Scavenger Receptors in Atherosclerosis
Beyond Lipid Uptake

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Abstract—Atherosclerotic vascular disease arises as a consequence of the deposition and retention of serum lipoproteins in the artery wall. Macrophages in lesions have been shown to express ≥6 structurally different scavenger receptors for uptake of modified forms of low-density lipoproteins (LDLs) that promote the cellular accumulation of cholesterol. Because cholesterol-laden macrophage foam cells are the primary component of the fatty streak, the earliest atherosclerotic lesion, lipid uptake by these pathways has long been considered a requisite and initiating event in the pathogenesis of atherosclerosis. Although the removal of proinflammatory modified LDLs from the artery wall via scavenger receptors would seem beneficial, the pathways distal to scavenger receptor uptake that metabolize the modified lipoproteins appear to become overwhelmed, leading to the accumulation of cholesterol-laden macrophages and establishment of a chronic inflammatory setting. These observations have led to the current dogma concerning scavenger receptors, which is that they are proatherogenic molecules. However, recent studies suggest that the effects of scavenger receptors on atherogenesis may be more complex. In addition to modified lipoprotein uptake, these proteins are now known to regulate apoptotic cell clearance, initiate signal transduction, and serve as pattern recognition receptors for pathogens, activities that may contribute both to proinflammatory and anti-inflammatory forces regulating atherogenesis. In this review, we focus on recent advances in our knowledge of scavenger receptor regulation and signal transduction, their roles in sterile inflammation and infection, and the potential impact of these pathways in regulating the balance of lipid accumulation and inflammation in the artery wall. (Arterioscler Thromb Vasc Biol. 2006;26:1702-1711.)

The deposition and retention of serum lipoproteins in the artery wall, where they are susceptible to modification through oxidization and enzymatic action, is believed to activate an immune response that initiates the atherosclerotic lesion. The current paradigm suggests that accumulation of oxidized lipoproteins in the artery wall sets off a cascade of proinflammatory events leading to the recruitment of macrophages, lipid uptake into these cells, and the initiation of the chronic inflammatory cascade that characterizes atherosclerosis. Electron microscopy studies have established that the earliest atherosclerotic lesion, the fatty streak, consists almost entirely of lipid-laden macrophages, thus implicating lipoprotein uptake by these immune cells in the origin of atherosclerosis. These findings led to a search for lipoprotein receptors distinct from the low-density lipoprotein (LDL) receptor that could mediate cholesterol loading of macrophages. Macrophage scavenger receptors (SRs), first described by Brown and Goldstein, were found to bind and internalize modified forms of LDL through mechanisms not inhibited by cellular cholesterol content, identifying these receptors as likely culprits in macrophage cholesterol accumulation.

See cover

Since the cloning of the first macrophage SR (MSR) in 1990, the SR family has expanded to include 8 different subclasses of structurally unrelated receptors that share the defining feature of being able to bind modified forms of LDL. This family was aptly named because these receptors have subsequently been found to bind and “scavenge” a broad array of other modified self and nonself ligands, including apoptotic cells, anionic phospholipids, and amyloid and pathogen components. The SRs are thus believed to be members of the group of pattern recognition receptors that mediate the innate immune host response through recognition of highly conserved pathogen-associated molecular patterns. This evolutionarily ancient but highly effective system of host defense enables the immune system to discriminate between “noninfectious self” and “infectious nonself.” However, there is a growing body of evidence to suggest that SRs may recognize endogenous neoantigens in oxidatively modified lipoproteins and apoptotic cells through molecular mimicry of microbial pathogen ligands. The EO6 monoclonal antibody that recognizes oxidized phosphorylcholine moi-
ieties present in oxidized LDL (oxLDL) that are known SR ligands has been shown to be identical to the T15 antibody identified independently in mice infected with *Streptococcus pneumoniae*. This suggests that the activation of innate immune pathways designed to protect us from pathogens may be responsible for initiating macrophage cholesterol loading and feeding the chronic inflammatory cascade that characterizes atherosclerosis.

Although the uptake of modified lipoproteins by SRs is thought to be central to foam cell formation, it is also widely believed to represent one of the major activation events stimulating the proinflammatory phenotype of lesional macrophages. In the last several years, it has come to be appreciated that SRs initiate signaling cascades that regulate macrophage activation, lipid metabolism, and inflammatory programs that may influence the development and stability of the atherosclerotic plaque. In addition, these receptors have roles in the induction of apoptosis, apoptotic cell clearance, and pathogen recognition that may differentially impact early and more complex lesions. These new insights suggest that the roles of SRs in atherosclerosis are more complex than originally envisioned, precipitating a renewed interest in understanding the contribution of these receptors to this multifactorial vascular disease.

Murphy et al recently published a comprehensive review of the biochemistry and cellular biology of SRs that details the genetics, protein expression, and membrane trafficking of SR family members. In this review, we focus on the SRs with established links to atherosclerosis (Figure 1) and the recent advances made in understanding the mechanisms by which these receptors may affect disease. The degree to which in vitro preparations of modified lipoproteins mimic in vivo lipoproteins is unknown, so particular emphasis is placed on receptors for which deletion has been shown to alter atherosclerosis in animal models. To date, there is genetic evidence that the A class SRs, SR-AI and SR-AII, and 2 members of the B class, CD36 and SR-BI, affect atherosclerotic lesion development. Roles have also been proposed for the class D, E, F, and G members, CD68, SR expressed by endothelial cells (SREC), SR-phosphatidylserine and oxidized lipoprotein (SR-PSOX), and lectin-like oxidized LDL receptor (LOX-1), respectively, based on their ability to bind modified LDL and their expression in atherosclerotic lesions, but thus far, studies showing a direct impact of these receptors on atherogenesis in vivo are lacking. For the purposes of this review, we do not discuss the class C *Drosophila* dSR-C, which does not have a human homologue, class H FEEL1 and FEEL2, which have roles primarily in bacterial binding, nor the class I CD163, which has a proposed role in hemoglobin binding.

**Class A SRs**

The cloning of the defining member of the SR family, SR-A, was first reported in 1990 and was originally named MSR. This gene gives rise to 3 differentially spliced mRNAs that code for type 1 transmembrane receptors predominantly expressed in macrophages. When it became apparent that these receptors were part of a larger receptor family, they were designated as class A SRs and renamed SR-AI, SR-AII, and SR-AIII. The A class of SRs has grown to include 5 members that share common collagen-like domains and a homotrimeric structure: SR-AI, SR-AII, SR-AIII, macrophage receptor with collagenous structure (MARCO), and SR with C-type lectin.

SR-AI and SR-AII have similar intracellular domains and collagen-domain containing stalks, but SR-AI has an additional cysteine-linked C-terminal extension of 110 amino acids. Despite this distinction, no major differences in ligand binding have been detected between these 2 splice products. The more recently described SR-AIII appears to be retained in the endoplasmic reticulum and is not accessible to extracellular ligands, thus its functional significance is uncertain. SR-AI and SR-AII are expressed on the cell surface of tissue macrophages, including macrophage foam cells, and have...
been detected on aortic endothelial cells and vascular smooth muscle cells within atherosclerotic plaque. Studies from our laboratory and others suggest that SR-AI and SR-AII account for the majority (>80%) of macrophage uptake of acetylated LDL but have a lower affinity for oxidized LDL (oxLDL). SR-AI and SR-AII preferentially bind more extensively to oxLDL, recognizing the modified apolipoprotein B (apoB) protein component of this particle. In addition, SR-AI and SR-AII also bind apoptotic cells, β-amyloid peptide, anionic phospholipids, and advanced glycation end-products. These receptors have also been implicated in both innate and adaptive immune responses through their recognition of pathogens and pathogen-associated molecules, including Gram-negative lipopolysaccharide and Neisseria meningitides and Gram-positive Staphylococcus aureus and Listeria monocytogenes.

Initial studies of SR-AI and SR-AII null (Msr/−) mice performed in atherosclerosis-susceptible apoE-deficient (Apo e/−) mice on a hybrid background (ICR/129) fed a chow diet showed a 58% decrease in aortic sinus atherosclerosis lesion area compared with Apo e/− littermates. However, subsequent evaluation in the LDL receptor null (Ldlr/−) atherosclerosis model after 4 and 12 weeks on a high-fat diet showed more modest reductions in atherosclerotic lesion size (28% and 23%, respectively). Despite the difference in the magnitude of the effect of the Msr deletion in these 2 models, these early studies established the paradigm that lipid uptake via SR-A was proatherosclerotic. However, a third study of Msr deletion in the apoE3 Leiden hyperlipidemic mouse model showed 35% and 86% increases in lesion area in male and female mice, respectively; however, the SDs in lesion measurements were sufficiently large so that they failed to obtain statistical significance. The reason for these different findings is unknown; however, the Msr/− mice used in all of these early studies were on a hybrid 129/ICR strain intercrossed into a genetically altered, hyperlipidemic mouse without extensive back-crossing into the atherosclerosis-susceptible C57BL/6 strain. It has since become appreciated that mouse strains differ in their atherosclerosis susceptibility, with 129 mice being more resistant than C57BL/6 mice, and that atherosclerotic lesion area can vary widely in same-generation mouse progeny of mixed backgrounds, with SDs of >70% being reported in F2 mice. Thus, these early investigations of SR-A function were likely confounded by variation at other genetic loci.

However, subsequent studies of SR-A deletion or overexpression in mice more fully back-crossed into the C57BL/6 background have led to equally confounding results, making the contribution of SR-A to atherogenesis controversial. Babaev et al reported 80% to 85% decline in lesion area in modestly hyperlipidemic Msr/− mice back-bred 6 generations and fed a butterfat diet for 30 weeks. Similar findings were also seen in Ldlr/− mice reconstituted with Msr/− hematopoietic fetal liver cells, suggesting that macrophage expression of SR-A contributes significantly to the proatherosclerotic effect of SR-A. However, studies of overexpression of Msr in either the Ldlr/− or Apo e/− mouse model have both failed to show any evidence for exacerbation of atherosclerosis and resulted in a 74% reduction in atherosclerosis in the aortic arch. The most recent study of Msr deletion comes from work performed in our laboratory on mice back-bred 7 generations into C57BL/6 in the Apo e−/− background. After 8 weeks on a Western diet, Msr−/− male mice showed a 40% increase in aortic sinus lesion area; however, no difference in aortic sinus lesion area was noted in similarly treated female mice, nor was a difference detected in lesion area in the aortic tree in mice of either gender. A particularly intriguing finding was that the increase of atherosclerotic lesion area in male Msr−/− mice corresponded with a profound reduction in peritoneal macrophage foam cell formation in vivo, as measured by cellular cholesterol and cholesterol ester content. This reduction in vivo foam cell formation was not apparent in female mice, and although the reason for this gender difference is unclear, the results suggest that lipid uptake by SRs, at least in male mice, may in fact protect against atherosclerosis lesion development.

The conflicting outcomes of these multiple studies on SR-A involvement in atherosclerosis are difficult to reconcile. The differences in genomic background, hypercholesterolemic mouse models, and diets used in the various studies are likely to have played a significant role in these divergent outcomes, and further studies will be needed to clarify this issue. Interestingly, comparisons of atherosclerosis-susceptible and -resistant mouse and rabbit models have shown that SR-A expression is increased in animals with low atherosclerotic responses, suggesting that this pathway is protective. Furthermore, overexpression of a secreted form of the human SR-A extracellular domain reduced monocyte/macrophage adherence to endothelial cells and atherosclerotic aortic lesion area in Ldlr−/− mice by 20%. Thus, the use of such decoy SRs may prove beneficial for retarding early atherosclerotic lesion development. However, because patients with overt coronary artery disease typically present at advanced stages of the disease when more complex plaques are present, this may not be an effective strategy for the treatment of human disease.

There is emerging evidence that SR-A plays different roles in early and advanced atherosclerotic lesions. In advanced atherosclerotic lesions, in which macrophage cell death leads to necrotic core formation and plaque destabilization, SR-A may have important roles in both the induction of apoptosis and the clearance of these dying cells. During hypercholesterolemia, macrophage pathways for metabolizing modified lipoproteins are believed to become overwhelmed, leading to a toxic accumulation of free cholesterol in the cell that results in endoplasmic reticular stress. In this setting, engagement of SR-A pathways by modified lipoproteins or fucoidan triggers apoptotic cell death, indicating that SR-A signaling contributes to macrophage death and necrotic core formation. However, this proatherosclerotic role is also balanced by the ability of SR-A to recognize and clear apoptotic cells in a nonphlogistic manner. These additional functions of SR-A must be considered when proposing therapies to block this pathway. Longer-term studies of SR-A manipulation (deletion or overexpression) will be required to determine the impact of this receptor at later stages of atherosclerosis.
Macrophage Receptor With Collagenous Structure

A novel member of the SR-A family was cloned in 1995 and named MARCO.4 This receptor is structurally similar to SR-AI in that it has an extracellular collagenous domain and a C-terminal cysteine-rich domain, but it lacks the α-helical coiled coil of the SR-As. In normal mice, MARCO expression is restricted to macrophages in the spleen marginal zone and lymph nodes, where it appears to play a role in cellular pathogen clearance. This receptor can bind both Gram-negative and -positive bacteria, and deletion of this gene in mice renders them more susceptible to infection with S. pneumoniae.4 However, the roles of MARCO in binding modified LDL and in atherogenesis have been less well studied.

Class B SRs

The B class of SRs was established with the identification of CD36 as a receptor for oxLDL.27 Unlike the SR-A family, CD36 is a type III (multiple transmembrane domains) receptor that traverses the membrane twice to form a heavily glycosylated extracellular loop with 2 short intracellular tails.4 This class contains 2 additional members with similar structure: SR-BI and lysosomal integral membrane protein—II. This gene family is believed to have evolved from a single ancestral gene that underwent duplication and dispersal in the genome. However, despite the high degree of homology of CD36 and SR-BI, these 2 receptors appear to play quite distinct roles in lipid metabolism and atherosclerosis.

CD36

CD36 was originally identified in the late 1980s as glycoprotein IV, a platelet receptor that bind thrombospondin and Plasmodium falciparum parasitized erythrocytes.28,29 However, its role in lipid uptake was not recognized until 1993, when it was shown to be a macrophage receptor for moderately oxidized LDL.27 Unlike SR-AI and SR-AII, CD36 does not bind acetylated LDL or extensively oxidized LDL with high affinity and has a wider cellular distribution, including monocytes, macrophages, adipocytes, microvascular endothelium, platelets, and erythroid precursors.4 CD36 binds several ligands common to SR-A (β-amyloid, anionic phospholipids, apoptotic cells, advanced glycation end-products),30–33 however, it is distinct from SR-A in its ability to bind native lipoproteins (LDL, high-density lipoprotein [HDL], and very low-density lipoprotein [VLDL]), as well as thrombospondin-1, collagen, fatty acids, and pathogen-derived ligands (P. falciparum peptides, bacterial lipopolysaccharides).28,34–36 As a result of its broad specificity, CD36 has been reported to contribute to a varied list of normal and pathologic processes such as apoptotic cell clearance, fatty acid transport, adhesion, angiogenesis, atherosclerosis, Alzheimer disease, and microbial defense.

Studies by our group and others indicate that CD36 plays a major role in the clearance of oxLDL, contributing 60% to 70% of cholesterol ester accumulation in macrophages exposed to LDL oxidized by Cu2+ and myeloperoxidase/peroxynitrite mechanism.11,37,38 A class of oxidized phosphatidylcholine molecules derived from oxidized PAPC (1-palmitoyl-2-
atherosclerosis in the descending aorta. Transplantation of \textit{Cd36} \textsuperscript{-/-} bone marrow into \textit{Apoe} \textsuperscript{-/-} mice resulted in a large reduction in aortic \textsuperscript{en face} lesion area in hypercholesterolemic mice, indicating that macrophage \textit{Cd36} contributes to lesion progression in the aortic tree.\textsuperscript{47} Moreover, treatment of \textit{Apoe} \textsuperscript{-/-} mice with a \textit{Cd36} ligand derived from growth hormone–releasing peptide EP80317 reduced aortic atherosclerotic lesion area by up to 50%.\textsuperscript{48} Together, these studies suggest that \textit{Cd36} may differentially contribute to lesion development in the aortic sinus and the descending aorta. Whether this effect is attributable entirely to its lipid uptake function is not known.

It has become increasingly appreciated that in addition to mediating lipid uptake and apoptotic cell clearance, \textit{Cd36} can promote proinflammatory signaling that may drive chronic inflammation in the artery wall. In the last several years, our group and others have described signaling pathways initiated by \textit{Cd36} in response to thrombospondin, amyloid peptides (\textit{\beta}-amyloid, fibrillar apoC-II), and pathogen-derived ligands from \textit{P. falciparum}, \textit{Mycoplasma pneumoniae}, and \textit{S. aureus}\textsuperscript{35,36,50–55}; however, the signaling pathways triggered by \textit{Cd36} engagement of oxLDL remain largely undefined.

The multiple signaling pathways induced via \textit{Cd36} are illustrated in Figure 2, and several common observations with regard to these \textit{Cd36} signaling pathways can be made: (1) \textit{Cd36} can associate with Src kinases (Lyn, Fyn, Yes)\textsuperscript{51,54}; (2) Src kinase activation leads to phosphorylation of mitogen-activated protein (MAP) kinase family members p38, p44/42, and \textit{c-Jun} \textit{N}-terminal kinase\textsuperscript{50,51,54,56}; (3) \textit{Cd36} interactions with Src and MAP kinases in different cell types can lead to diverse cellular and biologic consequences, including cell death,\textsuperscript{51} inflammatory gene expression,\textsuperscript{50,53,54,57} adhesion, and migration;\textsuperscript{56} and (4) \textit{Cd36} may interact with different coreceptors to initiate different signaling responses.\textsuperscript{36,50,55} Although these findings have underscored the ability of \textit{Cd36} to actively participate in signaling responses, many questions remain about the molecular mechanisms that regulate this process, particularly how \textit{Cd36} signaling induces such divergent responses as noninflammatory clearance of apoptotic cells, proinflammatory cytokine responses to pathogens, and angiostatic cell death. One possibility is that \textit{Cd36} cooper-
tion with coreceptors regulates activation of these different signal transduction pathways. Two such interactions have been confirmed: cooperation of CD36 with members of the Toll-like receptor (TLR2 and TLR6) family, and members of the integrin (α3β1 and α6β1) family. Recent reports from our group and others showed that CD36 activates signaling via TLR2 and TLR6 in response to the S aureus cell wall component lipoteichoic acid and the M pneumoniae diacylated lipopeptide macrophage-activity lipopeptide. The C-terminal cytoplasmic tail of CD36 was found to regulate both phagocytosis and activation of TLR2/6 signaling, and tyrosine 463 and cysteine 464 were identified as essential residues in this domain. Cysteine 464 was also identified as essential for CD36 association with β1-integrin and the antiangiostatic effect of thrombospondin-1. However, whether these residues mediate interactions with TLRs or β1-integrin or whether they promote kinase binding that regulates coreceptor activation is not known.

In addition to atherosclerosis, CD36 has also been implicated in promoting chronic inflammation in Alzheimer disease. There has been considerable interest in a link between these 2 diseases because recent epidemiological studies have suggested a convergence of risk factors for Alzheimer disease and atherosclerosis, indicating that they may have overlapping mechanisms of pathogenesis. Work from our group and others has shown that CD36 binding of β-amyloid fibrils that accumulate in Alzheimer disease initiates inflammatory signaling pathways leading to microglial activation, reactive oxygen production, and secretion of cytokines and chemokines. These responses contribute significantly to neuronal degeneration in the Alzheimer brain, and interruption of CD36 signaling pathways blocks the recruitment of microglia to amyloid deposits in the brain. Interestingly, amyloid ligands, including β-amyloid and fibrillar apolipoproteins (C-II, A-I), have also been detected in human atheroma, and these ligands can initiate proinflammatory CD36 signaling that may drive inflammation in the artery wall.

SR-BI and SR-BII
SR-BI was first discovered by its homology to CD36, and a differential splice variant differing in the C-terminal cytoplasmic domain was subsequently identified as SR-BII. SR-BI is more efficiently translated, representing 88% of immunodetectable SR-BI and SR-BII protein in mouse liver, and thus the majority of studies have focused on this isoform. SR-BI and SR-BII share ~30% amino acid sequence homology with CD36 and, like this receptor, can bind both modified forms of LDL as well as native HDL, LDL, and VLDL. In addition, SR-BI recognizes typical SR ligands, including apoptotic cells, advanced glycation end-products, anionic phospholipids, serum amyloid A, and β-amyloid. However, despite their high homology and similar ligand repertoire, CD36 and SR-BI have very distinct functions in lipoprotein metabolism. Although both bind HDL with high affinity, SR-BI facilitates selective cholesterol uptake from and transfer to HDL, marking it as an important player in reverse cholesterol transport.

SR-BI is highly expressed in the liver and macrophages, as well as steroidogenic tissues such as the adrenal glands, ovaries, and testes that have a continuous demand for cholesterol. This receptor has a major impact on lipoprotein metabolism through 2 mechanisms: (1) SR-BI mediates cholesterol transfer from cells to HDL, and (2) SR-BI facilitates the selective delivery of this cholesterol from HDL to steroidogenic tissues and to the liver for excretion into bile and feces. Unlike the endocytic mechanism used by the LDL receptor, SR-BI uptake of HDL cholesterol occurs by selective transfer of HDL-derived lipids into cells without HDL particle degradation. Gene deletion and overexpression studies have illustrated the physiological importance of the dual roles of SR-BI in HDL metabolism. Targeted deletion of SR-BI in mice leads to hypercholesterolemia primarily because of increased HDL levels and reduced biliary cholesterol secretion, whereas overexpression of SR-BI by transgenesis or adenoviral-mediated gene transfer is associated with decreased levels of HDL. In rabbits, an animal model that expresses cholesterol ester transfer protein as in humans, SR-BI overexpression is also associated with increased levels of apoB-containing lipoproteins. The impairment of SR-BI on atherosclerosis has been evaluated in several mouse models, and this gene is considered for the most part to play an antiatherosclerotic role. Although mice lacking SR-BI do not spontaneously develop atherosclerosis, when placed on a high-fat/high-cholesterol diet, they develop significantly greater atherosclerosis at the aortic sinus than their wild-type counterparts. Atherosclerosis is dramatically worsened in Srb−/− mice also deficient in apoE. On a chow diet, Srb1+/−Apoe−/− mice exhibit many of the hallmarks of human coronary disease, including occlusive coronary atherosclerosis, spontaneous myocardial infarction, and cardiac hypertrophy and dysfunction. This severe phenotype results in their premature death at 6 weeks of age, limiting the usefulness of these mice as a model of human disease. However, this constraint was recently overcome by crossing the Srb1−/− mice onto a hypomorphic apoE (ApoE R61K) background to generate a diet-inducible model of occlusive coronary atherosclerosis that should facilitate studies of the role of SR-BI in the pathophysiology of atherosclerosis.

The role of SR-BI in atherosclerosis has also been examined in the Ldlr−/− mouse model. Hepatic overexpression of SR-BI in these mice by either transgenesis or adenovirus-mediated gene transfer significantly protects against the development of atherosclerosis, whereas global deletion of SR-BI increases atherosclerotic lesion development. Although the antiatherogenic effects of SR-BI have been largely attributed to its ability to mediate cholesterol ester uptake from HDL to the liver, this receptor is highly expressed on macrophage foam cells in human and mouse atherosclerotic lesions, where it may influence lesion development through both the uptake of lipoproteins and the efflux of cholesterol to HDL. Two studies of Srb1−/− bone marrow transplantation into Ldlr−/− or ApoE−/− mice have suggested an atheroprotective role for macrophage SR-BI. However, a third transplantation study in Ldlr−/− mice that examined the effect of macrophage SR-BI on both early and advanced atherosclerosis suggests that its role may be more complex.
Although SR-BI on macrophages was found to reduce the development of advanced atherosclerotic lesions (9 and 12 weeks of Western diet), macrophage SR-BI appeared to promote fatty streak formation.\textsuperscript{80} Thus, depending on the context, macrophage SR-BI may be either proatherosclerotic or antiatherosclerotic, and this is likely a result of its multifunctional and multiligand qualities.

**Class D SRs: CD68 and Macrosialin**
CD68 and its murine homolog macrosialin are heavily glycosylated type I transmembrane proteins that are predominantly expressed in late endosomes and lysosomes of macrophages.\textsuperscript{81} These receptors were identified as oxLDL binding proteins through ligand blotting experiments; however, based on their expression pattern, they are unlikely to play a major role in oxLDL internalization.\textsuperscript{82} However, these proteins may contribute to oxLDL endolysosomal processing. Levels of macrosialin are upregulated by oxLDL, and this receptor is expressed in macrophage foam cells in atherosclerotic plaques of Apoe\textsuperscript{−/−} mice,\textsuperscript{82} but further studies of its role in atherogenesis await the generation of a macrosialin knockout mouse.

**Class E SRs: LOX-1**
LOX-1 is a lectin-like, type II transmembrane protein that was identified as a receptor for oxLDL in bovine aortic endothelial cells\textsuperscript{83} and subsequently shown to bind other SR ligands, including advanced glycation end-products, apoptotic cells, and bacteria.\textsuperscript{84} LOX-1 is also expressed on macrophages and vascular smooth muscle and is present in atherosclerotic lesions of humans and hyperlipidemic mice.\textsuperscript{85,86} Recently, endothelial overexpression of LOX-1 in Apoe\textsuperscript{−/−} mice was shown to enhance oxLDL uptake and accelerate intramyocardial vasculopathology.\textsuperscript{87} Further clarification of the role of LOX-1 in atherosclerosis awaits studies of a Lox1\textsuperscript{−/−} mouse.

**Class F SRs: SREC-I and SREC-II**
SRs expressed by endothelial cells, SREC-I, and SREC-II, are type I transmembrane receptors containing N-terminal epidermal growth factor–like domains, a transmembrane domain, and a long cytoplasmic tail postulated to induce signal transduction.\textsuperscript{4} These 2 receptors share 35% homology, and although both bind modified LDL, only SREC-I internalizes these ligands for degradation. Studies in Srec1\textsuperscript{−/−} macrophages demonstrated that this receptor accounts for only 6% of total acetylated LDL degradation, suggesting that it plays a minor role in foam cell formation; however, studies in mouse models of atherosclerosis are still pending.\textsuperscript{14}

**Class G SRs: SR-PSOX**
SR-PSOX was identified by its ability to bind oxLDL and was subsequently shown to be identical to the membrane-bound CXC chemokine CXCL16.\textsuperscript{4} This receptor is expressed in human and mouse atherosclerotic lesions, where it is present on endothelium, smooth muscle, and macrophages. To date, the contribution of SR-PSOX to macrophage oxLDL uptake, foam cell formation, and atherosclerosis is unclear; however, one study suggests an association of a CXCL16 gene polymorphism with severity of coronary artery stenosis.\textsuperscript{88}

**Alternative Pathways of Foam Cell Formation**
Despite the dominance of the SR paradigm, there is considerable evidence that LDL-derived lipids can enter macrophages via other pathways. Although monomeric LDL appears to require oxidation or acetylation to become a high-affinity ligand for the SRs, enzymatic modifications (eg, sphingomyelinase, phospholipase C, or secretory phospholipase A2) can lead to increased retention of lipoproteins by matrix proteoglycans and internalization by non–SR-mediated pathways.\textsuperscript{89} Furthermore, native LDL has been reported to be internalized via macropinocytosis of extracellular fluid.\textsuperscript{90} Because the concentrations of native LDL in human intimal samples typically exceed 100 mg/dL, these forms of LDL could provide substantially greater amounts of lipid than can be taken up by the SR pathways, which saturate at lipoprotein concentrations of 25 to 50 mg/mL.\textsuperscript{91} Thus, although there is substantial evidence that oxidized forms of LDL are produced in the arteries of both mice and men, definitive data to establish that the lipid that generates foam cells derives from these oxidized lipoproteins, as opposed to native, aggregated, or nonoxidatively modified forms of LDL, have not yet been obtained.

**Summary**
Our knowledge of SR biology and the role of these receptors in modified LDL clearance have increased greatly in the last 20 years. However, many questions remain regarding their roles in atherogenesis. Our current understanding suggests that SRs may be beneficial during the initial stages of atherogenesis through their ability to clear potentially deleterious modified lipoproteins that accumulate in the artery wall. As macrophage pathways for metabolizing lipoprotein-derived cholesterol become overwhelmed, the unregulated nature of these receptors results in their promotion of disease-causing foam cells and chronic inflammation. However, the effectiveness of therapies targeted at inhibiting SR pathways and decreasing modified lipoprotein clearance from the intima remain in question because the fate of these proinflammatory lipoproteins in the artery wall is unknown. Given the multiple cellular toxicities associated with exposure to oxidized lipoproteins, it is not clear why abrogating these uptake pathways should reduce damage to the artery wall. The emergence of conflicting results on the impact of these receptors in mouse models of atherosclerosis, combined with recent advances in our understanding of other functions of these SRs that may also affect lesion development, argue that additional work clarifying the role of these receptors in atherogenesis is still needed.

The recent discovery that CD36 cooperates with coreceptors, including the TLRs, to elicit signaling responses suggests a more complex model for SR function than previously presumed. SR responses may be influenced by the availability of these coreceptors, which could confer both tissue- and cell-specific regulation. The involvement of TLRs in mediating the SR response to modified-self ligands, such as
oxLDL and β-amyloid, is currently unknown. However, recent studies in mice lacking TLR4 or the TLR adaptor MyD88 suggest that TLR pathways play a role in atherogenesis in the absence of infection.91-92 The ligands activating these pathways and the involvement of SRs in mediating these responses are areas of intense investigation. Unraveling these additional pathways and their contributions to lipid metabolism and inflammation will likely be a central focus of SR research for several years to come.

Disclosures

None.

References

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