Microreview

Scavenger receptors: role in innate immunity and microbial pathogenesis

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Summary

Accumulating evidence shows that many scavenger receptors (SR), including SR-A, MARCO and CD36, represent an important part of the innate immune defence by acting as pattern-recognition receptors, in particular against bacterial pathogens. Several SR are expressed on macrophages and dendritic cells, where they act as phagocytic receptors mediating non-opsonic phagocytosis of pathogenic microbes. Another important function of some SR is to act as co-receptors to Toll-like receptors (TLR), modulating the inflammatory response to TLR agonists. On bacteria, the SR ligands have commonly been reported to be lipopolysaccharide and lipoteichoic acid, but recent advances in the field indicate that bacterial surface proteins play a more important role as target molecules for SR than previously thought. Interestingly, recent data show that major pathogens, including Streptococcus pyogenes and the group B streptococcus, have evolved mechanisms to evade SR-mediated recognition. Moreover, intracellular pathogens, such as hepatitis C virus and Plasmodium falciparum, utilize the SR to gain entry into host cells, focusing interest on the importance of SR also in the molecular pathogenesis of infectious diseases. This review highlights the complex interactions between SR and pathogenic microbes, and discusses the role of these interactions in host defence and microbial pathogenesis.

Introduction

The scavenger receptors (SR) comprise a large family of structurally diverse transmembrane cell surface glycoproteins restricted to macrophages (MΦ), dendritic cells (DC), endothelial cells and a few other cell types (Murphy et al., 2005). The concept of SR was initially put forward by Brown and Goldstein (Goldstein et al., 1979), who functionally defined the SR through their ability to bind modified low-density lipoproteins (LDL), e.g. oxidized LDL, but not native LDL. Today, the SR are divided into eight different classes (A–H) according to their overall multidomain structure (Murphy et al., 2005), and several other host molecules, including molecular chaperones and ECM proteins, have been identified as SR ligands (Plüddemann et al., 2007). Moreover, several reports show that some SR can also bind to unmodified lipoproteins. Most studies have been devoted to the role of SR-mediated endocytosis of modified LDL in foam cell formation and atherosclerosis, and the SR have also been implicated in Alzheimer’s disease and to be involved in adhesion and tissue maintenance (Plüddemann et al., 2007).

More recently, the SR have been demonstrated to play an important role in innate immune defence by acting as pattern recognition receptors (PRR) (Mukhopadhyay and Gordon, 2004). The SR have been reported to recognize several different microbial structures [pathogen-associated molecular patterns (PAMP)], including lipopolysaccharide (LPS), lipoteichoic acid (LTA), bacterial CpG DNA and yeast zymosan/β-glucan (Mukhopadhyay and Gordon, 2004; Areschoug and Gordon, 2008), but recent evidence suggests that for many SR microbial surface proteins are major ligands (Jeannin et al., 2005; Peiser et al., 2006; Areschoug et al., 2008; Plüddemann et al., 2009a). The most commonly described function for SR is to act as phagocytic receptors mediating direct non-opsonic phagocytosis of pathogenic microbes by MΦ and DC (Mukhopadhyay and Gordon,
2004; Areschoug and Gordon, 2008), but some SR have also been shown to be co-receptors for the Toll-like receptors (TLR), in particular TLR2, in pro-inflammatory cytokine responses to various PAMP (Hoebe et al., 2005; Jeannin et al., 2005). Interestingly, recent data show that several pathogens have evolved mechanisms to evade recognition by SR (Serghides et al., 2006; Pinheiro da Silva et al., 2007; Areschoug et al., 2008). Furthermore, there are several examples described in the literature where pathogenic microorganisms exploit SR for their own benefit, mainly as a portal of entry into host cells (Dubuisson et al., 2008; Rodrigues et al., 2008; Yalaoui et al., 2008). In this review, we focus on the interplay between SR and pathogenic microbes and discuss the role of these interactions in innate immunity and microbial pathogenesis. Our main focus will be on the class A and class B SR, which are the most extensively studied SR with regard to interactions with pathogenic microorganisms.

Class A SR

Scavenger receptor A (SR-A)
The class A SR SR-A is expressed on most MΦ subpopulations and on DC and was the first SR to be cloned and characterized molecularly. It is a trimeric type II transmembrane glycoprotein with several distinct domains: a cytoplasmic tail, transmembrane, spacer, α-helical coiled coil, collagenous and C-terminal SR cystein-rich (SRCR) domains. There are two functional splice variants of SR-A (SR-AI and SR-AII), where SR-AII lacks most of the SRCR (Murphy et al., 2005). These two isoforms are collectively referred to as SR-A in this review.

The first report that the SR are involved in host defence was presented by Hampton et al. (1991), who showed that SR-A bind to the purified lipid A moiety of LPS derived from the Gram-negative bacterium Escherichia coli. In a subsequent study (Dunne et al., 1994), it was shown that SR-A also bind to purified LTA from some Gram-positive bacteria. Recent data, however, indicate that bacterial surface proteins are major ligands for SR-A (Peiser et al., 2006; Areschoug et al., 2008; Plüddemann et al., 2009a) (see below). The main function of SR-A as a PRR has been shown to be as a phagocytic receptor (Fig. 1), mediating direct non-opsonic phagocytosis of several bacterial pathogens, including Neisseria meningitidis, Staphylococcus aureus, Streptococcus pneumoniae and E. coli, by MΦ (Peiser et al., 2000; 2002; Arredouani et al., 2006). SR-A may also bind to bacterial CpG DNA (Zhu et al., 2001) and

![Fig. 1. Summary of the most important functions of SR in the innate immune defence and the role of SR in infections caused by intracellular pathogens such as HCV and Plasmodium spp. See text for details.](image-url)
double-stranded RNA (Limmon et al., 2008), but the significance of these interactions is unclear. In addition to its role as a phagocytic receptor, SR-A may dampen the pro-inflammatory response to pathogenic microbes or their products from MΦ or DC (Becker et al., 2006; Ozeki et al., 2006; Hollifield et al., 2007; Villwock et al., 2008).

The generation of SR-A knockout mice has enabled the demonstration that SR-A is important for the defence against experimental bacterial infection. Suzuki et al. (1997) showed that SR-A−/− mice are significantly more susceptible than their wild-type (WT) counterparts to infection with Listeria monocytogenes, with increased bacterial loads in liver and spleen. In subsequent studies, SR-A has been shown to protect mice against infection with S. aureus (Thomas et al., 2000), S. pneumoniae (Arredouani et al., 2006) and N. meningitidis (Plüdde-mann et al., 2009a). In addition, SR-A has also been implicated in protection against endotoxic shock (Haworth et al., 1997), but conflicting data have been reported (Kobayashi et al., 2000). The role of SR-A in protection against parasitic infection has also been investigated. Nogami et al. (1998) reported that SR-A−/− mice are more sensitive to infection with Plasmodium berghei compared with WT mice, but subsequent studies have failed to show a protective role of SR-A against malaria in the mouse model (Su et al., 2002; Cunha-Rodrigues et al., 2006; Inoue et al., 2006).

Interestingly, two clinically important bacterial pathogens, Streptococcus pyogenes and the group B streptococcus (GBS; Streptococcus agalactiae), have evolved mechanisms to evade recognition by SR-A on MΦ (Fig. 2) (Areschoug et al., 2008). S. pyogenes express the surface M protein, which is an important virulence factor that prevents opsonin-dependent phagocytosis of S. pyogenes in human blood by inhibiting complement deposition at the bacterial surface (Carlsson et al., 2005). Similarly, all strains of GBS express a major surface virulence factor, the polysaccharide capsule, that prevents complement deposition and phagocytosis of GBS by neutrophils in presence of serum (Wessels et al., 1989). In addition to their role in preventing opsonin-dependent phagocytosis by neutrophils, recent data show that the GBS polysaccharide capsule and the S. pyogenes M protein prevent recognition and non-opsonic phagocytosis of streptococci by SR-A on MΦ, most probably by masking the SR-A ligand(s) at the bacterial surface (Areschoug et al., 2008). This is the first example of a microbial strategy to evade recognition by SR-A.

Fig. 2. Model of evasion mechanism in Streptococcus pyogenes to avoid SR-A-mediated recognition and non-opsonic phagocytosis by MΦ. (1) At low expression of the surface M protein, the SR-A ligand(s) at the bacterial surface are exposed, resulting in SR-A-mediated recognition and phagocytosis. (2) When M protein is expressed at high levels, it prevents SR-A-mediated phagocytosis of S. pyogenes by masking the ligand(s) for SR-A at the bacterial surface. See text for references.
MACRO

MARCO (MΦ receptor with collagenous structure) is another distinct member of the class A SR family implicated as a PRR. It has a structure similar to that of SR-A, but lacks an α-helical coiled coil domain and has a longer collagenous domain (Elomaa et al., 1995). In contrast to SR-A, MARCO is constitutively expressed only on some subpopulations of MΦ (van der Laan et al., 1997; 1999), but expression of MARCO is strongly upregulated in MΦ by various microbial stimuli in a TLR-dependent manner (Doyle et al., 2004; Mukhopadhyay et al., 2004). MARCO has been reported to bind soluble LPS and intact Gram-positive and -negative bacteria (Elomaa et al., 1995; Sankala et al., 2002). As shown for SR-A, MARCO acts as a phagocytic receptor for pathogenic bacteria, such as S. pneumoniae (Arredouani et al., 2004) and N. meningitidis (Mukhopadhyay et al., 2006).

In vivo evidence that MARCO is involved in host defence against bacterial infection was provided by Arredouani et al. (2004), who showed that MARCO−/− mice are significantly more sensitive to infection with S. pneumoniae compared with WT mice. Interestingly, a recent study suggests that pulmonary IFN-γ produced during T cell responses to influenza infection in mice inhibits bacterial clearance from lungs by alveolar MΦ, which was correlated with downregulation of MARCO on the MΦ (Sun and Metzger, 2008). Thus, downregulation of MARCO on alveolar MΦ may contribute to the enhanced susceptibility to secondary pneumococcal infection after an influenza infection.

In another interesting paper, it was reported that E. coli is able to engage CD16 (FcγRIII) on MΦ, which induces recruitment of SHP-1 to MARCO, resulting in inhibition of MARCO-mediated phagocytosis of these bacteria (Pinheiro da Silva et al., 2007). This may represent a novel microbial SR subversion mechanism, but the bacterial factor(s) interacting with CD16 has not been identified.

Other class A SR

In 2001, two independent research groups identified an SR-A-like receptor designated SRCL-I (Nakamura et al., 2001) or CL-PI (Ohtani et al., 2001), expressed by placenta, umbilical venous and arterial endothelium. Instead of an SRCR domain in the C-terminus, this receptor contains a C-type lectin domain. The role of SRCL-I/CL-PI as a PRR is unclear, but it has been shown to bind to heat-inactivated E. coli and S. aureus bacteria and Saccharomyces cerevisiae yeast particles (Ohtani et al., 2001). Interestingly, a recent study indicates that this receptor mediates non-opsonic phagocytosis of yeast zymosan by vascular endothelial cells, implicating a possible role of SRCL-I/CL-PI in antifungal defence (Jang et al., 2009). In addition, SCARA5 is a recently identified class A SR expressed in epithelial cells that binds to heat-killed E. coli and S. aureus, indicating a role of this SR as a PRR (Jiang et al., 2006).

Class B SR

CD36

The first class B SR to be cloned and molecularly characterized was CD36, which is a type III transmembrane receptor with two transmembrane domains, an extracellular loop with multiple glycosylation sites and two short intracellular tails. It is expressed on MΦ, platelets, adipocytes and some endothelial and epithelial cells (Murphy et al., 2005). CD36 has been shown to be a sensor for LTA and a diacylated lipopeptide (MALP-2) (Hoebe et al., 2005). Hoebe et al. (2005) showed that CD36 acts as a co-receptor for TLR2 in responses to microbial diacylglycerides (Fig. 1), as CD36 was found to be essential for TLR2 responses to both MALP-2 and LTA. Further studies suggested that upon stimulation with diacylglycerides, CD36 associates with TLR2/6 heterodimers in lipid rafts at the cellular surface, an interaction believed to be crucial for signalling in response to these microbial molecules (Triantafilou et al., 2006). Importantly, two independent groups showed that CD36-deficient mice are more susceptible to infection with S. aureus compared with WT mice, demonstrating that CD36 is important for the defence against this bacterial pathogen (Hoebe et al., 2005; Stuart et al., 2005). Interestingly, CD36 expressed on MΦ acts as a phagocytic receptor (Fig. 1) for S. aureus, but in contrast to pure diacylglycerides, TLR2/6 responses to whole S. aureus bacteria is dependent on CD36-mediated internalization of S. aureus into the phagosome (Stuart et al., 2005).

While CD36 is an important PRR for Gram-positive pathogens, its role in recognition of Gram-negative bacteria is unclear. In contrast to S. aureus, CD36 is not a major phagocytic receptor for E. coli in MΦ (Stuart et al., 2005). Other studies, however, have shown that when expressed in HEK293 cells, CD36 can bind to several Gram-negative pathogens, including E. coli, Klebsiella pneumoniae and Salmonella typhimurium (Philips et al., 2005; Baranova et al., 2008). Indeed, CD36 may act as a sensor for LPS (Baranova et al., 2008), but there are as yet no in vivo data supporting a host-protective role of CD36 against infection with a Gram-negative bacterium.

In addition to its role as a PRR for bacterial pathogens, CD36 has also received substantial attention in Plasmodium falciparum malaria as a receptor for parasitized erythrocytes (PE), but it is somewhat unclear whether CD36 contributes primarily to innate host defence or
rather the opposite, malaria pathophysiology (Serghides et al., 2003). CD36 was initially identified as a sequestration receptor for PE, contributing to the adhesion of PE to the venular endothelium within various organs, including heart, lung, liver and brain (Ockenhouse et al., 1991; Newbold et al., 1997; Serghides et al., 2003). Adherence of PE to the endothelium may cause microvascular occlusion, which is believed to contribute to the acute pathology of malaria (Serghides et al., 2003; Lovegrove et al., 2008). Baruch et al. (1996) identified the P. falciparum erythrocyte membrane protein-1 as the main ligand for CD36 on PE, an interaction suggested to be important for sequestration. However, CD36 has also been reported to act as a non-opsonic phagocytic receptor for PE on Mφ, mediating phagocytic clearance of PE (McGilvray et al., 2000; Patel et al., 2004). In a mouse model of malaria infection, CD36 mice showed more severe and fatal malaria compared with WT mice when challenged with P. chabaudi chabaudi AS, providing in vivo evidence for a protective role of CD36 against malaria (Patel et al., 2007). Possibly, some parasite isolates may evade CD36-mediated clearance of PE by the expression of novel variable surface antigens, including polymorphic forms of P. falciparum erythrocyte membrane protein-1 (Serghides et al., 2006). CD36 has also been shown to act as a sensor for P. falciparum glycosylphosphatidylinositol (pGPI), resulting in production of pro-inflammatory cytokines by Mφ (Patel et al., 2007). Interestingly, the pro-inflammatory response to pGPI from Mφ is largely dependent on TLR2 (Krishnegowda et al., 2005). Thus, CD36 may cooperate with TLR2 in pro-inflammatory cytokine responses to pGPI, similar to the proposed role in responses to diacylglycerides from Gram-positive bacteria. However, it is not clear whether the pro-inflammatory response elicited by pGPI contributes primarily to malaria pathogenesis or host defence.

Of note, CD36 may also be involved in antifungal defence, as it was recently suggested to bind β-glucan and to contribute to in vivo protection in mice against experimental Cryptococcus neoformans infection (Means et al., 2009).

**SR-BI (CLA-1)**

The second receptor in this class, SR-BI, has a similar loop structure to that of CD36 and consists of two splice variants designated SR-BI and SR-BII. SR-BI is primarily expressed on Mφ, DC, hepatocytes and steroidigenic tissue (Murphy et al., 2005). The first report describing the binding of a PAMP to SR-BI was presented by Vishnyakova et al. (2003), who showed that human SR-BI (designated CLA-1) binds pure LPS when expressed in HeLa cells. In a subsequent study, it was shown that CLA-1 mediates binding and uptake of both Gram-negative (E. coli and S. typhimurium) and Gram-positive (S. aureus and L. monocytogenes) bacteria in CLA-1 HeLa cells (Vishnyakova et al., 2006). However, peritoneal Mφ isolated from SR-BI mice demonstrated only a 30% decrease in bacterial uptake when compared with WT Mφ. In addition, when expressed in HEK293 cells, human SR-BI also binds to Mycobacterium fortuitum (Philips et al., 2005). The binding and uptake of bacterial pathogens into host cells via CLA-1/SR-BI has been suggested to represent a bacterial virulence mechanism (Philips et al., 2005; Vishnyakova et al., 2006), but in vivo evidence for this hypothesis is lacking.

SR-BI has received significant attention as a possible target receptor for hepatitis C virus (HCV) entry into host hepatocytes (Fig. 1) (Dubuisson et al., 2008). Scarselli et al. (2002) first reported human SR-BI as a putative receptor for the E2 glycoprotein of HCV. In this study, the investigators used soluble E2 glycoprotein to pull down a putative receptor on human hepatoma cells following coimmunoprecipitation. Several subsequent studies using HCV pseudoparticles, which consist of unmodified HCV envelope glycoproteins assembled onto retroviral core particles, support a role of SR-BI in HCV entry (Bartosch et al., 2003; Bartosch et al., 2005; Lavillette et al., 2005; Kapadia et al., 2007; Drex et al., 2009). However, the exact role of SR-BI in HCV entry is not understood. For example, HCV does not only rely on SR-BI for entry, but also other receptors such as CD81 and possibly members of the Claudin (CLDN) family (Dubuisson et al., 2008), but it is not known at what stage of entry SR-BI is required. Moreover, ectopic expression of SR-BI and CD81 in non-liver cell lines does not lead to HCV pseudoparticle entry, suggesting that additional receptors are required for HCV entry (Bartosch et al., 2003). Of note, SR-BI-mediated uptake of HCV has also been reported in human DC (Barth et al., 2008), resulting in cross-presentation of viral antigens. Thus, when expressed in DC, SR-BI may primarily mediate recognition and uptake of viral structures and contribute to host defence.

Whereas CD36 has been extensively studied in malaria pathogenesis, less is known about SR-BI in this context. However, two recent studies (Rodrigues et al., 2008; Yalaoui et al., 2008) report that SR-BI plays an important role in Plasmodium infection, as it promotes sporozoite invasion in hepatocytes and subsequent intracellular parasite development into exoerythrocytic forms and merozoites (Fig. 1). Thus, in malaria, SR-BI may mainly act as a target molecule for parasite infection, rather than in host defence. However, as described for HCV, CD81 is also required for hepatocyte entry of Plasmodium sporozoites (Yalaoui et al., 2008).
Other SR classes

Several other mammalian SR have been shown to recognize bacteria or isolated bacterial PAMP. The class E SR LOX-1 was originally identified as an endothelial cell-specific SR, but it can also be detected on Mφ, smooth muscle cells and platelets. It is a type II transmembrane protein with a short cytoplasmic N-terminus, a transmembrane domain, a neck domain and a C-proximal C-type lectin domain (Murphy et al., 2005). SREC-I is a class F SR expressed on endothelial cells and Mφ, and is composed of a large N-terminal extracellular domain containing 10 cysteine-rich repeats, five of which form EGF-like domains (Murphy et al., 2005). Both of these SR have been reported to bind heat-inactivated S. aureus and E. coli bacteria (Shimaoka et al., 2001; Jeannin et al., 2005). Interestingly, as described for SR-A and MARCO, LOX-1 and SREC-I can recognize bacterial surface proteins (Jeannin et al., 2005).

The class G SR SR-PSOX was originally identified as a transmembrane-type chemokine designated CXCL16 and is expressed in the endothelium, Mφ, DC, smooth muscle cells (Murphy et al., 2005), and has also been found in keratinocytes (Tohyama et al., 2007). It is a type I transmembrane protein with a chemokine domain adjoining a glycosylated mucin-like region (Murphy et al., 2005). When expressed in COS cells, SR-PSOX/CXCL16 mediates binding of S. aureus and E. coli, and antibodies to SR-PSOX/CXCL16 block uptake of bacteria by human DC, indicating that it may act as a phagocytic receptor (Shimaoka et al., 2003). Moreover, a study by Gursel et al. (2006) suggests that SR-PSOX/CXCL16 may act as an uptake receptor for bacterial CpG DNA, enhancing TLR9-mediated responses to this PAMP. Interestingly, a recent study suggests that the chemokine domain of SR-PSOX/CXCL16 may have direct antimicrobial activity against bacteria (Tohyama et al., 2007). Thus, SR-PSOX/CXCL16 might have dual roles in the innate immune defence, acting both as a PRR and a bactericidal host molecule.

The class H SR FEEL-1, and its parologue FEEL-2, are very large type I transmembrane proteins containing Fasciclins (Fas-1), EGF-like, laminin-type EGF-like and a hyaluronan-binding link domains. Both FEEL-1 and FEEL-2 bind to heat-killed bacteria (Adachi and Tsujimoto, 2002), but their role as PRR remains unclear.

Bacterial surface protein ligands for SR

As outlined above, many SR bind to purified LPS and/or LTA, but it is unclear whether these molecules act as SR ligands at the surface of intact bacteria. Indeed, SR-A-dependent binding and non-opsonic phagocytosis of whole N. meningitidis bacteria is independent of surface LPS, as shown for a lipid A-deficient isogenic mutant of N. meningitidis (Peiser et al., 2002). Thus, SR-A is dependent on surface structures distinct from LPS on N. meningitidis for its ability to directly bind and phagocytose these bacteria. Peiser et al. (2006) identified several conserved meningococcal surface proteins, including NMB0278 and NMB1220, as ligands for SR-A, focusing interest on microbial surface proteins as major target molecules for SR-A. To investigate the role of the meningococcal surface proteins in SR-A-mediated recognition of these bacteria in vivo, Plüddemann et al. (2009a) constructed N. meningitidis mutants lacking surface expression of NMB0278 and NMB1220. In a murine model of meningococcal septicemia employing WT and SR-A−/− mice, it was shown that SR-A contributes to recognition of the serogroup B WT strain MC58, with significantly lower health score and survival in SR-A−/− mice. In contrast, when mice were infected with an isogenic double-mutant (MC58-278-1220), lacking both NMB0278 and NMB1220, there was no difference in survival or health score between WT and SR-A−/− mice, indicating that SR-A lost the ability to recognize N. meningitidis when NMB0278 and NMB1220 are not surface-exposed (Plüddemann et al., 2009a). Thus, at least for N. meningitidis, the major ligands for SR-A are most likely surface proteins, rather than LPS. As shown for SR-A, MARCO also recognizes meningococcal surface proteins (Plüddemann et al., 2009b). The binding specificity to N. meningitidis surface proteins varies somewhat between SR-A and MARCO, adding to the complexity of ligand recognition of these SR (Plüddemann et al., 2009b).

The ligand for SR-A in Gram-positive bacteria has been reported to be LTA (Dunne et al., 1994), and this interaction was shown to be affected by D-alanyl moieties on the LTA structure (Greenberg et al., 1996). However, a recent study on GBS identified a surface lipoprotein, designated Blr, as an SR-A ligand (Areschoug et al., 2008). The Blr protein contains a leucine-rich repeat region, indicating that it may be involved in protein–protein interactions, but the biological role of Blr is not known (Waldemarsson et al., 2006). The ability of SR-A to recognize GBS was significantly reduced by employing an isogenic Blr-negative mutant compared with the WT GBS strain. Thus, the Blr protein is a ligand for SR-A at the surface of GBS, but SR-A also recognizes bacterial structures distinct from Blr, which might be LTA or other surface proteins (Areschoug et al., 2008).

In an interesting paper by Jeannin et al. (2005), it was shown that LOX-1 and SREC-I both bind to recombinant outer membrane protein A (OmpA) from K. pneumoniae. OmpA is a highly conserved surface protein in the Enterobacteriaceae family believed to be important for structural cell integrity and virulence (Jeannin et al., 2002). Employing an OmpA-negative mutant of E. coli, it was demon-
stated that OmpA also acts as a target molecule for LOX-1 and SREC-I at the bacterial surface (Jeannin et al., 2005). Interestingly, OmpA activates antigen-presenting cells via TLR2, but it does not bind to TLR2 (Jeannin et al., 2000), suggesting that LOX-1 and SREC-I may act as sensors for OmpA in TLR2 signalling. Thus, LOX-1 and SREC-I may, as described for CD36, act as co-receptors for a TLR2 agonist. In addition, SREC-I has been reported to interact with the PorB protein of Neisseria gonorrhoeae (Rechner et al., 2007), which also is a TLR2 agonist (Massari et al., 2006), but in this case it was suggested that the binding of PorB to SREC-I represents a bacterial invasion mechanism into epithelial cells.

Conclusions

A growing body of evidence demonstrates that several SR represent an important part in the innate immune defence by acting as phagocytic receptors or as co-receptors to TLR, especially in responses to bacteria. Several SR have been shown to recognize the same pathogens, e.g. S. aureus, but it is often difficult to evaluate the individual contributions of different SR in recognition of specific pathogens. Moreover, the molecular basis for recognition is still poorly understood for many SR, as these receptors have rather broad ligand-binding specificity, including LPS, LTA, nucleic acids, β-glucan and proteins. However, the emerging picture of the molecular basis for the ability of SR to recognize pathogens indicates that microbial surface proteins are major ligands, at least for SR-A, MARCO, CD36, LOX-1 and SREC-I. Interestingly, this finding may have implications for vaccine development, as several SR have been shown to promote antigen presentation (Nicoletti et al., 1999; Barth et al., 2008; Harvey et al., 2008). Thus, identification of microbial surface proteins recognized by SR might represent a novel method to identify vaccine candidates against important pathogens, as targeting of SR may result in efficient delivery of protein antigens to antigen-presenting cells. Of note, many of the ligands for SR and other PRR are not only found on pathogens, but also on commensal microbes. Therefore, instead of PAMP, ‘microbe associated molecular patterns’ has sometimes been used as an alternative term to describe microbial ligands for PRR (Fritz et al., 2008). It is not known, however, if recognition of pathogens and commensals, respectively, by SR result in different host responses.

The importance of SR in the immune defence is further underlined by the finding that several pathogens utilize their virulence factors to avoid recognition and phagocytosis via SR. Studies of the interactions between SR and pathogenic microbes may therefore become important model systems for general mechanisms by which pathogens can subvert pattern recognition and establish infections. Thus, to fully understand the interplay between microbes and SR, it is of importance to use clinically relevant strains, rather than attenuated laboratory strains, which have commonly been used in these studies. Moreover, the interest of SR in the molecular pathogenesis of infectious diseases has increased significantly in recent years by the findings that major intracellular pathogens, such as HCV and Plasmodium spp., utilize SR-BI to enter host cells, mechanisms believed to represent important virulence mechanisms by these pathogens.

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References

Adachi, H., and Tsujimoto, M. (2002) FEEL-1, a novel scavenger receptor with in vitro bacteria-binding and angiogenesis-modulating activities. J Biol Chem 277: 34264–34270.

Areschoug, T., and Gordon, S. (2008) Pattern recognition receptors and their role in innate immunity: focus on microbial protein ligands. Contrib Microbiol 15: 45–60.

Areschoug, T., Waldemarsson, J., and Gordon, S. (2008) Evasion of macrophage scavenger receptor A-mediated recognition by pathogenic streptococci. Eur J Immunol 38: 3068–3079.

Arredouani, M., Yang, Z., Ning, Y., Qin, G., Soinnen, R., Ttrygymason, K., and Kobzik, L. (2004) The scavenger receptor MARCO is required for lung defense against pneumococcal pneumonia and inhaled particles. J Exp Med 200: 267–272.

Arredouani, M.S., Yang, Z., Imrich, A., Ning, Y., Qin, G., and Kobzik, L. (2006) The macrophage scavenger receptor SR-AI/II and lung defense against pneumococci and particles. Am J Respir Cell Mol Biol 35: 474–478.

Baranova, I.N., Kurlander, R., Bocharov, A.V., Vishnyakova, T.G., Chen, Z., Remaley, A.T., et al. (2008) Role of human CD36 in bacterial recognition, phagocytosis, and pathogen-induced JNK-mediated signaling. J Immunol 181: 7147–7156.

Barth, H., Schnober, E.K., Neumann-Haefelin, C., Thumann, C., Zeisel, M.B., Diepolder, H.M., et al. (2008) Scavenger receptor class B is required for hepatitis C virus uptake and cross-presentation by human dendritic cells. J Virol 82: 3466–3479.

Bartosch, B., Vitelli, A., Granier, C., Goujon, C., Dubuisson, J., Pascale, S., et al. (2003) Cell entry of hepatitis C virus requires a set of co-receptors that include the CD81 tetraspanin and the SR-B1 scavenger receptor. J Biol Chem 278: 41624–41630.
Bartosch, B., Verney, G., Dreux, M., Donot, P., Morice, Y., Penin, F., et al. (2005) An interplay between hypervariable region 1 of the hepatitis C virus E2 glycoprotein, the scavenger receptor Bl, and high-density lipoprotein promotes both enhancement of infection and protection against neutralizing antibodies. J Virol 79: 8217–8229.

Baruch, D.I., Gormely, J.A., Ma, C., Howard, R.J., and Pasloske, B.L. (1996) Plasmodium falciparum erythrocyte membrane protein 1 is a parasitized erythrocyte receptor for adherence to CD36, thrombospondin, and intercellular adhesion molecule 1. Proc Natl Acad Sci USA 93: 3497–3502.

Becker, M., Cotena, A., Gordon, S., and Platt, N. (2006) Expression of the class A macrophage scavenger receptor on specific subpopulations of murine dendritic cells limits their endotoxin response. Eur J Immunol 36: 950–960.

Carlsson, F., Sandin, C., and Lindahl, G. (2005) Human fibrinogen bound to Streptococcus pyogenes M protein inhibits complement deposition via the classical pathway. Mol Microbiol 56: 28–39.

Cunha-Rodrigues, M., Portugal, S., Febbraio, M., and Mota, M.M. (2006) Infection by and protective immune responses against Plasmodium berghei ANKA are not affected in macrophage scavenger receptors A deficient mice. BMC Microbiol 6: 73.

Dreux, M., Dao Thi, V.L., Fresquet, J., Guérin, M., Julia, Z., Verney, G., et al. (2009) Toll-like receptors induce a phagocytic gene program through p38. J Exp Med 199: 81–90.

Fritz, J.H., Le Bourhis, L., Magalhaes, J.G., and Philpott, D.J. (2008) Innate immune recognition at the epithelial barrier drives adaptive immunity: APCs take the back seat. Trends Immunol 29: 41–49.

Goldstein, J.L., Ho, Y.K., Basu, S.K., and Brown, M.S. (1979) Binding site on macrophages that mediates uptake and degradation of acetylated low density lipoprotein, producing massive cholesterol deposition. Proc Natl Acad Sci USA 76: 333–337.

Greenberg, J.W., Fischer, W., and Joiner, K.A. (1996) Influence of lipoteichoic acid structure on recognition by the macrophage scavenger receptor. Infect Immun 64: 3318–3325.

Gursel, M., Gursel, I., Mostowski, H.S., and Klinman, D.M. (2006) CXCL16 influences the nature and specificity of CpG-induced immune activation. J Immunol 177: 1575–1580.

Hampton, R.Y., Golenbock, D.T., Penman, M., Krieger, M., and Raetz, C.R. (1991) Recognition and plasma clearance of endotoxin by scavenger receptors. Nature 352: 342–344.

Harvey, B.P., Quan, T.E., Rudenga, B.J., Roman, R.M., Craft, J., and Mamula, M.J. (2008) Editing antigen presentation: antigen transfer between human B lymphocytes and macrophages mediated by class A scavenger receptors. J Immunol 181: 4043–4051.

Haworth, R., Platt, N., Keshav, S., Hughes, D., Darley, E., Suzuki, H., et al. (1997) The macrophage scavenger receptor type A is expressed by activated macrophages and protects the host against lethal endotoxic shock. J Exp Med 186: 1431–1439.

Hoebe, K., Georgel, P., Du Rutschmann, S.X., Mudd, S., Crozat, K., et al. (2005) CD36 is a sensor of diacylglycerides. Nature 433: 523–527.

Hollifield, M., Bou Ghanem, E., de Villiers, W.J., and Garvy, B.A. (2007) Scavenger receptor A dampens induction of inflammation in response to the fungal pathogen Pneumocystis carinii. Infect Immun 75: 3999–4005.

Hone, M., Xuan, X., Fujisaki, K., Igarashi, I., and Suzuki, H. (2006) Short report: role of type I/II scavenger receptors in malarial infection in C57BL/6J mice. Am J Trop Med Hyg 75: 178–181.

Jang, S., Ohtani, K., Fukuoh, A., Yoshizaki, T., Fukuda, M., Motomura, W., et al. (2009) Scavenger receptor collectin placa 1 (CL-P1) predominantly mediates zymosan phagocytosis by human vascular endothelial cells. J Biol Chem 284: 3956–3965.

Jeannin, P., Renno, T., Goetsch, L., Miconnet, I., Aubry, J.P., Delneste, Y., et al. (2000) OmpA targets dendritic cells, induces their maturation and delivers antigen into the MHC class I presentation pathway. Nat Immunol 1: 502–509.

Jeannin, P., Magistrelli, G., Goetsch, L., Haeufw, J.F., Thieblement, N., Bonnefoi, J.Y., and Delneste, Y. (2002) Outer membrane protein A (OmpA): a new pathogen-associated molecular pattern that interacts with antigen presenting cells-impact on vaccine strategies. Vaccine 20 (Suppl. 4): A23–A27.

Jeannin, P., Bottazzi, B., Sironi, M., Doni, A., Rusnati, M., Presta, M., et al. (2005) Complexity and complementarity of outer membrane protein A recognition by cellular and humoral innate immunity receptors. Immunity 22: 551–560.

Jiang, Y., Oliver, P., Davies, K.E., and Platt, N. (2006) Identification and characterization of murine SCARAs, a novel class A scavenger receptor that is expressed by populations of epithelial cells. J Biol Chem 281: 11834–11845.

Kapadia, S.B., Barth, H., Baumert, T., McKeating, J.A., and Chisari, F.V. (2007) Initiation of hepatitis C virus infection is dependent on cholesterol and cooperativity between CD81 and scavenger receptor B type I. J Virol 81: 374–383.

Kobayashi, Y., Miyaji, C., Watanabe, H., Umezlu, H., Hasegawa, G., Abo, T., et al. (2000) Role of macrophage scavenger receptor in endotoxin shock. J Pathol 192: 263–272.
Krishnegowda, G., Hajjar, A.M., Zhu, J., Douglass, E.J., Uematsu, S., Akira, S., et al. (2005) Induction of proinflammatory responses in macrophages by the glycosylphosphatidylinositol of Plasmodium falciparum: cell signaling receptors, glycosylphosphatidylinositol (GPI) structural requirement, and regulation of GPI activity. J Biol Chem 280: 8606–8616.

van der Laan, L.J., Dopp, E.A., Haworth, R., Pikkarainen, T., Lavillette, D., Tarr, A.W., Voisset, C., Donot, P., Bartosch, B., Means, T.K., Mylonakis, E., Tampakakis, E., Colvin, R.A., Massari, P., Visintin, A., Gunawardana, J., Halmen, K.A., McGilvray, I.D., Serghides, L., Kapus, A., Rotstein, O.D., and Mukhopadhyay, S., and Gordon, S. (2004) Acti-

Nakamura, K., Funakoshi, H., Tokunaga, F., and Nakamura, T. (2001) Molecular cloning of a mouse scavenger receptor with C-type lectin (SRCL) (1), a novel member of the scavenger receptor family. Biochim Biophys Acta 1522: 53–58.

Newbold, C., Warn, P., Black, G., Berendt, A., Craig, A., Snow, B., et al. (1997) Receptor-specific adhesion and clinical disease in Plasmodium falciparum. Am J Trop Med Hyg 57: 389–398.

Nicoletti, A., Caligiuri, G., Tornberg, L., Kodama, T., Stemme, S., and Hansson, G.K. (1999) The macrophage scavenger receptor type A directs modified proteins to antigen presentation. Eur J Immunol 29: 512–521.

Nogami, S., Watanabe, J., Nakagaki, K., Nakata, K., Suzuki, H., Suzuki, H., et al. (1998) Involvement of macrophage scavenger receptors in protection against murine malaria. Am J Trop Med Hyg 59: 843–845.

Ockenhouse, C.F., Ho, M., Tandon, N.N., Van Seventer, G.A., Shaw, S., White, N.J., et al. (1991) Molecular basis of sequestration in severe and uncomplicated Plasmodium falciparum malaria: differential adhesion of infected erythrocytes to CD36 and ICAM-1. J Infect Dis 164: 163–169.

Ohtani, K., Suzuki, Y., Eda, S., Kawai, T., Kase, T., Keshi, H., et al. (2001) The membrane-type collectin CL-P1 is a scavenger receptor on vascular endothelial cells. J Biol Chem 276: 44222–44228.

Ozeki, Y., Tsutsumi, H., Kawada, N., Suzuki, H., Kataoka, M., Kodama, T., et al. (2006) Macrophage scavenger receptor down-regulates mycobacterial cord factor-induced proinflammatory cytokine production by alveolar and hepatic macrophages. Microb Pathog 40: 171–176.

Patel, S.N., Serghides, L., Smith, T.G., Silverstein, R.L., Kurzt, T.W., et al. (2004) CD36 mediates the phagocytosis of Plasmodium falciparum-infected erythrocytes by rodent macrophages. J Infect Dis 189: 204–213.

Patel, S.N., Lu, Z., Ayi, K., Serghides, L., Gowda, D.C., and Kain, K.C. (2007) Disruption of CD36 impairs cytokine response to Plasmodium falciparum glycosylphosphatidylinositol and confers susceptibility to severe and fatal malaria in vivo. J Infect Dis 187: 3954–3961.

Peiser, L., De Winther, M.P., Makepeace, K., Hollinshead, M., Coull, P., Pliested, J., et al. (2002) The class A macrophage scavenger receptor is a major pattern recognition receptor for Neisseria meningitidis which is independent of lipopolysaccharide and not required for secretory responses. Infect Immun 70: 5346–5354.

Peiser, L., Gough, P.J., Kodama, T., and Gordon, S. (2000) Macrophage class A scavenger receptor-mediated phagocytosis of Escherichia coli: role of cell heterogeneity, microbial strain, and culture conditions in vitro. Infect Immun 68: 1953–1963.

Peiser, L., Makepeace, K., Plüddemann, A., Savino, S., Wright, J.C., Pizza, M., et al. (2006) Identification of Neisseria meningitidis nonlipopolysaccharide ligands for class A macrophage scavenger receptor by using a novel assay. Infect Immun 74: 5191–5198.

Phillips, J.A., Rubin, E.J., and Perrimon, N. (2005) Drosophila RNAi screen reveals CD36 family member required for mycobacterial infection. Science 309: 1251–1253.

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Scavenger receptors and their interactions with pathogens 1169

Pinheiro da Silva, F., Aloulou, M., Skurnik, D., Benhamou, M., Andremont, A., Velasco, I.T., et al. (2007) CD16 promotes Escherichia coli sepsis through an FcγR inhibitory pathway that prevents phagocytosis and facilitates inflammation. Nat Med 13: 1368–1374.

Plüddemann, A., Neyen, C., and Gordon, S. (2007) Macrophage scavenger receptors and host-derived ligands. Methods 43: 207–217.

Plüddemann, A., Hoe, J.C., Makepeace, K., Moxon, E.R., and Gordon, S. (2009a) The macrophage scavenger receptor A is host-protective in experimental meningococcal septicaemia. PLoS Pathog 5: e1000297.

Plüddemann, A., Mukhopadhyay, S., Sankala, M., Savino, S., Piazza, M., Rappuoli, R., et al. (2009b) SR-A, MARCO, and TLRs differentially recognize selected surface proteins from Neisseria meningitidis: an example of fine specificity in microbial ligand recognition by innate immune receptors. J Innate Immun 1: 153–163.

Rechner, C., Kühlwein, C., Müller, A., Schild, H., and Rudel, T. (2007) Host glycoprotein Gp96 and scavenger receptor SREC interact with PorB of disseminating Neisseria gonorrohoeae in an epithelial invasion pathway. Cell Host Microbe 2: 393–403.

Rodrigues, C.D., Hannus, M., Prudêncio, M., Martin, C., Gonçalves, L.A., Portugal, S., et al. (2008) Host scavenger receptor SR-BI plays a dual role in the establishment of meningococcal septicaemia. J Innate Immun 1: 153–163.

Sankala, M., Brännström, A., Schulthess, T., Bergmann, U., Plüddemann, A., Mukhopadhyay, S., Sankala, M., Savino, S., Piazza, M., Rappuoli, R., et al. (2009a) CD16 promotes Escherichia coli sepsis through an FcγR inhibitory pathway that prevents phagocytosis and facilitates inflammation. Nat Med 13: 1368–1374.

Su, Z., Fortin, A., Gros, P., and Stevenson, M.M. (2002) Opsonin-independent phagocytosis: an effector mechanism against acute blood-stage Plasmodium chabaudi AS infection. J Infect Dis 186: 1321–1329.

Sun, K., and Metzger, D.W. (2008) Inhibition of pulmonary antibacterial defense by interferon-γ during recovery from influenza infection. Nat Med 14: 558–564.

Suzuki, H., Kurihara, Y., Takeya, M., Kamada, N., Kataoka, M., Jishage, K., et al. (1997) A role for macrophage scavenger receptors in atherosclerosis and susceptibility to infection. Nature 386: 292–296.

Thomas, C.A., Li, Y., Kodama, T., Suzuki, H., Silverstein, S.C., and El Khoury, J. (2000) Protection from lethal Gram-positive infection by macrophage scavenger receptor-dependent phagocytosis. J Exp Med 191: 147–156.

Tohyama, M., Sayama, K., Komatsuza, H., Hanakawa, Y., Shirakata, Y., Dai, X., et al. (2007) CXCL16 is a novel mediator of the innate immunity of epidermal keratinocytes. Int Immunol 19: 1095–1102.

Villwock, A., Schmitt, C., Schielke, S., Frosch, M., and Kurzai, O. (2008) Recognition via the class A scavenger receptor modulates cytokine secretion by human dendritic cells after contact with Neisseria meningitidis. Microbes Infect 10: 1158–1165.

Vishnyakova, T.G., Bocharov, A.V., Baranova, I.N., Chen, Z., Remaley, A.T., Csako, G., et al. (2003) Binding and internalization of lipopolysaccharide by CLA-1, a human ortholog of rodent scavenger receptor B1. J Biol Chem 278: 31002–31011.

Vishnyakova, T.G., Kurlander, R., Bocharov, A.V., Baranova, I.N., Chen, Z., Abu-Asab, M.S., et al. (2006) CLA-1 and its splicing variant CLA-2 mediate bacterial adhesion and cytotoxic bacterial invasion in mammalian cells. Proc Natl Acad Sci USA 103: 16888–16893.

Waldemarsson, J., Areschoug, T., Lindahl, G., and Johnsson, E. (2006) The streptococcal B1r and S1r proteins define a family of surface proteins with leucine-rich repeats: camouflaging by other surface structures. J Bacteriol 188: 378–388.

Wessels, M.R., Rubens, C.E., Benedi, V.J., and Kasper, D.L. (1989) Definition of a bacterial virulence factor: sialylation of the group B streptococcal capsule. Proc Natl Acad Sci USA 86: 8983–8987.

Yalaoui, S., Huby, T., Franetich, J.F., Gego, A., Rametti, A., Moreau, M., et al. (2008) Scavenger receptor BI boosts hepatocyte permissiveness to Plasmodium infection. Cell Host Microbe 4: 283–292.

Zhu, F.G., Reich, C.F., and Pisetsky, D.S. (2001) The role of the macrophage scavenger receptor in immune stimulation by bacterial DNA and synthetic oligonucleotides. Immunology 103: 226–234.