Hepatic and Extrahepatic Scavenger Receptors
Function in Relation to Disease

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Scavenger receptors (SRs) have been of major interest in the study of atherogenesis over the past decade. They were first described for macrophages as alternative receptors to the LDL receptor in the uptake of (excessive) cholesterol and lipid, leading to the development of foam cells. The name scavenger receptor was well chosen, because they recognize a broad array of ligands. In recent years, several new members of the SR family have been cloned on the basis of their ability to recognize modified lipoproteins. According to a proposal by Krieger[1] and recently reviewed by Greaves et al,[2] the members are classified as follows: SR class A consists of SR-AI, SR-AII, SR-AIII, and the macrophage receptor with collagenous structure (MARCO); class B consists of SR-BI and CD36; and class C contains only the Drosophila SR-C. Class D, E, and F receptors have only recently been identified, and none of these show any structural similarity with class A, B, or C receptors (see Figure for classes and structures).

The distinct, but partly overlapping, binding properties of the SR classes form a complication in defining their respective activity in terms of ligand uptake. Most SRs bind a variety of polyanionic ligands. SR classes A and B are expressed in atherosclerotic plaques and are involved in the development of lipid-laden foam cells. However, the expression of SRs is not restricted to cells within the arterial wall, making it difficult to prevent foam cell formation in atherosclerotic plaques by general inhibition of SRs. In general, injection of modified lipoproteins is followed by their rapid removal from the circulation by the liver. SRs present in the liver could have a protective role in atherosclerotic plaque formation by removing the atherogenic lipoproteins. SRs are particularly involved in the removal of modified (eg, oxidized, glycosylated) lipoproteins. Some of the SRs, such as CD36 and SR-B1, bind (in addition to these modified lipoproteins) native lipoproteins, such as HDL and LDL. The characterization of SRs in the liver is thus of particular interest, because failure of the liver protection system may increase atherogenesis. In addition, SRs have been implicated in adhesion, the clearance of dying cells, and host defense against bacterial infection. Thus, researchers in other areas of cell biology and medicine are becoming increasingly interested in the role of SRs in various diseases. In the present review, the characteristics of SRs will be discussed, with a specific emphasis on their role in the liver compared with their role in other tissues.

SRs: Structure, Expression, and Ligands

Table 1 summarizes the cellular expression of the various SRs within the liver and in extrahepatic tissues. Table 2 lists the SRs with their proposed ligands. Table 3 summarizes the cellular fate and intracellular signaling after ligand binding by SRs. Table 4 highlights the nonlipoprotein functions of the various SRs.

Class A SRs

SR-AI, SR-AII, and SR-AIII are all products of the same gene, generated by alternative splicing. SR-AI contains a 110–amino acid C-terminal cysteine-rich sequence that is absent in SR-AII.[3] There seems to be no major difference between these 2 forms in ligand binding, but Geng et al[4] reported steady high-level expression of the type II SR-A during monocyte differentiation, whereas type I expression gradually increased. Another study, which used P388D1 murine macrophages, showed differences in the expression levels of SR-AI and SR-AII,[5] with the type I receptor expression by P338D1 cells substantially less than that of the type II receptor. It was also observed that lipopolysaccharides derived from *Salmonella minnesota* Re 5g5 (Re mutant) was far more effective in inhibiting the binding of acetylated LDL (AcLDL) by the type II receptor than by the type I receptor, indicating different binding affinities for the 2 forms. SR-AIII, the third isoform of the SR-A gene, was recently identified.[6] It has a cysteine-rich C-terminal domain like SR-AI, but it lacks the C-terminal end of the collagenous structure, which has been implicated in the binding of polyanionic ligands.[7,8] SR-AIII is not expressed on the plasma membrane because of different intracellular processing and does not mediate ligand endocytosis. Expression of SR-AIII in soluble form inhibited ligand binding by SR-AI or SR-AII when cotransfected in Chinese hamster ovary (CHO) cells.

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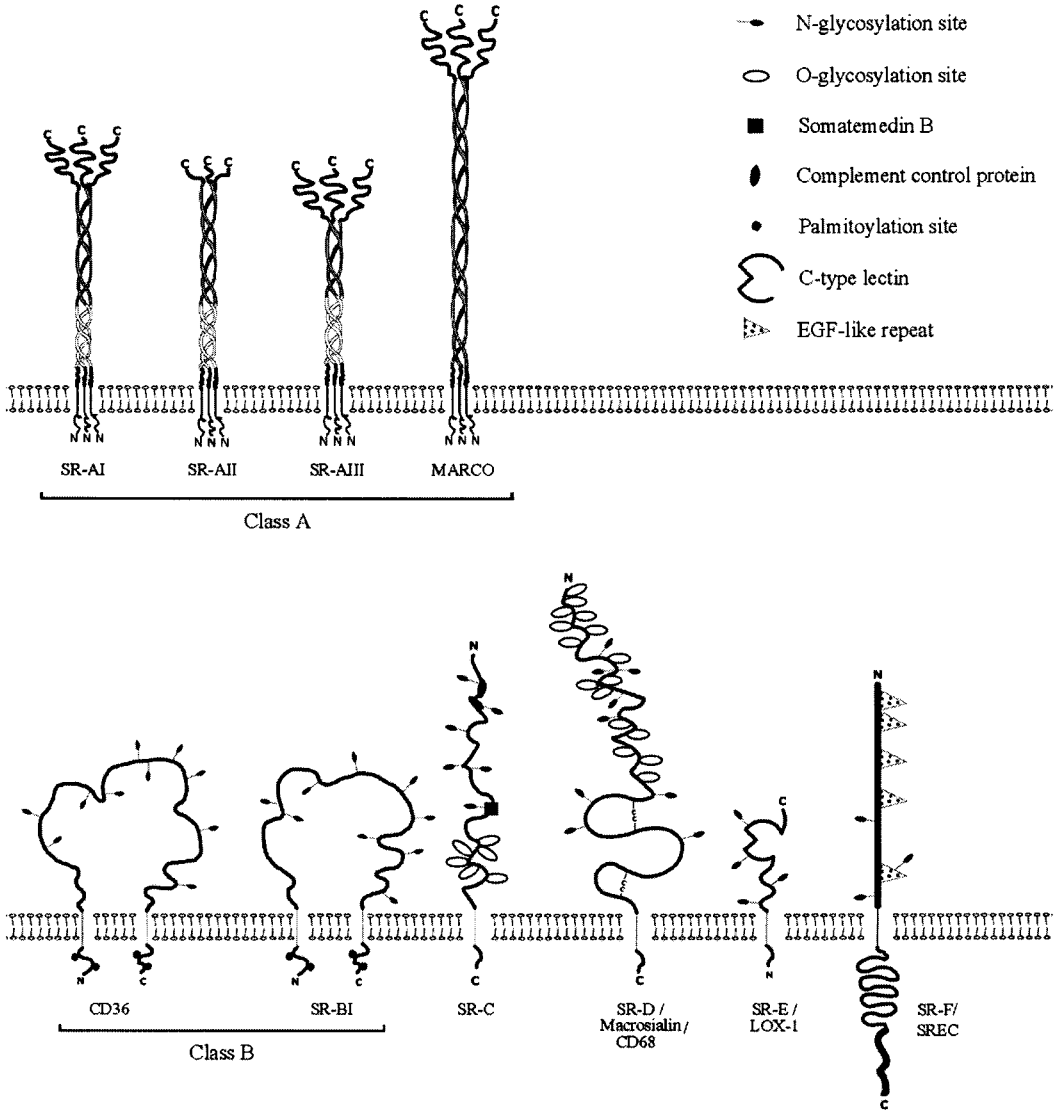

Classification of SRs and their proposed structures (based on a proposal by Krieger[1] and extended by Greaves et al[2]). EGF indicates epidermal growth factor.

SR-A is expressed by tissue macrophages, aortic endothelial cells, liver sinusoidal endothelial cells, and Kupffer cells.[9–11] Freshly isolated monocytes and macrophages express low levels of SR-A,[4,12] but mRNA and protein levels rapidly increase during culture.[13] SR-A is highly expressed in macrophage-derived foam cells in atherosclerotic plaques in humans,[9,13–15] and it has also been reported to be expressed by smooth muscle cells within atherosclerotic plaques.[16] Macrophage colony–stimulating factor[17] and phorbol esters[18] induce monocyte differentiation into macrophages and increase the functional expression of SR-A, whereas tumor necrosis factor-α,[19,20] transforming growth factor-β,[21] granulocyte-macrophage colony–stimulating factor,[22] and interferon-γ[23,24] decrease its expression. On human macrophages, the expression of SR-A decreases after stimulation with lipopolysaccharide (LPS).[19] Similarly, there is a transient downregulation of SR-A mRNA in mice after an in vivo challenge with LPS.[25] However, treatment of mice with inflammatory stimuli, such as Calmette-Guérin bacillus (BCG) or *Corynebacterium parvum*, results in increased SR-A expression on liver Kupffer cells.[26,27] Expression of SR-A is also increased by some of its own ligands, such as minimally and highly oxidized LDL.[28,29]

Many polyanionic molecules bind to class A SRs (see Table 2), but the affinity of SR-A for modified lipoproteins varies. For instance, binding of AcLDL competes for only half of the binding of oxidized LDL (OxLDL), whereas OxLDL is able to displace all of the binding of AcLDL,[30] which can be explained by the analysis of the SR-A/AII binding site.[7] SR-AI and SR-AII bind Gram-positive bacteria, lipoteichoic acid,[31,32] and lipid IV_A, a precursor of lipid A from LPS of Gram-negative bacteria.[33] Heparin,[34] advanced glycosylation end products,[35,36] and crocidolite asbestos[37] are also ligands for SR-AI and SR-AII.

MARCO shows structural features that are very similar to SR-AI and was therefore designated as a new member of the class A SRs. MARCO, like SR-A, forms a homotrimeric structure and is expressed on the plasma membrane of macrophages. It contains an extracellular collagenous domain and a C-terminal cysteine-rich domain, similar to SR-A.[38] However, there are also some important differences: MARCO lacks the α-helical coiled coil present in SR-AI, and

TABLE 1. Hepatic and Extrahepatic Expression of SRs

Class	Hepatic Expression	Extrahepatic Expression
Class A		
SR-AI SR-AII SR-AIII	Kupffer cells, sinusoidal endothelial cells	Tissue macrophages, foam cells
MARCO	Kupffer cells under inflammatory conditions	Macrophages in marginal zone of the spleen and lymph nodes
Class B		
SR-BI/CLA-1 SR-BII	Hepatocytes, Kupffer cells after cholesterol-rich diet or high-dose estrogen treatment	Adrenal glands, testes, ovaries, monocytes/macrophages
CD36	Kupffer cells, sinusoidal endothelial cells, hepatocytes during certain infectious diseases, hepatoma cells (HepG2)	Monocytes/macrophages, platelets, adipocytes, mammary epithelial cells, microvascular endothelial cells
Croquemort	?	Drosophila hemocytes/macrophages
Class C		
Drosophila SR-C	?	Drosophila hemocytes/macrophages
Class D		
CD68/macrosialin	Kupffer cells	Tissue macrophages
Class E		
LOX-1	Kupffer cells? Endothelial cells?	Vascular endothelial cells, monocytes/macrophages
Class F		
SREC	Endothelial cells?	Vascular endothelial cells

the collagenous domain of MARCO is much longer. MARCO also has a very restricted tissue expression. In mice, it is normally expressed only on macrophages in the marginal zone of the spleen and in lymph nodes.[38] In mice, the expression of MARCO in the liver can be increased by inflammatory stimuli, such as LPS, BCG, *C parvum*, or *Klebsiella pneumonia*.[26,27,39,40]

Moreover, a similar pattern of high MARCO expression was observed in the livers of 2 human newborns who died of sepsis.[41] MARCO binds Gram-positive and Gram-negative bacteria and AcLDL, but binding of OxLDL was not reported.[38] Recently, the bacteria-binding domain of MARCO has been located immediately proximal to the cysteine-rich domain,[41] which is the same region Doi et al[7] identified as the binding domain of SR-A.

Class B SRs

SR-BI belongs to the family of SRs on the basis of its property to bind modified LDL and maleylated BSA (M-BSA).[42] However, it soon became evident that SR-BI can also

TABLE 2. SRs and Their Proposed Ligands

Class	Ligands
Class A	
SR-AI SR-AII	AcLDL (1–5 μg/mL[160]), OxLDL (10 μg/mL[160]), AGE-modified proteins (1–5 μg/mL[35]); M-BSA, LPS (for ReLPS, 50–250 μg/mL[5]), LTA, whole bacteria, polyinosinic acid, polyguanosinic acid
SR-AIII	?
MARCO	AcLDL, LPS, whole bacteria
Class B	
SR-BI/CLA-1 SR-BII	HDL (30 μg/mL[93]), LDL (5 μg/mL[42]), VLDL, modified lipoproteins (5 μg/mL[42]), anionic phospholipids, apoptotic cells
CD36	HDL (2.9 μg/mL[99]), LDL (6.3 μg/mL[99]), VLDL (1.2 μg/mL[99]), modified lipoproteins (1.7 μg/mL[99]), anionic phospholipids, fatty acids, thrombospondin, collagen, *P falciparum*–infected RBCs, apoptotic cells
Croquemort	Apoptotic cells
Class C	
Drosophila SR-C	AcLDL (2 μg/mL[58])
Class D	
CD68/macrosialin	OxLDL, phosphatidylserine liposomes, malondialdehyde, BSA
Class E	
LOX-1	OxLDL (36 μg/mL[75]), carrageenan, polyinosinic acid, apoptotic cells
Class F	
SREC	AcLDL (3 μg/mL[77]), OxLDL (3 μg/mL[77])

AGE indicates advanced glycation end product; LTA, lypoteichoic acid; *P falciparum*, *Plasmodium falciparum*; and RBC, red blood cells. Affinities for various ligands are indicated in parentheses and are derived from data in which a single SR was expressed in COS or CHO cells.

TABLE 3. Cellular Fate and Intracellular Signaling After Ligand Binding by Various SRs

Class	Cellular Fate	Intracellular Signaling
Class A		
SR-AI SR-AII	Endocytosis, phagocytosis, involved in cell adhesion	Protein kinase C,[161,164] PPAR-γ,[162] PIP_2,[163] Ca^{2+} influx,[163] NF-κB binding,[163] plasminogen activation,[165,167–172] antigen presentation[166]
SR-AIII	Soluble form in plasma	...
MARCO	Endocytosis, phagocytosis	...
Class B		
SR-BI/CLA-1 SR-BII	Docking protein, endocytosis, phagocytosis, intracellular delivery of cholesterol (esters)	...
CD36	Slow endocytosis, phagocytosis	Oxidative burst,[173] activation of protein tyrosine kinases[174]
Croquemort	Phagocytosis	...
Class C		
Drosophila SR-C	Endocytosis	...
Class D		
CD68/Macrosialin	Endocytosis (mainly intracellular localization)	...
Class E		
LOX-1	Endocytosis, phagocytosis	...
Class F		
SREC	Endocytosis	...

NF indicates nuclear factor; PIP_2, phosphatidyl inositol diphosphate.

function as a receptor for HDL and is able to mediate selective uptake of cholesterol esters from HDL.[43] SR-BI was cloned from a variant CHO cell cDNA library.[42,44] It binds native and modified lipoproteins,[42,45] anionic phospholipids,[46] and apoptotic cells.[47] Using in situ hybridization, Ji et al[48] found expression of SR-BI mRNA in the thickened intima of apoE knockout mice, suggesting that SR-BI could contribute to the development of foam cells. In addition to the liver, SR-BI is also expressed at high levels in the adrenal glands, ovaries, and testes.[43,49] These tissues are involved in steroidogenesis and have a continuous need for cholesterol. CD36 and LIMP-II analogous-1 (CLA-1), the human homologue of SR-BI, is also expressed in these tissues as well as in cell lines of myeloid origin and in several carcinoma cells.[50] However, CLA-1 mRNA and protein expression decreased during the differentiation of monocytes into macrophages.[49]

SR-BII, a recently discovered isoform of the same gene as SR-BI, differs from SR-BI only in the C-terminal cytoplasmic tail. However, this does not affect its cellular localization (both forms are found in caveolae) or tissue distribution.[51] It represents ≈40% of total SR-BI/BII mRNA but only 12% of the immunodetectable SR-BI/BII protein in mouse liver. This could indicate that the SR-BII protein is less efficiently translated, because pulse-chase experiments showed no apparent differences between SR-BI and SR-BII in protein half-life.[52]

CD36 was previously known as the OKM5 antigen, platelet glycoprotein IV, or GP88 (reviewed in Reference 53). CD36 is expressed by mammary epithelial cells, adipocytes, platelets, erythrocyte precursors, monocytes/macrophages, and microvascular endothelial cells, to name a few. Evidently, the tissue distribution and cellular expression of CD36 are quite different from those of SR-BI, even though they are structurally strongly related. Immunohistochemical studies showed that CD36 expression in the liver is normally restricted to sinusoidal endothelial and Kupffer cells.[54,55] Under nonpathological conditions, CD36 is not expressed in the endothelium of the portal vein, hepatic arterioles, or central vein. During chronic hepatitis B virus infection, CD36 was also found on clusters of hepatocytes, which may indicate a role for CD36 in retention of inflammatory cells.[56] Ligands of CD36 include native and modified lipoproteins, anionic phospholipids, thrombospondin, collagen, apoptotic cells, and *Plasmodium falciparum*–infected red blood cells (see Table 2).

TABLE 4. Lipoprotein-Independent Ligands and Functions of SRs

Class	Function
Class A	
SR-AI SR-AII	Binding and uptake of Gram-negative and Gram-positive bacteria, antigen presentation, adhesion during homing of monocytes and possibly maturation, uptake of apoptotic thymocytes
MARCO	Binding and uptake of Gram-negative and Gram-positive bacteria
Class B	
SR-BI/CLA-1 SR-BII	Fatty acid transport, phagocytosis of apoptotic T cells and damaged red blood cells, adhesion of monocytes
CD36	Fatty acid transport, phagocytosis of apoptotic T cells and damaged red blood cells
Croquemort	Phagocytosis of apoptotic cells and aged red blood cells

Class C SRs

Drosophila embryonic macrophages were found to exhibit SR activity,[57] and a cDNA has since been isolated by expression cloning of a Drosophila Schneider L2 cell library.[58] The predicted protein sequence of Drosophila SR C (dSR-C) contains several interesting domains showing homology to known vertebrate sequences. There are 2 complement control protein domains, which are found in many complement proteins and clotting factors, and a serine/threonine-rich domain that is presumably heavily *O*-glycosylated and resembles a mucin structure. dSR-C, when expressed in CHO cells, showed high saturable binding and degradation of ^{125}I-AcLDL. It is expressed in Drosophila hemocyte/macrophages throughout embryonic development and perhaps plays a role here by clearing apoptotic cells or by taking part in other hemocyte functions in host defense and cell-matrix interactions. So far, a mammalian homologue to dSR-C has not been identified.

Class D SRs

Macrophages express another protein that was shown to bind OxLDL on ligand blots. By amino acid analysis, this protein was identified as macrosialin, the murine homologue of human CD68.[59] Antibodies against macrosialin/CD68 are widely used as macrophage markers, because virtually all tissue macrophages express this protein. Macrosialin/CD68 shows strong structural homology with the lysosomal-associated membrane protein family.[60] It is a highly glycosylated protein of ≈85 to 115 kDa and predominantly present in late endosomes and lysosomes.[61] Compared with resident peritoneal macrophages, thioglycolate-elicited peritoneal macrophages show an ≈17-fold increase in macrosialin expression.[62] Cell surface expression is low but detectable after stimulation.[63] Macrosialin is highly expressed in rat Kupffer cells but not in liver endothelial cells and recognizes OxLDL on ligand blots.[64,65] Membrane preparations of thioglycollate-elicited peritoneal macrophages were shown to bind OxLDL and phosphatidylserine (PS)-containing liposomes.[66]

One of the remarkable features of macrosialin/CD68 is its extensive glycosylation, which accounts for about two thirds of the mass of the mature protein.[67] Deglycosylation by treatment with *N*-glycosidase or *O*-glycosidase did not affect its ability to bind OxLDL on ligand blots,[65,68] suggesting that the binding of OxLDL is not mediated through the carbohydrate moiety. Recently, it has been shown that OxLDL increases macrosialin mRNA and protein levels in resident mouse peritoneal macrophages.[29] However, its functional role as an SR for OxLDL or other ligands on whole macrophages awaits further investigation.

Class E SRs

Recently, a new SR was cloned from a cDNA library of cultured bovine aortic endothelial cells.[69] The structure of the lectin-like OxLDL receptor (LOX) shows no similarity with other SRs. LOX-1 is a 50-kDa transmembrane protein with 4 potential *N*-glycosylation sites in the extracellular lectin-like domain and a C-terminal cytoplasmic tail, which contains several potential phosphorylation sites. Homology between bovine and human LOX-1 is especially well preserved in the lectin-like domain. Northern blots of human tissues detected LOX-1 mRNA in cultured aortic endothelial cells, normal thoracic and carotid vessels, and vascular-rich tissues, such as placenta, lungs, brain, and liver.[69] In endothelial cells, its expression was shown to be upregulated by OxLDL (10 to 40 μg/mL),[70] fluid shear stress,[71] tumor necrosis factor-α, and phorbol 12-myristate 13-acetate.[72] Interestingly, LOX-1 was recently shown to be expressed by human and murine macrophages.[73,74] Unfortunately, its expression in the liver is not further specified. LOX-1 showed high-affinity saturable binding of OxLDL (K_d ≈36 μg/mL) but apparently did not recognize AcLDL.[72,75]

LOX-1 differs from other SRs in that its binding of OxLDL is significantly inhibited by polyinosinic acid, carrageenan, and delipidated OxLDL but not by AcLDL, M-BSA, or fucoidin. Its lectin-like structure also distinguishes LOX-1 from other SRs. Interestingly, LOX-1 has recently been shown to mediate the recognition of apoptotic cells and aged red blood cells by endothelial cells,[76] implicating a possible dual role for this SR.

Class F SRs

Another endothelial SR, the SR expressed by endothelial cells (SREC), was cloned from human umbilical vein endothelial cells.[77] It consists of 830 amino acids and has a calculated mass of ≈86 kDa. The cytoplasmic tail of this protein is unusually long and contains several potential phosphorylation sites. The extracellular domain contains 5 epidermal growth factor–like repeats, which could be involved in ligand binding or mediate oligomerization of the molecule. When expressed in CHO cells, SREC bound and degraded AcLDL, which was completely inhibited by poly I, dextran sulfate, malondialdehyde-treated LDL, and M-BSA and only partially inhibited by OxLDL (50% reduction). This binding specificity is very similar to that reported for SR-AI/AII and differs from the binding specificity of LOX-1. It is not known whether SREC is expressed in liver endothelial cells. However, these 2 new SRs, SREC and LOX-1, could account for the observed high uptake of modified lipoproteins in vivo by liver sinusoidal endothelial cells[78] and in SR-AI/AII knockout mice.[79]

Functions of SRs

Lipoprotein Metabolism

Class A SRs

The potential role of SR-AI/AII in atherosclerotic plaque formation was confirmed in a study with apoE and SR-A double-knockout mice.[80] ApoE knockout mice have been reported to develop severe atherosclerotic plaques.[81,82] ApoE and SR-A double-knockout mice have been shown to develop 58% smaller atherosclerotic lesions compared with apoE knockout mice, in spite of a 46% higher level of plasma cholesterol. Similar findings were reported in LDL receptor/SR-A double-knockout mice,[83] although the atherosclerotic plaque formation in double-knockout mice was only ≈20% less than in LDL receptor knockout mice. Peritoneal macrophages lacking SR-A showed 80% less uptake of AcLDL and 30% less uptake of OxLDL,[84,85] and isolated liver endothelial cells and Kupffer cells showed a 40% to 50% reduction in the uptake of AcLDL.[79] Moreover, an antibody specific for SR-AI and SR-AII (2F8) was able to inhibit the uptake of

AcLDL by isolated wild-type Kupffer and liver endothelial cells to the level of the knockout cells (Y.K. Kruijt and T.J.C. van Berkel, unpublished data, 1999). Surprisingly, SR-A knockout mice and wild-type mice did not differ in in vivo clearance rates of modified LDL.[79,80,86] The kinetics of liver uptake and serum decay and the percentage of injected dose associated with the liver were similar in SR-A knockout and wild-type control mice. Apparently, there are other receptors expressed in the liver that are able to compensate completely for the absence of SR-A in the SR-A knockout mice.

Class B SRs

SR-BI binds HDL with high affinity (K_d ≈30 μg of HDL protein per milliliter),[43] unlike class A SRs, which do not bind native lipoproteins at all. In vivo studies established SR-B1 as an HDL receptor that mediates the selective uptake of cholesteryl esters without internalization of the HDL particle. Consistent with this observation, substrates for SR-BI (such as OxLDL and anionic phospholipids) strongly inhibit the in vitro uptake of HDL cholesteryl ester.[87] SR-BII has a tissue distribution similar to that of SR-BI and also mediates selective lipid uptake from HDL, but SR-BII is ≈4 times less efficient in the uptake of cholesteryl esters than is SR-B.I[52] SR-BI expression in rat liver is suppressed by a cholesterol-rich diet or 17α-ethinyl estradiol,[88,89] indicating a close link between cholesterol metabolism and the expression of SR-BI and suggesting a sterol regulatory element in the SR-BI gene. In steroidogenic tissues, adrenocorticotropic hormone,[90] estrogen, and human chorionic gonadotropin[89] upregulate SR-BI expression in concert with an increase in HDL binding and steroidogenesis. Indeed, it has recently been shown that steroidogenic factor-1, a transcription factor that activates many components of the steroidogenic complex, enhances the transcription of SR-BI in adrenocortical cells by binding to the SR-BI promoter.[91]

Much has been learned about SR-B1 through the generation of mice either lacking or (transiently) overexpressing SR-BI as well as other murine models, such as lecithin-cholesterol acyltransferase–deficient[92] or apoA-I–deficient[93,94] mice. Adenoviral overexpression of SR-BI in the liver strongly decreased plasma HDL levels and concomitantly increased biliary cholesterol secretion,[95] as did transgenic overexpression of SR-BI.[96] This indicates that SR-BI in vivo is functional in HDL metabolism and that, in the liver, SR-BI is an important determinant of cholesterol secretion. Mice in which the SR-BI gene is partially or completely disrupted show greatly increased levels of plasma HDL.[97,98] Disruption of the SR-BI gene had no effect on the concentration of apoA-I, but the HDL particles had increased in size considerably.[97]

The other known member of the class B SRs, CD36, has also been shown to recognize native and modified lipoproteins.[99] Using an expression cloning technique with fluorescently labeled OxLDL for selecting OxLDL binding proteins, Endemann et al[100] identified murine CD36 as a candidate SR. CD36-transfected 293 cells bound, internalized, and degraded OxLDL with a binding affinity of ≈1.5 μg/mL. Moreover, CD36-deficient monocytes and macrophages showed a reduction of ≈40% in OxLDL uptake and degradation and less cholesteryl ester accumulation when incubated with OxLDL.[101] Thus, CD36 was established as a new member of the SR family. It was also suggested that OxLDL bound to CD36 by its lipid moiety.[102] With the use of chimeric constructs of murine and human CD36, amino acid residues 155 to 183 were shown to be the OxLDL binding domain.[103] Considering the structural similarities between CD36 and SR-BI, it would be interesting to learn what exactly the SR-BI binding site is for HDL and whether other ligands, such as anionic phospholipids and OxLDL, bind to the same domain on SR-BI.

A recent report has shown that not only modified lipoproteins but also native LDL, VLDL, and HDL bind to CD36.[99] CD36 shares this broad recognition of lipoproteins with SR-BI.[45] Interestingly, SR-BI and CD36 significantly differ in their ability for selective lipid uptake.[104] For CD36, it has been shown that its ligand specificity for either collagen or thrombospondin depends on the phosphorylation state of an extracellular domain.[105] It is not known whether the phosphorylation state also affects CD36 lipoprotein binding. The binding domain for OxLDL does not coincide with the binding domain for thrombospondin, collagen, or *P falciparum*–infected erythrocytes, suggesting that there may be a different mechanism for regulating lipoprotein binding. Several recent reports showed that CD36 mRNA and protein expression increased after the incubation of cells with minimally or fully oxidized LDL.[29,106,107] Interestingly, one of the constituents of OxLDL, an oxidized lipid, is a ligand for peroxisome proliferator–activated receptor-γ (PPAR-γ) and through binding to PPAR-γ increases the expression of CD36.[108,109] Thus, the uptake of OxLDL through SRs could stimulate its own uptake by activating PPAR-γ and increasing the expression of CD36.

Adhesion and Differentiation

The role of SR-A in adhesion was first discovered when it was shown that the rat monoclonal antibody 2F8 completely inhibits the divalent cation-independent adhesion of murine macrophages to tissue culture plastic, in the presence of FCS. Immunoprecipitation experiments revealed that the antigen recognized by 2F8 is SR-A.[110] In another report, Hughes et al[10] demonstrated that 2F8 is able to inhibit the divalent cation–independent adhesion of macrophages to frozen tissue sections of different lymphoid and nonlymphoid organs. Experiments with SR-A–deficient mice confirmed the role of SR-A in adhesion, showing that the adhesion of thioglycollate-induced peritoneal macrophages from SR-A knockout mice to plastic is <50% of the adhesion of wild-type macrophages. In the presence of EDTA, the adhesion is even lower.[80] Other studies showed that SR-A mediates the adhesion of macrophages to glucose-modified basement membrane collagen IV[111] and the adhesion of microglia to β-amyloid fibrils.[112] Certain basement membrane proteoglycans (eg, nexin II, biglycan, and decorin) were shown to be ligands for SR-A.[113] Also, it was demonstrated that activated B lymphocytes are able to adhere to CHO cells transfected with SR-A[114] and that when SR-A is transfected into a human embryonic kidney cell line, which normally adheres only weakly to tissue culture plastic, it confers an adherent phenotype to these cells in culture.[115] Giry et al[116] showed that monocytes and macrophages from a human normolipidemic subject with planar xanthomas exhibit SR

overexpression. Monocytes from this subject show an increased rate of adhesion and maturation in culture.

In the liver, SR-A is also important for cell adhesion. Comparing SR-A–deficient mice with wild-type mice, it was demonstrated that SR-A plays a role in the adhesion of PMA-activated Kupffer cells to tissue culture plastic. In these activated Kupffer cells, SR-A is responsible for ≈35% of cell adhesion (A.G.v.V. et al, unpublished data, 2000). Finally, the group of Kodama (Hagiwara et al[27]) demonstrated that after injection of BCG, the formation of liver granulomas is delayed in SR-A–deficient mice compared with wild-type mice and that the size of the granulomas is decreased. Taken together, these results strongly suggest that SR-A is able to mediate the adhesion of different cell types to a number of substrates. In this way, SR-A may play an important role in the recruitment and retention of cells in different organs or at sites of pathological conditions, ie, sites of inflammation or atherosclerotic lesions.

CD36 has been implicated in adhesive processes because it can bind collagen[117] and thrombospondin,[118,119] a macromolecule involved in many adhesive processes. The expression of CD36 mRNA and of protein on the plasma membrane was shown to be upregulated on stimulation with phorbol esters in 2 monocytic cell lines, THP-1 and U937,[120] at the time when these cells became adherent. Increased monocyte CD36 expression has also been found after adhesion to tumor necrosis factor–activated endothelial cells,[121] further suggesting a role for CD36 in the adhesion of monocytic cells to extracellular matrix and increased retention of monocytes at inflammatory sites.

Host Defense

The Kupffer cells represent 80% to 90% of the total macrophage population, and because of their location (periportal, liver sinusoids), they are a first line of defense against circulating microorganisms. In vivo experiments with radiolabeled Gram-negative bacteria and LPS in mice and rats have shown that the liver (and within the liver, the Kupffer cell population) is mainly responsible for the clearance from the circulation.[122–124]

LPS can bind to several receptors, including CD14 and β_2-integrins.[125,126] Binding of LPS to these receptors elicits a strong cytokine release and concomitant inflammatory response. However, Hampton and colleagues[33,127] have demonstrated that lipid IV_A, an LPS precursor, can bind to the SR-A, resulting in uptake and intracellular dephosphorylation of the lipid IV_A, rendering it less toxic. Lipid IV_A, internalized through SR-A, failed to induce an inflammatory response in these cells, suggesting a protective role for SR-A in host defense. Besides LPS, SR-A also binds lipoteichoic acid (from Gram-positive bacteria)[31,32] and whole Gram-positive bacteria, such as *Staphylococcus aureus* and *Mycobacterium tuberculosis*.[31,128] MARCO is able to bind Gram-negative and Gram-positive bacteria.[38,40] Cross-competition studies with LPS and several other SR ligands have shown that there are other SRs, expressed on Kupffer and liver sinusoidal endothelial cells, involved in the binding of LPS as well.[123,129]

Little is known of the relative contribution of the receptors in the liver for the uptake of bacterial components in general and LPS especially. This is illustrated by in vivo experiments using blocking antibodies against MARCO, which did not affect the clearance of bacteria in mice.[40] Similarly, the liver uptake of LPS in SR-A–deficient mice was almost equal to that in control mice, indicating the involvement of parallel pathways.[124] Binding by SRs may actually form a protective mechanism by removing excess microorganisms or their components, thus preventing cytokine production and the development of septic shock. This was demonstrated by Haworth et al,[26] who showed that BCG-infected SR-A knockout mice are more susceptible to LPS. This suggests that if LPS cannot be cleared by SR-A, then CD14 and other receptors will bind, resulting in a potentially damaging inflammatory response. More recently, other ligands for CD14 have been discovered; these include lipoteichoic acid, peptidoglycans (both from Gram-positive bacteria), lipoarabinomannan (from *Mycobacterium tuberculosis*), and bacterial lipoproteins (from the pathogen *Borrelia burgdorferi*).[31,130–134] Validation of the role of the distinct receptors for microorganisms and their components is essential to understand the complex interactions between the proinflammatory and anti-inflammatory actions of these receptors. The fact that CD14 and SRs recognize and bind Gram-positive and Gram-negative bacteria or their components further strengthens the hypothesis that the SRs may have an anti-inflammatory role in host defense.

Although the class B SRs have not been shown to bind endotoxins or immunogenic pathogens directly, they could indirectly have an effect on mediating an inflammatory response. LPS is known to bind to HDL particles[135] in plasma. SR-BI, which binds HDL and selectively transfers cholesterol esters and phospholipids, could potentially mediate LPS transfer into the cell as well. Alternatively, by regulating HDL plasma levels (as shown in the SR-BI transgenic and SR-BI null and *att* mice), SR-BI could have a major impact on the HDL pool available for LPS binding. Plasma HDL has been shown to provide protection against endotoxin-induced sepsis, through binding endotoxin in the blood compartment.[136,137] When the HDL pool has decreased, this would leave higher concentrations of LPS present in the circulation to induce an inflammatory response and systemic sepsis.

Phagocytosis of Damaged Cells

Removal of dead cells is important both for embryological development and for maintaining tissue homeostasis. SRs have been implicated in the clearance of damaged and apoptotic cells.[138] This recognition by SRs may be explained by the structural similarities between cell membranes and lipoproteins. Both consist of phospholipids, cholesterol, and (glyco)protein. Oxidative damage to a lipoprotein particle may create epitopes that resemble the epitopes exposed by cells that undergo apoptosis or by senescent erythrocytes, such as membrane PS. PS is, under normal conditions, confined to the inner leaflet of cell membranes, but on apoptosis or aging, when the aminophospholipid asymmetry is destroyed, PS becomes exposed on the outer leaflet, providing a signal for removal.[139–142] Some SRs have been shown to bind liposomes containing PS,[46,47] and SR ligands, such as OxLDL and poly I, inhibit the binding of damaged and apoptotic cells,[66,138] further suggesting a role for SRs in the removal of damaged and apoptotic cells.

SR-A contributes to the recognition of apoptotic thymocytes by thymic macrophages and by thioglycollate-elicited peritoneal macrophages.[143] The 2F8 antibody, which recognizes SR-AI/AII, inhibited 50% of the apoptotic thymocyte uptake, and elicited peritoneal macrophages lacking SR-AI/AII showed 50% less phagocytosis of apoptotic thymocytes. In another in vitro study using resident peritoneal macrophages in the absence of serum, SR-AI/AII accounted for ≈20% of the apoptotic thymocyte binding.[85] The epitope on the apoptotic cells that is recognized by SR-A has not yet been determined.

Another apoptotic cell removal system is operated by CD36, in cooperation with the vitronectin receptor ($\alpha_b\beta_3$ integrin) and thrombospondin.[144–147] CD36 can also mediate the uptake of photoreceptor outer segments by epithelial cells in the retina,[148,149] an important process to maintain visibility. The epitope that was recognized by CD36 in these studies seemed to be PS, because liposomes containing PS completely inhibited the interaction. The other class B SRs, SR-BI and its human homologue CLA-1, were shown to bind apoptotic cells.[47,49] Binding of apoptotic thymocytes by HEK 293 cells, transfected with CLA-1, was inhibited by liposomes containing anionic phospholipids, suggesting that PS exposure on the outer leaflet of the apoptotic cell membrane was recognized by CLA-1.[49]

A recent study by Oka et al[76] convincingly showed that LOX-1 mediates the recognition of aged red blood cells and apoptotic HL-60 cells by bovine aortic endothelial cells and by CHO cells transfected with LOX-1. Binding and phagocytosis are effectively inhibited by OxLDL, fucoidin, poly I, and liposomes containing anionic phospholipids. Recognition of damaged cells does not depend on the type of cell or the type of damage, indicating that LOX-1 recognized a common structure in all of these ligands, possibly the exposure of PS on the outer leaflet of the apoptotic or aged cell membrane. Because these assays were performed in the presence of serum, one cannot completely exclude the possibility that a serum component (ie, β_2 glycoprotein I) binds to the damaged cells and mediates recognition by LOX-1.[150,151]

Oxidatively damaged red blood cells, a model for red cell senescence, are readily recognized by macrophages in vitro under nonopsonizing conditions.[66,138,152] This recognition is completely inhibited by OxLDL, poly I, and liposomes containing PS. This binding specificity markedly resembles that just described for LOX-1 on endothelial cells, but it is not known whether LOX-1, when expressed by macrophages, displays a similar recognition of damaged cells. We have recently shown that oxidatively damaged red blood cells in vivo are taken up by liver Kupffer cells and that this uptake was strongly inhibited by the same SR ligands, OxLDL, poly I, and PS liposomes (V.T. et al, unpublished data, 2000). The apparent redundancy of clearance mechanisms for apoptotic and damaged cells[153,154] raises difficulties in determining exactly which receptors are involved in vivo and may require crossbreeding of various types of SR knockout animals.

Relation to Disease

As mentioned earlier, cytokines greatly affect the expression level of class A SRs. In vivo, local concentrations of cytokines and growth factors may be different in various tissues. Depending on the localization of the macrophages, SR expression may be high or low, and SR activity may be either protective or damaging. This point is nicely demonstrated by the results obtained with hepatic overexpression of SR-A versus results obtained in SR-A null mice. The total lack of SR-A did prevent, to some extent, cholesterol accumulation in macrophages in the arterial wall, which was beneficial locally, but at the same time caused a systemic rise in plasma cholesterol and also rendered these mice more susceptible to infections.[80] On the other hand, selective overexpression of SR-A in the liver[155] prevented hyperlipidemia and atherosclerosis induced by a high-cholesterol diet. Then again, systemic overexpression of SR-A by monocytes and macrophages, as found in some patients with planar xanthomas,[116] is likely to result in pathological cholesterol accumulation in monocytes and macrophages in several tissues. Together, these findings indicate that whether SR activity is protective or damaging depends on its hepatic or extrahepatic localization. Hereby, the SRs in the liver may exert a protective role, whereas in extrahepatic tissues, including the vascular system, SR activity may result in pathological events.

High levels of plasma HDL correlate with a decreased risk for coronary artery disease.[156] If SR-BI/CLA-1 has the same important regulatory properties on plasma HDL levels in humans that was shown in mice, it could be a possible target for drug intervention in atherosclerosis. It is noteworthy that in mice the major cholesterol carrier is HDL, whereas in humans this is LDL. By overexpressing SR-BI, the natural cross talk between HDL cholesterol levels, biliary cholesterol secretion, and SR-BI expression may be perturbed, and studies like these should be considered with some care. Overexpression of SR-BI could, theoretically, be proatherogenic because of the decrease in plasma HDL levels, thereby reducing the ability for HDL to mediate cholesterol efflux as well as reducing the other protective effects of HDL, namely, its supposed role as an antioxidant[157] or as an inhibitor of cell adhesion[158] and anti-inflammatory agent.[159] On the other hand, overexpression of SR-BI in the liver could increase the flux of reverse cholesterol transport and the secretion of cholesterol into the bile and, therefore, have an antiatherogenic effect. Moreover, if somehow macrophages in atherosclerotic plaques could be induced to express high levels of SR-BI, perhaps foam cell formation could be prevented by promoting HDL-mediated cellular cholesterol efflux. What is more important: the ability of SR-BI to mediate cholesterol efflux from cells or its ability to mediate cellular cholesterol uptake from HDL? Again, localization of SRs, hepatic or extrahepatic, will probably determine their role in physiology and pathophysiology. Future studies in animals and humans will be necessary to establish the role of SR-BI/CLA-1 in lipid metabolism.

Conclusions

The SR family is a very heterogeneous group of proteins, both structurally and functionally. There is accumulating evidence that the class A SRs are involved in adhesion and host defense and that they mediate cellular responses within the macrophage. The class B SRs have been shown to affect plasma HDL levels and cholesterol uptake and efflux. Many SRs are expressed in the liver under normal and under pathological conditions. SRs, with their broad

ligand recognition, could assist in the function of the liver as a blood-filtering tissue and thereby protect the organism from harmful agents. They could also play a role in liver lipoprotein metabolism and reduce the risk of atherosclerosis by mediating efficient uptake of cholesterol from plasma. On the other hand, in extrahepatic tissues, it still needs to be determined whether their presence and activity are either protective or deleterious. Considering their diverse tissue distribution and the many processes in which they seem to be involved, there is a need for more in vivo studies to determine their role in physiology and pathophysiology. The use of tissue-specific or cell type–specific overexpression or deficiency of SRs in mice may be of great value.

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