

Fungal pathogen recognition by scavenger receptors in nematodes and mammals

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Macrophages are important cells in the host resistance to fungal infections, and fungal recognition by macrophages triggers phagocytosis, intracellular killing, induction of inflammatory cytokines and chemokines, and initiation of the adaptive immune response. All of the receptors that mediate binding and engulfment of fungal pathogens and the signaling pathways triggered by fungal pathogens are not fully understood. Using an RNAi screen we recently demonstrated that the *C. elegans* receptors CED-1 and C03F11.3, and their mammalian orthologues, the scavenger receptors SCARF1 and CD36 mediate host defense against the fungal pathogen, *Cryptococcus neoformans*. Finally, SCARF1 and CD36 function as co-receptors by binding and engulfing fungal pathogens to facilitate Toll-like receptor 2 signaling. Here we will summarize and expand upon our previous findings.

The innate immune response is the body's first line of defense against pathogen invasion and is mediated by both cytokines and cellular components. The cellular defenses involve circulating monocyte-derived phagocytic cells, which patrol the body at potential portals of pathogen entry. A key feature of these innate immune cells is the array of germ-line encoded receptors that are present on their surface that allow for recognition of a variety of conserved molecular ligands of both endogenous and microbial origin. Recognition of microbial pathogens by these pattern

recognition receptors (PRRs) triggers a tailored immune response program, which includes pathogen binding and internalization, pathogen killing, and initiation of intracellular signaling pathways that elicit the expression of inflammatory genes essential for host defense.¹ In addition, the inappropriate activation of these receptors by endogenous self ligands can contribute to chronic inflammatory syndromes and autoimmunity.²⁻⁴

Several families of PRRs have been described, including the Toll-like receptors (TLRs), C-type-lectins, NOD-like receptors (NLRs), and RNA helicases.^{1,5-7} Another class of PRRs are the scavenger receptor (SRs) family of proteins (Fig. 1).⁸ The first description of SRs was in 1979, when Brown and Goldstein described a receptor on macrophages for endocytosis of modified low-density lipoprotein (LDL) leading to foam cell formation.^{9,10} Since then the definition of SRs has broadened to: *SRs function in the uptake and clearance of polyanionic ligands of both pathogen and self origin*. In addition to their involvement in lipid metabolism,¹¹ SRs also bind and internalize microbial organisms and their products including Gram-negative bacteria (lipopolysaccharide), Gram-positive bacteria (lipoteichoic acid) and CpG DNA (Fig. 1).¹²⁻¹⁶ However, despite playing such a critical role in host defense against a variety of pathogens, and being the first PRRs to be described, SRs remain poorly understood.

While much work has been devoted in the past decade to uncovering the role of pattern recognition receptors in the innate response to bacteria and viruses, our

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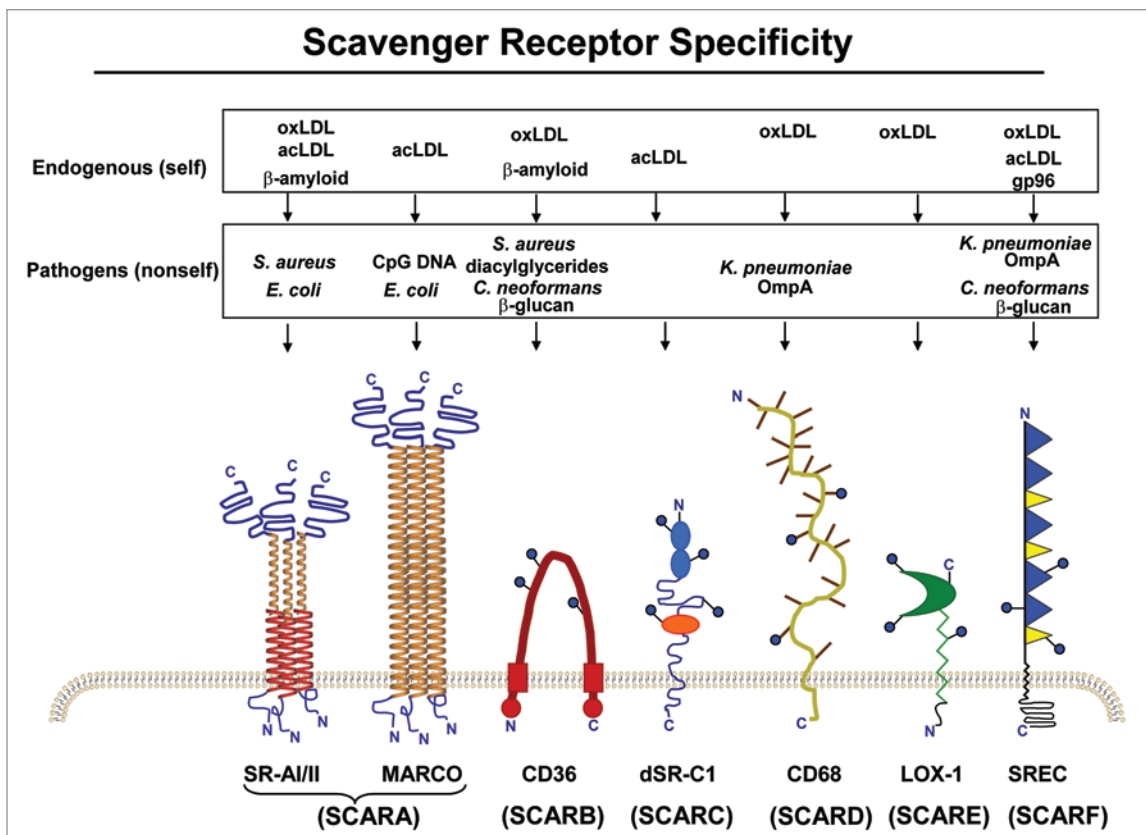


Figure 1. Scavenger Receptor Family and Ligand Specificity. The scavenger receptor family includes six classes A–F: macrophage scavenger receptor class A member 1 (SR-A1/SCARA1), macrophage receptor with collagenous structure class A member 2 (MARCO/SCARA2), scavenger receptor class B, member 3 (CD36/SCARB3), drosophila scavenger receptor class C, type I (dSR-C1), scavenger receptor class D, member 1 (CD68/SCARD1), scavenger receptor class E, member 1 (LOX-X/SCARE1), scavenger receptor class F, member 1 (SREC/SCARF1). Scavenger receptors are defined by their ability to bind modified (i.e., acetylated or oxidated) forms of endogenous self low density lipoproteins (acLDL or oxLDL). Scavenger receptors also bind several pathogenic ligands including Gram-negative *Escherichia coli* (*E. coli*), β-glucan, CpG-motif containing DNA, diacylglycerides, *Cryptococcus neoformans* (*C. neoformans*), *Klebsiella pneumoniae* outer membrane protein (*K. pneumoniae* OmpA), and fungal-derived β-glucans.

understanding of how the innate immune system senses fungal pathogens is less clear.¹⁷ Macrophage and DC interactions with fungal pathogens are an integral part of the host's resistance to fungal infections. Fungal recognition by macrophages triggers phagocytosis, intracellular killing, and induction of inflammatory cytokines and chemokines, while fungal stimulation of DCs results in DC maturation and the initiation of the adaptive immune response.^{18–20} There is also evidence that persistent infection is associated with the intracellular residence of fungal cells in macrophages. Furthermore, infected circulating macrophages can transfer these pathogens and cause dissemination of these infections hematogenously.²¹ Recently, the C-type lectin-like receptor Dectin-1 was shown to be a macrophage receptor for β-glucans (a carbohydrate found in

the fungal cell wall) and to bind several fungi.^{22–28} Other receptors, including the macrophage mannose receptor (MMR), complement receptor 3, Galectin-3, Mincle and DC-SIGN have been shown to bind fungal cells or to components of its capsule or cell wall (i.e., β-glucan and mannans).^{29–35} TLRs (TLR2, TLR4, TLR6 and TLR9) have also been shown to be involved in triggering macrophage activation by *Cryptococcus neoformans*, *Candida albicans* or fungal-derived molecules.^{36–38} While it has become apparent that these receptors contribute to the recognition of fungal pathogens in vitro, their role in host defense to fungal infections in vivo is less clear.^{28,39,40} Of note, mice deficient in TLR2 or MyD88, a signaling adaptor used by most TLRs and the IL-1R, succumbed to intranasal *C. neoformans* infection at an accelerated rate compared to wild-type

mice.^{41,42} Moreover, TLR4, TLR6, and TLR9 appear to play a relatively minor role to fungal infections in vivo. Together, these data suggest that all the receptors that mediate binding and engulfment of fungal pathogens and the signaling pathways triggered by fungal pathogens that regulate anti-fungal immunity have not been fully elucidated.

Pathogenic fungi such as *Cryptococcus neoformans* and *Candida albicans* are a significant cause of morbidity and mortality in immunocompromised individuals. Several fungal cell wall proteins are recognized by the innate immune system in mice and humans; however the molecular mechanisms and receptors used by immune cells to bind and trigger cell activation have not been fully elucidated. A direct role for SRs in the recognition of fungal pathogens has not been previously

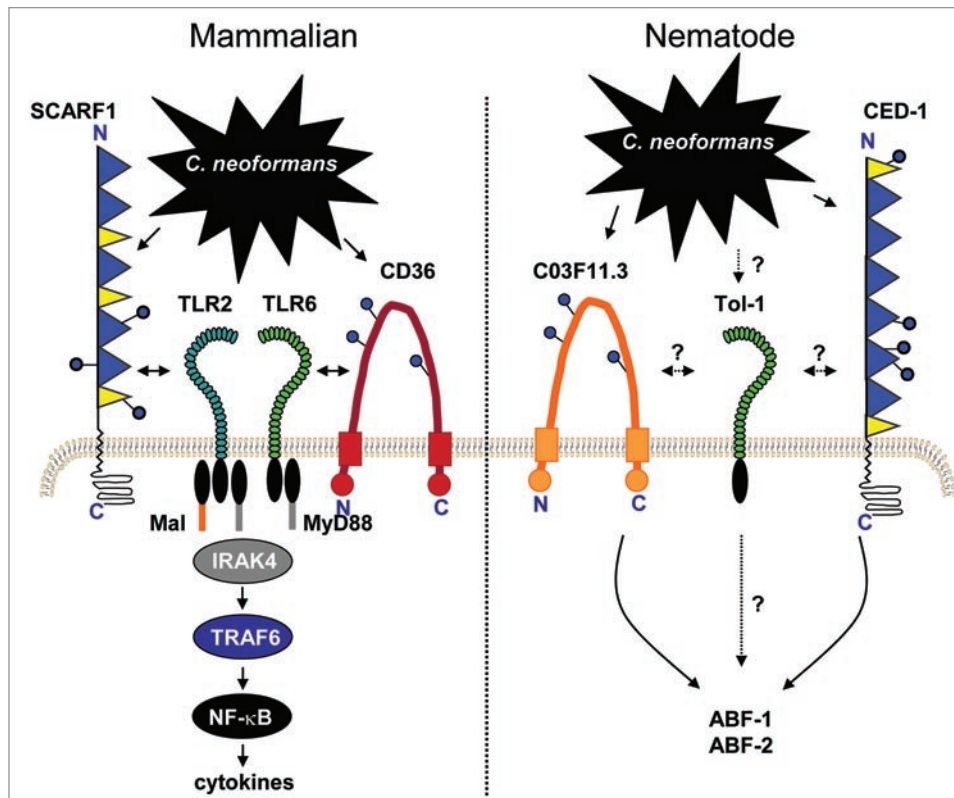


Figure 2. The scavenger receptors SCARF1 and CD36 are TLR2 co-receptors. In mammalian macrophages, SCARF1 and CD36 function as TLR2 co-receptors that promote fungal pathogen signaling. SCARF1 and CD36 direct fungal binding, internalization, and deliver *Cryptococcus neoformans* to TLR2/TLR6 to induce signaling and the production of cytokines. In *C. elegans*, the CD36 and SCARF1 orthologues C03F11.3 and CED-1, respectively, mediate *C. neoformans* recognition, induction of anti-fungal peptides (ABF-1 and ABF-2), and nematode survival. The *C. elegans* TLR orthologue Tol-1, is required for induction of ABF-2 in response to *Salmonella* infection, but its role in *C. neoformans* infection is unknown. More experiments are needed to determine whether C03F11.3, CED-1, or one of the other *C. elegans* SRs cooperate with Tol-1 to mediate recognition of microbial pathogens.

established, but Rice and colleagues found indirect evidence for the involvement of scavenger receptors in the innate sensing of fungal pathogens. They found that acetylated LDL, a common ligand for many SRs, inhibits binding of fungal-derived β -glucan to monocytes.⁴³ To determine whether any members of the SRs family were involved in fungal recognition we performed an RNAi screen to silence the expression of SRs individually in worms and murine macrophages.⁴⁴

SRs in *C. elegans*

C. elegans have been previously demonstrated to be an effective model host for studying fungal infections in vivo and nematodes respond to fungal infection by inducing the expression of host defense genes. The *C. elegans* genome contains seven putative SR orthologues. Silencing the expression of these receptors using RNAi demonstrated that CED-1,

a SCARF1 orthologue, and C03F11.3, a CD36 orthologue, were required for the innate sensing of *C. neoformans*. Worms deficient in CED-1 or C03F11.3 succumbed to *C. neoformans* infection at a significantly faster rate than wild-type worms. In addition, CED-1 and C03F11.3 expression was demonstrated to be required for fungal-induced expression of several antimicrobial peptides, including ABF-1 and ABF-2. It is currently not known whether CED-1 and C03F11.3 can signal directly, cooperate with each other, or collaborate with other receptors to activate signaling pathways innate host defense. One Toll orthologue exists in *C. elegans*, Tol-1, which has been shown to function as a sensor for pathogen avoidance.⁴⁵ Recently, Tenor et al. demonstrated that Tol-1 mutant nematodes are more susceptible to *Salmonella* infection.⁴⁶ Moreover, Tol-1 expression is required for the induction of the anti-microbial peptide ABF-2. Together, these results suggest

that Tol-1 has a direct role in microbial defense. Interestingly, Tol-1 mutant worms were not more susceptible to the fungi *Drechmeria coniospora* or *Pseudomonas aeruginosa*, however their susceptibility to other fungal pathogens such as *C. neoformans* or *C. albicans* remains unknown.⁴⁵ It is interesting to speculate that CED-1 and C03F11.3 may function as co-receptors with Tol-1 to mediate the recognition of specific fungal pathogens (Fig. 2). More work is needed to determine the receptors and signaling pathways involved in *C. elegans* innate host defense.

SCARF1 and CD36 and their Role as TLR Co-Receptors

SCARF1 (scavenger receptor class F, member 1), previously known as SREC-1 (scavenger receptor expressed by endothelial cell-1) since it was originally cloned from an endothelial cell cDNA library, is an 86 kDa single-pass type 1

transmembrane protein composed of 830 amino acids.^{47,48} The extracellular domain is made up of 406 amino acids and contains 5 epidermal growth factor (EGF)-like cysteine-rich repeats, followed by a long C-terminal cytoplasmic tail (391 amino acids) composed of serine/proline-rich regions. EGF-like domains have been shown to mediate homophilic and heterophilic protein-protein interactions, these domains in SCARF1 have been postulated to contribute to oligomerization of the protein or serve as the ligand binding domain. While SCARF1 was first shown to bind acetylated LDL, SCARF1 is also an endocytic receptor for calreticulin, gp96 and Tamm-Horsfall protein.⁴⁸⁻⁵¹ In addition to recognizing these endogenous host proteins, SCARF1 has also been shown to bind and internalize *Neisseria gonorrhoeae* bacterium via its interaction with gp96.⁵⁰ Similar to SCARF1, CD36 is a cell surface receptor with broad ligand specificity for endogenous (modified LDL, thrombospondin, apoptotic cells)⁵² and pathogenic (*Plasmodium falciparum*, mycobacterial lipopeptide, *Staphylococcus aureus*) ligands.^{15,53}

It has recently become appreciated that the specificity of TLR signaling is regulated, in part, through the association of TLRs with cell surface co-receptors. These co-receptors likely act to bind, concentrate, internalize, and deliver ligands to TLRs to initiate cell signaling. Both CD36 and SCARF1 have been implicated as co-receptors in TLR2 signaling (Fig. 2). SCARF1 appears to cooperate with TLR2 to trigger macrophage activation to outer membrane protein A (OmpA) from *Klebsiella pneumoniae*, while CD36 was demonstrated to cooperate with a heterodimer of TLR2 and TLR6, to trigger a signaling cascade essential for the host response to *Staphylococcus aureus* and the *Mycobacterium pneumoniae* diacylated lipopeptide MALP-2.^{15,53,54} In addition we found that SCARF1 and CD36 cooperate with TLR2, but not TLR4 or TLR9 to regulate the inflammatory responses to fungal pathogens (Fig. 2). We also found that SCARF1 and CD36 were required for the control of fungal burden and cytokine expression in mice after infection with *C. neoformans*.⁴⁴ While more studies are needed the evidence so far indicates that

SRs function as TLR co-receptors and may serve as beneficial targets for therapeutic intervention.

Summary

There is a pressing need for the development of new anti-fungal drugs to combat the increasing number of fungal infections and the increase in drug-resistant fungal species. Macrophage and DC interactions with fungal pathogens are an integral part of the host's resistance to fungal infections. Identifying all of the receptors and signaling pathways involved in regulating macrophage inflammatory responses to fungal pathogens will provide valuable insight into their role in fungal pathogenesis and possibly serve as therapeutic targets for novel drug design. Future studies are needed to characterize the role of scavenger receptors in the innate immune response to fungal infections.

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