The macrophage scavenger receptor at 30 years of age: current knowledge and future challenges

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Abstract **It is now thirty years since the original observation that macrophages take up and degrade modified forms of low density lipoprotein (LDL). Molecular cloning has identified multiple scavenger receptors that can endocytose modified LDL and binding studies continue to identify a wide range of scavenger receptor ligands displayed by bacterial pathogens, modified self proteins and apoptotic cells. Scavenger receptors drive macrophage foam cell development in vitro but their exact role in the development of atherosclerosis remains difficult to assess critically. This could be due in part to functional redundancy or it could perhaps reflect our incomplete appreciation of all the potential roles of this family of receptors in host defense and tissue homeostasis. In this brief overview of the extensive literature in this area we emphasize the continuing duality of scavenger receptors as sensors of both nonself (pathogens) and modified self (modified forms of LDL and apoptotic cells). We highlight some under-appreciated roles of scavenger receptors in macrophage biology (e.g., regulation of macrophage cytokine responses) and we speculate on potential approaches to target the activity of this diverse family of receptors for therapeutic benefit in cardiovascular disease.—** Greaves, D. R., and S. Gordon. **The macrophage scavenger receptor at 30 years of age: current knowledge and future challenges.** ***J. Lipid Res.*** **2009.** 50: **S282–S286.**

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A BRIEF HISTORY OF SCAVENGER RECEPTORS

In 1979, Brown and Goldstein (1, 2) published an important observation that heralded the birth of scavenger receptor biology. Working with resident mouse peritoneal cells they showed that the rate of ^{125}I-labeled-acetyl-LDL (AcLDL) uptake and degradation was 20 times higher than that of ^{125}I-labeled native LDL. Saturable macrophage binding of ^{125}I-AcLDL could be competed for by a wide range of polyanionic ligands including sulfated polysaccharides, maleylated BSA and maleylated LDL. The AcLDL binding site described by Brown and Goldstein was termed the macrophage scavenger receptor for its presumed role in scavenging modified forms of LDL that were ignored by the classical LDL receptor.

One immediate problem was that the chemically modified forms of LDL that acted as scavenger receptor ligands in vitro were not found in vivo. In 1981, work in the laboratory of Daniel Steinberg (3) showed that native LDL incubated with cultured endothelial cells was converted into a form of LDL that was recognized by the macrophage scavenger receptor to generate lipid-laden macrophage foam cells. Because this process could be blocked by antioxidants in vitro it was suggested that LDL modification (especially oxidation) in the subendothelial space generated modified forms of LDL that were scavenger receptor ligands and hence drove foam cell formation in the earliest stages of atherogenesis (4). The conversion of LDL into its various proatherogenic forms, collectively referred to as 'endothelial cell-modified LDL' or 'minimally modified LDL' has been the subject of extensive biochemical investigation. The importance of LDL oxidation, especially lipid oxidation, in the generation of scavenger receptor ligands led to the formulation of the oxidation hypothesis of atherogenesis. Despite notable successes for antioxidant therapy in some animal models of atherogenesis no clinical benefit of antioxidant therapy has been reported in clinical trials (5).

THE SR-A RECEPTOR–THE FIRST (AND FOREMOST?) AMONG EQUALS

In 1998, Kodama et al. (6) reported the purification of a trimeric 220 kDa AcLDL binding glycoprotein from bovine liver and lung membranes and the amino acid sequences of cyanogen bromide generated peptides were used to isolate cDNAs encoding two versions of the bovine macrophage scavenger receptor, SR-AI and SR-AII. SR-AI and

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SR-AII cDNAs encode very similar type II integral membrane proteins inserted into the cell membrane as homotrimers. The bovine SR-A cDNA sequence was used to isolate human SR-A cDNA clones and antibodies raised against human SR-AI peptides were used to show that the SR-AI macrophage scavenger receptor is expressed in macrophage-rich areas of human atherosclerotic lesions (7). The generalized structure of SR-A receptors consists of six recognizable protein motifs: an N-terminal cytoplasmic domain (domain I), a transmembrane spanning region (domain II), a spacer region (domain III), an α-helical coiled coil motif (domain IV), a collagenous domain (domain V), and a C-terminal cysteine-rich motif (domain VI). Domain VI is absent in the SR-AII protein structure due to alternative splicing of the primary RNA transcript of a single gene (8). Truncation of the extracellular domain of bovine and murine SR-A receptors demonstrated the importance of the receptor's collagenous domain, specifically a conserved stretch of lysine residues in domain V, for AcLDL binding (9).

In 1997, Suzuki et al. (10) reported the generation and initial phenotyping of mice in which the MSR gene had been deleted and hence no longer expressed either the SR-AI or SR-AII receptors. Macrophages of such MSR-A knockout mice displayed an ~80% decrease in ^{125}I-labeled AcLDL uptake in vitro but in vivo clearance of ^{125}I-labeled AcLDL was unaffected, an observation explained by the subsequent cloning and characterization of other scavenger receptors. Of note macrophages deleted for SRA I/II receptor expression display a profound (~90%) decrease in the uptake of advanced glycation end products (AGE)-modified BSA, perhaps hinting that physiological ligands for this receptor may be found in diabetes. MSR$^{-/-}$ mice showed reduced atherosclerotic lesion formation when the SR-A gene defect was crossed onto a C57Bl6 ApoE$^{-/-}$ background, although this original observation has been reevaluated in subsequent studies (11, 12). The original MSR-A knockout paper documented a clear deficiency in the knockout animals' response to a lethal dose of the bacterial pathogen *Listeria monocytogenes*. An early study using SR-A$^{-/-}$ mice showed loss of SR-A I/II expression led to an increased susceptibility to endotoxic shock in Bacillus Calmette-Guérin primed animals (13). Later, SR-A was implicated in protection against *Staphyloccus aureus* infection (14) and macrophage uptake of nonopsonised *Escherichia coli* (15) and *Neisseria meningitidis* by recognition of bacterial molecules other than endotoxin (16). In recent work, we have shown that SR-A I/II is the major pattern recognition receptor for nonopsonic uptake of Group B *Streptococcus* (GBS) and *Streptococcus pyogenes* (17). Interestingly, well-characterized virulence factors (the sialic acid containing capsule of GBS and the M protein of *S. pyogenes*) mask both microbial pathogens' SR-A I/II ligands from macrophages. Taken together, these findings suggest that the SR-A scavenger receptor is an important pattern recognition receptor for a wide range of pathogen associated molecular patterns that can also bind to altered self-proteins and lipoproteins.

THE EXPANDING FAMILY OF SCAVENGER RECEPTORS–MULTIPLE RECEPTORS FOR MULTIPLE PATHOGENS, MULTIPLE RECEPTORS FOR MULTIPLE FUNCTIONS, OR JUST RECEPTOR REDUNDANCY?

Since we last reviewed the scavenger receptor family (18), only one or two new scavenger receptors have been described. We have listed the best-characterized scavenger receptors in **Table 1** and indicated which of these dozen or so receptors have been shown to bind modified LDL and other modified self proteins to emphasize the dual role of these receptors as pattern recognition receptors for both modified self and pathogenic nonself signatures (19).

Reviewing the list of known scavenger receptors in Table 1 immediately begs the question, why do we need so many scavenger receptors? This question is made more perplexing when one realizes the wide range of ligands bound by the best characterized members of this family of receptors and the fact that mammals have a wide variety of other mechanisms for recognizing modified self proteins such as receptors for AGE and naturally occurring IgM antibodies

TABLE 1. Scavenger receptors and their ligands

Scavenger Receptor	Lipoprotein binding profile	Pathogen recognition
SR-A I/II	AcLDL, oxLDL, mlDL	Lipid A, *Listeria monocytogenes, Staphylococcus aureus, Neiserria meningitides, Streptococcus pyogenes, Group B Streptococcus*
MARCO	AcLDL (very low affinity - murine receptor)	LPS, LTA, *Streptococcus pneumoniae, Neiserria meningitides*
CD36	AcLDL, oxLDL	Microbial diacylglycerides, *Mycoplasma pneumoniae, Staphylococcus aureus*
SR-BI	AcLDL, oxLDL, native LDL, native HDL	Hepatitis C receptor
CD68	oxLDL*	Not reported
SR-PSOX (CXCL16)	oxLDL	*Staphylococcus aureus, E. coli*
LOX-1	oxLDL	Not reported
SREC-I	AcLDL	Not reported
CD163	None	*Streptococcus mutans, Staphylococcus aureus, E. coli*
CL-P1	oxLDL	*Staphylococcus aureus, E. coli*
FEEL-1	AcLDL	*Staphylococcus aureus, E. coli*
FEEL-2	AcLDL	*Staphylococcus aureus, E. coli*
SCARA5	None	*Staphylococcus aureus, E. coli*

Scavenger receptors are listed with an indication of their demonstrated ability to bind modified forms of lipoproteins (AcLDL, acetylated LDL; oxLDL, oxidized LDL; mlDL. maleylated LDL; * binding demonstrated only by ligand blotting) and their ability to recognize pathogen associated molecular patterns (PAMPs) or intact pathogens (LPS, lipopolysaccharide; LTA, lipoteichoic acid.

that recognize epitopes of modified forms of LDL. In a thoughtful and thought-provoking review, Witztum et al. (20) reason that oxidation generated neo-epitopes are found following all forms of inflammatory response and whenever cells undergo programmed cell death. Hence, the authors argue that the innate immune system has evolved multiple mechanisms to recognize and clear such oxidized self-antigens that might generate autoimmune responses if left to accumulate at sites of inflammation.

The final explanation for the multiplicity of scavenger receptors is the possibility of functional redundancy;, perhaps clearance of modified forms of LDL, modified self proteins, and apoptotic cells is too important a process to leave to only one receptor. Kunjathoor et al. (21) crossed CD36$^{-/-}$ mice with SR-A$^{-/-}$ mice and compared the uptake of different modified forms of LDL by macrophages from wild-type, SR-A$^{-/-}$ single knockout, CD36$^{-/-}$ single knockout and SR-A$^{-/-}$, CD36$^{-/-}$ double knockout mice. Macrophages from double knockout mice showed significantly reduced binding and degradation of AcLDL and LDL oxidized by a variety of different protocols compared with macrophages prepared from single scavenger receptor knockout animals while macrophage responses to lipopolysaccharide were unaltered.

In 2005, Moore et al. (11) revisited the original 1997 observations of Suzuki et al. (10) and analyzed aortic sinus atherosclerotic lesion size in mice carrying deletion of the SR-A gene on a C57Bl6 background. The authors reported that ApoE$^{-/-}$ animals deleted for either the CD36 or the SR-A gene had clear defects in peritoneal macrophage lipid uptake but increased atherosclerotic lesion size. This puzzling observation was explored in more detail by Kuchibhotia et al. (12) who generated ApoE$^{-/-}$ mice with either the CD36 or the SR-A gene deleted and triple knockout mice with both macrophage scavenger receptor genes deleted on an ApoE$^{-/-}$ C57Bl6 background. The authors were able to clearly demonstrate decreased atherosclerotic lesion formation throughout the aortic arch in ApoE$^{-/-}$, CD36$^{-/-}$ mice, but they saw no additional benefit from deletion of the SR-A gene. These data confirm a proatherogenic role for CD36 in vivo but they leave open the role of SR-A I/II in atherosclerotic plaque biology (12).

SCAVENGER RECEPTORS AND THE REGULATION OF MACROPHAGE CYTOKINE PRODUCTION

Tsujita et al. (22) compared the survival rates of wild-type and SR-A$^{-/-}$ mice following myocardial infarction (MI) induced by coronary artery ligation and observed a higher rate of post MI mortality due to left ventricle rupture in SR-A$^{-/-}$ mice compared with wild-type mice. Infarct size seven days post-MI was similar for the two groups of animals, the infracted sites contained similar numbers of inflammatory cells but the myocardium of infarcted SR-A$^{-/-}$ mice showed impaired healing. Enzyme zymography revealed higher levels of MMP-9 in SR-A$^{-/-}$ infarcts five days after infarction and this correlated with elevated levels of pro-inflammatory cytokines in the infarcted region and decreased IL-10 expression.

In a murine model of Streptococcal pneumonia, MARCO$^{-/-}$ mice display an impaired ability to clear bacteria from the lungs that is accompanied by increased pulmonary inflammation and cytokine release. Similar effects are seen following instillation of inert particles (23). The authors' conclusion from these observations is that removal of the bacterial pathogen or particulate irritant from the lung via MARCO expressed on alveolar macrophages removes the driver for cytokine production by bystander cells. An alternative explanation is that nonopsonic removal of pneumococci and inert particles in the lung via a Class A scavenger receptor results in reduced macrophage cytokine and chemokine responses.

An interesting example of the potential of the SR-A I/II receptor to modify macrophage cytokine production is seen in a *Pneumocytsis carinii* infection model. SR-A$^{-/-}$ mice cleared *P. carinii* infection faster than wild-type mice. This effect was not due to altered phagocytosis but rather alveolar macrophages in infected SR-A$^{-/-}$ had a more activated phenotype and produced higher levels of inflammatory cytokines in vivo (24). Taken together with previous observations in the myocardial infarction model it seems that the SR-A receptor is able to modulate pro- and antiinflammatory cytokine production at sites of inflammation.

TARGETING SCAVENGER RECEPTORS FOR THERAPEUTIC BENEFIT IN CARDIOVASCULAR DISEASE?

Hexarhelin is a six amino acid peptide that is a member of the growth hormone releasing peptide (GHRP) family, can act as a ligand at the CD36 receptor (25). Marleau et al. (26) tested the activity of a mutated hexapeptide devoid of secretagogue activity (EP 80317) in the ApoE$^{-/-}$ model of atherosclerosis. EP 80317 dosing was without effect in ApoE$^{-/-}$ Cd36$^{-/-}$ double knockout mice strongly suggesting that the anti-atherogenic effects of this synthetic peptide are CD36 dependent.

Reasoning that HDL is atheroprotective, Fogelman, Navab, and colleagues (27–29) have described the use of a synthetic 18 amino acid peptide that mimics the configuration of apo A-I amphipathic α-helices as a peptidomimetic alternative to HDL infusion. This D-4F peptide exhibits broadly antiatherogenic and antiinflammatory properties in a range of cellular assays and oral administration of the D-4F peptide has significant atheroprotective activity in the ApoE$^{-/-}$ model, both on its own and in combination with statin therapy. The mechanism of action of this class of peptides seems to be related to their ability to bind and remove proinflammatory oxidized lipids (30). Indeed, recent work has shown that apoA-I mimetic peptides bind oxidized lipids with a much higher affinity than native human apoA-I protein (31). This new class of peptides is active not only in models of atherogenesis but D-4F has also been demonstrated to have efficacy in the collagen induced arthritis model (32), influenza infection (33), and cardiac

allograft vasculopathy (34, recently reviewed in 29). This body of work suggests that apoA-I mimetic peptides render HDL more antiinflammatory and they do this by binding to oxidized lipids present at sites of inflammation. This class of peptide drugs can therefore be thought of as having anti-scavenger receptor activity by removing scavenger receptor ligands in vivo.

MACROPHAGE SCAVENGER RECEPTORS AT 30 YEARS OF AGE: FUTURE DIRECTIONS?

Like many other 30 year olds who have completed their higher education, most of the macrophage scavenger receptors are still trying to find a worthwhile job. While a strong case can be made for CD36 as a bona fide oxidized LDL receptor with a nonredundant function in atherogenesis it seems at first sight that SR-A plays no obvious role in atherogenesis and foam cell formation in vivo (11, 12). We suggest that the following topics may prove fruitful areas for macrophage scavenger receptor research in the coming years.

The use of scavenger receptors as probes for atherosclerotic plaques in vivo

There is an important clinical need to develop better methods to detect atherosclerotic plaques using non-invasive imaging techniques. The presence of macrophage scavenger receptors themselves or their atherogenic ligands within atherosclerotic plaques may represent good targets for molecular MRI. Lipinski et al. (35, 36) demonstrated the feasibility of detecting macrophages expressing SR-A I/II using gadolinium-containing immunomicelles in vitro and this work has subsequently been extended to in vivo imaging in ApoE$^{-/-}$ hypercholesterolemic mice.

The role of macrophage scavenger receptors in modified forms of inflammation, especially diabetes and other metabolic diseases

The role of the macrophage and inflammation in adipose tissue is currently the focus of much research and the role of macrophage scavenger receptors has not been explored in this context. The idea that SR-A I/II might play a role in diabetes and other metabolic diseases is suggested by the original observation that SR-A I/II is the major macrophage receptor for AGE-modified BSA (10) and a recent paper that showed reduced diabetic nephropathy in SR-A$^{-/-}$ mice compared with wild-type mice injected with streptozotocin (37). The reduced nephropathy in SR-A$^{-/-}$ mice was not associated with reduced blood glucose levels but rather was shown to be associated with reduced macrophage accumulation, possibly due to decreased macrophage adhesion to modified collagen IV.

Identification and validation of the true physiological ligands for all scavenger receptors

Identifying the full list of physiological ligands for all of the macrophage scavenger receptors has been challenging, not least because of the multiplicity of ligands identified to date and the issue of scavenger receptor redundancy. Experiments comparing the uptake of labeled bacteria by macrophages from SR-A$^{-/-}$ and wild-type mice have identified many new bacterial ligands for the SR-A I/II receptor and the recent development of a sensitive solid state assay for scavenger receptor ligands, together with a return to macrophage adhesion assays, may well identify new scavenger receptor ligands of physiological and pathophysiological importance (38).

The use of scavenger receptors to scavenge inflammatory oxidized lipids at sites of inflammation

It is becoming increasingly clear that oxidized lipids are found at all sites of inflammation, not just in the subendothelial space of atherosclerosis prone arteries. This accumulation of oxidized lipids may exacerbate inflammation by delaying the clearance of apoptotic cells, a process that rapidly initiates an antiinflammatory program of macrophage gene expression (39). Therapeutic strategies that can reduce the generation of oxidized lipids and oxidized lipoproteins at sites of inflammation in vivo or enhance the clearance of these molecules may therefore find application in many chronic inflammatory diseases.

The authors believe that a better understanding of the physiological roles of macrophage scavenger receptors will lead to new opportunities for therapeutic intervention in cardiovascular disease, diabetes, and other diseases characterized by chronic inflammation.

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