Lipoprotein Receptors, Macrophages, and Sphingomyelinase

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Cholesterol ester–filled macrophages are the hallmark of atherosclerotic lesions. Unraveling the pathways responsible for lipid accumulation in macrophages has been viewed as an important aspect for understanding a piece of the atherosclerotic process. Investigations into the mechanisms through which macrophages accumulate cholesterol esters from lipoproteins have delineated the involvement of several different receptor- and non–receptor-mediated pathways. For instance, macrophages express LDL receptors as well as several other members of the LDL receptor family, such as the LDL receptor–related protein (LRP) and the VLDL receptor. The LDL receptor family recognizes apolipoprotein (apo) B-100– and particularly apoE-containing lipoproteins. The uptake of lipoproteins via LDL receptor family members is facilitated by additional apoE, as well as by the presence of lipoprotein lipase. Each member of the LDL receptor family appears to be capable of contributing to a portion of the uptake of lipoproteins by macrophages; however, the contribution of each particular member will vary depending on the underlying pathophysiological condition. For instance, the LDL receptor is not functional in LDL receptor deficiency, and the contribution of either the LRP or the VLDL receptor would be expected to be low in apoE deficiency. In addition, macrophages express an apoE-independent pathway for the uptake of triglyceride-rich lipoproteins that recognizes apoB-48 or the similar domain on apoB-100 and has been termed the apoB-48 receptor. Finally, macrophages express several different scavenger receptors that recognize modified lipoproteins, particularly lipoproteins that have been modified by oxidation. Other lipoprotein modifications, such as aggregation, proteoglycan complex formation, and glycation, can lead to lipid accumulation in macrophages via these as well as other receptor and nonreceptor pathways.

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Lipoprotein aggregation has been proposed to be an important step in atherogenesis, occurring in the subendothelial space where circulating lipoproteins diffuse into the space and interact with matrix molecules, eg, proteoglycans, lipases, and proteases. Aggregated lipoproteins have been shown to be potent inducers of macrophage foam cell formation, and aggregated lipoproteins have been observed in atherosclerotic lesions in humans, fat-fed rabbits, and apoE-deficient mice. Aggregated lipoproteins have been shown to have an increased binding affinity for proteoglycans, and the larger size of the aggregated particles physically inhibits their release from the subendothelial space. In addition, proteoglycans released by macrophages can stimulate lipoprotein aggregation in the subendothelial space. Several different mechanisms have been suggested to be involved in the uptake of aggregated lipoproteins by macrophages. Aggregated lipoproteins have been shown to be taken up via phagocytosis, by scavenger receptors, and/or through other unidentified receptors. In addition, the internalization of aggregated lipoproteins in macrophages has been reported to be mediated by the LDL receptor, while others have suggested a process different from phagocytosis and independent of LDL receptors.

In the current issue of Arteriosclerosis, Thrombosis, and Vascular Biology, Marathe et al have addressed the question of why lipoproteins isolated from apoE-deficient mice cause only modest cholesterol ester accumulation in macrophages while apoE-deficient mice develop massive atherosclerosis and foam cell formation. The authors hypothesized that hydrolysis of apoE-deficient lipoproteins by sphingomyelinase would facilitate their uptake by macrophages. Sphingomyelinase is an enzyme that hydrolyzes sphingomyelin to phosphocholine and ceramide (acylphosphogolne) that has attracted much attention as an important component of intracellular signaling pathways. At least 7 different sphingomyelinases have been identified, with acid lysosomal sphingomyelinase being the best studied. Acid sphingomyelinase is found ubiquitously in tissues and is deficient in patients with Niemann-Pick disease (types A and B), a lysosomal sphingomyelin storage disease. Interestingly, sphingomyelinase activity is also present in serum, where it is presumably not involved in cell signaling. Tabas and coworkers have shown that serum sphingomyelinase is a secretory product of the acid sphingomyelinase gene and in a series of studies have characterized the effects of sphingomyelinase on lipoproteins. Exposure of lipoproteins to sphingomyelinase results in hydrolysis of sphingomyelin, the generation of ceramide, and the fusion and aggregation of lipoprotein particles. Lipoproteins isolated from apoE-deficient mice are enriched in sphingomyelin and are highly susceptible to hydrolysis and aggregation by sphingomyelinase.

In their current studies, Marathe et al show that by incubating lipoproteins from apoE-knockout mice with sphingomyelinase, the ability of the lipoproteins to be taken up and degraded and to cause cholesterol ester accumulation in macrophages is dramatically increased. Because the kinetics and biochemical characteristics of the uptake of the sphingomyelinase-treated lipoproteins were consistent with those for a receptor-mediated process, they explored the...
possible pathways mediating uptake by using several different competitors, as well as macrophages from genetically engineered mice. Neither LDL nor oxidized LDL competed with sphingomyelinase-treated lipoproteins, suggesting that neither LDL nor scavenger receptors were involved in the process. As further confirmation, the degradation of sphingomyelinase-treated lipoproteins was similar in macrophages from wild-type, apoE-knockout, and LDL receptor–knockout mice, suggesting that members of the LDL receptor family are not involved in uptake. Macrophages from scavenger receptor A–knockout and CD36-knockout mice also degraded sphingomyelinase-treated lipoproteins in a fashion similar to that of wild-type macrophages, suggesting that scavenger receptors were not involved. In addition, because uptake was unaffected by treatment with chondroitin ABC lyase and heparitinase, glycosaminoglycans also do not appear to mediate this interaction. However, incubation with anti-apoB antibodies partially decreased the degradation of sphingomyelinase-treated lipoproteins by macrophages, and native as well as trypsinized hypertriglyceridemic VLDL effectively competed with sphingomyelinase-treated lipoproteins for uptake by macrophages from wild-type, apoE-knockout, and LDL receptor–knockout mice. Interestingly, hypertriglyceridemic VLDL did not compete with monomeric lipoproteins from apoE-knockout mice that had not been treated with sphingomyelinase. These results are consistent with the newly identified apoB-48 receptor being responsible for the uptake of sphingomyelinase-treated lipoproteins from apoE-knockout mice.

These findings highlight the likely importance of both the involvement of secretory sphingomyelinase in modifying lipoproteins within the vessel wall to increase their atherogenic potential and the role of the apoB-48, or the triglyceride-rich lipoprotein, receptor in macrophage lipid accumulation. Additional studies will be needed to clarify these conclusions and to address additional questions. First, does sphingomyelinase directly contribute to atherosclerosis in vivo? If so, does this occur via the mechanisms identified in vitro? Does the contribution of sphingomyelinase vary depending on the type of lipoprotein abnormality; ie, are the effects different in settings with elevated LDL versus elevations in VLDL or low HDL? Second, is the apoB-48 receptor involved in atherosclerosis? Is it important only in apoE deficiency when lipoprotein uptake via LDL receptor family members is diminished? What is the relative contribution of the apoB-48 receptor to atherosclerosis or macrophage foam cell formation compared with those of other receptor pathways? The answers to these questions will undoubtedly be forthcoming and illuminating as studies with sphingomyelinase-knockout and apoB-48 receptor–knockout mice are performed.

References


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Arterioscler Thromb Vasc Biol. 2000;20:2509-2510
doi: 10.1161/01.ATV.20.12.2509
Arteriosclerosis, Thrombosis, and Vascular Biology is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1079-5642. Online ISSN: 1524-4636

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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