REVIEW ARTICLE

Scavenger Receptors: Promiscuous Players During Microbial Pathogenesis

Rita Pombinho[a], Sandra Sousa[a], Didier Cabanes[a*]

[a] *Instituto de Investigação e Inovação em Saúde, i3S; Instituto de Biologia Molecular e Celular, IBMC; Group of Molecular Microbiology; Universidade do Porto; Porto, Portugal*

Contact: *Didier Cabanes; didier@ibmc.up.pt; Rua Alfredo Allen, 208, 4200-135 Porto, Portugal

Abstract

Innate immunity is the most broadly effective host defense, being essential to clear the majority of microbial infections. Scavenger Receptors comprise a family of sensors expressed in a multitude of host cells, whose dual role during microbial pathogenesis gained importance over recent years. SRs regulate the recruitment of immune cells and control both host inflammatory response and bacterial load. In turn, pathogens have evolved different strategies to overcome immune response, avoid recognition by SRs and exploit them to favor infection. Here, we discuss the most relevant findings regarding the interplay between SRs and pathogens, discussing how these multifunctional proteins recognize a panoply of ligands and act as bacterial phagocytic receptors.

Key words: Innate immune response, Scavenger Receptors, pathogens, microbial pathogenesis

Scavenger Receptors: an emergent family of Pattern Recognition Receptors

Host cells are effective guardians of the immune response through the expression of complex surveillance systems, including the Pattern Recognition Receptors (PRRs) (Pluddemann et al. 2011). SRs include a diverse and evolutionary conserved family of PRRs that are functionally and structurally distinct. They are soluble or cell surface associated proteins originally implicated on the recognition and binding of modified lipoproteins. Indeed, the scavenger activity of these receptors was first associated to their ability to bind and internalize oxidized low-density lipoproteins (Brown and Goldstein 1979). Oxidized low-density lipoproteins were implicated in the pathogenesis of atherosclerosis by challenging normal homeostasis (Kzhyshkowska et al. 2012). By recognizing specific epitopes, SRs can differentiate between unaltered and modified self-molecules (Greaves and Gordon 2009). However, the range of ligands that SRs recognize is extremely diverse and it is now appreciated that SRs eliminate a number of altered self- and non-self-ligands (extensively reviewed elsewhere) (Areschoug and Gordon 2008, 2009; Mukhopadhyay and Gordon 2004; Pluddemann et al. 2006). Diverse cell processes ranging from

endocytosis to phagocytosis or macropinocytosis are usually undertaken to eliminate unwanted ligands and maintain homeostasis (Prabhudas et al. 2014). Importantly, SRs are widely expressed in cells patrolling potential portals of pathogen entry, such as macrophages, neutrophils, dendritic cells, microglia and B cells, but they are also expressed in endothelial and epithelial cells (Mukhopadhyay and Gordon 2004; Murphy et al. 2005; Platt and Gordon 2001). Currently, SRs are categorized into 10 classes (A-J) grouped according to their sequence similarity or common structural features (Fig. 1) (Prabhudas, et al. 2014). Several SRs have been reported to play opposite roles during bacterial infection: whereas at portals of pathogen invasion SRs recognize a myriad of microbial proteins activating downstream immune responses to fight and eliminate the pathogen, some pathogens hijack SRs function exploiting them to bind and invade cells, thus promoting intracellular survival and proliferation. Having in mind that SRs have a primordial role to maintain homeostasis by controlling cell integrity, which may impact pathogen infection (Trahtemberg and Mevorach 2017), this review focuses on SRs as an emergent family of PRRs, and their interplay with different pathogens to either promote an effective innate immune response or by the contrary, favor microbial pathogenesis.

Scavenger Receptors from Class A

Class A SR includes five membrane proteins containing a collagen-like domain with collagen-binding activity (Fig. 1) (Gowen et al. 2001; Kodama et al. 1990; Zani et al. 2015). These proteins are primarily expressed in tissue-resident macrophages and dendritic cells (Hughes et al. 1995). Their role in bacterial pathogenesis was essentially reported for Scavenger Receptor A (SR-A) and Macrophage Receptor with Collagenous Structure (MARCO).

SR-A

SR-A has long been shown to bind to *Escherichia coli* lipopolysaccharide (LPS) and lipoteichoic acids from some Gram-positive bacteria and was thus suggested to be implicated in host defense (Dunne et al. 1994; Hampton and Raetz 1991). Further studies revealed its involvement in the pathogenesis of different microorganisms and importantly, pointed to the dual role of SR-A in infection, either by favoring the host response contributing to pathogen elimination or by promoting pathogen survival and dissemination.

In particular, SR-A was reported to be detrimental for the host during ***Mycobacterium tuberculosis*** (*Mtb*) infection of alveolar macrophages. Indeed, SR-A knock-out (KO) mice display increased survival to pulmonary tuberculosis (Ulrichs and Kaufmann 2006). Histopathology analysis of infected lungs showed *Mtb* within cholesterol clefts and multinucleated foam cells in SR-A KO mice, whilst necrotic macrophages obstructing alveolar and bronchial spaces were detected in wild type (WT) mice (Sever-Chroneos et al. 2011). In addition, the analysis of cell populations in infected lungs revealed increased recruitment of CD4+ lymphocytes and antigen-presenting cells (APCs) in SR-A KO mice, suggesting SR-A as a negative regulator of pulmonary adaptive immunity during chronic *Mtb* infection (Fig. 2) (Sever-Chroneos, et al. 2011). SR-A was also reported to be disadvantageous for the host during ***Cryptococcus***

neoformans and ***Pneumocystis carinii*** infections. As described for *Mtb* infection, SR-A KO mice displayed improved pulmonary fungal clearance, which is intimately associated with stronger accumulation of $CD4^+$ T cells and $CD11b^+$ myeloid cells in the lungs (Hollifield et al. 2007; Qiu et al. 2013). Together, these reports suggest that SR-A confers an advantage for pathogens infecting host lungs and reinforce the idea that SRs can be exploited by pathogens to promote their survival within the host. SR-A KO mice were less prone to ***Brucella abortus*** infection, which is attributed to decreased bacterial internalization and intracellular replication within SR-A-deficient macrophages (Kim et al. 2004). SR-A was also implicated in the non-opsonic phagocytosis of two major Gram-positive pathogens, ***Streptococcus agalactiae*** (GBS) and ***Streptococcus pyogenes***, by murine bone marrow-derived macrophages. The polysaccharide capsule or the bacterial surface lipoprotein Blr of GBS and the surface M protein of *S. pyogenes* were shown to prevent SR-A-mediated recognition and non-opsonic phagocytosis (Fig. 2) (Areschoug and Gordon 2008; Carlsson et al. 2005).

Reversely, SR-A also appears to be crucial to protect the host from pathogen damage. ***Neisseria meningitidis*** binds bone marrow-derived macrophages almost exclusively through SR-A and independently from LPS, suggesting that SR-A-expressing macrophages may be critical in the innate host immune response to meningococci (Peiser et al. 2002). Additionally, binding assays aiming to uncover SR-A ligands identified three *N. meningitidis* proteins: NMB1220, NMB0278 and NMB0667 (Fig. 2). Soluble forms of these proteins were shown to block the binding of meningococci to CHO cells stably transfected with SR-A. Nevertheless, the authors claimed that only NMB1220 induced SR-A-mediated endocytosis in macrophages (Peiser et al. 2006). SR-A-mediated phagocytosis of viable *N. meningitidis* highly stimulates DCs, considered the first line of defense against invading *N. meningitidis,* and the release of pro-inflammatory cytokines, including TNF-α, IL-1β and IL-6 (Fig. 2). Interestingly, SR-A was reported transiently dephosphorylated shortly after meningococci contact, suggesting that SR-A engagement in response to bacterial binding elicits intracellular signaling to trigger a cellular response (Villwock et al. 2008). Importantly, *N. meningitidis* infected SR-A KO mice showed reduced survival as compared to WT mice, exhibiting higher levels of bacteremia and circulating IL-6, which is commonly associated with meningococcal septicemia in humans (Fig. 2) (Pluddemann et al. 2009; Prins et al. 1998). Additionally, the lack of SR-A was reported to impair host survival against infections by ***Mycoplasma pulmonis*** and ***Staphylococcus aureus*** (Fig. 2) (Booth et al. 2014; Thomas et al. 2000).

Concerning ***Listeria monocytogenes*** infection, different studies pointed to the beneficial role of different SR-A isoforms in host protection. SR-AI (SR-A1) KO mice showed higher susceptibility to *L. monocytogenes* infection, with highly increased bacterial burden and decreased host survival (Suzuki et al. 1997). The increased susceptibility of SR-AI KO mice to *L. monocytogenes* infection was related with a defect in the uptake or killing of bacteria by macrophages (Fig. 2) (Suzuki, et al. 1997). Mice KO for both SR-AI and SR-AII (SR-A1.1) were also shown to be more susceptible to *L. monocytogenes* infection and displayed increased hepatic granuloma formation regarding their number, dimension and persistence throughout the infection (Fig. 2) (Ishiguro et al. 2001). Concomitantly, Kupffer cells and peritoneal

macrophages from SR-AI/II KO mice showed decreased *L. monocytogenes* phagocytosis. Moreover, the listericidal phagocytic activity of WT macrophages was impaired in the presence of an anti-SR-AI/II blocking antibody (Ishiguro, et al. 2001). SR-AI/II were thus proposed to play a crucial role in host defense against *L. monocytogenes* infection not only by acting as a receptor for its phagocytosis, but also by mediating listericidal mechanisms (Fig. 2) (Ishiguro, et al. 2001).

SR-A was also suggested to orchestrate innate and adaptive immune response to specific infections. Indeed, SR-A was elegantly shown to directly interact with interferon-regulatory factor 5 (IRF5) in ***Schistosoma japonicum*** infected macrophages, thus impairing IRF5 nuclear translocation, interfering with macrophage polarization and ultimately stimulating T-helper responses from type 2. In this context, SR-A acts to modulate macrophage polarization and fine-tune T-cell differentiation. SR-A KO mice displayed exacerbated death upon *S. japonicum* infection (Z. Xu et al. 2017).

Pulmonary surfactant is composed by a variety of lipids and proteins, including surfactant protein A (SP-A), which prevents alveoli collapsing during expiration (Kuroki and Voelker 1994). It was reported that SP-A increases cell surface localization of SR-A and potentiates SR-A-mediated phagocytosis of ***Streptococcus pneumoniae*** by alveolar macrophages promoting bacterial clearance (Kuronuma et al. 2004). In agreement, SR-A KO mice displayed increased mortality rate upon *S. pneumoniae* infection, possibly due to an impaired phagocytosis, that lead to reduced clearance of live bacteria from the lungs and highly increased lung inflammation (Fig. 2) (Arredouani et al. 2006). Altogether, the data compiled above show that SR-A enhances host resistance to several pathogens, being essential to limit the severity of certain infections.

Other reports point to the interplay between SR-A and other pathogens, however specific outcomes in the context of infection need further analysis. ***Clostridium perfringens***, which has the ability to survive within murine macrophage-like cell lines (O'Brien and Melville 2000), was shown to bind to CHO cells in a SR-A-dependent manner (Fig. 2) (O'Brien and Melville 2003). ***Porphyromonas gingivalis*** induces the expression of SR-A by macrophages (Bodet et al. 2007). This increase is partially dependent on the major fimbriae of *P. gingivalis* FimA and promotes TNF-α, thus suggesting a role for SR-A in inflammation (Fig. 2) (Baer et al. 2009).

Finally, SR-A was reported to act as a receptor for pathogen phagocytosis. This was shown for ***Escherichia coli*** and ***Francisella tularensis*** in dendritic cells and macrophages, respectively (Amiel et al. 2007; Pierini 2006). Binding and phagocytosis of yeast ***Saccharomyces cerevisiae*** and ***Candida albicans*** was also shown to be dependent on SR-A (Fig. 2) (Wang and Chandawarkar 2010). In addition, SR-A was shown to bind bacterial DNA (Zhu et al. 2001) and double-stranded RNA (DeWitte-Orr et al. 2010; Limmon et al. 2008) and was involved in virus recognition, namely in the uptake of **Adenovirus type 5** (Ad5) and endocytosis of **Adeno-associated virus serotype 8** (Haisma et al. 2009; van Dijk et al. 2013).

SR-A appears thus as a SR capable to recognize a wide range of microbes, and contributes to pathogen containment by modulating the recruitment and activation of phagocytic cells and regulating

inflammatory response through cytokine secretion. To counteract this function, some microbes evolved strategies to evade SR-A dependent recognition and phagocytosis.

MARCO

MARCO (SR-A6) has also an ambiguous involvement in pathogen infections, either being beneficial or detrimental for the host response. It is constitutively expressed in specific macrophage subpopulations and was primarily reported to bind soluble LPS and intact Gram-positive and Gram-negative bacteria. (Elomaa et al. 1995; Sankala et al. 2002). Recent studies deployed an effort to clarify the impact of this SR in infection. The lack of MARCO was shown to induce different outcomes upon SR interaction with bacteria, virus, fungus and even parasites.

MARCO induces increased morbidity and mortality of mice with **Influenza A** associated pneumonia, due to a diminished neutrophilic inflammatory response (Ghosh et al. 2011). In addition, it is exploited by **Herpes Simplex Virus** type 1 glycoprotein C to promote cell surface adsorption and infection in the skin (Fig.3) (MacLeod et al. 2013). These data suggest that MARCO suppresses an early inflammatory response against these viral infections. Curiously, MARCO was shown to significantly enhance **Adenovirus** infection, contributing to an efficient innate virus recognition by macrophages, that in turn potentiates a pro-inflammatory response (Maler et al. 2017).

In opposition, MARCO improves host resistance and promotes pathogen clearance through its capacity to recognize, bind and internalize different bacteria. MARCO KO mice intranasally infected with ***Streptococcus pneumoniae*** displayed a diminished survival rate, due to an impaired ability to clear bacteria from the lungs and consequently increased pulmonary inflammation (Fig. 3). Both *in vitro* binding of *S. pneumoniae* and *in vivo* uptake of non-opsonized particles were drastically impaired in MARCO KO alveolar macrophages (Arredouani et al. 2004). Later, MARCO was revealed crucial against *S. pneumoniae* in the murine model, MARCO KO mice showing a defect on bacterial clearance from the nasopharynx. In addition, MARCO deficiency abrogates cytokine production and cellular recruitment to the nasopharynx following colonization. Maximal TLR2- and NOD2-dependent NF-κB activation was shown to be MARCO-dependent (Fig. 3) (Dorrington et al. 2013).

Regarding ***Mycobacterium tuberculosis (Mtb)***, MARCO-deficient macrophages are unable to mount an efficient inflammatory response to bacterial infection. MARCO, which is a tethering receptor for the cell wall glycolipid TDM (trehalose 6,6′-dimycolate) of *Mtb*, presumably presents lipids to the CD14/TLR2 complex (Bowdish et al. 2009). MARCO is essential for phagocytosis of ***Mycobacterium marinum*** by zebrafish macrophages, being crucial to control bacterial growth and inflammatory response (Benard et al. 2014). Moreover, peritoneal macrophages from MARCO KO mice showed impaired ***Clostridium sordellii*** phagocytosis, which correlated with MARCO KO mice being more susceptible to *C. sordellii* uterine infection (Thelen et al. 2010). MARCO also efficiently contributes to limit ***Cryptococcus neoformans*** infection, controlling the recruitment of monocytes and dendritic cells and regulating the levels of IFN-γ. Additionally, MARCO is involved in *C. neoformans* phagocytosis by resident pulmonary

macrophages and dendritic cells (Xu et al. 2017). These findings confer an important role for MARCO as a phagocytic receptor essential to clear pathogens.

Microbial infection is intimately associated with an increased MARCO expression, which suggests its role in host defense. *In vivo* studies showed a transient but substantial expression of MARCO in liver Kupffer cells and red pulp macrophages of the spleen following intravenous infection by ***Listeria monocytogenes*** (Fig. 3) (Ito et al. 1999). In line with this, MARCO/SR-A double KO mice intraperitoneally inoculated with *L. monocytogenes* displayed slightly higher bacterial loads in the spleen and liver than the WT mice, although WT and KO mice showed equal survival rates (Chen et al. 2010). The expression of MARCO is also rapidly induced on macrophages, including Kupffer cells, upon **Bacillus Calmette-Guérin** (BCG) infection or injection of purified LPS (van der Laan et al. 1999), and in response to both *in vitro* and *in vivo* ***Leishmania major*** infections. *L. major* infection of macrophages is partially reduced *in vitro* by specific anti-MARCO monoclonal antibody, supporting a role of MARCO in macrophage infection by this parasite (Fig. 3) (Gomes et al. 2009). Besides macrophages, a strong increase in *MARCO* expression was reported in astrocytes during meningococcal-associated meningitis, showing that ***Neisseria meningitidis*** induces glial cell activation *via* MARCO (Fig. 3) (Braun et al. 2011). Given that MARCO has the ability to recognize *N. meningitidis* independently from LPS (Mukhopadhyay et al. 2006) glial cell activation may dependent on specific meningococcal components.

Contrarily, the lipoprotein PpiA of ***Streptococcus mutans*** negatively regulates the expression of MARCO at the transcriptional and translational levels, which in turn contributes for the suppression of MARCO-mediated phagocytosis by macrophages (Fig. 3) (Mukouhara et al. 2011).

So far, MARCO has been involved in the recognition and pathogenesis of both Gram-positive and Gram-negative bacteria, parasites, fungi and various viruses. It usually behaves as a protective molecule for the host, stimulating phagocytosis, cellular recruitment and cytokine production. Several studies have shown that MARCO is differentially regulated/expressed in response to certain pathogens, suggesting its potential as a host innate immune receptor. This SR is also overcome and/or exploited by some pathogens to promote infection.

Other class A SRs

Among the less characterized members of SRs class A, SCARA5 (SR-A5), which is exclusively expressed by epithelial cells, was reported to bind heat-killed ***Escherichia coli*** **and** ***Staphylococcus aureus*** (Jiang et al. 2006) and SRCL (SR-A4) has the ability to bind and phagocytose bacteria and yeast, suggesting its possible role in host defense (Jang et al. 2009; Nakamura et al. 2001; Ohtani et al. 2001).

Scavenger Receptors from class B

The members that belong to class B SRs are characterized by the presence of two transmembrane domains flanking an extracellular loop, with both the amino and carboxyl terminal located within the cytosol (Fig.

1) (Asch et al. 1987). CD36 is the prototype of class B SR and has been largely involved in microbial pathogenesis.

CD36

CD36 (SR-B2) senses both Gram-positive LTA and Gram-negative LPS, acting as a phagocytic receptor for a number of pathogenic bacteria, such as ***Escherichia coli***, ***Klebsiella pneumoniae***, ***Salmonella typhimurium***, ***Staphylococcus aureus*** **and** ***Enterococcus faecalis*** (Fig. 4) (Baranova et al. 2008). Bacterial chaperonin 60, GroEL, and LPS potentially contribute to bacteria-induced inflammation by triggering SR-Bs (SR-BI, SR-BII and CD36), which mediate inflammatory signaling thus strongly impacting innate immunity and host defense (Baranova et al. 2012). CD36 has a protective role in skin infections caused by Hla-producing *S. aureus* which are characterized by a local inflammatory response that often precedes the formation of necrotic lesions. CD36 KO mice intoxicated with sterile *S. aureus* supernatant showed enhanced dermonecrosis, with increased neutrophil accumulation and local IL-1β expression. The contribution of neutrophils to tissue injury was confirmed since dermonecrosis is almost abolished upon neutrophil depletion (Fig. 4) (Castleman et al. 2015). CD36 also provides host protection against ***Klebsiella pneumoniae*** and ***Streptococcus pneumoniae*** intrapulmonary infections, modulating host inflammatory response and enhancing macrophage phagocytosis (Olonisakin et al. 2016; Sharif et al. 2013).

In turn, CD36 was also reported to benefit the pathogens during infection. This is the case for *S. aureus* infection of lung epithelial cells that was suggested to be driven by Tet38 efflux pump by interacting with CD36 (Truong-Bolduc et al. 2017), and for ***Listeria monocytogenes*** invasion of HeLa cells which increases by 20-fold in CD36 overexpressing cells (Vishnyakova et al. 2006). In addition, CD36 deficiency confers resistance to ***Mycobacterium tuberculosis*** infection. CD36 KO mice display reduced bacterial burden in both spleen and liver, decreased density of granulomas and diminished levels of circulating tumor necrosis factor (TNF) (Fig. 4) (Hawkes et al. 2010). Of note, ***Porphyromonas gingivalis*** infected macrophages *up-regulate* CD36 expression *via* ERK/NF-kβ pathway (Liang et al. 2016).

Regarding parasite infection, CD36 was demonstrated to be the most common target of the PfEMP1 proteins of ***Plasmodium falciparum***, tethering parasite-infected erythrocytes to endothelial receptors, thus preventing their splenic clearance and allowing increased parasitaemia (Fig. 4) (Hsieh et al. 2016). Taken together these data support a dual role for CD36 in infection, being useful or not for pathogen elimination.

SR-B

Several studies pointed to the involvement of SR-B in viral infection. It was previously recognized essential for virus uptake, cell-to-cell transmission and cross-presentation by human dendritic cells. In addition, SR-B expression is modulated upon cell contact with **Hepatitis C virus** (HCV) (Barth et al. 2008; Fan et al. 2017; Schwarz et al. 2009).

In bacterial infections, SR-B may act as a multi-recognition receptor crucial to potentiate host response or to promote pathogen invasiveness and survival. SR-BI (SR-B1) KO mice showed increased mortality throughout ***Klebsiella pneumoniae*** infection, which correlates with high bacterial burden in the lung and in the blood, increased serum cytokines, neutrophils recruitment to the infected airspace, impaired phagocytic clearance and markedly organ injury (Gowdy et al. 2015).

Reversely, SR-B promotes infection by ***Chlamydia pneumoniae*** improving bacterial attachment, internalization and growth into epithelial cells, and by ***Brucella abortus*** increasing the phagocytic activity of trophoblasts giant cells (Korhonen et al. 2012; Watanabe et al. 2010). Although SR-B was reported to recognize *Mtb*, the effects in infection remain to be addressed (Schafer et al. 2009).

SR-BI, which is a high-density lipoprotein receptor able regulate the formation of lipid domains including cholesterol-rich domains (Acton et al. 1996; Urban et al. 2000), was described to mediate bacterial adhesion and invasion to mammalian cell (Urban, et al. 2000). In a recent study using ***Listeria monocytogenes*** intraperitoneal mice infection, SR-BI was proposed to prevent tissue damage without altering pathogen burden. SR-BI would activate autophagy mechanisms to protect organs, such as the liver and spleen, from the collateral damage induced by antibacterial defenses (Pfeiler et al. 2016). SR-BI-induced autophagy suppresses tissue damage by preventing necrosis at the infectious foci, stimulating the internalization and clearance of apoptotic cells and inhibiting extravasation and accumulation of neutrophils and inflammatory macrophages in infected tissues (Pfeiler, et al. 2016).

The interplay between SR-B and parasites was also addressed. SR-BI significantly boosts hepatocyte permissiveness to ***Plasmodium falciparum***, ***Plasmodium yoelii***, *and* ***Plasmodium berghei*** and promotes parasite development. Interestingly, SR-B is responsible for the regulation of CD81 localization at the plasma membrane, mediating a membrane rearrangement that facilitates sporozoites penetration (Yalaoui et al. 2008). So far, these data indicate that SR-B not only favors host response but also pathogen dissemination.

Scavenger Receptors from classes D and I

CD68 (SR-D1), the only member of class D SR, is a glycosylated membrane protein that belongs to the lysosome-associated membrane protein family (LAMP) (Fig. 1) (Song et al. 2011). Its role in microbial pathogenesis is largely unknown. A peptide from ***Plasmodium*** was shown to interact with CD68 at the surface of Kupffer cells. The exogenous addition of this peptide inhibited sporozoite entry and subsequent traversal of Kupffer cells and liver infection, which strongly supports a role for CD68 as a *Plasmodium* receptor in the liver (Cha et al. 2015).

Class I SRs are also transmembrane proteins characterized by an extracellular region with multiple scavenger receptor cysteine-rich (SRCR) domains (Fig.1) (Kristiansen et al. 2001). Among them, CD163 (SR-I1) is a membrane receptor exclusively expressed in monocytes and macrophages but may be shed from cell surface upon cell activation. It plays important roles in the down-regulation of inflammation (Etzerodt and Moestrup 2013), but also functions as a sensor for Gram-positive and Gram-negative

bacteria (Fabriek et al. 2009). In particular, it was demonstrated that soluble CD163 recognizes a specific fragment of fibronectin bound to ***Staphylococcus aureus*** surface molecules, leading to increased phagocytosis and effective bacterial killing by professional phagocytes (Kneidl et al. 2012). In addition, interactions of CD163 with some viral species are also known. CD163 is one of the receptors for Porcine reproductive and respiratory syndrome virus **(PRRSV)** (Calvert et al. 2007) and its absence is sufficient to protect fetuses following maternal infection with the virus (Prather et al. 2017). The infection process by African swine fever virus **(ASFV)** and Simian hemorrhagic fever virus **(SHFV)** is also dependent on CD163 expression, being knockout cells less permissive to viral infection (Cai et al. 2015; Sanchez-Torres et al. 2003). Human immunodeficiency virus-1 **(HIV)** infection is also enhanced in macrophages through the induction of CD163 expression, suggesting a role for this SR as a broad viral receptor that favors pathogen dissemination (Tuluc et al. 2014).

Although CD5 and CD6 are both implicated on the modulation and signalling of T and B cell receptors, CD5 is well adapted to interact with fungal associated ligands, while CD6 has evolved to recognize bacterial ones (Sarrias et al. 2007; Vera et al. 2009). T cells expressing CD5 were shown to be more permissive to Hepatitis C virus **(HCV)** infection, promoting pathogen dissemination (Sarhan et al. 2012). On the other hand DMBT1 (Salivary Agglutinin or gp340) was previously found to inhibit human immunodeficiency virus-1 **(HIV-1)** infection (Chu et al. 2013) and to be associated with the activation of the complement (Leito et al. 2011). This SR was shown to interact and agglutinate several Gram-positive and Gram-negative bacteria, including ***Streptococcus mutants*** (Ericson and Rundegren 1983; Madsen et al. 2010). Human Spα has the same domain organization as the extracellular region of CD5 and CD6 and may regulate monocyte activation, function and survival (Fig. 1) (Gebe et al. 1997). Human recombinant Spα, that is the homologue of the mouse protein AIM, was found to interact *in vitro* with Gram-negative and Gram-positive bacteria, including ***Listeria monocytogenes*** (Bessa Pereira et al. 2016; Sarrias et al. 2005).

Scavenger Receptors from classes E, F, G, H and J

While class E of SRs includes type II membrane proteins with C-type lectin-like domains, classes F and H are type I membrane proteins that contain extracellular domains with multiple Epidermal Growth Factor (EGF)-like repeats either alone (class F) or in combination with Fasciclin and laminin EGF-like domains (Class H) (Fig. 1) (Politz et al. 2002; Sawamura et al. 1997). Class G is composed by a single member that is not structural similar with other SRs. It is a type I transmembrane glycoprotein with a CXC chemokine domain and a mucin-like domain (Bazan et al. 1997). The only member of class J of SRs is composed by a single transmembrane domain and belongs to the immunoglobulin superfamily (Fig.1) (Ibrahim et al. 2013).

LOX-1

LOX-1 (SR-E1) was previously implicated on adhesion of ***Staphylococcus aureus*** and ***Escherichia coli*** (Shimaoka et al. 2001). Its expression was shown to be *up-regulate*d in response to ***Aspergillus fumigatus, Chlamydia pneumoniae*** and **Herpes simplex virus I** (HSV-1) infection, suggesting a role for LOX-1 in host defense mechanisms against pathogen infections (Campbell et al. 2013; Chirathaworn et al. 2004; Gao et al. 2016; Li et al. 2015; Yoshida et al. 2006). In addition, *E. coli* surface-associated GroEL is recognized by LOX-1 on macrophages, stimulating their phagocytic capacity and enhancing bacterial clearance (Fig. 4) (Zhu et al. 2013). OmpA from ***Klebsiella pneumoniae*** was also reported to bind LOX1 and SREC, activating macrophages and dendritic cells (DCs) in a TLR2-dependent way. Cellular recognition of *K. pneumoniae* OmpA activates a pro-inflammatory response beneficial for the host innate immune response (Jeannin et al. 2005).

DECTIN-1

Dectin-1 (SR-E2) binds to β-glucans from various fungal pathogens, usually protecting the host from infection. Therefore, Dectin-1 KO mice were shown to be more susceptible to infections with ***Candida albicans, Candida glabrata*** and ***Aspergillus fumigatus*** (Chen et al. 2017; Taylor et al. 2007; Werner et al. 2009). Phagocytosis stimulation, ROS and cytokine production, inflammasome activation and T helper cell differentiation are some of the anti-fungal responses generated by this receptor (Geijtenbeek and Gringhuis 2009).

CD206

The human mannose receptor, CD206 (SR-E3) is involved in the recognition of glycans at the surface of some pathogens, such as ***Mycobacterium tuberculosis, Streptococcus pneumonia, Yersinia pestis, Candida albicans, Pneumocystis carinii,*** **Influenza virus** and ***Leishmania*** promoting their phagocytosis (Medzhitov 2007). Moreover, CD206 protects against ***Cryptococcus neoformans*** infection due to its role in the development of CD4+ T cells that specifically work to eliminate the pathogen (Dan et al. 2008).

SREC

SREC (SR-F1) was previously described to recognize and internalize molecular chaperones and heat shock proteins (Gong et al. 2009). Curiously, ***Neisseria meningitidis*** expressing the serotype A of the major outer membrane porin PorB ($PorB_{IA}$) interacts with SREC via Gp96 allowing adherence to host cells. However, the invasion process requires the dissociation of Gp96 from SREC, since SREC is masked by surface-exposed Gp96, impairing $PorB_{IA}$ binding (Fig. 4). In that sense, the depletion of Gp96 from host cells prevented adherence but significantly triggered gonococcal invasion.(Rechner et al. 2007) Gp96 is an endoplasmic reticulum (ER) resident chaperone previously reported to modulate the interaction between pathogens with their host cells. It was shown to interact with the Outer Membrane Protein A (OmpA) of ***Escherichia coli*** and with the Vip surface protein of *L. monocytogenes*, thereby

supporting invasion, however its interaction with SREC was not described in those cases (Cabanes et al. 2005; Prasadarao et al. 2003). SREC may also have a role in Leptospirosis since it has the potential to bind to ***Leptospira*** LipL32, which is an immunogenic outer membrane protein (Fig. 4) (Chaemchuen et al. 2011). Notable is the cooperation of both SR-AI and SREC-I with TLR2 to recognize **Hepatitis C virus** non-structural protein 3 (NS3) and induce myeloid cell activation (Beauvillain et al. 2010). More recently, SREC-I was found to bind ***Staphylococcus aureus*** wall teichoic acids (WTAs) and mediate adhesion to nasal epithelial cells *in vitro* (Fig. 4). Additionally, the inhibition of WTA-mediated adhesion with a specific SREC-I antibody reduces nasal colonization in the animal model (Baur et al. 2014).

SR-PSOX

SR-PSOX (SR-G1) mediates adhesion and phagocytosis of both Gram-positive and Gram-negative bacteria and it was shown to play a particular role in T and NKT cells chemotaxis, suggesting a role for this SR in innate and adaptive immunity during microbial infection (Shimaoka et al. 2003; Xu et al. 2005). Expression levels of this SR were associated with different pathogenic conditions. High levels of SR-PSOX were correlated with lung transplant recipients affected by **Human Cytomegalovirus (HCMV)** (Weseslindtner et al. 2014). In addition, a virulence factor named zonula occludens toxin, produced by **Campylobacter concisus,** induced an upregulation of SR-PSOX, which may provide some insights on the bacterial mechanisms that affect the host (Deshpande et al. 2016). Higher expression levels of this SR were also associated with a more efficient cell migration to the secondary lymphoid organs and infected tissues upon **Leptospira** infection (Domingos et al. 2017).

STABILIN-1

Stabilin-1 (SR-H1) was found to bind to Gram-positive and Gram-negative bacteria, suggesting a role for this receptor in the defense mechanism against bacterial infection (Adachi and Tsujimoto 2002).

RAGE

RAGE (SR-J1) plays an important role in inflammation and infection having a dual role in bacterial infection. It plays a detrimental role in host response to ***Streptococcus pneumoniae*** and **influenza A virus** by promoting bacterial dissemination and potentiating pulmonary inflammatory response (van Zoelen et al. 2009a; van Zoelen et al. 2009b). On the other hand, it has a protective role during ***Staphylococcus aureus*** infection promoting lung injury in the early infection phase and contributing to effective antibacterial defense during ***Klebsiella pneumoniae*** pneumonia (Achouiti et al. 2016; Achouiti et al. 2013).

Conclusion

Throughout lifetime we are permanently in contact with a multitude of microbial species, which are usually targeted by our immune defenses in an effective way to prevent infection. PRRs are key players

in the initiation of the host innate immune response. SRs compose a diverse family of PRRs mainly expressed in cells patrolling pathogen invasion and with an increasing role in pathogen recognition and elimination. Whereas, some microbes developed strategies to evade SR-dependent recognition, SRs mainly appear as PRRs capable to recognize a wide range of microbes, and contributes to pathogen containment by modulating the recruitment and the activation of phagocytic cells, and regulating inflammatory response through cytokine secretion. Interestingly, different SRs are capable to recognize the same kind of ligands, and different pathogens are recognized by SRs binding various ligands. This suggest that, in addition to other PRRs, the host use a range of SRs to recognize specific ligands and activate downstream signaling pathways accordingly to their tissue-specific and cell type-specific expression. In the future, it will be interesting to understand the mechanisms that regulate these pathways, and identify potential crosstalk between SRs that recognize the same ligands or pathogens.

It is highly probable that other/new SRs will be implicated in microbial pathogenesis, increasing our understanding of the host/pathogen interplay and providing crucial insights into the immune responses orchestrated by the host to avoid microbial predation. Understanding the complexity of this network may pave the way for the identification of novel targets and pathways to limit pathogenic infection by amplifying protective the host cell response.

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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Figure Legends

Figure 1. Schematic overview of SRs families. SRs are either transmembrane or soluble proteins distributed into 10 classes, from A to J, according to their sequence or structural similarities. Protein and carbohydrate domains that compose SR members are indicated.

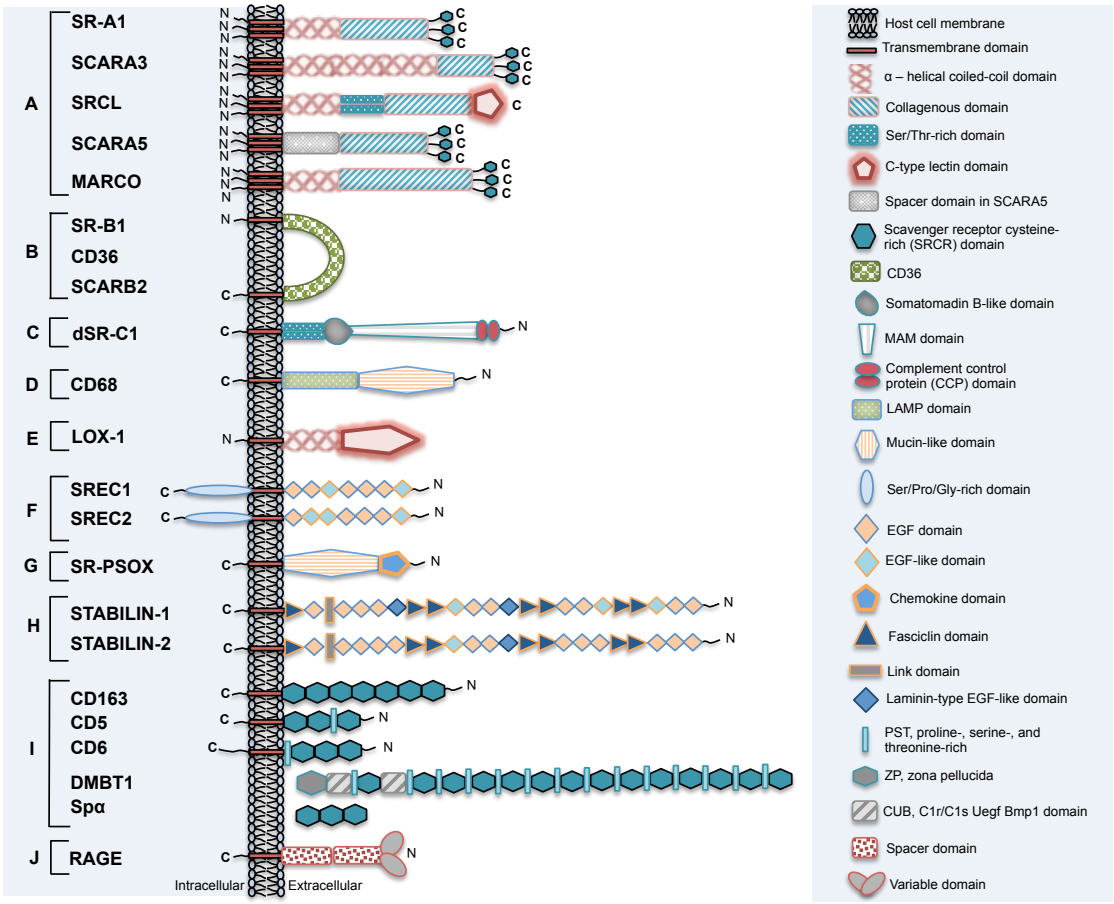
Figure 2. The most relevant functions of SR-A in microbial pathogenesis. SR-A binds to different pathogen components and act as receptor for different bacteria, virus and yeasts. SR-A is a negative regulator of chronic *Mtb, C. neoformans* and *P. carinii* infections, as SR-A KO mice show increase lymphocyte and APCs recruitment. Contrarily, SR-A positively regulates immune response against *S. pneumoniae, N. meningitidis, M. pulmonis, S. aureus* and *L. monocytogenes* mainly by potentiating bacterial phagocytosis and clearance. *In vitro* assays show that SR-A exposed at the surface of epithelial cells mediates adherence to *C. perfringens* and in the case of *N. meningitidis* and *P. gingivalis*, SR-A interacts with bacterial proteins, stimulating inflammatory response. *S. pyogenes* and *S. agalactiae* display evasion mechanisms to avoid SR-A-mediated phagocytosis through the expression of M protein and polysaccharide capsule, respectively. SR-A, Scavenger Receptor A; WT, wild-type; KO, knock-down; LPS, lipopolysaccharide; LTA, lipoteichoic acid; dsRNA, double-stranded ribonucleic acid; DNA, deoxyribonucleic acid; APCs, antigen-presenting cells; FimA, fimbrillin; SP-A, surfactant protein A. See text for details.

Figure 3. The most relevant functions of MARCO in microbial pathogenesis. MARCO binds to *E. coli* LPS and to *S. aureus* and, it promotes cell surface adsorption and skin infection by HSV. MARCO is a negative regulator of the inflammatory response against Influenza A virus. However, MARCO is essential for controlling host immune response to *M. marinum, S. pneumoniae, C. sordellii, L. monocytogenes* and *C. neoformans* infections, being WT mice or WT morpholino highly resistant to infection. *S. pneumoniae* clearance, which is MARCO-dependent, stimulates TLR2- and NOD2-dependent NF-κB activation and signaling. MARCO expression is *up-regulated* in macrophages, spleen and glial cells in response to *L. major, N. meningitides, L. monocytogenes* and *S. pneumoniae* infections. The lipoprotein PpiA of *Streptococcus mutans* contributes to the anti-phagocytic activity mediated by MARCO. MARCO, macrophage receptor with collagenous structure; WT, wild-type; KO, knock-down; LPS, lipopolysaccharide; NOD2, nucleotide-binding oligomerization domain-containing protein 2; TLR2, Toll-like receptor 2; NF-kB, nuclear factor kappa B; PpiA, peptidyl-prolyl *cis/trans*-isomerase. See text for details.

Figure 4. The most relevant functions of CD36, LOX-1 and SREC in microbial pathogenesis. CD36 is a receptor for a number of Gram-positive and Gram-negative bacteria. CD36 negatively regulates dermonecrosis upon mice intoxication with *S. aureus*-producing α-hemolysin. PfEMP1 proteins of

Plasmodium falciparum target CD36, tethering parasite-infected red-blood cells to endothelial receptors to avoid splenic clearance. CD36 plays a crucial role in host defense against *K. pneumoniae* and *S. pneumoniae,* while it diminishes mice survival upon *M. tuberculosis* infection. LOX-1 and SREC bind to *E. coli* and *S. aureus. LOX-1* expression is increased in response to *A. fumigatus*, HSV and *C. pneumoniae* within different cell types. GroEL from *E. coli* is recognized by LOX-1 and stimulates bacterial phagocytosis, weather OmpA from *K. pneumoniae* interact with both LOX-1 and SREC to activate cells in a TLR2-dependent way. $PorB_{IA}$ from *N. gonorrhoeae* interacts with SREC via Gp96 allowing adherence to host cells. For bacterial invasion Gp96 needs to dissociate from SREC. SREC also interacts with LipL32 from *Leptospira* and with WTA of *S. aureus*, stimulating nasal colonization. CD36, cluster of differentiation 36; LOX-1, oxidized low-density lipoprotein receptor 1; SREC, scavenger receptor expressed by endothelial cells; WT, wild-type; KO, knock-down; RBC, red-blood cell; pfEMP1, *Plasmodium falciparum* erythrocyte membrane protein 1; TLR2, toll-like receptor 2; GroEL, large oligomeric chaperone; OmpA, outer membrane protein A*;* PorB (IA), serotype A of the major outer membrane porin; Gp96, glycoprotein 96; LipL32, leptospiral lipoprotein; WTA, wall teichoic acids.

Word count: 5111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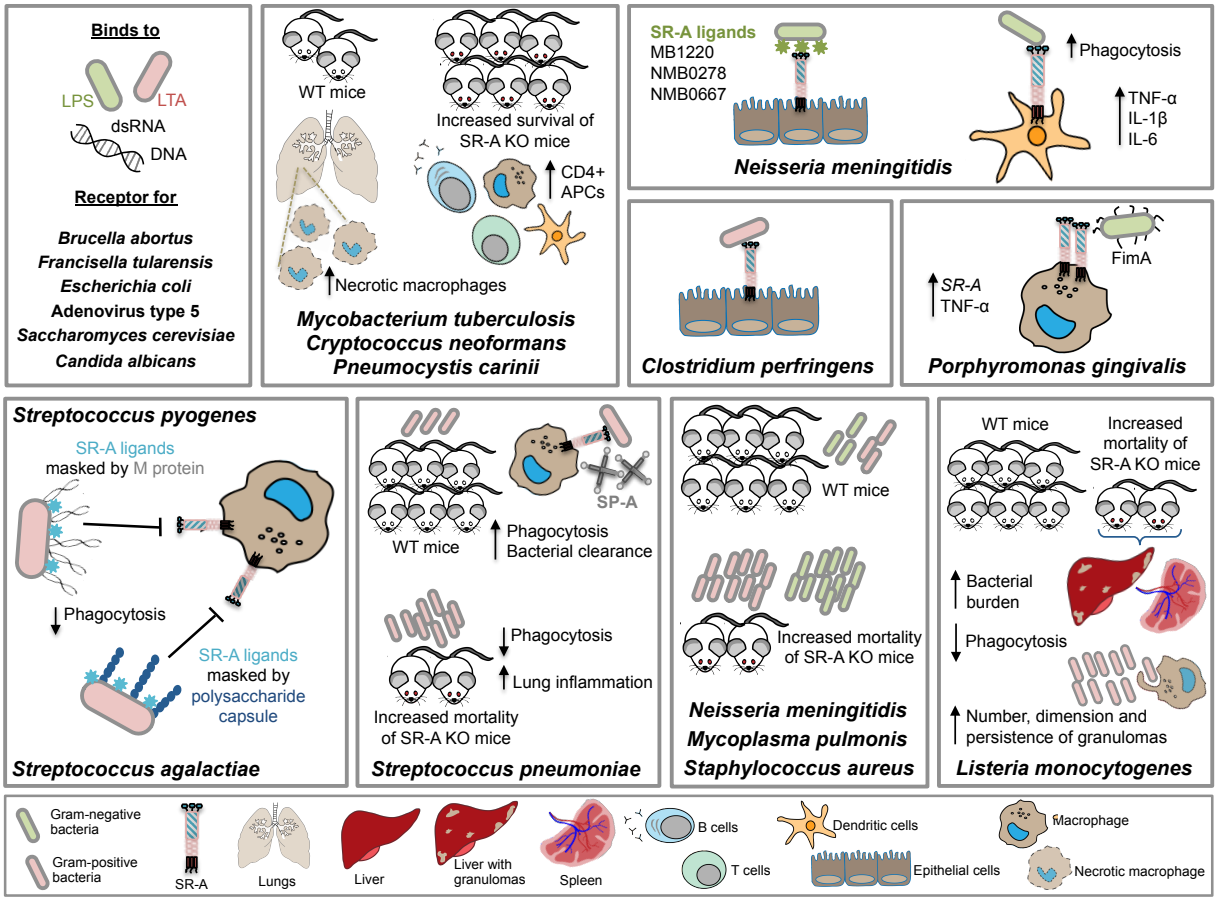
E
LOX-1
F
SREC1
SREC2
G
SR-PSOX
H
STABILIN-1
STABILIN-2
I
CD163
CD5
CD6
DMBT1
Spα
J
RAGE
Intracellular
Extracellular
Host cell membrane
Transmembrane domain
α – helical coiled-coil domain
Collagenous domain
Ser/Thr-rich domain
C-type lectin domain
Spacer domain in SCARA5
Scavenger receptor cysteine-rich (SRCR) domain
CD36
Somatomadin B-like domain
MAM domain
Complement control protein (CCP) domain
LAMP domain
Mucin-like domain
Ser/Pro/Gly-rich domain
EGF domain
EGF-like domain
Chemokine domain
Fasciclin domain
Link domain
Laminin-type EGF-like domain
PST, proline-, serine-, and threonine-rich
ZP, zona pellucida
CUB, C1r/C1s Uegf Bmp1 domain
Spacer domain
Variable domain

Figure 1.


Binds to
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LTA
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Receptor for
Brucella abortus
Francisella tularensis
Escherichia coli
Adenovirus type 5
Saccharomyces cerevisiae
Candida albicans
WT mice
Increased survival of SR-A KO mice
CD4+ APCs
Necrotic macrophages
Mycobacterium tuberculosis
Cryptococcus neoformans
Pneumocystis carinii
SR-A ligands
MB1220
NMB0278
NMB0667
Phagocytosis
TNF-α
IL-1β
IL-6
Neisseria meningitidis
Clostridium perfringens
SR-A
TNF-α
FimA
Porphyromonas gingivalis
Streptococcus pyogenes
SR-A ligands masked by M protein
Phagocytosis
SR-A ligands masked by polysaccharide capsule
Streptococcus agalactiae
WT mice
SP-A
Phagocytosis
Bacterial clearance
Phagocytosis
Lung inflammation
Increased mortality of SR-A KO mice
Streptococcus pneumoniae
WT mice
Increased mortality of SR-A KO mice
Neisseria meningitidis
Mycoplasma pulmonis
Staphylococcus aureus
WT mice
Increased mortality of SR-A KO mice
Bacterial burden
Phagocytosis
Number, dimension and persistence of granulomas
Listeria monocytogenes
Gram-negative bacteria
Gram-positive bacteria
SR-A
Lungs
Liver
Liver with granulomas
Spleen
B cells
T cells
Dendritic cells
Epithelial cells
Macrophage
Necrotic macrophage

Figure 2.

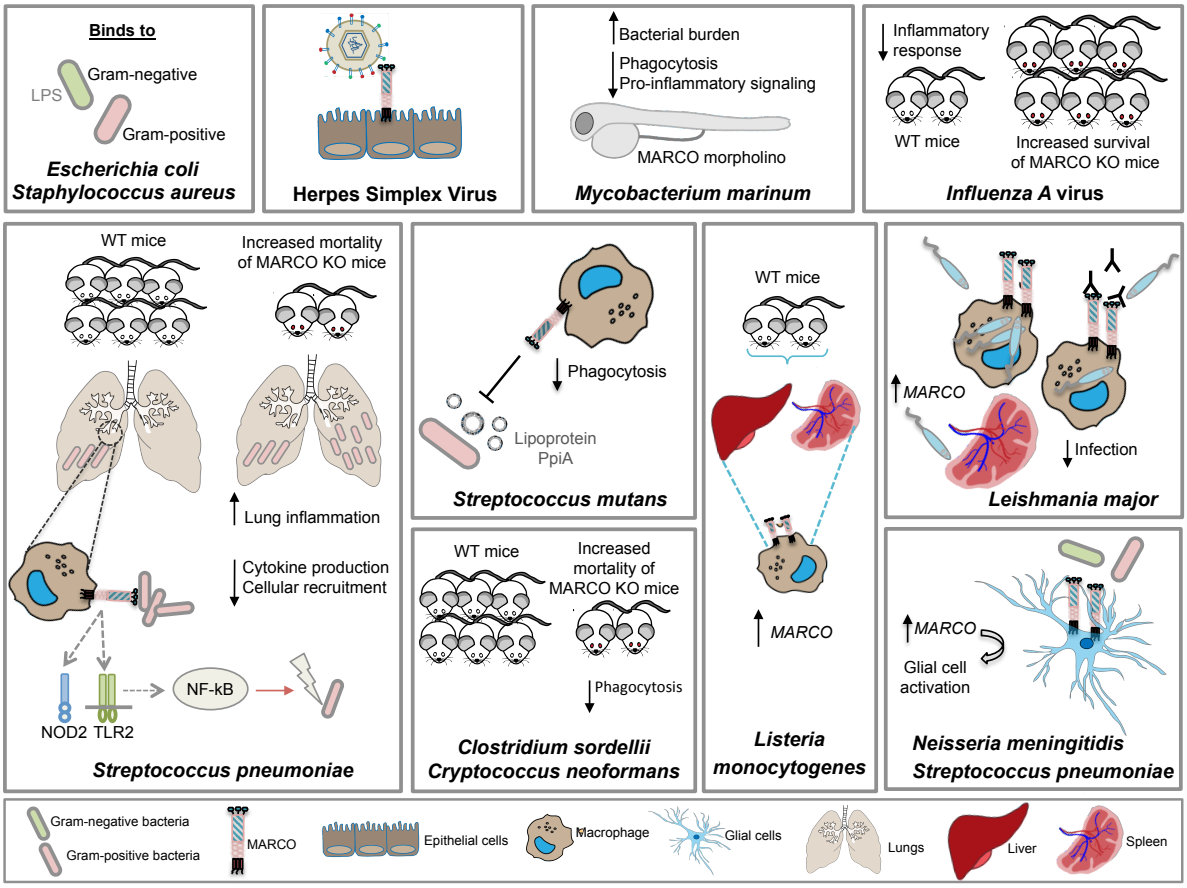
Binds to
Gram-negative
LPS
Gram-positive
Escherichia coli
Staphylococcus aureus
Herpes Simplex Virus
Bacterial burden
Phagocytosis
Pro-inflammatory signaling
MARCO morpholino
Mycobacterium marinum
Inflammatory response
WT mice
Increased survival of MARCO KO mice
Influenza A virus
WT mice
Increased mortality of MARCO KO mice
Lung inflammation
Cytokine production
Cellular recruitment
NF-kB
NOD2 TLR2
Streptococcus pneumoniae
Phagocytosis
Lipoprotein
PpiA
Streptococcus mutans
WT mice
Increased mortality of MARCO KO mice
Phagocytosis
Clostridium sordellii
Cryptococcus neoformans
WT mice
MARCO
Listeria monocytogenes
MARCO
Infection
Leishmania major
MARCO
Glial cell activation
Neisseria meningitidis
Streptococcus pneumoniae
Gram-negative bacteria
Gram-positive bacteria
MARCO
Epithelial cells
Macrophage
Glial cells
Lungs
Liver
Spleen

Figure 3.

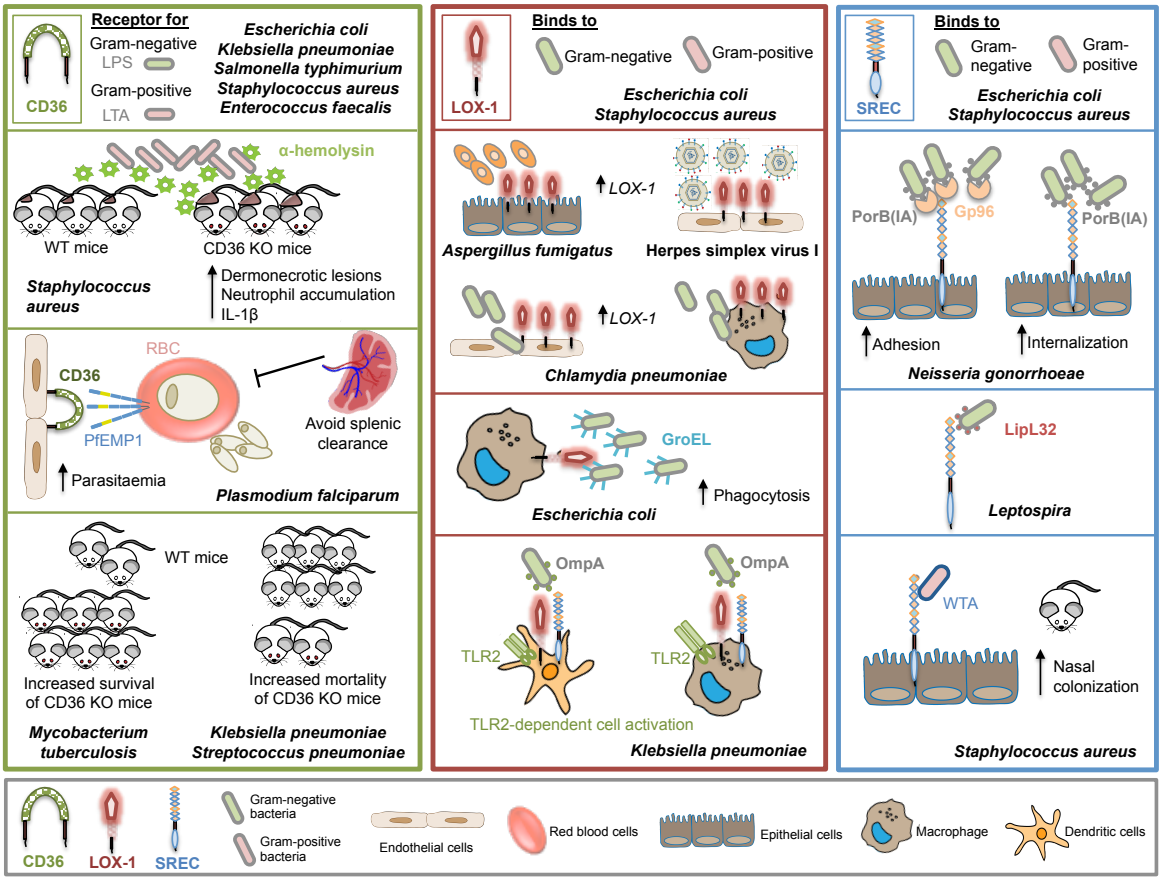
CD36
Receptor for
Gram-negative
LPS
Gram-positive
LTA
Escherichia coli
Klebsiella pneumoniae
Salmonella typhimurium
Staphylococcus aureus
Enterococcus faecalis
α-hemolysin
WT mice
CD36 KO mice
Staphylococcus aureus
Dermonecrotic lesions
Neutrophil accumulation
IL-1β
RBC
CD36
PfEMP1
Parasitaemia
Avoid splenic clearance
Plasmodium falciparum
WT mice
Increased survival of CD36 KO mice
Increased mortality of CD36 KO mice
Mycobacterium tuberculosis
Klebsiella pneumoniae
Streptococcus pneumoniae
LOX-1
Binds to
Gram-negative
Gram-positive
Escherichia coli
Staphylococcus aureus
LOX-1
Aspergillus fumigatus
Herpes simplex virus I
LOX-1
Chlamydia pneumoniae
GroEL
Phagocytosis
Escherichia coli
OmpA
OmpA
TLR2
TLR2
TLR2-dependent cell activation
Klebsiella pneumoniae
SREC
Binds to
Gram-negative
Gram-positive
Escherichia coli
Staphylococcus aureus
PorB(IA)
Gp96
PorB(IA)
Adhesion
Internalization
Neisseria gonorrhoeae
LipL32
Leptospira
WTA
Nasal colonization
Staphylococcus aureus
CD36
LOX-1
SREC
Gram-negative bacteria
Gram-positive bacteria
Endothelial cells
Red blood cells
Epithelial cells
Macrophage
Dendritic cells

Figure 4.