APO A-I AND APO E INTERACTION: BEYOND LIPOPROTEINS

Naoki Tamasawa, M.D., Third Department of Internal Medicine, Hirosaki University School of Medicine, Zaifu-5, Hirosaki, 036-8562, Japan, E-mail: tmsw@cc.hirosaki-u.ac.jp

Introduction

Apolipoproteins (Apo) A-I, A-II, A-IV, and E possess repeated amphipathic helical regions with the same genomic structure and are members of a multigene family that probably evolved from a common ancestral gene [1]. These apolipoproteins play pivotal roles in lipid transport and lipoprotein metabolism, and their carboxyl-terminal domain is critical for lipid binding [2]. The purpose of this commentary is to give a brief summary of the part of lipid metabolism in which apolipoproteins are involved as a major regulatory component.

Apo A-I

Apo A-I and apo A-II, the major apolipoproteins of high-density lipoprotein (HDL), are synthesized in the liver. Part of Apo A-I is produced in the small intestine. They are secreted as components of triglyceride-rich lipoproteins, and then transferred, along with phospholipid and cholesterol, into HDL during lipolysis. Alternatively, they may be secreted as free apolipoproteins, and then acquire lipids through the interaction with the cellular ATP-binding cassette transporter, ABCA1 [3].

Reverse cholesterol transport is a pathway by which cholesterol is transported from peripheral tissues and macrophages to the liver for excretion, thus preventing lipid accumulation in peripheral tissues and development of atherosclerosis. Apo A-I and HDL are major players of reverse cholesterol transport as well as enzymes like lecithin:cholesterol acyltransferase (LCAT), phospholipid transfer protein (PLTP), hepatic lipase (HL), and cholesterol ester transfer protein (CETP) [4].

Recently, many studies have been performed to evaluate cholesterol efflux from lipid-laden macrophages by adding exogenous Apo A-I and nascent HDL. The mechanism of the ABCA1-mediated efflux of cellular cholesterol and phospholipids is now considered as follows: Apo A-I first binds to ABCA1 and hydrophobic α-helices in the C-terminal domain of Apo A-I are inserted into the region of the perturbed phospholipid bilayer created by the phospholipid transport activity of ABCA1, thereby leading to the second step of lipidation of Apo A-I and formation of nascent HDL particles [5,6].

Apo E

Most of circulating Apo E is synthesized in the liver [7]; however, a number of other peripheral tissues have been shown to express this protein. The expression of Apo E gene in monocyte-derived macrophages is highly induced in response to granulocyte-macrophage colony stimulating factor [8,9]. Several agents are able to modulate Apo E secretion. For example, sterol loading and cholesterol acceptor, such as Apo A-I or HDL, stimulate Apo E secretion [10,11], whereas cytokines have a negative regulatory effect [12]. Macrophages, especially cholesterol-loaded foam cells, express a significant amount of Apo E [13], resulting in plasma levels under 10% of normal (or less than 0.5 mg/dL). Very little Apo E is sufficient to protect from diet-induced atherosclerosis in the apo E -/- mouse [14].
Apo E is a key component of cholesterol-rich lipoproteins and serves as a ligand for the removal of these lipoprotein particles from the circulation by the liver through a specific receptor, LDL receptor-related protein (LRP), in the hepatocyte plasma membrane [15]. Apo E may contribute to the clearance of cholesterol from peripheral tissue macrophages [16,17].

We examined the secretion of Apo E by monocyte-derived macrophages from patients with type 2 diabetes, who commonly have low plasma HDL and Apo A-I levels. We found that Apo E secretion by macrophages was reduced in patients with low plasma HDL and Apo A-I levels; there was positive correlation between the Apo E secretion and plasma HDL-cholesterol (n = 42, r² = 0.33, p = 0.03) or Apo A-I levels (r² = 0.31, p = 0.03). Furthermore, we found that ApoE secretion increased concomitantly with an increase in HDL or ApoA-I during treatment for diabetes: 1.99 ± 1.86 to 3.40 ± 1.77 ng/mg cell protein (n = 24, p < 0.05). There was no correlation between the macrophage ApoE and plasma total cholesterol, LDL-cholesterol, or HbA1c levels, though there was a positive correlation between the ApoE secretion and plasma HDL-cholesterol or ApoA-I levels. The enhanced macrophage Apo E secretion may be considered as one of the major signs of improved lipid metabolism associated with glycemic control in diabetics [18].

Apo A-I and Macrophage Apo E

A possible interaction between exogenous Apo A-I and macrophage-derived Apo E has been hypothesized to inhibit cholesterol accumulation in the vessel wall in vivo [19]. ABCA1 is required for sterol efflux from macrophages elicited by exogenous lipid-free Apo A-I, however, there is less information regarding whether ABCA1 is required for the sterol efflux associated with endogenous expression of ApoE in macrophages. Kockx et al. [20] showed that Apo A-I stimulates the mobilization and secretion of a mobile smaller pool of cell surface Apo E, as well as a larger intracellular pool. This process is likely to be regulated by a post-transcriptional mechanism. They reported that Apo A-I stimulates secretion of Apo E independently of cholesterol efflux, and that this represents ABCA1-independent, positive feedback pathway for stimulation of Apo E secretion by α-helix-containing apolipoproteins, Apo A-I and Apo E [21] (Figure 1).
We reported a female patient with Tangier disease who had a mutation in ABCA1 [22]. Cultures of fibroblasts from the patient showed no efflux of cholesterol [22]; however, her monocyte-derived macrophages secreted Apo E. Also, we confirmed sterol efflux along with the endogenous macrophage Apo E expression is independent of ABCA1 (the result will be reported elsewhere).

Apo E is considered to play a protective role against atherosclerosis in the arterial wall since it promotes cholesterol efflux from foam cells and other cells leading to reverse cholesterol transport and local clearance of cellular lipids [12]. Other anti-atherogenic effects of Apo E include the inhibition of local inflammatory responses, the proliferation and migration of smooth muscle cells, platelet aggregation, and oxidative stress [14]. These effects of macrophages were reproduced by the animal data collected in Apo E-null mice and the mice transplanted with Apo E-expressing bone marrow [7,23,24]. In fact, Apo E protein and mRNA are abundant within human atherosclerotic lesions, especially in lesions rich in macrophage-derived foam cells, and this fact may suggest the adaptive upregulation of Apo E in macrophages within atherosclerotic lesions.

**Summary**

Numerous epidemiological and interventional studies revealed that low HDL level is an important risk factor for premature atherosclerosis as well as for cardiovascular morbidity and mortality, independent of serum LDL [25] or triglyceride levels [26]. Low serum levels of HDL are frequently encountered, especially in patients who are obese or have the metabolic syndrome [27]. Consequently, many attempts have been made to enhance ApoA-I and HDL levels as anti-atherogenesis therapy [28,29,30].

It should be considered that the effects of non-lipidated Apo A-I and Apo E by themselves
and possible interaction between them are potentially important, independently of lowering plasma lipids, for the prevention of atherosclerosis [31].

References


