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Hepatic ABC transporters and triglyceride metabolism

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Abstract

Purpose of review—Elevated plasma triglyceride and reduced HDL concentrations are prominent features of metabolic syndrome and type 2 diabetes. Individuals with Tangier disease also have elevated plasma triglyceride concentrations and very low HDL, resulting from mutations in ATP-binding cassette transporter A1 (ABCA1), an integral membrane protein that facilitates nascent HDL particle assembly. Past studies attributed the inverse relationship between plasma HDL and triglyceride to intravascular lipid exchange and catabolic events. However, recent studies also suggest that hepatic signaling and lipid mobilization and secretion may explain how HDL affects plasma triglyceride concentrations.

Recent findings—Hepatocyte-specific ABCA1 knockout mice have markedly reduced plasma HDL and a two-fold increase in triglyceride due to failure to assemble nascent HDL particles by hepatocytes, causing increased catabolism of HDL apolipoprotein A-I and increased hepatic production of triglyceride-enriched VLDL. In-vitro studies suggest that nascent HDL particles may induce signaling to decrease triglyceride secretion. Inhibition of microRNA 33 expression in nonhuman primates augments hepatic ABCA1, genes involved in fatty acid oxidation, and decreases expression of lipogenic genes, causing increased plasma HDL and decreased triglyceride levels.

Summary—New evidence suggests potential mechanisms by which hepatic ABCA1-mediated nascent HDL formation regulates VLDL–triglyceride production and contributes to the inverse relationship between plasma HDL and triglyceride.

Keywords

ATP-binding cassette transporter A1; high-density lipoprotein formation; mRNA; Tangier disease; very low-density lipoprotein production

INTRODUCTION

ATP-binding cassette (ABC) transporters constitute a large family of integral membrane proteins that transport a variety of small molecules across cell membranes. ATP-binding

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Conflicts of interest

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cassette transporter A1 (ABCA1) is a member of the ABC transporter family that is required for the formation of plasma HDL. Mutations in *ABCA1* cause Tangier disease, an autosomal recessive disorder characterized by severe HDL deficiency, sterol deposition in tissues, and premature coronary atherosclerosis [1]. In addition to HDL deficiency, Tangier disease patients have significantly elevated plasma triglyceride concentrations [1–3]. An inverse relationship between dysfunctional *ABCA1* alleles and plasma triglyceride concentrations has been reported [2], but the underlying mechanisms for the increased plasma triglyceride concentrations in Tangier disease patients have not been established. Metabolic syndrome and type 2 diabetes are also characterized by elevated VLDL triglyceride and reduced HDL concentrations [4,5], a plasma lipoprotein phenotype similar to Tangier disease.

One explanation for the inverse association between plasma HDL and triglyceride involves intravascular metabolism. Elevated plasma VLDL–triglyceride levels in type 2 diabetes appear due to enhanced hepatic production of large, triglyceride-enriched VLDL particles, referred to as $VLDL_1$ [6,7]. Intravascular exchange of excess VLDL–triglyceride and HDL cholesteryl ester, mediated by cholesteryl ester transfer protein, leads to HDL-triglyceride enrichment, followed by lipolysis of HDL–triglyceride. This creates smaller HDL particles that are more rapidly removed from the circulation [8]. Hydrolysis of VLDL or HDL–triglyceride also generates redundant phospholipid surface that can serve as substrate for plasma HDL production [9]. Over the past several years, however, new information has emerged implicating a key role for the liver in regulating the reciprocal relationship between plasma triglyceride and HDL. This review will summarize recently published studies on the regulation of plasma triglyceride and HDL by ABCA1 and miR-33 expression.

HEPATIC ATP-BINDING CASSETTE TRANSPORTER A1 AND TRIGLYCERIDE METABOLISM: IN-VITRO STUDIES

Sahoo *et al.* [10] previously reported that hepatocyte ABCA1-dependent cholesterol efflux decreased VLDL secretion, presumably by limiting cholesterol availability for VLDL particle assembly. These findings provided the first potential mechanistic link between hepatic ABCA1 and VLDL secretion. Recent in-vitro studies using oleic acid-stimulated McArdle RH7777 (McA) rat hepatoma cells have provided new insights into the relationship between hepatic ABCA1 expression and triglyceride secretion [11']. Silencing of ABCA1 in McA cells with siRNA reduced ABCA1 protein expression by more than 70% and increased triglyceride secretion two-fold compared with control siRNA-treated cells [11'], whereas apoB protein secretion was only modestly increased (~15%). In addition, the ABCA1- silenced McA cells secreted larger (1.6-fold) VLDL particles that floated in the $VLDL_1$ fraction. The increased VLDL–triglyceride secretion from ABCA1-silenced McA cells was not due to changes in expression of microsomal transfer protein or signaling through mammalian target of rapamycin or mitogen-activated protein kinase/extracellular signal-regulated kinase pathways. However, phosphoinositide 3 (PI3) kinase activation was diminished with ABCA1 silencing, and chemical inhibition of PI3 kinase increased triglyceride secretion in control siRNA transfected McA cells to levels observed for ABCA1-silenced McA cells. These results suggested that ABCA1 expression affected triglyceride mobilization for the second step of VLDL particle maturation, a process that was previously shown to be impacted by insulin and PI3 kinase signaling [12,13]. Because ABCA1 has no known direct role in triglyceride transport, the authors hypothesized that silencing of ABCA1 reduced nascent HDL production, which in turn, resulted in increased triglyceride secretion. To explore this hypothesis, oleic acid-stimulated McA cells were incubated with apolipoprotein A-I (apoA-I), resulting in assembly of heterogeneous-sized (7–16 nm diameter) nascent HDL particles, similar to those reported for ABCA1-transfected HEK293 cells [14]. When nascent HDL-containing conditioned medium from either McA rat hepatoma cells or HEK293 cells transfected with ABCA1 were incubated with ABCA1-

silenced McA cells, both were effective in increasing PI3 kinase activation and reducing VLDL–triglyceride secretion, whereas nonconditioned medium lacking nascent HDL was not. Addition of isolated large (>10 nm diameter) nascent HDL particles to ABCA1-silenced McA hepatoma cells inhibited VLDL–triglyceride secretion to a greater extent than small (<10 nm diameter) nascent HDL. Similarly, addition of recombinant HDL made *in vitro* with synthetic lipids and apoA-I, but not human plasma HDL, was effective in attenuating triglyceride secretion and increasing PI3 kinase activation in ABCA1-silenced McA cells.

Collectively, these data suggest that large nascent HDL particles, assembled by ABCA1 but not mature plasma HDL, generate a PI3 kinase-mediated autocrine/paracrine signal that attenuates VLDL maturation and triglyceride secretion. These results provided a novel potential mechanistic link between nascent HDL particle formation by hepatic ABCA1 and VLDL–triglyceride secretion.

HEPATIC ATP-BINDING CASSETTE TRANSPORTER A1 AND TRIGLYCERIDE METABOLISM: IN-VIVO STUDIES

Because ABCA1 is expressed in many tissues to varying degrees [15], in-vivo evidence for its role in hepatic triglyceride metabolism was lacking until hepatocyte-specific ABCA1 knockout (HSKO) mice were generated [16]. Relative to wild-type controls, HSKO mice have reduced plasma HDL (20% of wild type) and LDL (50% of wild type) and a two-fold increase in plasma triglyceride concentrations [17'']. The reduction in plasma HDL resulted from failure of hepatocytes to efflux free cholesterol and phospholipid to form nascent HDL particles, leading to increased kidney catabolism of apoA-I [16,18']. The reduction in plasma LDL concentrations in HSKO mice was due to increased hepatic LDL receptor expression, which caused greater hepatic removal of LDL from the circulation. Genetic deletion of LDL receptors in HSKO mice raised plasma LDL concentrations to levels comparable to LDL receptor knockout mice, providing additional mechanistic support for the idea that increased LDL receptor expression in HSKO mice causes reduced plasma LDL concentrations. The increased plasma triglyceride observed in HSKO mice was attributed to a two-fold increase in hepatic triglyceride production *in vivo* and in isolated hepatocytes, *in vitro* [17'']. The augmented hepatic triglyceride production was due to greater secretion of large $VLDL_1$ particles, with no significant alteration in hepatic lipid content or microsomal triglyceride transfer protein expression [17'']. Furthermore, hepatic PI3 kinase activation was attenuated in HSKO mice compared with wild-type mice after acute insulin injection or in response to fasting and refeeding. Acute pharmacological inhibition of PI3 kinase with wortmannin, *in vivo*, resulted in increased hepatic triglyceride secretion in wild-type mice, similar to that observed in HSKO mice without PI3 kinase inhibition. These data are remarkably similar to those obtained with silencing of ABCA1 in McA cells and support an essential role for hepatic ABCA1 in regulating VLDL triglyceride secretion.

An additional mechanism for the elevated plasma triglyceride concentrations in HSKO mice was decreased postheparin hepatic lipase and lipoprotein lipase activity compared with wild-type mice [17'']. This finding was further supported by delayed in-vivo clearance of postprandial triglyceride after an oral fat load. The molecular explanation for this decreased lipolytic activity is unknown; however, these observations in HSKO mice agree with similar data demonstrating decreased lipoprotein lipase activity [19] and delayed clearance of postprandial lipid in Tangier disease patients [3].

Because the plasma lipid phenotype in Tangier disease is similar to that in HSKO mice, it appears that much of the Tangier disease lipid phenotype is due to ABCA1 deficiency in hepatocytes. In addition, studies in HSKO mice suggest that two distinct mechanisms are responsible for the elevated plasma triglyceride concentrations and reduced LDL levels in

ABCA1-deficient states: hepatic overproduction of triglyceride and reduced triglyceride lipolysis for the former, and increased hepatic LDL receptor expression for the latter.

In another recent study, adenovirus-mediated overexpression of murine ABCA1 in male apoE knockout mice resulted in a two-fold increase in liver ABCA1 protein expression and increased plasma LDL and HDL concentrations, a phenotype that, as expected, is opposite of that observed in HSKO mice and which caused enhanced atherosclerosis [20]. A quantitatively greater increase in LDL compared with HDL, along with formation of dysfunctional HDL under conditions of ABCA1 excess, may partially explain the increased atherosclerosis in mice overexpressing ABCA1 [20]. Interestingly, however, plasma triglyceride levels were unchanged in these animals, in agreement with some [21–23], but not all [24], previous ABCA1 overexpression (transgenic or adenovirus) studies. The absence of a triglyceride phenotype upon ABCA1 overexpression suggests that normal levels of ABCA1-generated nascent HDL may be sufficient to fully attenuate hepatic triglyceride secretion, with no further impact upon ABCA1 overexpression.

REGULATION OF ATP-BINDING CASSETTE TRANSPORTER A1 AND TRIGLYCERIDE BY MICRORNA-33

microRNAs are small noncoding RNA molecules that are important post-transcriptional regulators of gene expression [25']. Two microRNAs (miR-33a and miR-33b) are known to be important in regulating HDL concentrations. miR-33a and 33b are encoded within introns of sterol regulatory element-binding protein (SREBP) 2 and SREBP1, respectively. SREBP1 and 2 are master transcription factors that control pathways of lipogenesis and sterol biogenesis, respectively [26]. miR-33a is highly conserved throughout evolution, whereas miR-33b is only expressed in nonrodent mammals. Once transcribed miR-33s are processed, they bind to the 3′ untranslated region of mRNA-encoding genes involved in cellular cholesterol export (i.e., ABCA1, ABCG1, NPC1) and fatty acid oxidation (CPT1, CROT, HADHB), repressing their expression. Antagonism of miR-33 with anti-miR-33 oligonucleotides increased hepatic ABCA1 expression and plasma HDL concentrations, and decreased atherosclerosis in atherogenic diet-fed LDL receptor knockout mice, compared with mice treated with control anti-miR; however, plasma triglyceride concentrations were unaltered [27'']. An explanation for this apparent discrepancy is that miR-33b is not expressed in mice, so potential anti-miR-33 effects that might accompany SREBP1-mediated lipogenesis and hepatic triglyceride production would be absent. Recently, inhibition of miR-33a/b was reported in African green monkeys, a species that, like humans, expresses miR-33b [28'']. miR-33a/b inhibition resulted in increased expression of hepatic ABCA1 protein and increased plasma HDL concentrations [28''], similar to previous results in mice [27'']. In addition, miR-33a/b inhibition in monkeys increased expression of genes involved in fatty acid oxidation and reduced expression of genes involved in hepatic lipogenesis, resulting in marked reduction in plasma VLDL–triglyceride. Interestingly, hepatic expression of SREBP1 mRNA and protein was reduced in monkeys treated with anti-miR-33a/b, but the reasons for this response are not clear. These results represent another example of coordinated hepatic regulation of HDL production and triglyceride secretion that helps explain the reciprocal relationship between plasma HDL and triglyceride in nonhuman primates and humans.

GENETIC VARIATION IN ATP-BINDING CASSETTE TRANSPORTER A1 AND PLASMA TRIGLYCERIDE CONCENTRATIONS

Previous genome-wide association studies have reported a significant association between single nucleotide polymorphisms in *ABCA1* and plasma HDL concentrations [29]. On the

contrary, genetic associations between *ABCA1* and plasma triglyceride concentrations were not apparent [30'] until a recent study in a Chinese population found variants in *ABCA1* that were associated with plasma triglyceride and HDL [31]. Another study reported that *ABCA1* gene variants are associated with postprandial lipoprotein clearance from plasma of healthy men [32']. The lack of consistent association between sequence variants of *ABCA1* and plasma triglyceride concentrations may due to the inherent variability in triglyceride levels in individuals in various states of postprandial dietary lipid absorption. In Tangier disease patients who lack functional ABCA1, plasma triglyceride concentrations average two-fold higher than in controls; however, even in individuals lacking ABCA1, plasma triglyceride concentrations are quite variable [1].

CONCLUSION

Elevated plasma triglyceride and reduced HDL concentrations are prominent features of metabolic syndrome and type 2 diabetes. The mechanism behind the reciprocal relationship of these two lipid/lipoprotein components is poorly understood. Recent studies suggest two independent mechanisms that involve hepatic ABCA1 expression. First, lack of hepatic ABCA1 expression results in increased liver secretion of VLDL–triglyceride in a process that involves PI3 kinase activation. Second, inhibition of hepatic miR-33 expression in nonhuman primates increases expression of cholesterol export and fatty acid oxidation genes, reducing plasma triglyceride and elevating HDL. These findings not only establish a mechanistic link between plasma HDL and triglyceride but offer new potential therapeutic avenues for individuals with metabolic syndrome and type 2 diabetes. In these individuals, insulin resistance drives hyperinsulinemia, which in turn stimulates hepatic lipogenesis through increased SREBP1 expression [33]. Coincident with increased SREBP1 transcription, increased miR-33b will diminish HDL production and increase triglyceride secretion. Antagonism of miR-33 offers hope for reversing this phenotype, resulting in increased HDL and reduced triglyceride concentrations.

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Papers of particular interest, published within the annual period of review, have been highlighted as:

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Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 249–250).

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KEY POINTS

- Hepatic ABCA1 expression regulates VLDL triglyceride production through a PI3 kinase-signaling step that involves nascent HDL.
- The similarity in plasma lipid phenotype between Tangier disease patients and hepatocyte-specific ABCA1 knockout mice supports a major role for hepatic ABCA1 expression in the regulation of plasma VLDL, LDL, and HDL concentrations.
- Hepatic microRNA (miR) 33 expression results in reciprocal regulation of plasma HDL and triglyceride concentrations in nonhuman primates.
- Silencing of miR-33 may be a new therapeutic option for raising plasma HDL and lowering triglyceride levels in individuals with metabolic syndrome.