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Editorial

The Promise of Apolipoprotein AI-Based Therapy

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Editorial

Apolipoprotein A-I (ApoAI) is an anti-atherosclerotic protein that promotes cholesterol efflux from tissues to the liver for excretion [1]. ApoAI is the main structural and functional protein of High-Density Lipoproteins (HDL), representing ~70% of total HDL proteins [2,3]. Circulating apoAI protein is an amphipathic protein (28kDa) comprising eight alpha-helical domains of 22 amino acids and two repeats of 11 amino acids [4]. Consequently, ApoAI binds avidly to lipids and readily moves between lipoprotein particles; however, ~5-10% of human plasma ApoAI exists in a free state (lipoprotein-unbound) [5]. ApoAI protein is more than a structural scaffold that maintains lipid packaging, as it plays an important role in the transport of cellular cholesterol from the artery wall to the liver for catabolism [6-8]. Antioxidant and anti-inflammatory properties were also attributed to apoAI [9,10]. In addition, a protective role of apoAI against cancer was proposed [11]. ApoAI is synthesized mainly in the liver and small intestine and there are a lot of regulatory elements and transcription factors that control apoAI gene expression, as reviewed in [12]. Treatment with BPA (bisphenol A), one of the most widespread environmental chemicals, downregulates ApoAI gene expression, aggravating the atherosclerotic plaques in LDLR-/- mice [13]. Interestingly, the ratio of HDL-cholesterol to apoAI protein levels is an indicator of the risk of the cardiovascular disorder [14].

Lack of ApoAI augmented atherosclerosis in various hypercholesterolemic mice, such as mice expressing human apoB or ApoAI$^{-/-}$/LDLR$^{-/-}$ mice [15,16]. In humans, familial ApoAI deficiency is associated with premature coronary heart disease [17]. Interestingly, low levels of apoAI and atherogenic dyslipidemia were found in obese individuals, but increases in apoAI levels and enhancements of cholesterol efflux capacity of HDL were reported at three months after bariatric surgery [18].

Considering the anti-atherogenic properties of apoAI, various apoAI-based therapies were proposed for reduction of atherogenesis: i) overexpression of ApoAI, ii) infusions of ApoAI protein, ApoAI mimetic peptides, or ApoAI-containing HDL [19-21], iii) oral small molecules that stimulate ApoAI production [22]. Overexpression of ApoAI reduced atherogenesis in apoE$^{-/-}$ or LDLR$^{-/-}$ atherosclerotic mice [23-31]. Infusions of ApoAI mimetic peptides led to the regression of aortic valve stenosis in rabbits [32]. Liver-directed adenoviral gene transfer of ApoAI resulted in the regression of preexisting atheroma in LDLR-/- mice [33]. Undoubtedly, local delivery of apoAI protein to the vascular wall represents a more efficient apoAI-based therapy than its systemic delivery. Remarkably, transduction of vascular endothelial cells with ApoAI expressing adenovirus reduced inflammation and protected against atherosclerosis in hyperlipidemic rabbits [34,35]. The oral drug RVX-208 significantly increased apoAI production in monkeys but presented disappointing efficacy in a phase II trial [36]. Notwithstanding there are good results obtained in studies using animal models, several apoAI-based clinical trials failed to regress atherosclerotic plaques in humans [37,38]. Despite tremendous advances regarding the understanding of apoAI, the promise of apoAI-based therapy awaits new studies and trials.

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References

1. Lund-Katz S, Phillips MC. High density lipoprotein structure-function and role in reverse cholesterol transport. Subcell Biochem. 2010; 51: 183-227.
2. Davidson WS, Thompson TB. The structure of apolipoprotein A-I in high density lipoproteins. J Biol Chem. 2007; 282: 22249-22253.
3. Frank PG, Marcel YL. Apolipoprotein A-I: structure-function relationships. J Lipid Res. 2000; 41: 853-872.
4. Thomas MJ, Bhat S, Sorci-Thomas MG. Three-dimensional models of HDL apoA-I: implications for its assembly and function. J Lipid Res. 2008; 49: 1875-1883.
5. Nguyen D, et al. Interactions of apolipoprotein A-I with high-density lipoprotein particles. Biochemistry. 2013; 52: 1963-1972.
6. Curtiss LK, et al. What is so special about apolipoprotein AI in reverse cholesterol transport? Arterioscler Thromb Vasc Biol. 2006; 26: 12-9.
7. von Eckardstein A, Nofer JR, Assmann G. High density lipoproteins and arteriosclerosis. Role of cholesterol efflux and reverse cholesterol transport. Arterioscler Thromb Vasc Biol. 2001; 21: 13-27.
8. Sviridov D, Nestel P. Dynamics of reverse cholesterol transport: protection against atherosclerosis. Atherosclerosis. 2002; 161: 245-254.
9. Gordon SM, Davidson WS. Apolipoprotein A-I mimetics and high-density lipoprotein function. Curr Opin Endocrinol Diabetes Obes. 2012; 19: 109-114.
10. Navab M, et al. HDL and cardiovascular disease: atherogenic and atheroprotective mechanisms. Nat Rev Cardiol. 2011; 8: 222-232.
11. Georgila K, Vyrla D, Drakos E. Apolipoprotein A-I (ApoA-I), Immunity, Inflammation and Cancer. Cancers (Basel). 2019; 11: 1097.
12. Kardassis D, et al. Regulation of HDL genes: transcriptional, posttranscriptional, and posttranslational. Handb Exp Pharmacol. 2015; 224: 113-179.
13. Trusca VG, et al. The Mechanism of Bisphenol A Atherogenicity Involves Apolipoprotein A-I Downregulation through NF-kappaB Activation. Int J Mol Sci. 2019; 20: 6281.
14. Rhee EJ, Byrne CD, Sung KC. The HDL cholesterol/apolipoprotein A-I ratio: an indicator of cardiovascular disease. Curr Opin Endocrinol Diabetes Obes. 2017; 24: 148-153.
15. Voyiaziakis E, et al. ApoA-I deficiency causes both hypertriglyceridemia and increased atherosclerosis in human apoB transgenic mice. J Lipid Res. 1998; 39: 313-321.
16. Moore RE, et al. Apolipoprotein A-I deficiency results in markedly increased

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atherosclerosis in mice lacking the LDL receptor. Arterioscler Thromb Vasc Biol. 2003; 23: 1914-1920.

17. Schaefer EJ, Santos RD, Asztalos BF. Marked HDL deficiency and premature coronary heart disease. Curr Opin Lipidol. 2010; 21: 289-297.

18. Thakkar H, et al. Improvements in cholesterol efflux capacity of HDL and adiponectin contribute to mitigation in cardiovascular disease risk after bariatric surgery in a cohort with morbid obesity. Diabetol Metab Syndr. 2021; 13: 46.

19. Stoekenbroek RM, Stroes ES, Hovingh GK. ApoA-I mimetics. Handb Exp Pharmacol. 2015; 224: 631-648.

20. Valanti EK, Dalakoura-Karagkouni K, Sanoudou D. Current and Emerging Reconstituted HDL-apoA-I and HDL-apoE Approaches to Treat Atherosclerosis. J Pers Med. 2018; 8: 34.

21. Kuai R, et al. High-Density Lipoproteins: Nature's Multifunctional Nanoparticles. ACS Nano. 2016; 10: 3015-3041.

22. Bailey D, et al. RVX-208: a small molecule that increases apolipoprotein A-I and high-density lipoprotein cholesterol in vitro and in vivo. J Am Coll Cardiol. 2010; 55: 2580-2589.

23. Rubin EM, et al. Inhibition of early atherogenesis in transgenic mice by human apolipoprotein AI. Nature. 1991; 353: 265-267.

24. Plump AS, Scott CJ, Breslow JL. Human apolipoprotein A-I gene expression increases high density lipoprotein and suppresses atherosclerosis in the apolipoprotein E-deficient mouse. Proc Natl Acad Sci USA. 1994; 91: 9607-9611.

25. Paszty C, et al. Apolipoprotein AI transgene corrects apolipoprotein E deficiency-induced atherosclerosis in mice. J Clin Invest. 1994; 94: 899-903.

26. Benoit P, et al. Somatic gene transfer of human ApoA-I inhibits atherosclerosis progression in mouse models. Circulation. 1999; 99: 105-110.

27. Boisvert WA, Black AS, Curtiss LK. ApoA1 reduces free cholesterol accumulation in atherosclerotic lesions of ApoE-deficient mice transplanted with ApoE-expressing macrophages. Arterioscler Thromb Vasc Biol. 1999; 19: 525-530.

28. Li H, et al. Suppression of induced atherosclerosis in h-apo AI transgenic mice by overexpression of human apo AI in the aortic wall. Chin Med J (Engl). 2000; 113: 657-661.

29. Belalcazar LM, et al. Long-term stable expression of human apolipoprotein A-I mediated by helper-dependent adenovirus gene transfer inhibits atherosclerosis progression and remodels atherosclerotic plaques in a mouse model of familial hypercholesterolemia. Circulation. 2003; 107: 2726-2732.

30. Pastore L, et al. Helper-dependent adenoviral vector-mediated long-term expression of human apolipoprotein A-I reduces atherosclerosis in apo E-deficient mice. Gene. 2004; 327: 153-160.

31. Valenta DT, et al. Overexpression of human ApoAI transgene provides long-term atheroprotection in LDL receptor-deficient mice. Atherosclerosis. 2006; 189: 255-263.

32. Busseuil D, et al. Regression of aortic valve stenosis by ApoA-I mimetic peptide infusions in rabbits. Br J Pharmacol. 2008; 154: 765-773.

33. Tangirala RK, et al. Regression of atherosclerosis induced by liver-directed gene transfer of apolipoprotein A-I in mice. Circulation. 1999; 100: 1816-1822.

34. Wacker BK, et al. Apo A-I (Apolipoprotein A-I) Vascular Gene Therapy Provides Durable Protection Against Atherosclerosis in Hyperlipidemic Rabbits. Arterioscler Thromb Vasc Biol. 2018; 38: 206-217.

35. Flynn R, et al. Expression of apolipoprotein A-I in rabbit carotid endothelium protects against atherosclerosis. Mol Ther. 2011; 19: 1833-1841.

36. Nicholls SJ, et al. Efficacy and safety of a novel oral inducer of apolipoprotein a-I synthesis in statin-treated patients with stable coronary artery disease a randomized controlled trial. J Am Coll Cardiol. 2011; 57: 1111-1119.