Monocyte-derived macrophages are among the first cells to accumulate in atherosclerotic lesions. Primarily, they appear to scavenge lipids and lipoproteins from fatty streaks, but their long-term presence and accumulation of cholesterol and cholesteryl esters is the hallmark of atherosclerosis. Atherogenesis begins by a perturbation in the endothelium. Subsequently, blood monocytes and later T lymphocytes adhere to the endothelium and migrate into the intima. Macrophages accumulate cholesteryl esters and triglyceride in cytoplasmic droplets, leading to the formation of foam cells. Although questions still remain regarding the relative contribution of environmental and/or genetic factors to the cholesterol accumulation and initiation of the atherogenic process, it is believed that foam cell development and ultimately atherosclerosis result from a defective control in the intimal round-trip of cholesterol.

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Cholesterol accumulation in macrophages occurs independently of LDL receptors and results from the uptake of retained and modified apoB-containing lipoproteins by scavenger receptors, which are not under a cholesterol-feedback regulation. The scavenger receptor superfamily is composed of many members with diverse structures, expression patterns, and functions. Scavenger receptor class A types I and II, the class B scavenger receptors (CD36 and CD68), LOX-1, and possible others are implicated in the unrestrictive cholesteryl ester accumulation in macrophages, lipid droplet formation and ultimately, atherosclerosis. As intracellular cholesterol levels increase, endogenous cholesterol biosynthesis and LDL receptor expression are repressed through inhibition of the sterol regulatory element-binding protein (SREBP) pathway. This mechanism is insufficient to maintain cholesterol homeostasis in the face of continued cholesterol uptake by scavenger-receptor–dependent mechanisms. As mammalian cells do not have the ability to degrade the sterol ring, and most excess sterols can only be eliminated from the body by biliary excretion, macrophages must export cholesterol to extracellular acceptors to maintain their intracellular levels. HDL and its apoproteins provide the main route by which cholesterol is removed from macrophages and delivered to the liver either directly, or indirectly through CETP-mediated transfer to other lipoproteins.

Multiple mechanisms exist to efflux cholesterol from macrophages. They involve either the bidirectional or unidirectional movement of cholesterol across the plasma membrane. Passive diffusion through the unstirred water layer surrounding the cells occurs in all cell types, it is dependent on concentration and nature of acceptor particles and is driven by the cholesterol concentration gradient. This process is relatively inefficient and contributes little to overall cholesterol homeostasis. ABCA1, a newly discovered member of the ABC transporter family, promotes unidirectional efflux of cholesterol from cell membranes to apoproteins, plays a critical role in HDL biogenesis and influences the development of atherosclerosis. In addition, bidirectional cholesterol movement occurs and is accelerated in cells expressing SR-BI, a member of the scavenger receptor class B, type I family. SR-BI, a 509-amino-acid-long member of the CD36 superfamily of proteins, binds to a variety of ligands such as native, acetylated, or oxidized LDL and anionic phospholipids. SR-BI binds HDL with high affinity and represents a physiologically relevant cell surface receptor for HDL. There is also evidence for a cross-talk between SR-BI and ABCA1. Several studies including gene deletion and/or bone marrow-transplantation have been used to understand the contribution of unidirectional and bidirectional efflux pathways to the development of atherosclerosis.

In this issue of *Atherosclerosis, Thrombosis, and Vascular Biology*, Covey et al. present new and conclusive evidence supporting the functional role of SR-BI in macrophages in the development of atherosclerosis. The authors used bone marrow transplantation to selectively eliminate SR-BI expression in bone marrow–derived cells in a hyperlipidemic mouse model: the LDL receptor–deficient mice. Taken together, the study demonstrates that the absence of SR-BI in bone marrow–derived cells is associated with increases in atherosclerosis despite no significant changes in plasma lipids. These findings support the hypothesis that SR-BI plays an antiatherogenic role in macrophages, probably through its role in the efflux of cholesterol. Although the antiatherogenic role of SR-BI has already been demonstrated and largely attributed to increases in reverse cholesterol transport, this study is the first to demonstrate that the absence of SR-BI in macrophages directly affects the development of atherosclerosis. It is intriguing, however, to consider whether a similar experiment in which SR-BI is overexpressed in bone marrow–derived cells will either slow or prevent the development of atherosclerosis. Should the antiatherogenic role of SR-BI in macrophages be solely due to its role promoting cholesterol efflux remains unclear. Besides cholesterol efflux, SR-BI facilitates the selective transport of lipid moieties from lipoproteins, delivers antioxidants such as α-tocopherol, promotes vascular relaxation and activation of eNOS in the endothelium, and alters the distribution of cholesterol in plasma membranes.
membrane domains. These mechanisms alone or in combination with increased cholesterol efflux could contribute to the authors’ observation. The study by Covey et al and many others point to the crucial relevance of influx or efflux pathways on the balance of cholesterol in macrophages and atherosclerosis. The net accumulation of cholesterol, which is characteristic of the atherosclerotic foam cell, indicates a failure of those mechanisms to regulate cellular cholesterol content and an early indicator of phenotypic changes in macrophages. Changes in cytokine expression and production were colocalized with macrophages in human atherosclerotic plaques. Simultaneously, elevated expression and production of extracellular matrix-degrading enzymes such as metalloproteinases, components of the plasmin activation system and lysosomal proteases were shown in macrophages and in certain cases with a subpopulation of macrophage foam cells. It remains intriguing whether foam cell macrophages have an inflammatory profile distinct from other tissue macrophages or circulating monocytes. It is also curious whether changes in the production of inflammatory mediators occurs earlier in circulating monocytes as a response to sterol loading, which would affect their maturation, differentiation and recruitment to lesion-prone sites.

The role of SR-BI in HDL metabolism and atherosclerosis has been well established in murine models, however, it remains unclear whether SR-BI plays an equally important role in lipid transport in normal physiology and pathological conditions such as atherosclerosis in humans. Expression patterns and tissue distribution closely parallel those observed in mice; selective cholesteryl ester uptake and cholesterol efflux mechanisms are operational in human cells suggesting that SR-BI is indeed involved with the metabolism of HDL in humans. Although recent promising studies suggest that SR-BI might influence the lipoprotein metabolism in humans, the association between functional genetic variants of the SR-BI gene, plasma HDL levels and risk for cardiovascular diseases are still scarce, and require more studies to assess its importance in humans.

References

SR-BI: A New Player in an Old Game
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