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Editorial

High-Density Lipoprotein-Based Therapeutics: Can a Novel Mechanism Succeed Where Previous Approaches Have Failed?

Liam R. Brunham, MD, PhD, FRCPC

UBC Centre for Heart Lung Innovation, St Paul's Hospital, Vancouver, British Columbia, Canada

See article by Hafiane et al., pages 770–781 of this issue.

For more than 50 years, high-density lipoprotein (HDL) has tantalized the cardiovascular community as a therapeutic target for the prevention and treatment of atherosclerosis, because of the inverse relationship between HDL cholesterol levels and cardiovascular disease, and because of the purported ability of HDL to participate in reverse cholesterol transport. More recent advances in our understanding of the important role of HDL in such diverse processes as inflammation,[1] infection,[2] diabetes,[3] and neurocognitive disorders,[4] have only heightened the appeal of how an HDL-based therapy could prevent disease and ameliorate health. However, enthusiasts of HDL have been met with repeated disappointment by the failure of clinical trials of HDL-based therapies, including inhibitors of cholesteryl ester transfer protein, niacin, and apolipoprotein A-I infusion therapies.[5,6]

An important limitation of HDL-based therapies tested to date is that, although they increase the HDL cholesterol concentration, they may not enhance flux through the HDL pathway. A key player in this pathway is the ATP-binding cassette, sub-family A, member 1 (ABCA1) transporter—the rate-limiting step in HDL biosynthesis. ABCA1 is a plasma membrane transporter that effluxes cholesterol and phospholipids to generate nascent HDL in the liver and intestine. Approaches to enhance the activity of ABCA1 have been viewed as potential therapies that might succeed where previous HDL-based therapies have failed.

In the current issue of the *Canadian Journal of Cardiology*, Hafiane and colleagues report the findings of their carefully conducted cellular studies on a new class of HDL-based therapies, namely, small peptides based on the C-terminal domain of apolipoprotein E, that act as agonists of the ABCA1 transporter.[7] They show that the CS-6253 peptide is able to elicit the release of cholesterol-containing microparticles from various cell types in an ABCA1-dependent manner.

Microparticles are cholesterol- and phospholipid-containing membrane vesicles, generated by the activity of ABCA1, that are devoid of apolipoproteins and are thought to be important components of the cholesterol efflux pathway.[8] Interestingly, Hafiane and colleagues show that the release of these microparticles followed the process of HDL biogenesis, suggesting that these processes are mechanistically linked.

They provide detailed data analyzing the size and composition of these microparticles, and show that the release of microparticles triggered by CS-6253 can be abrogated by inhibiting ABCA1 with probucol. Depletion of membrane cholesterol though the use of cylcodextrin prevented the release of microparticles, whereas cholesterol loading of cells increased microparticle release, consistent with the concept that the lipids within microparticles originate from specific domains in the plasma membrane.

What are the potential implications of this work? The finding that the CS-6253 peptide enhances microparticle release and HDL biogenesis provides support for the concept that these peptides might represent therapies to enhance cholesterol removal from cells in an ABCA1-dependent manner. In this regard, they are attractive as potential agonists of the ABCA1 pathway. However, the physiological and clinical relevance of such a treatment remains far from clear, and substantial additional preclinical work will be required before testing of such peptides in humans could be contemplated. The prospect of a completely novel approach to raising plasma HDL concentration is potentially exciting, and might succeed where other approaches have failed. However, because of the disappointing track record of HDL-based therapies to date, the clinical cardiac community might well await more data before renewing its enthusiasm for HDL as a target for therapy.

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Corresponding author: Dr Liam R. Brunham, University of British Columbia (UBC) Centre for Heart Lung Innovation, St Paul's Hospital, Rm 166 - 1081 Burrard St, Vancouver, British Columbia V6Z 1Y6, Canada. Tel.: +1-604-806-2344 ×63929; fax: +1-604-806-8351.

E-mail: liam.brunham@ubc.ca

See page 706 for disclosure information.

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Disclosures

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