Scavenger receptors in innate immunity

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Scavenger receptors (SR) are expressed by myeloid cells (macrophages and dendritic cells) and certain endothelial cells. They play an important role in uptake and clearance of effete components, such as modified host molecules and apoptotic cells. They bind and internalise micro-organisms and their products including Gram-positive bacteria (lipoteichoic acid), Gram-negative bacteria (lipopolysaccharide), intracellular bacteria and CpG DNA. SR can alter cell morphology and their expression is affected by various cytokines. SR are involved in lipid metabolism and bind modified low-density lipoproteins.

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Abbreviations

Ac-LDL	acetylated LDL
CL-P1	collectin from placenta receptor 1
DC	dendritic cells
dSR-C I	*Drosophila* SR-C I
EC	endothelial cells
LDL	low-density lipoproteins
LOX-1	lectin-like oxidised LDL-receptor 1
LPS	lipopolysaccharide
LTA	lipoteichoic acid
MARCO	MØ receptor with a collagenous structure
MØ	macrophages
PRR	pattern-recognition receptors
PS	phosphatidylserine
SR	scavenger receptors
SR-CL I	SR with C-type lectin I
SRCR domain	SR cysteine-rich domain
TLR	Toll-like receptors

Introduction

Our knowledge of the family of scavenger receptors (SR) has grown considerably since the initial characterisation of the SR of macrophages (MØ) (these SR are now termed SR-A I and SR-A II). SR encompass a broad range of molecules involved in receptor-mediated endocytosis of selected polyanionic ligands, including modified low-density lipoproteins (LDL) [1]. Several of these receptors are also involved in phagocytosis of apoptotic cells and of bacteria, as well as in cell adhesion [2]. These transmembrane receptors vary markedly in structure, including molecules with collagenous, cysteine-rich, C-type-lectin or other domains. Related molecules have been discovered in *Drosophila melanogaster*, where they have been implicated in clearance of apoptotic cells and in innate immunity [3].

For the present, it is useful to retain the term 'SR' to classify molecules that share related functions. In the past year our knowledge of structures and regulation of known SR has extended, and several reviews of earlier work have been published [4•,5•]. In addition, novel receptors have been described, with related functions.

Although the role of SR in atherogenesis continues to drive much of the research in this area, their role in host defence has received increasing attention. In this review of recent work, we emphasise the role of SR in innate immunity. This should be seen in the context of ongoing developments in the study of opsonin-mediated phagocytosis and of other opsonin-independent pattern-recognition receptors (PRR) — Toll-like receptors (TLR), lectins, CR3, CD14 and so on. We do not here consider other cell-interaction molecules with cysteine-rich domains [1], or endocytic receptors for α2-macroglobulin-proteinase [6] or haemoglobin–haptoglobin complexes [7••], that play analogous roles in homeostasis.

MØ and innate immunity

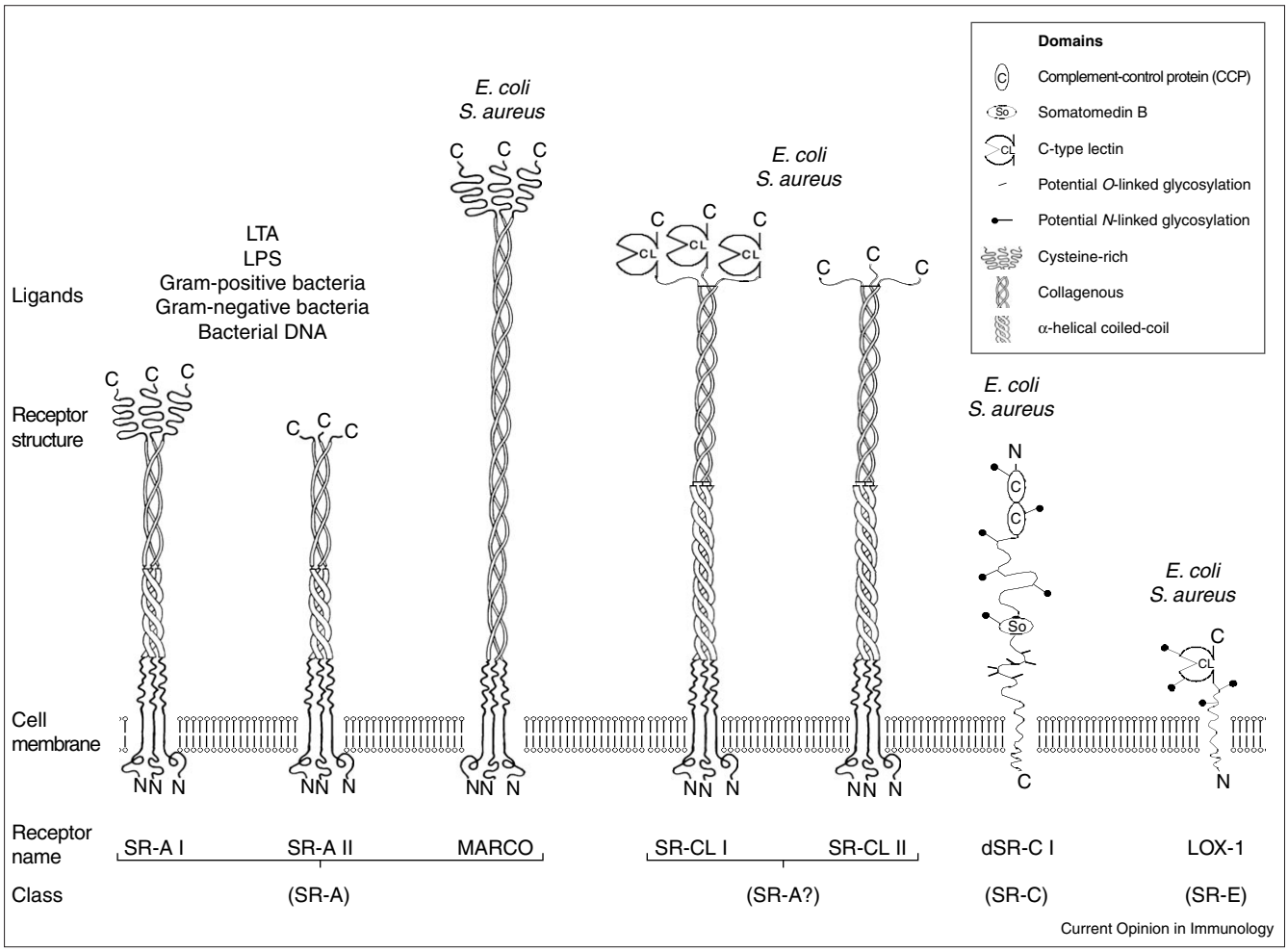
MØ are widely distributed in lympho-haemopoietic and other organs, where they play a role in tissue homeostasis as specialised phagocytic cells able to produce trophic, cytotoxic and regulatory molecules that mediate inflammation and repair [8•]. By virtue of their presence at portals of entry as in the lung and gastro-intestinal tract, they provide a first line of defence against microbial invaders.

Dendritic cells (DC) of myeloid origin, such as Langerhans cells in skin and epithelia, are closely related to tissue MØ and express many of the same genes; they are specialised for capture and delivery of antigens to secondary lymphoid organs, and for antigen processing and presentation — in association with MHC molecules — to naive T lymphocytes.

MØ and DC express a range of PRR involved both in pathogen recognition and in the induction of adaptive immunity; their uptake of apoptotic and necrotic cells can result in antigen destruction or cross-presentation to T cells, depending on the nature of the phagocytic cell and microenvironment [9•]. The cellular mechanisms involved in phagocytosis, intracellular signalling, altered gene expression and activation of immunological effector functions are under intensive study. Our understanding of the contributions of SR to these processes is still limited. Recent work has begun to explore their role in bacterial uptake and cytokine responses, and the possible significance of the involvement of SR and similar receptors in the phagocytosis of apoptotic cells [10•].

Although not conventionally regarded as part of innate immunity, some of the features of atherogenesis can be considered to represent a modified form of inflammation (even without accepting a role for potential pathogens in the disease process) and provide relevant information in regard to functions of SR.

Figure 1



This figure shows, schematically, those SR that have been implicated in microbial recognition. SR-CL I is very similar, if not identical to CL-P1, a recently described collectin-like scavenger receptor. Adapted from Peiser and Gordon [2].

Interactions of SR with bacteria

Figure 1 illustrates the range of SR that have been implicated in bacterial uptake by MØ, DC and/or endothelial cells (EC). The work hitherto has been done mainly with model Gram-negative (*Escherichia coli*) and Gram-positive (*Staphylococcus aureus*) organisms; the absence of bacterial binding by other SR, not discussed here, may be due to lack of study rather than their inability to interact with micro-organisms. Below, we briefly summarise knowledge of particular SR and emphasise recently published studies.

SR-A

SR-A I and SR-A II

These classical SR-A molecules differ in regard to the presence or absence of the SR cysteine-rich domain (SRCR domain), which still has no known function [4•]. The binding site for selected polyanionic ligands has been attributed to the collagenous domain, whereas the coiled-coil domain is important for receptor trimerisation. The cytoplasmic tail has no known internalisation motifs, but contains potential protein kinase C (PKC)-interaction sites. These receptors are expressed on most populations of tissue MØ, but not monocytes or neutrophils; *in-vitro*-cultured DC express SR-A I and II, as does sinusoidal endothelium, for example in liver.

Hampton and colleagues [11] were the first to implicate SR-A in the binding of lipid A, a component of lipopolysaccharide (LPS). Subsequently, Dunne *et al.* [12] demonstrated that SR-A binds Gram-positive bacteria, in particular lipoteichoic acid (LTA). Greenberg and co-workers [13] showed that different LTA structures have different specificity for SR-A, depending on the negative charge and its distribution. Similarly, Shnyra and Lindberg [14] showed that binding of LPS by undefined SR on Kupffer cells and EC depends on anionic groups in the lipid A moiety.

The production of SR-A I,II$^{-/-}$ mice (i.e. lacking SR-A I and SR-A II) by Suzuki and associates [15] made it

possible to examine mouse survival and systemic release of cytokines following infection *in vivo*; these knockout mice are more susceptible to *Listeria monocytogenes*, with increased bacterial burdens in liver and spleen. Similarly, Thomas *et al.* [16•] showed enhanced susceptibility to *S. aureus*, with impaired clearance from the peritoneal cavity; these studies dealt with initial responses in unprimed mice. Haworth *et al.* [17] found that *Bacillus Calmette–Guérin* (BCG)-primed SRA I,II$^{-/-}$ animals formed normal granulomata, but were more susceptible to additional LPS challenge and septic shock, in part mediated by TNFα. These studies were consistent with a host-protective role for SR-A, perhaps in LPS clearance; this report, however, needs to be reconciled with other studies on shock [18] and granuloma formation [19].

In order to examine the role of SR-A in bacterial uptake directly, Peiser *et al.* [20•] used a FACS-based *in vitro* assay with different strains of *E. coli*, as well as *S. aureus*, and bone-marrow-culture-derived MØ (BMDM) from wild-type and SR-A I,II$^{-/-}$ mice. This study showed that SR-A contributed variably to the binding of different bacteria, depending on the microbial strain, source of MØ and their in *vitro* culture conditions, which influence SR-A expression. BMDM generated in L-cell-conditioned medium — a source of M-CSF (MØ-colony-stimulating factor) — expressed high levels of SR-A and showed a greater contribution from SR-A in *E. coli* uptake than biogel-polyacrylamide-elicited peritoneal MØ, which express a wider range of receptors. The microbial ligands for SR-A have not been determined; SR-A has also been shown to bind bacterial CpG DNA, but it is not required for TNFα release, unlike TLR [21].

In MØ that express SR-A I/II and a range of other PRR and phagocytosis-enhancing factors, bacterial binding results in rapid ingestion; SR-A-transfected fibroblast-like cells bind bacteria efficiently, but uptake is inefficient. The role of SR-A I/II in intracellular signalling and actin assembly is unexplored, as are its roles in bacterial killing. Limited studies have begun to investigate its ability to induce adaptive immune responses to SR-A ligands [22,23].

Apart from M-CSF, cytokine regulation of SR-A expression and phagocytic functions is poorly understood. LPS itself has opposite effects on SR-A expression in different populations of MØ [24], perhaps acting via induced cytokines such as TNFα.

MARCO

MARCO (MØ receptor with a collagenous structure) is a distinct type-A SR, with collagenous and SRCR domains, but is very similar to SR-A I/II in its overall structure (Figure 1) [25]. The mouse molecule is able to bind Gram-positive and Gram-negative bacteria, but is normally expressed by only a subpopulation of MØ — for example in spleen marginal zone and freshly harvested peritoneal populations. It is rapidly induced in most tissue MØ by BCG infection, bacterial sepsis, or treatment with bacteria or LPS *in vitro* [26•].

Species differences may account for differences in MARCO expression (e.g. by alveolar MØ) among mice, humans and hamsters. Noninfectious stimuli (e.g. particulates, joint inflammation and murine atherosclerotic plaques) can also upregulate its expression. The human MARCO molecule binds bacteria, but does not take up acetylated LDL (Ac-LDL), unlike the mouse molecule [27•]. The role of MARCO in host resistance to infection *in vivo* awaits studies in knocout mice. Ectopic expression *in vitro*, in nonmyeloid cell lines, induces dramatic changes in cell shape and induces the formation of lamellipodia and long dendritic processes [28]. These changes suggest that expression of MARCO by DC could contribute to their distinctive cellular responses to microbial stimuli. Enhanced expression of SR-A I/II by transfection of MØ also induces extensive spreading [29•], consistent with a role in adhesion and migration of myeloid cells.

SR-A-like SR

A novel collagenous receptor — SR-CL I (SR with C-type lectin I) — was cloned from human placental cDNA and resembles type-A SR in structure, but differs from it in the carboxyl terminus (Figure 1) [30•]. A related receptor (SR-CL II) lacks the C-type-carbohydrate-recognition domain. Northern blot analysis revealed that both mRNAs are abundantly expressed in various adult human tissues. Ligand-binding studies of CHO-K1 cells expressing human (h)SR-CL I and II demonstrated specific binding of *E. coli* and *S. aureus*, although ingestion of bacteria was not evident.

An independent group has characterised a molecule similar if not identical to SR-CL, termed CL-P1 (collectin from placenta receptor 1), as a collagenous scavenger receptor that is highly conserved between man and mouse [31•]. Northern-blot analysis, RT-PCR and immunohistochemistry showed that CL-P1 is expressed in vascular EC, but not in MØ. Immunoblotting and FACS revealed a membrane glycoprotein of ~140 kDa in human umbilical vein and arterial endothelium, in placenta and in transfected cells. This study showed binding and phagocytosis not only of bacteria (*E. coli* and *S. aureus*), but also of *Saccharomyces cerevisiae*. This receptor reacted with oxidised LDL, not Ac-LDL, and was inhibited by selected polyanions. CL-P1 is therefore a membrane-bound collectin, which may share functions in innate immunity with well-characterised soluble collectins.

LOX-1

LOX-1 (lectin-like oxidised LDL-receptor 1) (Figure 1) was cloned from bovine aortic EC and human lung. It is expressed by vascular endothelium and mature MØ, and by smooth-muscle cells in atherosclerotic lesions. A potential role for LOX-1 in innate immunity was revealed when Shimaoka *et al.* [32•] showed, using CHO-K1 cells stably transfected with human LOX-1 (as well as using bovine EC) that LOX-1 can bind both *S. aureus* and *E. coli*. Binding was blocked by polyinosinic acid, a nonspecific polyanion

inhibitor, and by anti-LOX-1 monoclonal antibodies. However, it does not bind Ac-LDL or LPS. Its expression can be induced by LPS and TNFα, as well as TGF-β.

dSR-C I

A structurally unrelated *Drosophila* (d)SR-C I has been identified in *D. melanogaster* (Figure 1) [3]. This molecule contains domains found in complement-control proteins and a somatomedin-B domain, and has been implicated in phagocytosis and in innate immunity.

Other SR

Class-B receptors (e.g. CD36, SR-B1 and Croquemort), a class-D receptor (macrosialin), a class-F receptor (SREC) and a newly described SR that binds phosphatidylserine and oxidised lipoprotein (SR-PSOX) [33•] bind oxidized LDL and various polyanions, but have not been reported as able to bind bacteria. They are variably expressed by MØ, EC and cells involved in lipid homeostasis.

Apoptotic-cell clearance and innate immunity

Several SR have been implicated in the uptake of apoptotic cells, including SR-A, dSR-C I and CD36 [10•]. In addition, integrins (αvβ3, αvβ5 and CR3), a phosphatidylserine (PS) receptor [34••,35•,36•,37••], CD14 and selected ABC transporters [38•] have been shown to play a role in phagocytosis of various apoptotic targets. Other receptors shown to mediate microbial recognition (Figure 1) have not been examined for their ability to take up apoptotic cells.

Our appreciation of the relevance of apoptotic-cell clearance in innate immunity has grown recently, through the following observations: first, evidence that apoptotic-cell uptake via some of these pathways signals the release of anti-inflammatory products (e.g. TGFβ and PGE2) [35•]; second, evidence that uptake by DC rather than MØ results in cross-presentation of viral and potential tumour antigens to naive T lymphocytes [9•]; and third, evidence that engagement of receptors during apoptotic-cell phagocytosis can enhance the growth of intracellular pathogens within MØ [39••]. This could provide a novel survival mechanism for a range of organisms, including parasites such as *Trypanosoma cruzi*.

The contributions of individual receptors, some of which are distributed on myeloid cells alone and some more broadly, deserve a great deal of further work. The use of receptor-knockout mice and specific reagents (antibodies, agonists and antagonists) will facilitate their analysis in disease models *in vivo*, and in cellular studies *in vitro*. A detailed comparison of gene expression in defined populations of MØ and DC in response to apoptotic versus microbial stimuli has been initiated recently [40••,41•].

Lessons from atherogenesis

Ongoing studies of host and cellular responses to lipid-loading in different mouse strains, including SR-knockout animals, have uncovered additional complexity of receptor functions *in vivo* and contributed to our understanding of ligand formation, thus bearing on our understanding of the function of SR in the innate immune response [42,43•]. Apart from genes for SR themselves, other genes may modify expression and function of SR; thus perhaps accounting for some of the variability observed in different murine models of disease. For example, SR-A has been found to be pro-atherogenic or anti-atherogenic and similar contradictions will surely be found in bacterial-challenge experiments. Polymorphisms and multiple natural mutations in SRA I/II have been described in C57 black mice, compared with other strains [44,45], but with no clear functional differences.

Although many artificial ligands have been identified for the promiscuous members of the SR family, there is a dearth of information regarding naturally occurring ligands. The careful model studies on oxidised LDL that implicate pyrrole or pyrimidine adducts in CD36 binding may clarify the stages by which labile and transient ligands are formed *in vivo* [46•]. These may be relevant to ligand generation during microbial interactions with myeloid cells that express potent oxidative capacities during phagocytosis [47].

Effects of microbial phagocytosis on expression of SR

Apart from a few studies on the effects of LPS on SR-A expression [24] there is very little knowledge of the consequences of ligation on the biosynthesis and functions of SR. One intriguing example is the rapid upregulation of MARCO expression after LPS or microbial uptake [26•]. It will be important to examine intact organisms as well as individual microbial components, such as LPS and LTA, in experimental models. It may be anticipated that different PRR, including SR and TLR, can influence one another, through cross-talk as well as induced responses. A detailed comparison of innate and acquired immune activation remains to be made.

Conclusions

These studies point to the dynamic complexity that underlies host cell, pathogen and cytokine interactions. It is often assumed that SR, as well as other PRR, play a key proximal role in determining various adaptive immune responses that can follow innate recognition. The differential responses initiated by clearance of endogenous host ligands and exogenous microbial invaders are poorly understood, but lie at the heart of immunosuppression and autoimmunity as well as immune activation. Distinct myeloid cell types (MØ, DC and neutrophils) utilise a range of surface receptors, including SR, in homeostasis and host defence; intriguingly, some EC are also implicated in related functions.

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