JACC: BASIC TO TRANSLATIONAL SCIENCE VOL. 9, NO. 12, 2024

EDITORIAL COMMENT

Knowing Your ABCs

Macrophage ABCA1-Mediated Cholesterol Efflux as a Therapeutic Target in Atherosclerotic Cardiovascular Disease

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Atherosclerotic cardiovascular disease (ASCVD) is the leading cause of death worldwide. Lipid accumulation and lipoprotein oxidation in the subendothelial space, excess cholesterol loading on arterial macrophages, and foam cell transformation are inciting events in the development of atherosclerotic plaque. Contemporary therapies for atherosclerosis and related cardiovascular risk are largely preventative and focus on lowering plasma lipid levels. Most of them broadly affect cholesterol metabolism, dyslipidemia, modifications, and function of low-density lipoprotein (LDL) and very low-density lipoprotein. Yet, ASCVD risk remains high among individuals with low LDL cholesterol. Therefore, additional and novel therapeutic targets aiming at prevalent atherosclerotic plaque resolution are the mandate of upcoming therapies.

High-density lipoprotein cholesterol (HDL-C) levels and function are inversely associated with ASCVD.[1] HDL removes cholesterol from foam cells in plaque—a function known as cholesterol efflux capacity (CEC)—and may attenuate atherosclerosis progression.[1] CEC is inversely associated with plaque size, lipid content, macrophage burden, and ASCVD risk, independently from HDL-C levels.[2] ATP-binding cassette A1 (ABCA1) membrane transporter initiates cholesterol efflux from macrophages to apolipoprotein A-I (ApoA-I) or lipid-poor pre-β HDL discoidal particles, promoting their maturation to spherical HDL3. These subsequently accept more cholesterol through the ATP-binding cassette G1 (ABCG1) transporter, leading to fully mature HDL2 particles able to dispose of cholesterol to hepatocytes via scavenger receptor type B class 1.[1] Therefore, ABCA1 activity is beneficial through both direct cell cholesterol discharge (via ApoA-I and pre-β HDL) and the formation of mature HDL, which is quantitatively predominant in serum, further promoting cell cholesterol efflux through ABCG1. Loss-of-function mutation of ABCA1 protein in humans (Tangier disease) is associated with reduced serum HDL-C and premature coronary atherosclerosis.[1]

In this issue of *JACC: Basic to Translational Science*, Wang et al[3] identified and characterized a novel superenhancer RNA (seRNA) as an epigenetic regulator of cholesterol efflux. ABCA1-seRNA up-regulated ABCA1 expression and promoted ABCA1-CEC in vitro, optimized lipid levels, and attenuated atherosclerosis in both normal (C57BL/6) and atherosclerosis-prone ApoE$^{-/-}$ mice in vivo and was negatively associated with coronary atherosclerosis in humans. They showed that ABCA1-seRNA interacted with mediator complex subunit 23 (MED23) and recruited transcription factors retinoid X receptor α (RXRα) and liver X receptor α (LXRα) to promote ABCA1 transcription by directly binding to ABCA1 locus. ABCA1-seRNA knockdown was associated with lower ABCA1 protein expression, ABCA1-CEC in human THP-1 macrophages, and HDL production. In contrast, ABCA1-seRNA overexpression up-regulated both ABCA1 protein and ABCA1-CEC. Beyond effects on cholesterol efflux, ABCA1-seRNA suppressed NF-κB activity by promoting ubiquitination of its P65 subunit and degradation via the ubiquitin-proteasome pathway. ABCA1-seRNA knockdown in THP-1 macrophages associated with NF-κB activation and increased production of proinflammatory

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

ISSN 2452-302X https://doi.org/10.1016/j.jacbts.2024.09.008

cytokines, enhanced M1 macrophage polarization, migration, and adherence to endothelial cells.

Importantly, the benefits of ABCA1-seRNA described in in vitro systems were replicated in vivo, in both murine and human systems. Overexpression of human ABCA1-seRNA in both normal (C57BL/6) and atherosclerosis-prone ApoE$^{-/-}$ mice significantly decreased total cholesterol and LDL-C levels, proinflammatory cytokines, aortic plaque burden and inflammatory infiltrates within plaque. Likewise, ABCA1-seRNA expression in peripheral blood mononuclear cells from patients with coronary artery disease positively correlated with ABCA1 protein and serum HDL-C and inversely correlated with proinflammatory cytokines and Gensini and SYNTAX atherosclerosis scores.

It appears, therefore, that ABCA1 is a plausible therapeutic target for atherosclerosis. So far, few ABCA1 regulators have been studied. LXR-623 (WAY-252623), a dual LXRα/β agonist, was tested in a phase I clinical trial that was prematurely terminated owing to central nervous system toxicity.[4] A selective LXRβ agonist (BMS-779788) was tested in a clinical trial, but results are not available.[4] Notably, medications currently used for cardiometabolic diseases may target ABCA1—among other effects—although none have been explicitly or prospectively studied in humans in that capacity. Metformin up-regulated fibroblast growth factor 21, which increased ABCA1 and ABCG1 expression and cholesterol efflux in macrophages and attenuated atherosclerosis burden in ApoE$^{-/-}$ mice.[5] Atorvastatin increased ABCA1 expression and cholesterol efflux in macrophages via inhibition of Ras homolog gene family member A (RhoA) signaling, leading to increased peroxisome proliferator-activated receptor γ activity and enhanced LXR activation.[5] Finally, high-dose rosuvastatin increased ABCA1 protein expression in human plaque macrophages by suppressing miR-33b-5p, a microRNA that down-regulates ABCA1-mRNA translation.[5] The various antiatherogenic effects of ABCA1-seRNA described by Wang et al[3] suggest a promising novel therapeutic strategy, assuming successful fine-tuning of potential challenges with in vivo stability, delivery, and tissue- or organ-specific targeting of ABCA1-seRNA mimetics.

However, it is important to consider that ABCA1 transporter expression is only one of the requirements for the benefits deriving from ABCA1 activity. The second requirement is the presence of suitable extracellular cholesterol acceptors, specifically functional ApoA-I or lipid-poor pre-β HDL particles. For example, ABCA1-CE is low in the presence of sera from LDL-R$^{-/-}$ApoA-I$^{-/-}$ mice[6] and can vary in the presence of human sera with similar HDL-C, depending on their pre-β HDL concentration.[7] Notably, pre-β HDL concentration may be high, but their functionality reduced, as reported in patients with myocardial infarction.[8] The third requirement is a seamless HDL maturation and a conserved functionality of mature HDL. As mentioned above, ABCA1 activity favors HDL maturation and consequently ABCG1-CEC, which is important for cell cholesterol discharge, as mature HDL particles represent the overwhelming majority of circulating HDL. In the presence of a block in pre-β HDL maturation, eg, in patients with lecithin cholesterol acyl transferase (LCAT) deficiency, high levels of pre-β HDL and ABCA1-CEC associate with low levels of mature HDL and ABCG1-CEC. A block in the transition of pre-β to mature HDL may be due to genetic or epigenetic mechanisms. In both clinical scenarios, cardiovascular risk was increased: LCAT-deficient carriers exhibited 32% greater atherosclerosis burden compared with family control subjects.[9] In rheumatoid arthritis, where inflammation is associated with reduced LCAT activity, a concurrent increase in ABCA1-CEC[10] and decrease in ABCG1-CEC was linked to higher coronary atherosclerosis burden and ASCVD risk. Therefore, provided that the collaborative and complementary function of the ABCA1/ABCG1 transporter system and overall HDL function are preserved, specifically promoting ABCA1-mediated CE may foster comprehensive protection against ASCVD risk.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

Dr Karpouzas has received consulting and speaker fees from Sanofi-Genzyme-Regeneron, Bristol-Meyer-Squibb, and Janssen (<$10,000 each) and research grant support from Pfizer, none of which are relevant to the contents of this paper. Dr Ronda has reported that she has no relationships relevant to the contents of this paper to disclose.

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JACC: BASIC TO TRANSLATIONAL SCIENCE VOL. 9, NO. 12, 2024
DECEMBER 2024:1406–1408

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KEY WORDS ATP-binding cassette transporter A1, atherosclerosis, cardiovascular disease, cell cholesterol efflux