter-cellular Adhesion Molecule 1; IDOL, Inducible Degrader of the LDL Receptor; IL6/IL8, Interleukin 6/8; INSIG, Insulin Induced Gene; LDL, Low Density Lipoprotein; LDLR, Low Density Lipoprotein Receptor; LRP8, LDLR-related protein 8; LXR, Liver X Receptor; MCP-1, Monocyte Chemotactic Protein 1; MR, Mineralocorticoid Receptor; NPC1, Niemann Pick C Type I; NPC2, Niemann Pick C Type II; PCSK9, Proprotein Convertase Subtilisin/Kexin Type 9; PR, Progesterone Receptor; PXR, Pregnane X Receptor; RXR, Retinoid X Receptor; SCAP, SREBP Cleavage-activating Protein; SR-B1, Scavenger Receptor B1; SREBP, Sterol Regulatory Element Binding Protein; TLR4, Toll-like receptor 4; TNFα, Tumor necrosis factor α; VDR, Vitamin D Receptor

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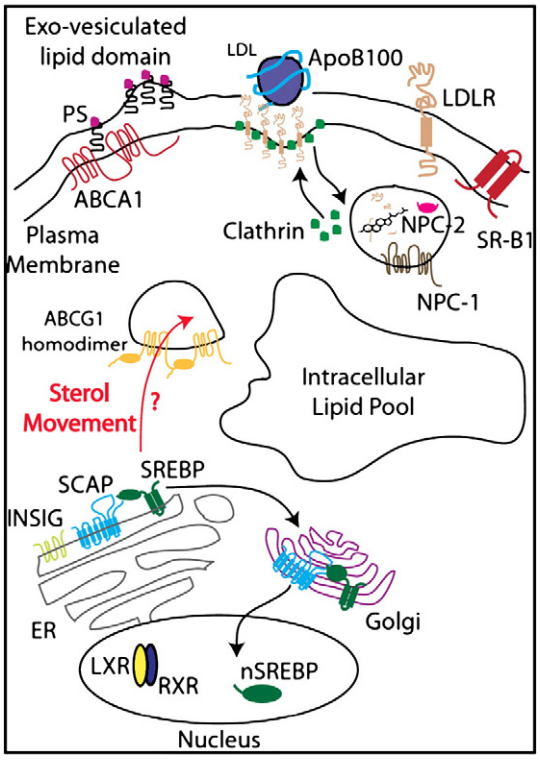

Fig. 1. Intracellular cholesterol metabolism. The control of intracellular levels of cholesterol is tightly regulated. Cells can either synthesize cholesterol de novo from acetate or derive cholesterol from plasma low-density lipoprotein (LDL). ApoB100 on the surface of LDL is recognized by the LDL receptor, which is then taken into the cell by clathrin-mediated endocytosis. Cholesterol is hydrolyzed in lysosomes and is exported out of the lysosome by a "hydrophobic handoff" mechanism between NPC-2 and NPC-1. Levels of genes encoding the enzymes that synthesize cholesterol are under the transcriptional control of SREBP. SREBP is processed to its mature transcriptionally active form when endoplasmic reticulum (ER) cholesterol content falls below 5% of total ER lipids (on a molar basis). If cholesterol levels in the ER increase above 5%, the binding of SCAP to INSIG is promoted and SREBP is retained in the ER. Increased cholesterol levels inside the cell also result in the production of oxysterol ligands for the nuclear receptor LXR. Activation of LXR increases the expression of genes involved in the removal of cholesterol from the cell, such as ABCA1 and ABCG1. The model shows ABCG1 localizing to intracellular vesicles. Overexpression of ABCG1 results in increased expression of SREBP-2 target genes [71], presumably by activating SREBP-2 maturation through promoting "sterol movement" away from the endoplasmic reticulum (ER).

facilitate the movement of sterols and/or phospholipids across membrane bilayers, v) two proteins (NPC1, NPC2) that function in concert to efflux lipoprotein-derived cholesterol out of lysosomes [15–18], and vi) NPC1L1 (Niemann–Pick C1-like 1) that is required for cholesterol absorption from the intestinal lumen into enterocytes and, in humans, where it also mediates resorption of cholesterol from bile across the bile cannalicular membranes back into hepatocytes [19].

Oxysterols and cholesterol also function to regulate the processing and nuclear localization of SREBP-2, a transcription factor that regulates expression of many genes involved in lipid metabolism [20–22]. Classic studies from Goldstein and Brown and colleagues have shown that immediately after synthesis the polytopic protein SREBP-2 binds to a sterol-sensing protein named SREBP cleavage-activating protein (SCAP) in the endoplasmic reticulum [23]. A small decrease in the sterol levels in the endoplasmic reticulum results in transport of the SCAP-SREBP-2 complex to the Golgi where SREBP-2 is processed by two proteases to release a transcriptionally active amino-terminal fragment [22]. This soluble fragment enters the nucleus, binds to sterol response elements (SREs) in target genes and activates transcription [24]. Target genes include the LDL receptor, SREBP-2, HMG-CoA reductase and the approximate 27 other genes involved in the biosynthesis of cholesterol from acetate.

A small increase in the cholesterol/oxysterol levels in the endoplasmic reticulum however, leads to retention of the SCAP-SREBP-2 complex in the endoplasmic reticulum as a result of an interaction of SCAP with INSIG, yet another polytopic protein [21]. Under these latter conditions, transport and processing of SREBP-2 in the Golgi is reduced and transcription of SREBP-2 target genes declines [21,24]. Lanosterol and cholesterol play additional regulatory roles by feeding back to promote the degradation of HMG-CoA reductase, the rate limiting enzyme of cholesterol biosynthesis [25].

Recent studies identified a novel additional level of feedback control on the regulation of cholesterol metabolism [26–30]. Five groups reported nearly simultaneously that microRNA miR-33a is co-transcribed from within an intron of the SREBP-2 transcript [26–31]. Thus, low cellular sterol levels not only result in increased SREBP-2 mRNA levels, but also to increased levels of miR-33a. It was shown that miR-33a binds to complimentary sequences in the 3'UTR of the mRNAs encoding ABCA1 and/or ABCG1, leading to degradation of these mRNAs and reduced protein levels [26–30]. Thus, a small decrease in sterol levels in the endoplasmic reticulum not only leads to increased nuclear levels of SREBP-2 and induction of genes involved in cholesterol synthesis and uptake of cholesterol-rich lipoproteins, but also to a decrease in proteins such as ABCA1 and ABCG1 that facilitate the efflux of cholesterol from cells [26,28–30]. To summarize, small changes in endoplasmic reticulum sterol levels result in multiple compensatory mechanisms that return cellular/membrane sterol levels to normal. The consequences of abnormal cellular sterol levels are discussed below.

Hepatic and intestinal levels of ABCA1 are known to regulate plasma HDL levels [32]. Therefore, it is not surprising that changes in hepatic miR-33a levels have significant effects on plasma HDL [26–30]. These recent studies also showed that hepatic overexpression of miR-33a in mice resulted in a significant decrease in plasma HDL levels [27–30]. In contrast, plasma HDL levels are increased in mice that fail to express miR-33a [27] or after knockdown of miR-33a [27–30]. These latter findings open up the exciting possibility that knockdown of hepatic miR-33a in humans will result in increased hepatic ABCA1 protein levels that will in turn lead to an increase in plasma HDL levels and decreased cardiovascular disease.

Functional loss of many of these proteins severely alters sterol homeostasis and results in specific diseases/phenotypes. Examples include familial hypercholesterolemia (loss of LDLR) [33,34], Tangier's disease or hypoalphalipoproteinemia (loss of ABCA1) [35], sitosterolemia (loss of ABCG5 and/or ABCG8) [36], Niemann–Pick type C (loss of NPC1 or NPC2) [37,38], hypercholesterolemia (activating mutations of PCSK9) [11], hypocholesterolemia (inactivating mutations of PCSK9) [39]. In addition, recent genome wide association studies (GWAS) have linked IDOL with altered plasma cholesterol levels [40]. Presumably, an increase in IDOL expression will promote hepatic LDLR degradation, reduce the normal clearance of LDL from the blood and result in hypercholesterolemia. Finally, the observations that mutations/loss of function of cholesterol ester transfer protein (CETP), that is normally found in human but not mouse plasma, results in elevated plasma HDL levels has led to the development of CETP inhibitors [41,42].

1.3. ABC transporters

A number of excellent reviews on ABC proteins, ABCG1 and/or the ABCG subfamily of ABC transporters have been published in the last few years [43–49]. ABC transporters represent a large superfamily of proteins present in numerous organisms that include bacteria, yeast, plants, fish, and mammals. They have been sub-divided into 7 families A-G which function to transport substrate(s) across a membrane by a process dependent upon ATP hydrolysis. They can also be divided into 3 main functional categories. (1) In prokaryotes, ABC importers mediate the uptake of nutrients (ions, peptides, sugars, amino acids) into cells, (2) ABC exporters/effluxers, present in both prokaryotes and eukaryotes, function as pumps to remove toxins from cells, (3) a