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Review

Scavenger receptor family proteins: roles for atherosclerosis, host defence and disorders of the central nervous system

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Abstract. In this review, we summarize the structure and function of the scavenger receptor family of proteins including class A (type I and II macrophage scavenger receptors, MARCO), class B (CD36, scavenger receptor class BI), mucinlike (CD68/macrosialin, dSR-CI) and endothelial (LOX-1) receptors. Two motifs have been identified as ligand-binding domains: a charged collagen structure of type I and II receptors, and an immunodominant domain of CD36. These structures can recognize a wide range of negatively charged macromolecules, including oxidized low-density lipoproteins, damaged or apoptotic cells, and pathogenic microorganisms. After binding, these ligands can be either internalized by endocytosis or phagocytosis, or remain at the cell surface and mediate adhesion or lipid transfer through caveolae. Under physiological conditions, scavenger receptors serve to scavenge or clean up cellular debris and other related materials, and they play a role in host defence. In pathological states, they mediate the recruitment, activation and transformation of macrophages and other cells which may be related to the development of atherosclerosis and to disorders caused by the accumulation of denatured materials, such as Alzheimer's disease.

Key words. Macrophage; endothelial cell; atherosclerosis; lipoprotein metabolism; cholesterol; apoptosis; host defence; Alzheimer's disease.

Introduction

The scavenger receptor was first discovered in 1979, during attempts to learn how cholesterol from low-density lipoproteins (LDL) accumulates in macrophages in atherosclerotic plaques. Macrophages actively uptake a wide range of negatively charged macromolecules, including modified LDL, and the receptor for acetyl-LDL recognizes the conformation as well as the charge [1–4]. Steinberg and co-workers discovered that oxidized LDL competes for the binding of acetyl-LDL and delivers sufficient cholesterol to produce foam cells [5]. Oxygen radicals which are generated either by chemical or by enzymatic reaction mediate the modification of apo B100 [6–8]. From cross-competition experiments, it is evident that macrophages express several scavenger receptors [9, 10].

Macrophage scavenger receptors type I and II are trimeric 220–250-kD proteins which preferentially bind acetyl-LDL. They have a collagenous domain, which is essential for ligand binding [11–19]. Type I scavenger

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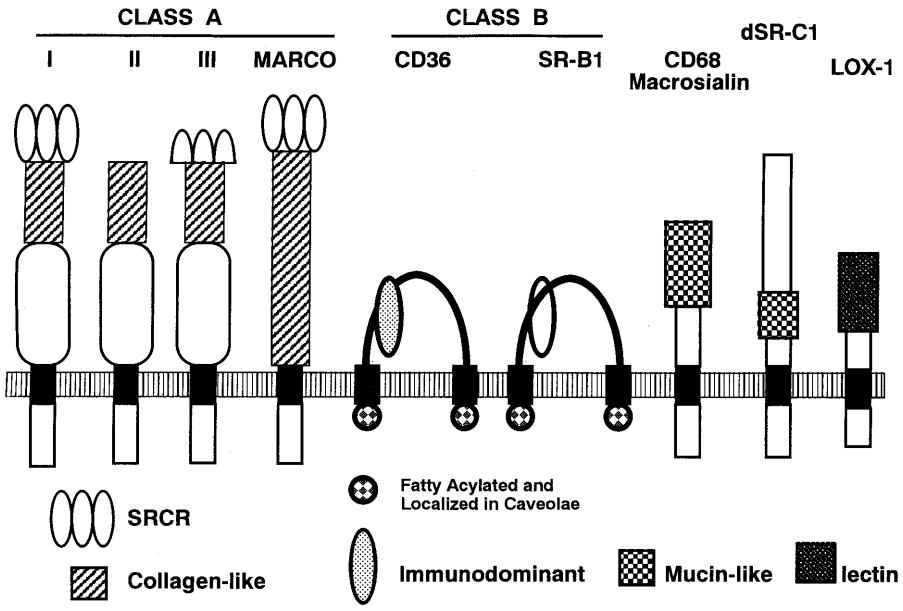

Figure 1. Structure of scavenger receptors. Type I, II and III macrophage scavenger receptors and MARCO belong to class A. All class A receptors are trimeric proteins with a collagenous domain which is essential for ligand binding. Type I, II and III receptors are generated by alternate splicing. A novel isoform, type III, has been identified (P. Gough and S. Gordon, personal communication). Type I and MARCO have C-terminal cysteine-rich domains. CD36 and SR-B1 belong to class B. Both of them have two transmembrane domains and fatty acylated N- and C-terminal cytoplasmic domains. These fatty acylated cytoplasmic domains localize in caveolae. CD36 has an immunodominant domain which is recognized by the anti-CD36 isoantibody. Other scavenger receptors, such as CD68/macrosialin, dSR-CI and LOX-1, are single-membrane spanning proteins. CD68/macrosialin and dSR-CI have a mucinlike structure which may be responsible for the binding of modified LDL. LOX-1 has a structure conserved in the c-type lectin family. All scavenger receptor family proteins except for LOX-1 express on macrophages or their lineage cells. LOX-1 is the first oxidized LDL receptor which expresses on aortic endothelial cells.

receptors have a scavenger receptor cysteine-rich (SRCR) domain, which can be found in a series of cell surface receptors and soluble proteins [20, 21]. Another macrophage receptor, MARCO [22], has collagen-like and SRCR domains, and is classified as a class A receptor.

The expression cloning of oxidized LDL receptors led to the isolation of complementary DNAs (cDNAs) encoding class B scavenger receptors including CD36 [23], and a novel CD36-related protein, scavenger receptor class BI (SR-BI) [24]. Both proteins are concentrated in a specific plasma membrane microdomain, the caveolae. CD36 has been implicated in adhesion, phagocytosis of apoptotic cells and in the metabolism of long-chain fatty acids [25]. SR-BI can interact not only with oxidized LDL but also with acetyl-LDL and normal LDL as well as with high-density lipoproteins (HDL) [26]. Recent studies have indicated the involvement of SR-BI in HDL metabolism in vivo [27–29].

Purification of the macrophage cell surface oxidized LDL receptor led to the identification of CD68 and its mouse homologue macrosialin as an oxidized LDL receptor [30]. CD68/macrosialin has a unique N-terminal mucinlike domain, which cannot be detected in other lamp proteins [31]. A drosophila class C scavenger receptor, named dSR-C1 [32], also has a mucinlike structure. LOX-1 was isolated from an aortic endothelial cell, and encodes an endothelial cell-specific scavenger receptor [33]. The FcgRII-B2 macrophage Fc receptor can also bind oxidized LDL [34]. Figures 1 and 2 indicate the structure and intracellular localization of receptor proteins belonging to this family.

Recently the involvement of the class A receptors in atherogenesis was confirmed using type I and II knockout mice [35]. Scavenger receptors are also expressed in normal brain and in the brain of Alzheimer's patients [36–40]. The aim of this review is to provide a perspective of this multiligand, multifunction receptor system under physiological and pathological conditions.

Structure and function of scavenger receptor family proteins

Class A: collagenous scavenger receptors

Gene structure and expression. Class A receptors are mainly expressed in macrophages and related cells. The human type I and II gene [41] consists of 11 exons, and

two messenger RNA (mRNA) species are generated by alternate splicing from exon 8 to either exon 9 (type II) or exons 10 and 11 (type I).

Type I and II receptor proteins are constitutively present in resident macrophages, including Kupffer cells of the liver, as well as in peritoneal, alveolar and other macrophages [36, 42]. Epidermal Langerhans cells and dendritic cells express very low or undetectable levels, however. In normal brain, type I and II receptors are expressed in the perivascular macrophages surrounding arterioles, called MATO cells, but not in microglial cells [38]. Type I and II receptors are also expressed in sinusoidal endothelial cells of the liver and the adrenal gland [36], and in high endothelial cells of postcapillary venules in lymph nodes [43].

Type I and II receptor mRNA expression is upregulated by macrophage-colony stimulating factor (M-CSF), and downregulated by interferon gamma (IFN-γ), and tumor necrosis factor alpha (TNF-α), transforming growth factor beta (TGF-β) and interleukin-10 (IL-10) [44–46; W. J. S. de Villiers, personal communication]. Type I receptor mRNA can be dramatically induced during monocyte macrophage differentiation. In contrast, type II mRNA can be detected in monocytes, and a mild increase occurs during differentiation [47].

In the THP-1 human monocytic leukemic cell line, the transformation into macrophage-like cells by means of phorbol esters is mediated by the PU-1 motif and a composite AP-1/ets motif. The inhibition of type I and II mRNA expression by IFNγ is mediated by competition between AP-1/ets factors and STAT1 for limiting amounts of CBP and p300 [48–52]. In murine macrophage-like P388D1 cells, AP-1 and GATA elements [53], and a novel macrophage-specific element [54], have been reported to regulate the type I and II receptor expression.

Upregulation of type I and II receptor expression is induced by phorbol ester in cultured smooth muscle cells and fibroblasts, and is mediated by protein kinase C [55–58]. Vascular smooth muscle cells in the arterial intima of cholesterol-fed rabbits express type I and II receptors, but in vitro smooth muscle cells do not [59]. Platelet-derived growth factor-BB (PDGF-BB) and other cytokines synergistically induce type I and II receptor mRNA expression in cultured smooth muscle cells [60–62].

Expression of MARCO [22] in normal animals is limited to marginal zone macrophages in the spleen and lymph nodes, and to peritoneal macrophages. Marginal zone macrophages are positioned in the anatomical compartment where blood leaves the small arterioles and the mononuclear phagocyte system first encounters blood-borne pathogens. When animals are infected with bacteria or injected with lipopolysaccharide (LPS) or BCG, MARCO expression is induced in macrophages of various organs, including Kupffer cells and alveolar macrophages [22].

Structure and function of class A receptors. Class A receptors are trimeric membrane proteins with an N-terminal cytoplasmic domain and glycosylated fibrous coiled coil extracellular domains [12–22]. Electron microscopy using rotary shadowing and negative staining showed that the type I and II fibrous domains are joined by an extremely flexible hinge. The angle between these domains varies from 0 to 180 degrees [63].

Collagenous domain mediates ligand binding. Type I and II receptors have 23 (human) or 24 (bovine, rabbit, murine) uninterrupted Gly-X-Y tripeptide repeats that form a collagenous triple helix, whereas murine MARCO has 89 Gly-X-Y repeats interrupted at one location (residues 174–176] by Ala-Glu-Lys. The C-terminal 22 amino acids of the collagen-like domain, which contain five basic amino acids that are highly conserved among animal species, is essential for both oxidized LDL and acetyl-LDL binding [16]. Substitution of Lys 337 in the centre of this lysine cluster to alanine abolished acetyl-LDL binding. Oxidized LDL-binding activity was abolished by an additional substitution of the adjacent lysine residue. Based on these findings and crystallographic data of the collagen backbone, a computer-generated model of the ligand-binding domain was built as a 'charged collagen' molecule. In this model, a coiled groove surrounded by lysine 337 side chains just reaches the centre of this positively charged three-turn coil space, where negatively charged macromolecules, including the apoB100 fragment of

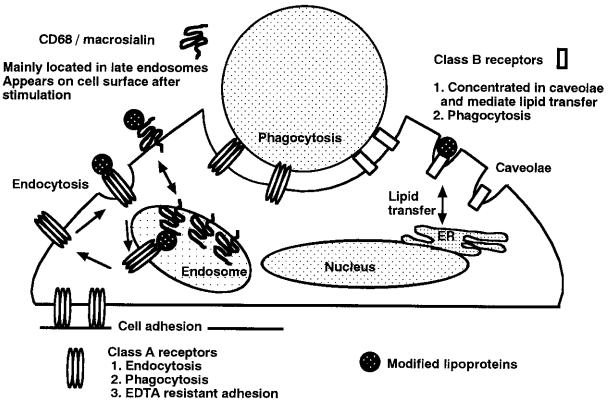

Figure 2. Intracellular localization and functions of scavenger receptors. Class A receptors are mainly located on the cell surface and endosomes. These receptors relate to phagocytosis, receptor-mediated endocytosis and cation-independent cell adhesion of macrophages. Class B receptors are richly present in the caveolae and may mediate lipid transfer. Class B receptors may also relate to phagocytosis. CD68/macrosialin is located mainly in endosomes, and after stimulation it appears on the cell surface. Their reported intracellular pathways are also indicated.

modified LDL, polyglutamic acid and polyinosinic acid can bind. This charged collagen structure was synthesized by cross-linking of three synthetic peptide chains at the C-terminus or N-terminus. The triple-stranded peptide can bind acetyl-LDL, but a single-stranded peptide cannot [64, 65].

MARCO has a larger collagen-like stretch, and at the C-terminal end there is a GQKGEKGQK sequence, which is closely related to charged collagen structure of the type I and II receptors.

The scavenger receptor cysteine rich domain. Analysis of the C-terminal cysteine-rich domain of the type I receptor helped to define a previously unrecognized, ancient and highly conserved family of cysteine-rich protein domains, named scavenger receptor cysteine-rich (SRCR) domains [20, 21]. Type II receptors lack the SRCR domain, which is present in MARCO. More than 50 SRCR superfamily proteins including CD6 have been described. In the case of CD6, the SRCR domain mediates the binding of an immunoglobulin-like domain of the activated leukocyte adhesion molecule [66]. The SRCR domain in the scavenger receptor may mediate some other ligand recognition mechanism.

α-Helical coiled coil domain. Type I and II receptors have a 163-amino acid α-helical coiled coil domain. Doi et al. [16, 67] showed that this domain is essential for both trimer formation and acid-dependent ligand dissociation. Studies using immunoelectron microscopy indicate that acetyl-LDL dissociates within an endosomal compartment, and the type I and II receptor returns to the cell surface via the trans-Golgi apparatus [37]. A histidine (His 260)-disrupting leucine or isoleucine heptad repeats are essential for this acid-dependent ligand dissociation. Substitution of His260 into Ala abolishes the ligand dissociation at acidic pH. In acidic conditions, protonation of His 260, which is located adjacent to the ligand binding collagen-like domain, causes a conformational change in the α-helical coiled coil domain, which in turn causes allosteric ligand dissociation. The α-helical coiled coil domain also plays a role in macrophage adhesion. The monoclonal antibody 2F8, which can inhibit divalent cation-independent murine macrophage adhesion [68], recognizes murine type I and II receptors. 2F8 binds the α-helical coiled coil domain (S. Gordon et al., unpublished observation). It is not yet clear whether the binding of 2F8 directly inhibits adhesion or has some allosteric effect on adhesion.

The cytoplasmic domain. The predicted secondary structure of the cytoplasmic domain suggests the presence of a tight turn motif consisting of residues 12 to 18 of the bovine type I receptor. The deletion of this motif results in a marked reduction of cell surface expression of type I receptor [69]. Substitution of Val21 and Phe22 by Ala markedly reduced the internalization index, suggesting that these residues may be essential for the interaction of cytoplasmic proteins (T. Doi, unpublished observations).

Functions of the class A receptors studied in knockout mice

Binding and endocytosis of multiple ligands. Type I and II receptor knockout mice [36] grow normally and are fertile. Peritoneal macrophages of homozygote mice have less than 20% activity of normal acetyl-LDL degradation. In contrast, these macrophages still have significant oxidized LDL degradation activity, 40–70% the activity of the normal control. The uptake of advanced glycation product bovine serum albumin (BSA) by type I and type II receptor deficient macrophages was about 1/3 that of normal control levels (S. Horiuchi, unpublished observation). The specificity of oxidized LDL-binding activity remaining in type I and II receptor deficient macrophages is similar to the reported specificity of macrosialin/CD68 [70]. Acetyl- and oxidized LDL are rapidly cleared by the liver in mice deficient for type I and II receptors, and there was no difference in negative mice as compared with control mice with respect to clearance of acetyl-LDL from plasma [71]. The average size of atherosclerotic lesions in type I- and II-deficient mice was decreased (see below).

Phagocytosis of apoptotic cells. Uptake of steroid-treated apoptotic thymocytes by normal thymic macrophages is partially inhibited by the monoclonal anti-type I and II receptor 2F8 antibody [72]. Type I and II receptor deficient macrophages also show a 50% reduction in phagocytosis of apoptotic thymocytes in vitro. In contrast, type I and II receptors do not mediate the uptake of oxidized red blood cell phagocytosis [73]. Other classes of receptors are also known to mediate phagocytosis of apoptotic cells and oxidized red blood cells [74–76].

Cell adhesion. The antimurine type I and II receptor monoclonal antibody, 2F8, inhibits divalent cation-independent adhesion of murine macrophages to plastic [68]. Peritoneal macrophages obtained after thioglycolate stimulation adhere tightly to a plastic tissue culture plate after overnight incubation, and many protrusions and distortions of shape are apparent. Macrophages deficient for type I and II receptors are still round in shape and less adhesive after a single overnight incubation (12–20 h). It takes more than 40 h for type I and II deficient macrophages to adhere to a plastic dish and change shape [36]. The adhesion mediated by the type I and II receptors is prominent in an early phase of this process, less than 24 h after initiation of cultivation.

Host defence function. Macrophages play an important role in the host defence system in both normal and pathological processes [77]. Type I and II receptors can

bind both bacterial endotoxin [78] and gram-positive bacteria, and recognize lipoteichoic acid [79, 80]. The binding of endotoxin to type I and II receptors did not mediate endotoxin signalling, and this pathway may serve as a route for the cleaning up of excess endotoxin [81]. Homozygote type I and II receptor deficient mice are more susceptible to injection of macrophage tropic pathogens, *Listeria monocytogenes* and herpes simplex virus type 1 (HSV-1). The clearance of *L. monocytogenes* from plasma did not change in deficient mice, and the number of microorganella in the host organ was increased [36]. MARCO can also bind bacteria and is implicated in bacterial clearance from plasma [22].

Type I and II receptors in the brain. In normal brain cortex, type I and II receptor proteins and mRNA are expressed by the perivascular macrophage lineage cells surrounding arterioles [39], known as MATO cells [80]. MATO cells mediate the uptake of macromolecules, including modified LDL, horseradish peroxidase and ferritin injected either into the blood or into the cerebral ventricles. Accumulation of scavenged material with aging results in the formation of honeycomb-like foam cells and the narrowing of the lumen of arterioles in the brain cortex. In type I and II receptor deficient mice, the development of MATO cells is retarded by up to 4 weeks [82]. In contrast, resident microglia do not express type I and II proteins. They display a specialized, apparently downregulated, phenotype compared with other macrophage populations. Expression of type I and II receptors is upregulated by intracerebral administration of LPS or cytokines [83–85].

CD36 family/class B receptors

Expression. CD36 was initially characterized as a hydrophobic membrane glycoprotein on the surface of platelets [86]. CD36 is expressed in capillary endothelial cells, mammary secretory epithelial cells, differentiated adipose cells, B cells and several types of tumour cells. In the monocytic and megakaryocytic lineage, expression is upregulated during differentiation, whereas in the erythrocytic lineage CD36 is expressed by erythroblasts. Expression of monocyte CD36 is regulated by M-CSF and IL-4 [87] and through adherence to activated endothelial cells [88]. Most capillary endothelial cells express CD36, but CD36 is not expressed by endothelial cells of large blood vessels [89, 90]. Analysis of the CD36 gene promoter revealed the importance of the PEBP2/CBF transcription factor for constitutive expression [89].

Within the cell, CD36 is concentrated in plasma membrane microdomains called caveolae [90]. Caveolae have been implicated in a number of transport and signalling phenomena, and recent studies suggest that the caveolae participate in intracellular cholesterol transport and the efflux of unesterified cholesterol [91, 92].

SR-BI is expressed most abundantly in the adrenal gland and ovary, where it is upregulated by adrenocorticotropic hormone (ACTH), human chorionic gonadotropin (hCG) and estrogen and downregulated by dexamethasone, and in the liver where its expression is suppressed by estrogen [26, 28, 94, 95]. In addition to these organs, CLA-1, a human homologue of SR-BI, is also expressed in circulating monocytes and to a lesser extent in differentiated macrophages [95]. SRB1, like CD36, is also concentrated in caveolae [94].

Structure and function of CD36 family/class B receptors

Structure of CD36 and SR-BI. Human CD36 has two transmembrane domains, and several cysteines in the N- and C-terminal cytoplasmic domain are palmitoylated [96–98]. A hydrophobic sequence (amino acids 184–204) has been proposed to be membrane associated or alternatively to form hydrophobic pockets. The anti CD36 isoantibody generated in a CD36 deficient subject [97, 98] recognizes a highly antigenic structure, called the immunodominant domain (residues 155–183).

Murine SR-BI has essentially the same structural characteristics as CD36. SR-BI also has two transmembrane domains and is fatty-acylated by both palmitate and myristate at Cys462 and Cys470 in the C-terminal cytoplasmic domain [24, 95]. SR-BI is copurified and colocalizes with caveolin-1. Dual palmitoylation and myristoylation is necessary and sufficient to localize p59fyn and endothelial NO synthase to caveolae, and may be related to the localization of CD36 and SR-BI to caveolae [91, 95].

Lipid and lipoprotein binding. Expression of murine or human CD36 in CD36-deficient cells results in specific and high-affinity binding of oxidized LDL, followed by internalization and degradation [23, 98]. Using human-mouse chimeric constructs and neutralizing antibodies, the immunodominant domain has been identified as the oxidized LDL-binding site [98]. CD36 also binds to long-chain fatty acids [97a]. CD36 expression by endothelial cells is upregulated in tissues involved in fatty-acid transport and metabolism [99].

CD36 deficiency can be seen in about 3% of the Japanese population, and 0.3% of Caucasians, who are phenotypically normal [100–102]. The type I variant is characterized by a platelet and monocyte CD36 deficiency, whereas type II is not expressed on the surface of platelets but is present on monocytes. Type I individuals develop anti-CD36 antibody after blood transfusion or during pregnancy. Monocyte-derived macrophages from type I subjects have a reduced capacity to bind and internalize oxidized LDL [103]. The binding and adhesion function of CD36-deficient platelets remains normal [104].

Cytoadhesion and phagocytosis. CD36 is implicated in platelet adhesion and aggregation, cytoadherence to *Plasmodium falciparum*-infected erythrocytes [105], and in phagocytosis of apoptotic cells and the outer segment of shed photoreceptor [25]. Red blood cells infected with *P. falciparum* are sequestered within the microvasculature, which contributes to the survival of the parasite by preventing clearance in the spleen. CD36 mediates the binding of infected erythrocytes, and the anti-CD36 monoclonal antibody against the immunodominant domain can inhibit this process [106]. Infected red blood cells express PfEMP1 protein [107], which mediates the binding of capillary endothelial cells to CD36. The binding of infected erythrocytes or anti-CD36 antibodies can induce an oxidative burst of monocytes and platelet activation [108, 109].

COS cells transfected with CD36 cDNA can phagocytose apoptotic cells [98]. The immunodominant domain is essential for the phagocytosis of apoptotic polymorphonuclear cells. The recognition of anionic phospholipids including phosphatidylserine expressed on the outer surface of apoptotic cells may mediate phagocytosis [110]. Croquemort, a *Drosophila* homologue of the CD36/SR-BI family of proteins expressed in hemocyte/macrophage, recognizes apoptotic cells [111].

SR-BI as a receptor for HDL. SR-BI can mediate the binding not only of oxidized LDL but also acetyl-LDL, normal LDL and HDL [27]. SR-BI are receptors for anionic phospholipids [27a]. SR-BI mediate the high-affinity binding of HDL and selective cholesterol uptake from HDL by a mechanism that is distinct from the endocytotic pathway [27, 28]. The binding of HDL to SR-BI resulted in the intracellular accumulation of HDL-derived cholesterol esters without internalization or degradation of 125I-apolipoproteins [27, 105]. Tissue distribution of SR-BI, which is predominantly expressed in the liver, adrenal gland and ovary, is compatible with a role in the transport of HDL-derived cholesterol [93]. SR-BI localizes in plasma membrane caveolae and is copurified with caveolin 1, and may mediate lipid transfer through caveolae [94]. Mice deficient for apo A-I overexpressed SR-BI, and further studies about the relationship between apo A-I and SR-BI gene expression will be needed. Mice strains deficient for apo A-II, apo E, LDL receptor or cholesterol ester transfer protein did not exhibit any change in SR-BI mRNA expression [112]. Adenovirus-mediated overexpression of SR-BI in mouse liver results in a marked reduction of plasma HDL and an increase in biliary cholesterol [29]. A targeted mutation in the murine gene encoding the HDL receptor reveals its key role in HDL metabolism [113]. CLA-1, a human homologue of SR-BI, can bind apoptotic thymocytes, and this binding is inhibited by liposomes containing phosphatidylinositol or phosphatidylserine like CD36 or CD68 [95].

CD68/macrosialin as a mucinlike scavenger receptor family protein

Various types of macrophages, including mouse peritoneal macrophages, foam cells in rabbit atherosclerotic lesions, carrageenan granulomas and rat liver Kupffer cells have a '95-kDa oxidized LDL receptor' [114, 115]. Ramprasad et al. [30] purified this protein from RAW264.7 mouse macrophage cells and indicated that it is identical to macrosialin, the mouse homologue of human CD68 [31].

Murine macrosialin is widely expressed by most macrophages, as well as dendritic and osteoclasts, and is mainly present in late endosomes [116]. Fluorescence-activated cell sorting (FACS) analysis revealed that only 4% of CD68 molecules are localized to the surface of THP-1 human cultured monocytic leukaemic cells. However, 10–15% of total CD68/macrosialin is present on the surface of thioglycollate-elicited peritoneal macrophages, and more than 20% of all CD68 molecules, 4000–8000 molecules, are on the surface of a single phorbol ester-treated THP-1 cell [117].

Macrosialin/CD68 is a heavily glycosylated transmembrane protein of 87–115 kDa, which is highly and specifically expressed by tissue macrophages, and has significant homology to the lysosomal associated protein (lamp-1) family [34]. The predicted polypeptide sequence of murine macrosialin consists of 326 residues including a hydrophobic signal sequence, extracellular domain (271 amino acids), a transmembrane domain and a 10-amino acid cytoplasmic domain. An additional cDNA containing only two amino acid cytoplasmic domains has been cloned, but its physiological function remains obscure [31]. There are nine potential N-glycosylation sites, and N-linked sugars that account for 21 kDa. The polypeptide backbone is only 35 kDa, whereas the observed mature glycoprotein is between 87 and 115 kDa. The extracellular domain has numerous runs of serine, threonine and proline, which could act as sites for attachment for O-linked sugars, and approximately 40% of the molecular mass is due to O-linked sugars. Cell surface expression of CD68/macrosialin increases upon the activation of macrophages, and upon activation extensive remodelling of N- and O-linked sugars occurs involving the acquisition of numerous terminal sialic acid residues and polylactosaminoglycans [32]. The mucinlike structure of CD68/macrosialin is not found in other lamp family proteins.

The mucinlike domain may be related to binding ability. The specific binding at 4 °C of ^{125}I-oxidized LDL in phorbol ester-treated THP-1 cells is inhibited 30 to 50% by the anti-CD68 monoclonal antibodies EBM11 or KP1 [117]. In murine macrophages, Macrosialin/CD68 is one of the candidate receptors which are responsible for the uptake of oxidized LDL [70].

dSR-CI: a macrophage specific scavenger receptor (class C) of *Drosophila melanogaster* [32]

A *Drosophila* cDNA, dSR-CI, was cloned using fluorescent-labelled DiI-acetyl LDL as a probe. Expression of dSR-CI was restricted to macrophage/haemocytes during embryonic development. When expressed in mammalian cells, dSR-CI expressed high-affinity binding to acetyl-LDL and mediated degradation. Acetyl-LDL binding to Chinese hamster ovary (CHO) cells transfected with dSR-CI was inhibited by maleyl-BSA, polyinosinic acid, poly d(A5G37) and the polysaccharide dextran sulfate by $>85\%$. Poly(d-glutamic acid) also inhibited dSR-CI, although it is not a class A type I and II receptor inhibitor. The dSR-CI clone encodes a 629-residue polypeptide including a 20-amino acid putative signal sequence, two complement control protein domains, a MAM family extracellular domain, a spacer domain, a somatomedin B-like domain, a serine/threonine-rich domain (129 residues), a second spacer domain, a transmembrane domain and a 64-residue cytoplasmic domain. Threonine and serine comprise 55 and 12% of the serine/threonine-rich domain, respectively, which is reminiscent of both vertebrate and *Drosophila* mucins. CD68/macrosialin also has a mucinous structure, and this structure may be responsible for the binding of modified LDL.

LOX-1: an endothelial cell-specific scavenger receptor [33]

Sawamura et al. [33] cloned the LOX-1 cDNA from a bovine endothelial cell cDNA library by expression cloning using fluorescent labelled oxidized LDL. LOX-1 binds, internalizes and degrades oxidized LDL but not native or acetyl-LDL. Northern blot analysis indicated that the mRNA is expressed in the aortic intima and vascular-rich organs. Reverse transcription-polymerase chain reaction (RT-PCR) indicated that human LOX-1 mRNA is expressed in normal aorta and atheromatous lesions, and in cultured aortic endothelial cells. The bovine LOX-1 mRNA 3′ noncoding region has seven mRNA-destabilizing AUUUA signals. Activation of cultured bovine aortic endothelial cells by TNF-α or phorbol ester results in upregulation of LOX-1 mRNA expression and cell surface protein expression. Bovine LOX-1 has 270 amino acid residues with a hydrophobic 26-amino acid transmembrane domain. Although the calculated M_r of this protein is 30,872, the M_r of mature protein estimated by SDS-polyacrylamide gel electrophoresis (PAGE) is 50K. This discrepancy may result from glycosylation of four potential N-linked glycosylation sites located on C-terminal domain [34]. In the N-terminal cytoplasmic domain, there are several potential phosphorylation sites; at Thr21 and Ser28 for protein kinase C, and at Thr2 for casein kinase II. Bovine and human LOX-1 have a structure that is conserved in the C-type lectin family [118]. CHO cells expressing LOX-1 can bind, internalize and degrade oxidized LDL efficiently, but they do not take up acetyl-LDL. The binding of oxidized LDL is suppressed by polyinosinic acid and carrageenan but not by native LDL, acetyl LDL maleyl-BSA or fucoidan (N. Kume et al., personal communication). Two independent monoclonal antibodies against LOX-1 can inhibit oxidized LDL binding to cultured bovine aortic endothelial cells by 50 to 70%.

A macrophage Fc receptor for IgG, FcgRII-B2, also binds oxidized LDL [34]

Murine FcgRII-B2 was identified as a cell surface binding site for oxidized LDL by expression cloning using rhodamine-labelled oxidized LDL as a probe. Approximately 15% of the internalized oxidized LDL was degraded. FcgRII-B2 is a 50-kDa macrophage-specific glycoprotein with a single transmembrane domain, which mediates immune complex uptake via recognition of the Fc region of IgG [119]. However recent analysis revealed that human Fcg receptor does not express oxidized LDL receptor activity [120].

Scavenger receptors in disease

Atherosclerosis

Scavenger receptors were originally implicated in the pathological deposition of cholesterol in the foam cells of atherosclerotic lesions through receptor-mediated uptake of modified LDL [121, 122]. Multiple functions of scavenger receptors, including endocytosis, phagocytosis, and adhesion and signal transduction triggered by the binding and uptake of modified LDL may also be involved in the development of atherogenesis.

Atherosclerotic lesions in type I and II receptor knockout mice [36]. Type I and II receptor proteins [17, 42] and mRNA [123, 124] are expressed in macrophages in atherosclerotic lesions. We mated type I and II deficient mice to atherosclerosis model LDL receptor deficient mice or apolipoprotein E (apo E) deficient mice [123]. With apo E deficiency, plaque formation was observed without a high cholesterol diet. The plasma cholesterol level of the type I and II/apoE double knockout mice was slightly higher than the apoE single knockout mice. However the average size of the atherosclerotic lesions decreased by 60%. In type I and II/LDL receptor knockout mice, a 1.25% high cholesterol diet was started at 10 weeks of age, and the lesion size was smaller than in LDL receptor single knockout mice, but the difference (a decrease of 25%) was less prominent. MARCO and macrosialin were expressed by the macrophages in the atherosclerotic lesion in knockout mice [125].

Although the plasma cholesterol level and plasma clearance of acetyl- or oxidized LDL in type I and II deficient mice did not differ from that of wild-type controls, the lesion size diminished. This result is compatible with the hypothesis that modification of LDL which accumulates in the vessel wall is essential for lesion formation.

Oxidized LDL is known to stimulate macrophage proliferation through the uptake mediated by type I and II receptors. The signal is mainly mediated by the uptake of lysophosphatidyl choline [124].

Other scavenger receptors and atherosclerosis. The ligand specificity of oxidized LDL receptor that remains in type I and II receptor deficient macrophages is similar to that of CD68 [70]. CD36 is also expressed both in the monocytes and in the core of advanced lesions, suggesting that this receptor can also mediate oxidized LDL uptake. Recent identification of SR-BI as an HDL receptor [28, 30] suggests that SR-BI may rather involve reverse cholesterol transport. Further study will be necessary to clarify this point.

Scavenger receptors mediate the phagocytosis and uptake of apoptotic cells. During macrophage transmigration, macrophages can uptake matrix proteins digested by macrophage metalloproteases, and LDL attached to the matrix can be concurrently taken up. Many apoptotic cells are found in atherosclerotic lesions and macrophages uptake these cells by scavenger receptors, and this process also provides cholesterol to macrophages.

Scavenger receptor expression in smooth muscle cells and endothelial cells. Type I and II receptor expression can be induced in smooth muscle cells by the synergic effects of cytokines, which may cause the uptake of modified LDL in the lesion [55–61]. Aortic endothelial cells are most sensitive to the toxicity of oxidized LDL. Many effects of oxidized LDL are mediated by the lipid components of oxidized LDL which can enter the cell by the scavenger receptor-mediated system. Minimally modified LDL [126] can mediate the stimulation of various cytokines and chemokines by endothelial cells. If LOX-1 can take up these minimally modified LDL species, this receptor may be involved in the initial events of atherosclerosis.

Scavenger receptors in Alzheimer's disease and other disorders of the central nervous system

Microglial cells can bind and internalize aggregated β-amyloid protein, and microglia surrounding senile plaques of Alzheimer's disease express type I and II receptors [39]. Type I and II receptors may mediate rodent and human monocyte binding to β-amyloid fibril-coated surface, with subsequent secretion of reactive oxygen species [39, 40, 127]. Activated microglias express the receptor for advanced glycation end product (AGE), which can be activated by AGE-modified β-amyloid protein and other cytokines [128]. Because type I and II receptors can also mediate the adhesion and uptake of AGE-modified proteins [129], they may also be involved in the processing of AGE-modified β-amyloid proteins. The expression of type I and II receptors in the brain, including the hippocampal areas CA1 and CA3, is also upregulated after kainic acid treatment [130] and after ischaemia caused by cerebrovascular disease [M. Honda et al., unpublished].

Scavenger receptors are expressed in perivascular MATO cells in normal brain [38]. With aging, MATO cells accumulate honeycomb-like inclusion bodies which emit fluorescence. The enlargement of MATO cells may result in the narrowing of blood vessels. These changes may also affect the blood flow in the brain cortex.

Scavenger receptors in host defence

Scavenger receptors are involved in both host defence [25a] and sequestration, and survival of pathogens [25, 78]. As described in previous papers, type I and II receptors can bind endotoxin [78], Gram-positive microorganisms and lipoteicoic acids [79]. Endotoxin binding to scavenger receptors does not transmit signals, suggesting that this is a disposal system for toxic, pathogenic substances. MARCO can bind *Escherichia coli* and *Staphylococcus aureus* [22], and is implicated as a bacterial docking site in lymphatic tissue. Type I and II receptor deficient mice are susceptible to *Listeria monocytegenes* and HSV-1 infection due to ineffective killing of pathogens in monocytes/macrophages. This suggests that scavenger receptors are not only involved in pathogen uptake but also in killing activity in endolysosomal compartments [35].

Vascular endothelial cells expressing CD36 mediate the sequestration of *P. falciparum*-infected erythrocytes, which results in the escape of the pathogen from the splenic surveillance [25]. In spleen, MARCO and other scavenger receptors may mediate surveillance. *Plasmodium* may use the existence of scavenger receptor family members in nonlymphatic tissue to escape surveillance.

The scavenger receptor in lung disease

In humans type I and II receptors are most abundantly expressed in the lung. Expression is suppressed in alveolar macrophages obtained from patients with alveolar proteinosis. Type I and II receptors can mediate the uptake of crocidolite asbestos, which is the causative agent for asbestosis [131].

Involvement in xanthoma; familial overexpression of type I and II receptors with generalized xanthomatosis

Extensive xanthelasmas and planar xanthomas in the absence of hyperlipidaemia has been reported in two siblings, and was characterized by an overexpression of type I and II receptor protein and mRNA in monocytes and macrophages [132]. Monocytes from family members displayed an unusual phenotype characterized by increased adhesion and rapid maturation into large macrophages which overaccumulated lipids. This is the first demonstration of an inherited abnormality in scavenger receptor expression and its occurrence in association with planar xanthomas. The phenotype is not linked to polymorphisms of the type I and II receptor gene, suggesting that this overexpression may be caused by an abnormality in factors regulating the expression of this gene (A. Minnich et al., unpublished observation). Expression of type I and II receptors and CD68 in foam cells of verruciform xanthoma has been also reported [133]. Scavenger receptors are actively involved in the formation of xanthoma lesions.

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