Hepatic Lipase, Lipoprotein Metabolism, and Atherogenesis

Silvia Santamarina-Fojo, Herminia González-Navarro, Lita Freeman, Elke Wagner, Zengxuan Nong

Abstract—The role of hepatic lipase as a multifunctional protein that modulates lipoprotein metabolism and atherosclerosis has been extensively documented over the last decade. Hepatic lipase functions as a lipolytic enzyme that hydrolyzes triglycerides and phospholipids present in circulating plasma lipoproteins. Hepatic lipase also serves as a ligand that facilitates lipoprotein uptake by cell surface receptors and proteoglycans, thereby directly affecting cellular lipid delivery. Recently, another process by which hepatic lipase modulates atherogenic risk has been identified. Bone marrow transplantation studies demonstrate that hepatic lipase present in aortic lesions markedly alters aortic lesion formation even in the absence of changes in plasma lipids. These multiple functions of hepatic lipase, which facilitate not only plasma lipid metabolism but also cellular lipid uptake, can be anticipated to have a major and complex impact on atherogenesis. Consistently, human and animal studies support proatherogenic and antiatherogenic roles for hepatic lipase. The concept of hepatic lipase as mainly a lipolytic enzyme that reduces atherogenic risk has evolved into that of a complex protein with multiple functions that, depending on genetic background and sites of expression, can have a variable effect on atherosclerosis. (Arterioscler Thromb Vasc Biol. 2004;24:1-5.)

Key Words: transgenic mouse models ■ lipolytic enzyme ■ ligand-binding function ■ macrophages ■ bone marrow transplantation ■ aortic atherosclerosis

Coronary artery disease (CAD) is a major cause of mortality in advanced societies.1–3 Multiple factors contribute to the formation of lesions that ultimately lead to CAD. One of the initial events in the development of atherosclerosis is the accumulation of cells containing excess lipids within the arterial wall.4 Plasma lipoproteins play a major role in the deposition and removal of lipids that accumulate in atherosclerotic lesions. Apolipoprotein B (apoB)–containing lipoproteins and high-density lipoprotein (HDL) have opposite effects on CAD and are independent risk factors for this disease.5–7 Both classes of lipoproteins have been major targets for the development of new therapeutic approaches for treatment of CAD.

During the last decade, a great deal of interest has focused on hepatic lipase and its impact on lipoprotein metabolism, including intermediate-density lipoproteins (IDLs), chylomicron remnants and HDLs, and atherogenesis. Hepatic lipase has been shown in several studies to modulate atherogenic risk; however, its role as either a protective or proatherogenic agent remains unclear. Published human and animal studies support proatherogenic and antiatherogenic functions for hepatic lipase.8–14 In humans, low hepatic lipase activity has been associated with increased risk of CAD.15–18 Furthermore, premature CAD has been reported in patients with complete hepatic lipase deficiency,19 although the manner in which these very few individuals have been identified raises the issue of ascertainment bias. Other studies have concluded that decreased hepatic lipase activity does not influence susceptibility to CAD.20 Finally, increased hepatic lipase activity has been reported in patients with CAD.21,22 A proatherogenic role for hepatic lipase has been suggested from the inverse correlation between increased hepatic lipase activity and the plasma levels of the antiatherogenic HDL and the positive correlation with small dense proatherogenic low-density lipoprotein (LDL).11,22,23 Analyses of transgenic (Tg) and knockout (KO) animal models have also provided conflicting data regarding the role of hepatic lipase in atherosclerosis. Hepatic lipase overexpression beneficially alters the plasma lipid profile in mice and rabbits by reducing the amount of cholesterol present in apoB-containing lipoproteins.24,26 In addition, overexpression of human hepatic lipase reduced the aortic cholesterol content in cholesterol-fed mice.27 However, hepatic lipase deficiency in lecithin: cholesterol acyltransferase (LCAT)–Tg and apoE–KO mice significantly reduced aortic atherosclerosis despite the increase in cholesterol content in the apoB-containing lipoproteins.28,29 In the latter mouse model, cholesterol accumulated in distinct phospholipid-rich lamellar apoB-containing particles.30 In addition, although the atherogenicity of dense LDL has not been investigated in animals, hepatic lipase activity has been shown to enhance the formation of small, dense LDL particles in mice and rabbits.31–33 Recent work elucidating the multifunctional roles of hepatic lipase may help to resolve these discrepant observations.

Hepatic lipase plays a major role in lipoprotein metabolism as a lipolytic enzyme that hydrolyzes triglycerides and
LDLs, and HDLs.\textsuperscript{12,34} LDL,\textsuperscript{53} uptake of chylomicrons, chylomicron remnants, VLDL, have demonstrated that hepatic lipase enhances the binding or surface receptors or proteoglycans (Figure 2). In vitro studies facilitates the uptake of lipoproteins and lipoprotein lipids by cell types. Cell surface receptors, including the LDL receptor (LDLr)\textsuperscript{55,60} LDLr-related protein (LRP)\textsuperscript{53,60} and scavenger receptor B1 (SR-B1),\textsuperscript{59,61} as well as cell surface proteoglycans,\textsuperscript{54,60} have been implicated in these processes. Initial evidence supporting a role of the ligand-binding function of hepatic lipase, independent of the lipolytic function of the lipase, in cellular lipid uptake and lipoprotein metabolism was provided by studies using heat-inactivated hepatic lipase\textsuperscript{56} and antilipase lipase antibodies.\textsuperscript{55,58} These data were subsequently confirmed by in vivo experiments that demonstrated that expression of the catalytically inactive form of hepatic lipase, HL-145G, reduced the plasma levels of apoB-containing lipoprotein cholesterol and apoE (apoE-KO mice) decreased the plasma concentrations of HDL-C as well as remnant lipoproteins by mechanisms independent of lipolysis. Similar findings were observed in apoE-KO and LDLr-KO Tg mice with long-term expression of the catalytically inactive hepatic lipase.\textsuperscript{24,26} In these latter studies, the effect of the catalytically inactive hepatic lipase on plasma lipoprotein metabolism was confounded by expression of the endogenous, fully active mouse hepatic lipase. Recently, Dichek et al\textsuperscript{64} reported that overexpression of the catalytically inactive hepatic lipase in LDLr-KO, LDLr-KO×apoB-100 and LDLr-KO×apoB-48 mice lacking endogenous HL facilitates the clearance of apoB-48-containing and apoB-100-containing lipoproteins. In humans, the presence or absence of hepatic lipase protein in patients with functional deficiency of hepatic lipase also leads to significant differences in the cholesterol content of the apoB-containing lipoproteins.\textsuperscript{65} These combined animal and human studies support an important physiological role for the ligand-binding function of hepatic lipase in vivo.

Despite these recent advances in elucidating the role of hepatic lipase in lipoprotein metabolism, little is known about the independent contributions of the ligand-binding function versus the lipolytic function of hepatic lipase to the development of atherosclerosis. Current studies have begun to address these questions. Recently, González-Navarro et al\textsuperscript{66} showed that hepatic expression of catalytically inactive HL-145G in mice deficient in apoE and hepatic lipase (apoE-KO×HL-KO mice) markedly lowers the plasma concentrations of cholesterol-rich remnants and significantly reduces proximal aortic atherosclerosis. Thus, in this animal model, the ligand-binding function of hepatic lipase protects against lesion development.

The involvement of hepatic lipase in a novel proatherogenic pathway was first inferred from the unexpected finding that despite increased levels of the proatherogenic apoB-containing lipoproteins, hepatic lipase deficiency reduces aortic lesion formation in apoE-KO mice and LCAT Tg mice.\textsuperscript{29} These findings suggested the possibility that this
Findings identify a new pathway by which hepatic lipase expression yields a great deal of insight into the role of hepatic lipase in CAD. The last decade has provided a partial explanation for the conflicting data on the role of hepatic lipase in CAD. The future challenge will be to use these insights to achieve new treatments for CAD.

Summary

The role of hepatic lipase in CAD has long been controversial, with evidence supporting a proatherogenic and antiatherogenic role for hepatic lipase. Recent studies have revealed that in addition to its role as a lipolytic enzyme that remodels LDL and HDL, hepatic lipase also has a ligand-binding function that enhances lipid and lipoprotein uptake by cell surface receptors and proteoglycans. In addition, the recent finding that hepatic lipase is present in the vessel wall and that its presence is atherogenic provides a partial explanation for the conflicting data on the role of hepatic lipase in CAD. The last decade has yielded a great deal of insight into the role of hepatic lipase in lipoprotein metabolism and atherogenesis. The concept of hepatic lipase as mainly a lipolytic enzyme that reduces lipase might have a localized effect on the arterial wall that could overwhelm the hepatic lipase-mediated effects on the plasma lipoproteins. We thus evaluated hepatic lipase expression in the various cell types that comprise aortic lesions. Hepatic lipase mRNA was detected in peritoneal macrophages and in 2 immortalized mouse macrophage cell lines (RAW 264.7 and IC-21). Moreover, Western analysis of partially purified cell lysates from mouse peritoneal macrophages and RAW 264.7 cells, as well as human monocytic-derived macrophages and THP cells, revealed a 62-kDa protein immunoreactive to the antihepatic lipase antibody. As a functional test to determine whether macrophage expression of hepatic lipase was proatherogenic, bone marrow from HL-KO donor mice was transplanted into irradiated HL-wild-type mice and vice versa, in apoE-KO and LCAT-Tg backgrounds. Interestingly, macrophage hepatic lipase expression in the arterial wall enhanced early lesion formation in apoE-KO and LCAT-Tg mice without modification of plasma lipoprotein lipids or hepatic lipase activities. These findings identify a new pathway by which hepatic lipase modulates atherogenic risk in vivo.

Localized production of hepatic lipase within the vessel wall has many implications. Like lipoprotein lipase, hepatic lipase expression in the arterial wall may result in localized increased production of free fatty acids (FFAs), increased cholesterol uptake, retention of LDL in the subendothelial wall, and macrophage recruitment, all of which would enhance lesion formation. Aviram et al reported that hepatic lipase enhances the uptake and accumulation of LDL-C by macrophages, and Nong et al have shown that the uptake of oxidized LDL-C differed significantly in peritoneal macrophages isolated from hepatic lipase KO mice compared with control mice. Accumulation of cholesterol by macrophage has been demonstrated to alter macrophage gene expression and promote atherosclerosis. Thus, in addition to its classical role as a lipolytic enzyme and of its ligand-binding function, our data provide evidence that hepatic lipase may modulate atherogenic risk, independent of changes in the plasma lipid profile by altering macrophage cholesterol accumulation (Figure 3). Hepatic lipase present in the arterial wall may significantly alter lesion formation. Future studies will be required to further elucidate the mechanism by which hepatic lipase may exert this effect.

Figure 3. Schematic illustration of the multiple roles of hepatic lipase (HL) in lipoprotein metabolism and cellular lipid uptake in liver as well as macrophages present in the vessel wall. HL, present in the basolateral surface of hepatocytes and the luminal and subluminal surfaces of endothelial cells or freely circulating in the bloodstream, hydrolyzes triglycerides and phospholipids present in circulating plasma lipoproteins, including IDL, chylomicron remnants (data not shown), and HDL. During lipolysis, a small fraction of HL may dissociate, attach to circulating lipoproteins, and bind proteoglycans (Figure 2). The lipase–lipoprotein complex can then undergo internalization, a process that is independent of lipoprotein lipase and can be mediated by proteoglycans, the LDLr, and LRP, as well as SR-B1, which facilitates selective lipid uptake. Within the atheromatous plaque, HL facilitates cholesterol accumulation in macrophages, altering macrophage gene expression and enhancing the atherosclerotic process.

The atherogenic risk has evolved into that of a complex protein with multiple functions with variable effects on atherosclerosis. The future challenge will be to use these insights to achieve new treatments for CAD.

References


