REVIEW

Scavenger receptors in host defense: from functional aspects to mode of action

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Abstract

Scavenger receptors belong to a superfamily of proteins that are structurally heterogeneous and encompass the miscellaneous group of transmembrane proteins and soluble secretory extracellular domain. They are functionally diverse as they are involved in various disorders and biological pathways and their major function in innate immunity and homeostasis. Numerous scavenger receptors have been discovered so far and are apportioned in various classes (A-L). Scavenger receptors are documented as pattern recognition receptors and known to act in coordination with other co-receptors such as Toll-like receptors in generating the immune responses against a repertoire of ligands such as microbial pathogens, non-self, intracellular and modified self-molecules through various diverse mechanisms like adhesion, endocytosis and phagocytosis etc. Unlike, most of the scavenger receptors discussed below have both membrane and soluble forms that participate in scavenging; the role of a potential scavenging receptor Angiotensin-Converting Enzyme-2 has also been discussed whereby only its soluble form might participate in preventing the pathogen entry and replication, unlike its membrane-bound form. This review majorly gives an insight on the functional aspect of scavenger receptors in host defence and describes their mode of action extensively in various immune pathways involved with each receptor type.

Keywords: Scavenger receptors, Immunity, PAMPs, Signalling pathways, ACE-2
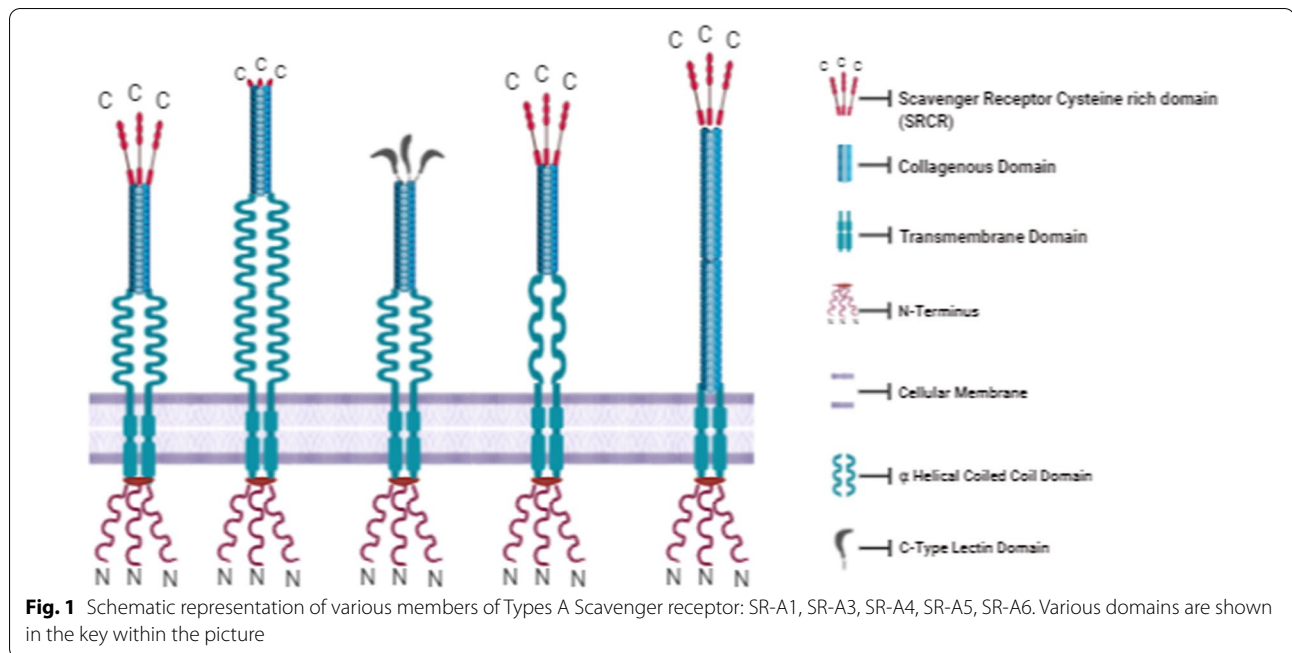
Background

Scavenger receptors (SRs) were shown for the first time on macrophages to function in endocytosis and degradation of modified (acetylated) low-density lipoproteins (LDLs) [1]. SRs are a structurally heterogeneous superfamily of proteins that belong to different classes with very little or no structural resemblance. The only characteristic that designates various classes is their competence to bind mutual ligands. SRs show interactions with modified self-molecules, damage-associated molecular patterns (DAMPs), non-self molecules like preserved pathogen-associated molecular patterns (PAMPs) on microbial pathogens (lipopolysaccharide (LPS) and lipoteichoic acid (LTA)). They also recognize unmodified endogenous proteins, lipoproteins, apoptotic cells and polyionic ligands such as carbohydrates, proteoglycans, cholesterol ester and phospholipids etc. Host cells are effective guardians of the immune response through the expression of complex surveillance systems, including the Pattern Recognition Receptors (PRRs) [2]. Scavenger receptors are membrane-associated pattern recognition receptors (PRRs) [3–5] that act as phagocytic receptors mediating direct non-opsonic uptake of pathogenic microbes and/or their products. SRs may partner with other PRRs like TLRs (Toll-like receptors) or multimolecular complexes on various cell types and participate in diverse functions like signalling other than scavenging. Recognition of pathogens by SRs

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Fig. 1 Schematic representation of various members of Types A Scavenger receptor: SR-A1, SR-A3, SR-A4, SR-A5, SR-A6. Various domains are shown in the key within the picture

on antigen-presenting cells leads to inflammatory response followed by phagocytosis, processing of antigens and subsequent presentation on MHC class I and II molecules thus, linking innate and adaptive immune responses [6]. SRs show expression on various cell types that are potential portals of pathogen entry like macrophages, dendritic cells, neutrophils, microglia, B cells, endothelial and epithelial cells [7, 8]. SRs play a significant role in host defence by recognizing countless microbial antigens at the portals of pathogen invasion and activating downstream immune responses to fight and eliminate the pathogens [9].

Due to their functional diversity and involvement in various diseased conditions and immunity-related signalling pathways this review extensively focus upon the emergence of mammalian scavenger receptor as PRRs, their involvement in host defence and mode of action in various immune pathways involved with each receptor type.

Types of Scavenger receptors

Scavenger receptors are classified based on their nucleotide sequence alignment and protein structure [10, 11]. Each class is divided into subclasses that include members, which share structural features [12]. Based on the current understanding of scavenger receptors and proposed nomenclature, this review discusses 12 classes and their subclasses of mammalian scavenger

receptors and one potential scavenger receptor, Angiotensin-converting enzyme-2 (ACE-2).
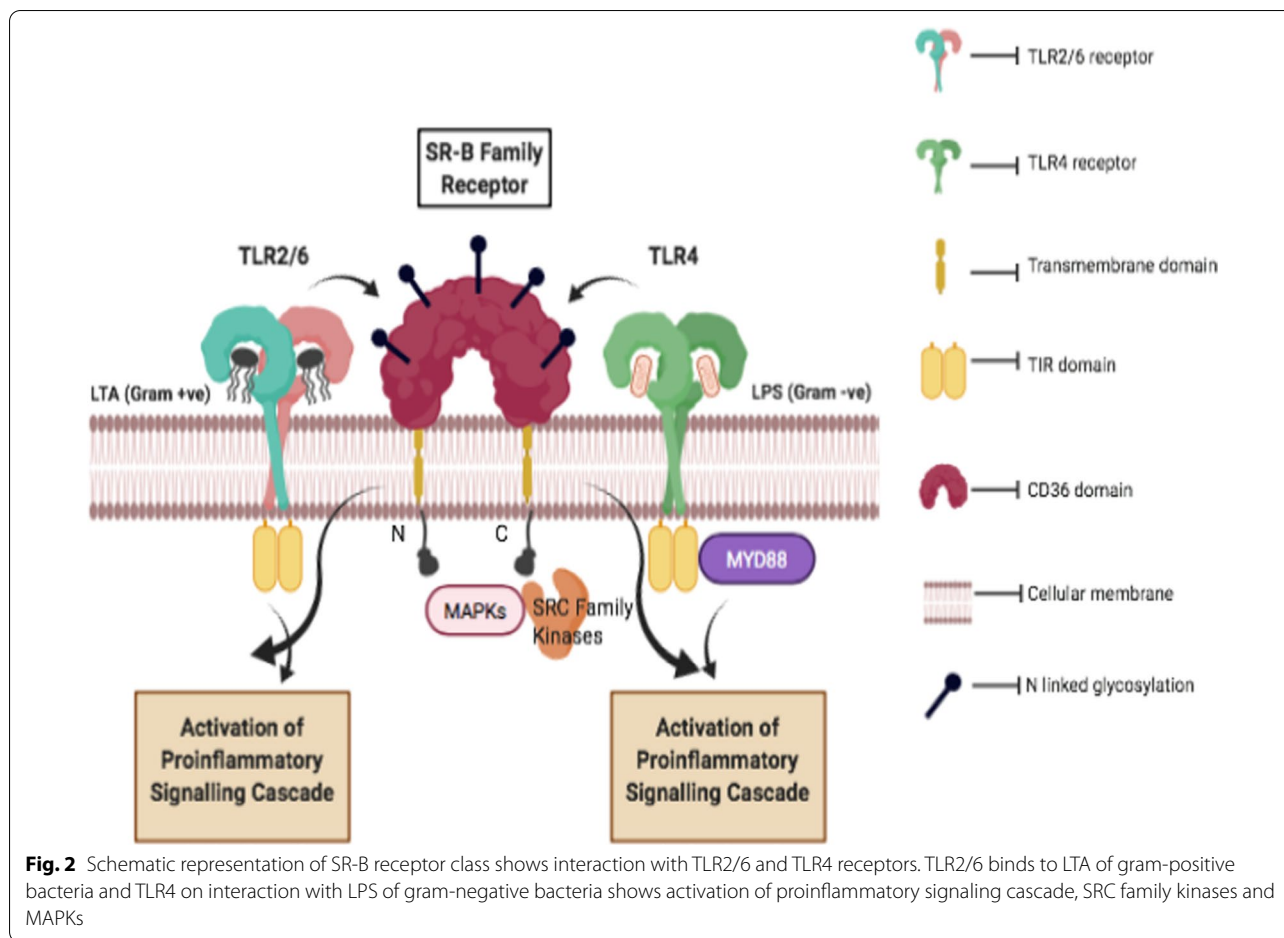
Class A

Class A scavenger receptors have an N-terminus cytoplasmic domain, single transmembrane section and a big extracellular C-terminus part involved in ligand identification. Class A SRs contains a collagen domain, and a type-A cysteine-rich domain (SRCR) or a C-type lectin domain (CLEC). Members include SR-A1 (SCAR-A1 OR MSR1), SR-A3 (SCAR-A3 or CSR1), SR-A4 (SRCL), SR-A5 (SCAR-A5) and SR-A6 (MACRO) (Fig. 1). The linked SRCR domain of SR-A1 facilitates communications with other membrane-bound receptors while the collagen domain is responsible for ligand recognition. SR-A1 binds to lipopolysaccharide (LPS), lipoteichoic acid (LTA) and bacterial CpG DNA. In the presence of LPS, SR-A1 interacts with Toll-like receptor 4 (TLR4) and stimulates NF-κB and inflammatory cytokine production in macrophages in presence of LPS [13]. Also, it binds to the purified lipid A moiety of LPS from *E. coli* where it is involved in the clearance and detoxification of endotoxins [14]. Similarly, SR-A1 also participates in host defence by binding and clearance of LTA and/or gram-positive bacteria from tissues and the circulation such as (*Streptococcus pyogenes, Streptococcus agalactiae, Staphylococcus aureus, Enterococcus hirae and Listeria monocytogenes*) [15]. SR-A1 can facilitate the internalization of *Neisseria*

meningitides, *Listeria monocytogenes* and *Staphylococcus aureus* [16–18]. The SRCR domain of SR-A6 mediates the attachment of bacteria and LPS. The positive arginine area that exists outwardly on the exterior of SR-A6 is deficient in the case of SR-A1 [19]. SR-A1 and SR-A6 are also involved in the aberrant dispersal of splenic macrophages if depleted. In mice, deficiency of SR-A1 and SR-A6 results in distorted spleen morphology and low circulating antibody levels (IgM and IgG3) for bacterial polysaccharides. Ligand specificities and structural features suggest that SR-A1 and SR-A6 show functional dissimilarity contrary to a study, which recognizes overlapping, but separate endogenous and microbial ligands, comprising some *N. meningitides* external proteins binding to both of these receptors [20]. SR-A1 can generate an adaptive immune response by stimulating antigen binding, internalization and antigen presentation in alliance with HSP70 members [21]. SR-A1 also cooperates with TLR4 to phagocytize *Escherichia coli*, while SR-A1 and TLR2 collaborate in the phagocytosis of *Staphylococcus aureus* [22]. SR-A6 partners with TLR2 and CD14 in the identification of the *Mycobacterium tuberculosis* glycolipid to produce a pro-inflammatory reaction [23]. Macrophage associated cell surface SR-A6 is inhibited by Herpes simplex virus type 1 (HSV-1) jointly with proteoglycans to facilitate adsorption of the virus to keratinocytes epithelial cells [24]. SR-A1 participates in the internalization via clathrin-dependent endocytosis (CDE) or clathrin-independent endocytosis (CIE) methods and the latter stimulates apoptosis. In antigen-presenting cells (APCs), SR-A1 facilitates internalization and phagocytosis by a lipid raft-dependent method. It was reported that cumulative surface expression of SR-A1 along with its co-receptor MERTK M2 resulted in the engulfment of apoptotic bodies by macrophages [25]. As for SCAR-A3 or CSR1 (cellular stress response protein), its expression could be improved by oxidative stress and functions as a cellular stress response gene to scavenge reactive oxygen species (ROS). A recent study reported SCAR-A3 as the potential prognostic indicator in Hand Foot and Mouth Disease (HFMD) and a boosted expression of SCAR-A3 was observed in severe HFMD patients compared with the control group [26]. SCAR-A4 or SRCL (scavenger receptor with C-type lectin) belongs to collectin family PRRs and the C-terminal domain contains a C-type lectin, instead of an SRCR domain. It generates an immune response on binding to heat-killed *S. aureus, E. coli* and *S. cerevisiae* yeast particles [27] and facilitates non-opsonic phagocytosis of zymosan [28]. SCAR-A5 is a newly recognized class A scavenger receptor that binds to modified

LDL particles instead of heat-inactivated *E. coli* and *S. aureus*, signifying its part as a PRR in innate immunity [29]. Increased SCAR-A5 expression causes inactivation of signal transducer and activator of transcription 3 (STAT3), a chief transcriptional watchdog in pro-inflammatory gene expression [30].

Class B

Class B scavenger receptors comprise a conserved CD36 domain (Fig. 2). It comprises three members: SR-B1 (SCAR-B1), LIMP2 (SCAR-B2), and CD36 (SCAR-B3). This class binds to a wide array of ligands like viruses and bacteria, HDL particles and correlates with the amplified danger of infertility, atherosclerosis and reduced natural immunity. CD36 (SCAR-B3) has two transmembrane domains and both its N and C terminus are cytoplasmic. The C-terminal tail might be the spot of signal transduction and links with SRC family kinases, including FYN, YES and LYN [31]. The C-terminus of CD36 holds a CXCX5K motif, which is located on the cytosolic ends of the T cell co-receptors CD4 and CD8 that play a role as a docking place for SRC kinases. CD36 is known to stimulate mitogen-activated protein kinases (MAPKs) and binds with a noticeable array of transmembrane proteins that comprise TLR2, TLR4 TLR6, β1 integrin, β2 integrin, β5 integrin and CD9, CD81. In response to lipoteichoic acid or diacylated lipoproteins, CD36 generates an immune response in association with the TLR2-TLR6 heterodimer complex [32, 33]. The SR-B1 (SCAR-B1) has two splice variants entitled SR-BI and SR-BII and has an indistinguishable loop structure as of CD36. A variety of pathogenic ligands comprising Alexa Fluor 488-labeled live *E. coli* K12, K1, S. *aureus,* S. *typhimurium* and *Listeria monocytogenes* bind and internalize CLA-1 and CAL-2 stably transfected HeLa and HEK293 cells. These cells also bind to and internalize dead bacteria and are involved in its clearance hence their role in infection and sepsis [34]. Another study demonstrated internalization of *E. coli*, LPS, and chaperonin 60 (GroEL) in HeLa cells due to overexpression of CLA-1, CLA-2, and CD36 receptors indicating that SR-B1 receptors plays part in pathogen detection and facilitate bacteria-associated inflammation and signalling [35]. Hepatic SR-B1 acts as a critical defensive factor in sepsis thus endorsing hepatic SR-B1 facilitated LPS clearance that delivers a therapeutic approach for sepsis [36]. SR-BI plays role in hepatitis C virus (HCV) internalization and cross-presentation by human dendritic cells (DCs) and may influence the design of HCV vaccines and immunotherapeutic methods [37]. The role of SR-B1 and LOX1 on bronchial epithelial cells (BECs) showed that SRs participate in the in vitro activation of human airway cells triggered by TLR3 ligand, dsRNA and SRs act as

Fig. 2 Schematic representation of SR-B receptor class shows interaction with TLR2/6 and TLR4 receptors. TLR2/6 binds to LTA of gram-positive bacteria and TLR4 on interaction with LPS of gram-negative bacteria shows activation of proinflammatory signaling cascade, SRC family kinases and MAPKs

transporters, enabling dsRNA entrance and transport to the dsRNA-sensing receptors on BECs [38]. In malaria, SR-B1 acts against host defence for *Plasmodium* infection by stimulating sporozoite penetration in liver cells and consequent intracellular parasite growth [39]. SR-B1 binds to the diverse spectrum of receptors; it binds and recognizes *Mycobacterium tuberculosis* in vitro but is known to play only an insignificant role in anti-myco-bacterial immunity in vivo [40]. Overexpressed SR-B1 in epithelial cells of pyometra-affected uteri is potentially involved in endometrial bacterial adhesion and involve-ment in the pathogenesis of pyometra in general [41]. In our study on milk derived goat mammary epithelial cells (GMECs) we have validated the presence and expres-sion of SR-B1 and its role in *E. coli* infection. Through esiRNA based silencing technique, SCARB1 expression significantly affects the TLR4-MyD88 and TRIF pathway genes following infection with *E.coli*. Also, this receptor is involved in mediating endocytosis of live bacteria in GMECs. Intriguingly, CD36 has a role to play in the clear-ance of numerous bacterial and protozoan pathogens. A variety of bacteria like *E. coli*, *Klebsiella pneumoniae*,

S. typhimurium, *S. aureus*, and *Enterococcus faecalis* are phagocytized in CD36 overexpressing HeLa cells via JNK-Mediated Signaling and in association with TLR2/4 [42]. Also, the binding to beta-glucan of *Cryptococcus neoformans* provided evidence of its role in antifun-gal defence in an experimental mice model in vivo [43]. CD36 deficit presents resistance to mycobacterial infec-tivity, which is due to decreased intracellular existence of *Mycobacterium* in the *Cd36 -/-* macrophages [44]. In goat mammary epithelial cells, CD36 is involved in LPS based pro-inflammatory response and TLR4 mediated *E. coli* endocytosis in GMECs [45].

LIMP-2 (lysosome membrane protein 2) or SCAR-B2 is known to be a receptor for enterovirus 71 (EV71) and shows binding with both of its soluble and cell sur-face forms. LIMP2 is recognized for enterovirus 71 so that its expression is propagated in normal unsusceptible cell lines, development of cytopathic effects. It is also a receptor for development of infection for coxsackievirus A16 (CVA16) (a weak pathogen). Enterovirus 71 belongs to human enterovirus species A and along with CVA16, is recurrently linked with human foot and mouth disease

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[46]. L929 cells expressing human LIMP-2 infected with coxsackievirus A7, coxsackievirus A14 and coxsackievirus 16 require the receptor for entrance into host cells and the expansion of human foot and mouth disease [47]. Subsequently, during EV71 infection, LIMP-2 along with acidic conditions also function as a receptor for viral binding, virus internalization, viral uncoating and therefore infection efficiency [48].

Class C
Class C scavenger receptors have only been described in *Drosophila melanogaster* and lacks mammalian counterparts. *Drosophila* SR-CI (dSR-CI) on Schneider 2 cells (derived from a primary culture of late stage *Drosophila* embryos) is expressed as an undefined bacterial PRR for both gram-positive and gram-negative bacteria. Cross-competition experiments and dsRNAi-mediated gene silencing methods have suggested dSR-CI to be a common candidate PRR for *E. coli* and *S. aureus* binding and optimal bacterial phagocytosis by S2 Cells. Additionally, dSR-CII is detected on early embryos and is predicted to be a transmembrane protein with no role in innate immunity at later stages. Also, dSR-CIII and dSR-CIV classes are predicted to be present in secreted soluble form [49].
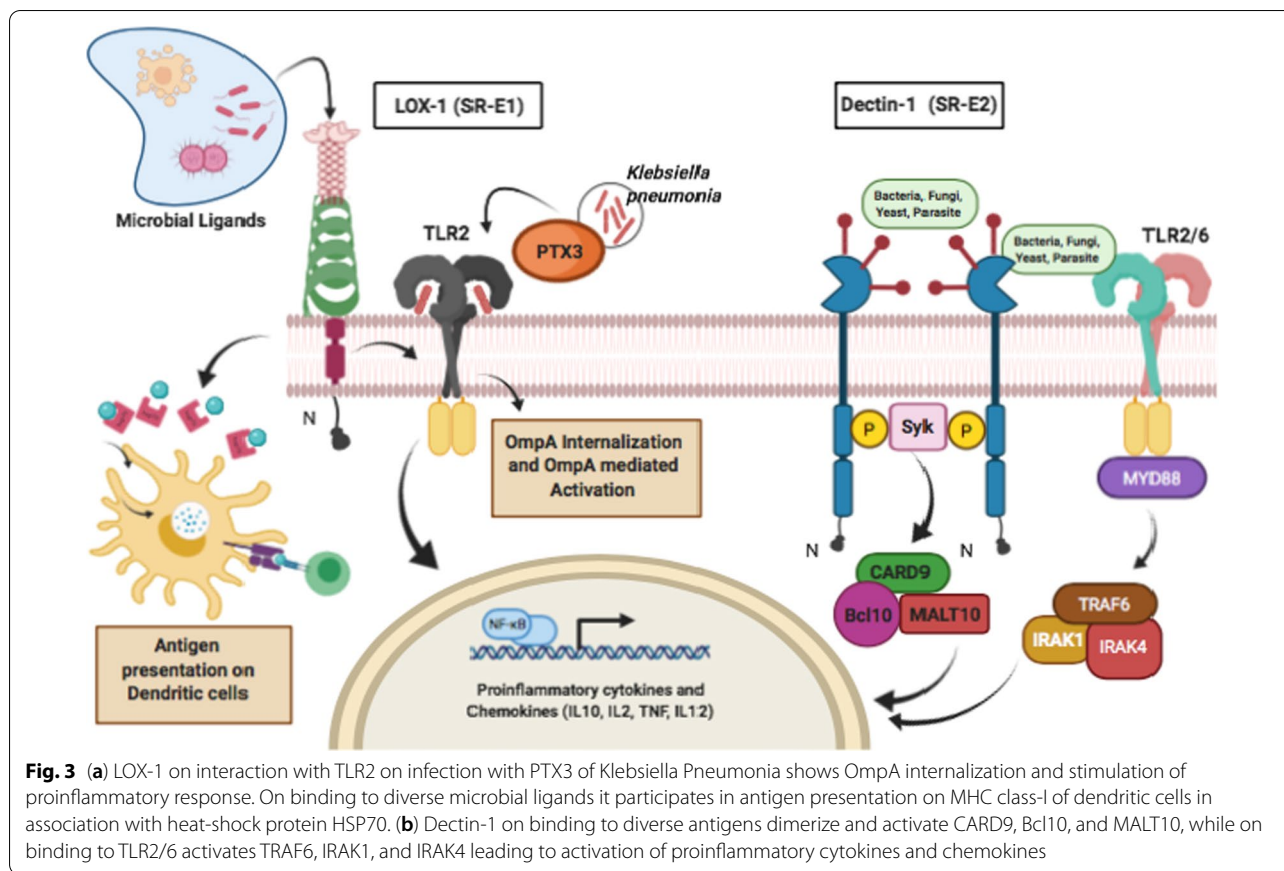
Class D
CD68 (named Macrosialin in the mouse) is the only member belonging to class D of scavenger receptors. Class D scavenger receptors contain a mucin-like domain, a proline-rich center, lysosome-associated membrane glycoprotein (LAMP) domains, single transmembrane and a small cytoplasmic tail [50]. CD68 receptor is abundant on immune cells like free monocytes, tissue-specific macrophages in the peritoneum, liver, lungs, spleen, Langerhans cells, and microglia where it scavenges oxLDL binds to lectins, selectins and mediate endocytosis and phagocytosis. CD68 being a macrophage marker is involved in differentiation of hematopoietic cells of the monocyte/macrophage descent. The function of CD68 in antigen presenting and processing is ambiguous. But, the involvement of lysosomal associated membrane proteins (LAMP) in CD68 related activities are highly assumed due to their structural homology. In CD68 knockout mice, phagosome lysosome fusion and overall phagolysosome formation are regulated by LAMP-1/2. Lower levels of CD68 are also expressed in $CD4^+$ T lymphocytes, $CD19^+$ B lymphocytes, basophils and intestinal neutrophils from patients with inflammatory bowel syndrome. While as in normal mucosal tissue CD68 + neutrophils are absent [51]. In vivo CD68 participates in discriminating M1 and M2 macrophage divergence in association with transcription factor markers such as pSTAT1, CMAF and RBP-J [52] and association of TLR4 in (microglial cell) macrophages in brain tissue in response to stimuli like LPS and IFN-γ upregulates the CD68 expression significantly [53]. CD68 plays a role in host resistance by preventing the uptake of malarial sporozoite in liver tissue macrophages hence acting as a potential receptor for malarial pathogen [54]. Contrary to this in small intestinal epithelial cells, CD68 was reported to be putatively involved in antigen processing and presentation together with other factors in the processing of intestinal pathogens [55]. In summary, the participation of CD68 in immunity and inflammation is still ambiguous and needs further validation.

Class E
Class E scavenger receptors belong to the NK cell C-type lectin-like (CLEC) receptor family. It has four members: SR-E1 (LOX-1) (Fig. 3a), SR-E2 (Dectin-1), SR-E3 (MRC1) and SR-E4 (ASGPR1). The SR-E1 is also called lectin-like oxidized low-density lipoprotein receptor (LOX-1). Human SR-E1 has an N-cytoplasmic region, a transmembrane region, an extracellular coiled-coil 'neck' region and a C-type lectin-like domain. SR-E1 binds diverse ligands like apoptotic cells, gram-positive, gram-negative bacteria and acute phase C-reactive proteins. SR-E1 participates in antigen presentation on MHC class-I of dendritic cells in association with HSP70 [56]. SR-E1 also mediates signal transduction that triggers an important feature of pro-inflammatory response in immune and vascular cells i.e., NF-κB activation [57]. It acts as an intermediate between NF- κB and its targets. In Chinese hamster ovary-K1 (CHO-K1) cells, stably expressing LOX-1 can bind FITC-labeled *S. aureus* and *E. coli* in both static and non-static conditions, and bovine aortic endothelial cells (BAEC) also bind to labelled *S. aureus* that is supported by the fact that binding was repressed with poly (I) and an anti-LOX-1 mAb [58]. Knockout of LOX-1 decreased pro-inflammatory response, reduced inflammation during sepsis, lung oedema, stopped neutrophil overreaction, and amplified neutrophil employment to infection sites in a murine model of polymicrobial sepsis. Thus, indicating that SR-E1 is a significant intermediary of intracellular signalling during infection and promotes immune suppression if absent [59]. In the brain abscess model, TLR2-dependent signals affect the degree of SR-E1 induction, suggesting possible cross-talk amongst TLRs and SRs. Both SR-A1 and SR-E1 together generate an antibacterial immune response in the CNS parenchyma [56]. Also, TLR2 activation is triggered when SR-E1 together with SR-F1 binds to outer membrane protein A (OmpA) of *Enterobacteriaceae (Klebsiella pneumonia)* and thus controls many phases of the innate immune response [60].

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Fig. 3 (**a**) LOX-1 on interaction with TLR2 on infection with PTX3 of Klebsiella Pneumonia shows OmpA internalization and stimulation of proinflammatory response. On binding to diverse microbial ligands it participates in antigen presentation on MHC class-I of dendritic cells in association with heat-shock protein HSP70. (**b**) Dectin-1 on binding to diverse antigens dimerize and activate CARD9, Bcl10, and MALT10, while on binding to TLR2/6 activates TRAF6, IRAK1, and IRAK4 leading to activation of proinflammatory cytokines and chemokines

SR-E2 or Dectin-1 being an innate immunity PRR is expressed principally on macrophages, DCs, and neutrophils. This receptor mediates both the internalization and cellular responses of various bacteria, fungi and parasites through unique processes [61]. Dectin-1 stimulates diversity of cellular reactions like phagocytosis; cytokine production and the respiratory burst via Syk/CARD9 dependent and Syk- independent signalling pathways [62]. Dentin-1 recognizes unidentified endogenous ligands on CD4+and CD8+T cells hence acting as a co-stimulatory molecule through an unknown response. Due to its prevalence on DCs and macrophages of medullary areas of the thymus, it functions in thymocyte growth and its expression on CD11c (+) splenic DCs in areas of the spleen and lymph nodes suggests it to act as a co-receptor for triggering T cells [63]. Dectin-1 plays a major role against the systemic *Candida glabrata* challenge. Splenocytes were collected from infected dectin-1-deficient and wild-type mice and the levels of TNF- α, IL-6, IFN-ϒ and IL-17 in supernatant indicated lower Th cell responses. Also, dectin-1-and dectin-2 deficient mice showed considerably increased fungal loads while dectin-1 renders the host sensitive to *C. glabrata* infection, unlike dectin-2 [64] (Fig. 3b).

SR-E3 or MRC1, the human mannose receptor (CD206) is another transmembrane glycoprotein belonging to this class. Most tissue macrophages, DCs and selected lymphatic or liver endothelial cells express it predominantly. It is involved in phagocytosis of mannosylated glycoproteins, or receptor-mediated antigen presentation. As a homeostatic PRR on macrophages, it binds to high mannose *N*-linked glycoproteins on the surface of pathogens, pituitary hormones in the circulation and scavenges via phagocytosis and lysosomal degradation. SR-E3 after participation in recognizing and processing antigenic bacteria help in the removal of myeloperoxidases that are released by the pathogenic bacteria to prevent complement activation and damage to host tissue. CD206 binds to a variety of pathogens like M. *tuberculosis,* S*. pneumonia, Yersinia pestis, Candida albicans, Pneumocystis carinii, Cryptococcus neoformans*, HIV, influenza virus, dengue virus, and *Leishmania* species. MR-mediated uptake by macrophages in tissues during infection is a striking method for effective and targeted delivery of drug transporters such as liposomes, microparticles, nanoparticles and dendrimers for infectious diseases like tuberculosis and also for cancer imaging, diagnosis and therapy [65]. SR-E3 is expressed on

dendritic epidermal cells in a condition called atopic dermatitis where it acts as a differentiation marker of immature monocyte-derived DCs [66] and in COPD (severe chronic obstructive pulmonary disease) overexpression of SR-E3 along with other CD markers on alveolar macrophages function in COPD pathogenesis [67]. In hepatitis B virus mouse model F4/80$^+$SR-E3$^+$CD80$^{lo/+}$ hepatic macrophages endorse the immunosuppressive action of regulatory T cells thus offering novel understandings into the immunomodulation in HBV infection [68].

SR-E4 or asialoglycoprotein receptor 1 (ASGPR1) also designated the Ashwell receptor is found on the surface of hepatocytes that recognize, internalize and transport glycoproteins deficient in terminal sialic acid residues and those which have galactose or N-acetylgalactosamine residues via the route of receptor-mediated endocytosis. SR-E4 binds to a range of clinically essential plasma proteins like transferrin, IgA, apoptotic cells, fibronectin, alkaline phosphatase and many immune cells. During liver diseases impaired SR-E4 receptor is related to the increased pro-inflammatory release of TNF-α and IL-6 in kupffer cells [69]. Additionally, when mice deficient in functional hepatic SR-E4 (receptor-deficient, RD), and wild-type (WT) controls were intravenously administered with mitogens, the former displayed increased pro-inflammatory cytokine expression, caspase activation and buildup of CD8 + T cells versus normal WT mice. Thus, deficiency of this receptor may lead to liver diseases as it has protective effects against T cell-mediated hepatitis [70]. Similarly, in SR-E4 knockout hepatitis E virus-infected PLC/PRF/5 cells various assays revealed direct attachment of ASGR1 and ASGR2 to ORF2 protein of virus and participation in regulating the viral attachment and internalization steps and not in viral emancipation. Also, HeLa cell lines stably expressing SR-E4 scavenger receptors demonstrated amplified virus-binding competence [71].

Class F

Class F scavenger receptors have three members: SREC1 (SCAR-F1), SREC2 (SCAR-F2) and SCAR-F3 (also called MEGF10) and have epidermal growth factor (EGF) and EGF-like domains. One of the distinct structural properties of these receptors is that they lack visible signalling motifs on short cytosolic ends. They also have a higher inclination to oligomerize and bind large, multivalent ligands. SCAR-F1 is a membrane-bound receptor with EGF-like domains on the outside and unusually extended proline- and serine-rich cytoplasmic extensions. SCAR-F1 binds to a variety of pathogens, both exogenous and endogenous. It binds to fungal pathogens in a β-glucan dependent approach and facilitates host defence alongside *Candida albicans* and *Cryptococcus neoformans.*
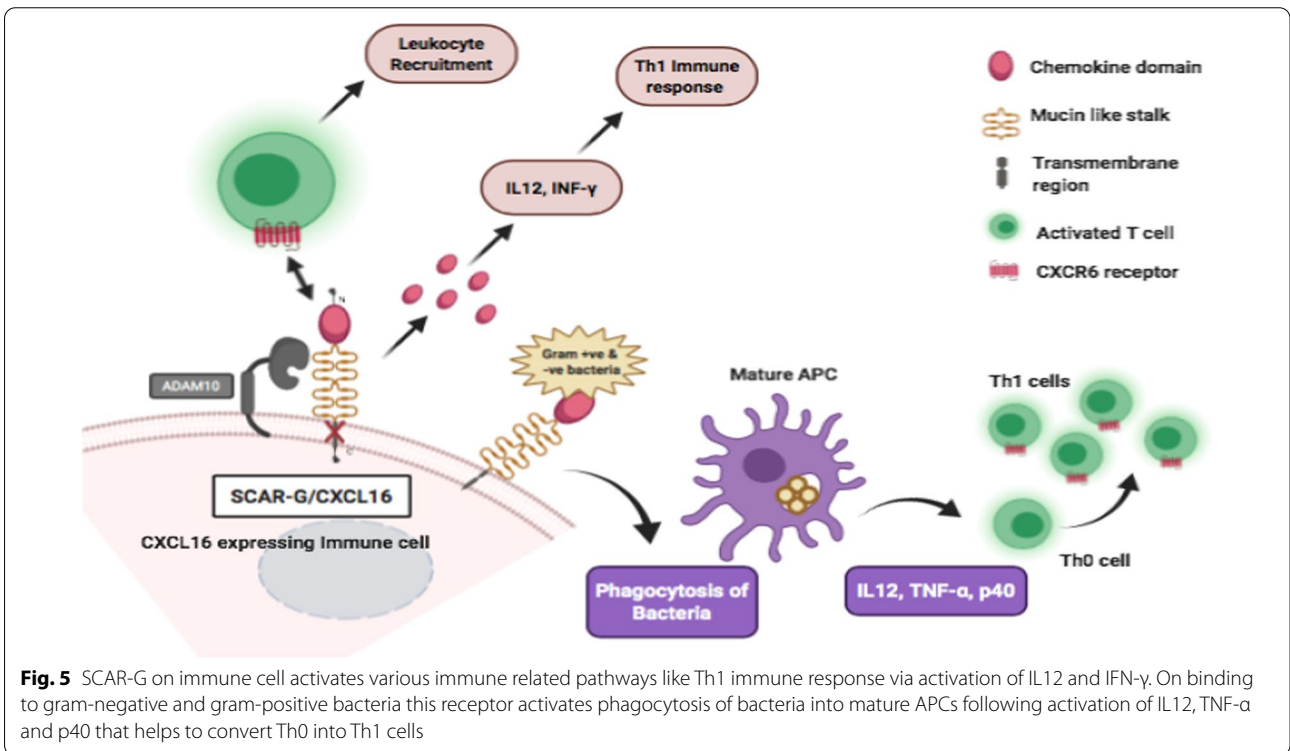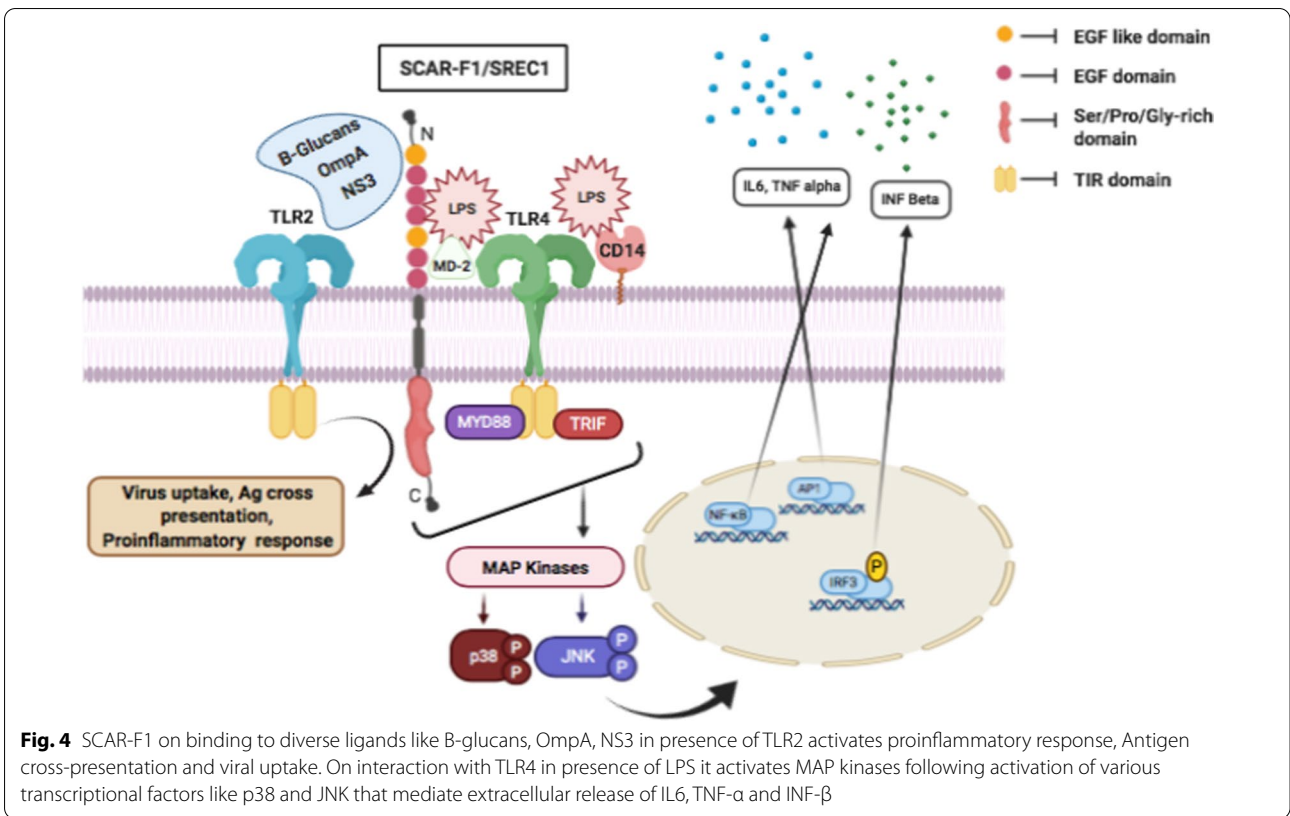
SCAR-F1 along with SCAR-B3 mediated cytokine production and innate immunity in response to fungal infections [72]. Also, SCAR-F1 through an endocytic receptor in co-operation with TLR2 binds to non-structural protein 3 (NS3) of hepatitis C virus and participate in virus uptake and cross-presentation [43]. SCAR-F1 in association with TLR4 leads to LPS induced pro-infalmmatory response through NF-kB and P kinase pathways on RAW and HEK 293 cells and function in the endocytosis of peptides and antigen presentation [73]. SCAR-F1 is present on DCs and helps in the removal of apoptotic cells in association with C1q/phosphatidylserine complexes. Deficiency of SCAR-F1 has been shown to impair efferocytosis in vitro and in vivo and trigger systemic lupus erythematosus, an autoimmune disorder in SCAR-F1 deficient mice [74] (Fig. 4).

SCAR-F2 is originally recognized on endothelial cells and is expressed by macrophages as well but its scavenging function is yet to be reported. It favourably forms heterodimers with SCAR-F1 in *trans* and these heterodimers lack SR activities losing the competence to mediate ligand recognition [75].

MEGF10 (Multiple EGF-like domains 10) or SCAR-F3 is the third newest member in this group that was recently reported to express on brain macrophages (myosatellite and astrocytes). It plays a role as a receptor for binding to a complement protein called C1Q and is hence involved in apoptotic cell clearance in the mouse cerebellum and deficiency of MEGF10 in mice showed paucity in the apoptotic cells clearance in the mammalian brain [76]. MEGF10 is reported as an astrocytic phagocytic receptor for neuronal debris and unnecessary synapses in ischemic injured and developing brain [77]. MEGF10 is an ortholog of *Drosophila* Draper [78] and *C. elegans* CED-1 [79] that help to mediate axon pruning by glial cells in flies and phagocytosis of apoptotic cells in worms. It is a critical protein in the synapse remodeling underlying neural circuit refinement and has important implications for understanding learning and memory as well as neurological disease processes. Developing mice deficient in MEGF10 receptor fail to normally refine their retinogeniculate connections and retain excess functional synapses [80].

Class G

Chemokine 16 (CXCL16) is a single receptor in this class that has a CXC-chemokine domain with conserved arginine residues (Fig. 5). It is also called SR-PSOX (scavenger receptor for phosphatidylserine and oxidized LDL) due to their amino acid sequence similarity. It was primarily recognized in human monocytic cell line THP-1 as a receptor for scavenging and delivery of oxLDL and as a chemoattractant for stimulated T cells and bone

Fig. 4 SCAR-F1 on binding to diverse ligands like B-glucans, OmpA, NS3 in presence of TLR2 activates proinflammatory response, Antigen cross-presentation and viral uptake. On interaction with TLR4 in presence of LPS it activates MAP kinases following activation of various transcriptional factors like p38 and JNK that mediate extracellular release of IL6, TNF-α and INF-β

Fig. 5 SCAR-G on immune cell activates various immune related pathways like Th1 immune response via activation of IL12 and IFN-γ. On binding to gram-negative and gram-positive bacteria this receptor activates phagocytosis of bacteria into mature APCs following activation of IL12, TNF-α and p40 that helps to convert Th0 into Th1 cells

marrow plasma cells via receptor interaction with CXC-chemokine receptor 6 (CXCR6). It is likewise expressed on various immune cells like DCs, macrophages, [81] smooth muscle cells and endothelial cells. Novel CXCL16 on the surface of APCs function as an adhesion molecule that can be converted into a soluble form through proteolytic degradation of transmembrane CXCL16 mediated through (A Disintegrin and metalloproteinase domain-containing protein 10) ADAM10, which acts as a CXCL16 sheddase. The soluble chemokine, SR-PSOX/CXCL16 is interferon-regulated that triggers the CXCR6 receptor expressed by T cells, natural killer T cells [82] and a range of CXCR6 (+) leukocytes. In chronic inflammation, a characteristic of inflammatory bowel disease is that the serum concentrations of soluble SR-PSOX/CXCL16 are elevated in patients and that this soluble cytokine triggers phagocytosis of bacterial pathogens as well as Th 1 immune response through the production of IL 12, TNF- α and INF γ [83]. The deficiency of SR-PSOX/CXCL16 however, results in a reduced number of natural killer T cells in the liver and diminished release of cytokines like IFN- γ and IL-4 thus explaining its critical role in Th1 immune response [84]. Also, SR-PSOX/CXC ligand CXCL16 not only attracts but also facilitates the strong adhesion of CXCL16 expressing macrophages and DCs with CXCR6 expressing activated T cells and natural killer T cells [85]. In the liver, a specific NK cell population (liver-resident NK) is critical for local innate immunity that expresses a unique repertoire of chemokine receptors including CXCR6 that regulates selective movement in reaction to the chemotactic stimuli [86].

Class H

Class H scavenger receptors are transmembrane protein receptors with fasciclin, EGF-like, and lamin-type EGF-like domains comprising scavenger receptor 1, FEEL-1 (also called stabilin-1 and CLEVER1) and FEEL-2 (also called stabilin-2 and HARE). Both are structurally homologous and display analogous domain organization in extracellular regions.
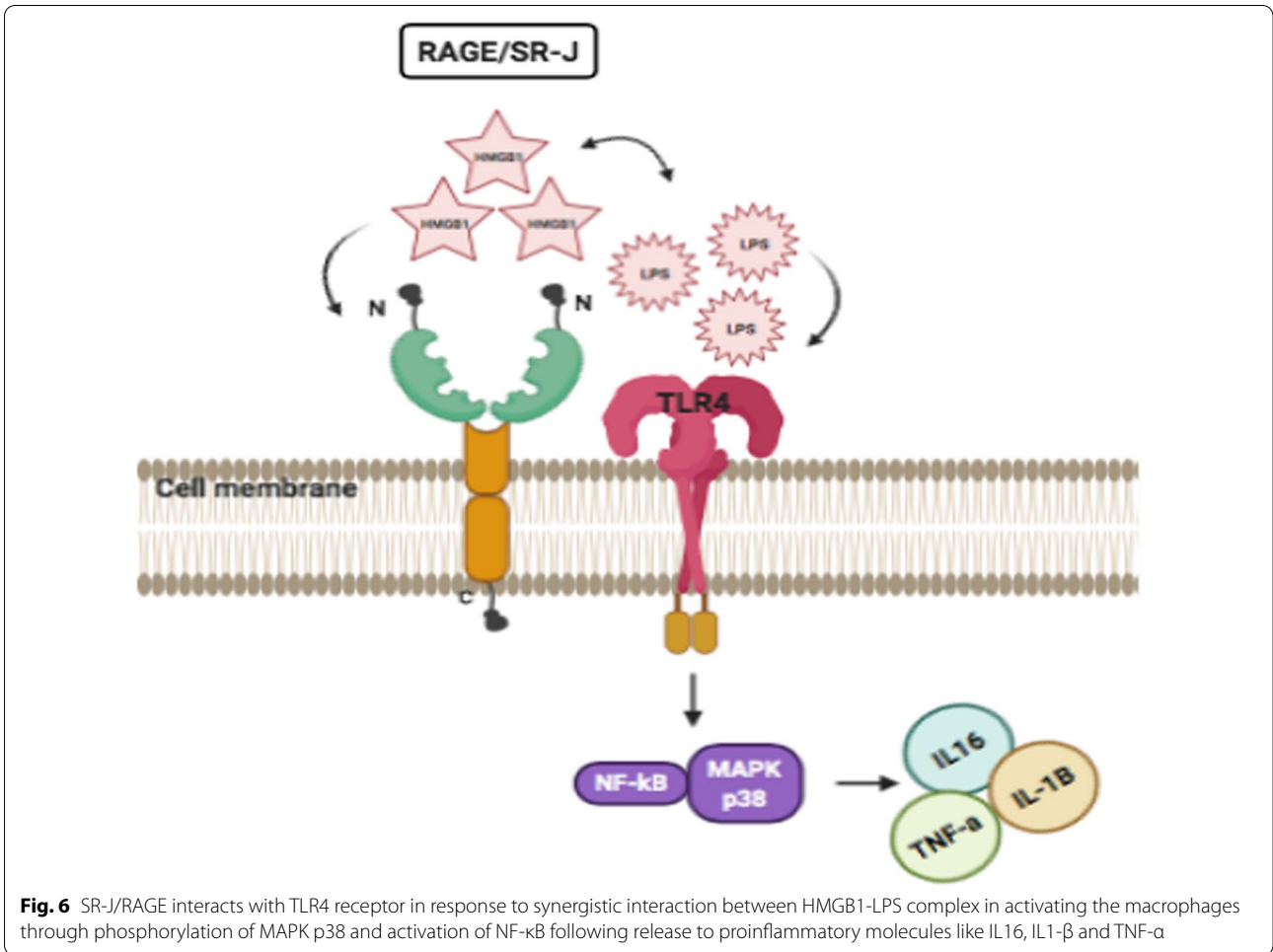
FEEL-1/Stablin-1 is principally expressed on macrophages, mononuclear cells, hematopoietic stem cells, and endothelial cells. Its expression is inducible in reaction to diverse proinflammatory stimuli. Stablin-1 as a leucocyte adhesion molecule is involved in regulating lymphocyte recirculation and trans movement to inflammation sites in vitro [87]. Another study by Karikoshi et al. confirmed that stablin-1 participates in the movement of T cells and B cells across HEVs in vivo and blockade of this receptor inhibited the relocation of blood monocytes and lymphocytes into the spot of infection [88]. Stabilin-1 binds a broad spectrum of ligands, such

as modified LDLs, apoptotic cells and microparticles from gram-positive and negative bacteria. Stablin-1 provides a defence mechanism to cells against bacteria and the direct interaction of stablin-1 and S. *aureus* is confirmed by using a blocking antibody against the transiently expressing receptor on CHO-1 cells [89].

FEEL-2/Stablin-2 has a conventional NPxY-like endocytic motif in the cytoplasmic region and like stablin-1 it is expressed on HS endothelial cells facilitating lymphocyte trafficking to the liver sinusoidal endothelium [90] and binding a variety of ligands such as acLDLs, heparin, apoptotic, necrotic cells and microparticles of gram-positive and negative bacteria. Stablin-2 also participates in regulating lymphocyte recirculation and migration to the liver sinusoidal endothelium via interaction with fasciclin 1 (FAS1) domains of stabilin-2 with lymphocyte expressed αMβ2 integrin. Future findings are necessitated to examine and authenticate the possible function of stabilin-2 in leukocyte trafficking to other tissues like the spleen and lymph nodes [91].

Class I

Class I receptors are the CD163 family of molecules that are categorized by the presence of numerous group B SRCR in their extracellular region. SCAR-I1 (also known as CD163A) is a transmembrane type 1-membrane glycoprotein with nine SRCR domains that are predominantly expressed in monocytes and macrophages acting as an endocytic receptor for haptoglobin-haemoglobin complexes to endorse the clearance of plasma haemoglobin. It was also called the 'haemoglobin scavenger receptor' due to its part as a haemoglobin receptor. It contributes to functions like apoptotic cell sequestration, clearance and inactivation of pro-inflammatory cytokine and TNF-related weak inducer of apoptosis (TWEAK) [92]. Like scavenger receptor SR-PSOX, SCAR-I1 is highly predisposed to cleavage by exofacial proteases and exists in soluble forms in plasma thus acting as a potential biomarker for infection and autoimmune diseases [93]. However, the proteolytic products function contrarily than the precursor receptor as the soluble form can counteract the growth of pathogens by acting as an iron chelator [94]. CD163A in host–pathogen interactions deliver host protection through its function as a macrophage receptor for gram-negative and positive bacteria. Its expression on human monocytes also provides defence through bacteria-induced proinflammatory cytokine production confirmed through using antagonistic antibodies against CD163A. It also has an immunomodulatory function as it activates intracellular protein tyrosine kinase-dependent signalling secretion of IL-6 and IL-10 [95]. CD163-L1 (also known as CD163B) is another member of this class with 12 SRCR domains. The cytoplasmic splice variants

Fig. 6 SR-J/RAGE interacts with TLR4 receptor in response to synergistic interaction between HMGB1-LPS complex in activating the macrophages through phosphorylation of MAPK p38 and activation of NF-κB following release to proinflammatory molecules like IL16, IL1-β and TNF-α

recognized so far are the full-tail length variant (CD163-L1α) and the short-tail variant (CD163-L1β). The subcellular location of these two variants in HEK293 cells differs as the former is an exterior receptor and the latter is in the intracellular section [96]. It is highly expressed in co-localization with CD163 in various types of macrophages like in alveolar macrophages, glia, and kupffer cells. Its involvement in the differentiation of monocytes into macrophages is dependent on various exogenous stimuli; M-CSF, IL6 and IL10 but is repressed by the cytokines such as IL-4, IL-13, TNF-α, LPS/IFN-γ [97]. Being an endocytic receptor, it is internalized through a clathrin-mediated pathway unlike other members of this group, CD163 and CD5 and also does show the same ligand preferences as of CD163 ligands such as the haptoglobin–haemoglobin complex or numerous bacteria.

The third CD163 family member is CD163c-a (SCART1) or CD5 with five SRCR domains. Two isoforms differ in the number of SRCR domains, one with two domains and another with four SRCR domains. SCART1 and SCART2 are the isoforms of this class expressed on

mice γδ T cells, lymph node, trachea, and lungs [98] and CD163 and SCART1 genes are expressed in bovine γδ T cells, monocytes, lymph node, lungs, and intestinal lymphocytes [99]. These SRCR families of receptors exist in both bound and soluble forms, whereby the membrane-bound form is involved in ligand binding. CD5 binds to numerous fungal cells such as *Schizosaccharomyces pombe*, *Candida albicans*, and *Cryptococcus neoformans* through its ectodomain and purified zymosan but not gram-negative or positive bacteria or purified LPS, LTA or peptidoglycans components. CD5 binds to fungal particles through conserved fungal components on the surface called β-glucans and trigger phosphorylation of MEK and ERK1/2 and thus triggers MAPK signalling cascade. This interaction further results in the significant release of cytokine IL-8 from HEK293 cells expressing CD5. Whether CD5 binds to microbial ligands in association with TLRs and participate in adaptive immune responses needs further investigation [100]. The fourth human CD163 family molecule is CD163c-b (SCART2) or CD6 that has high structural and functional homology
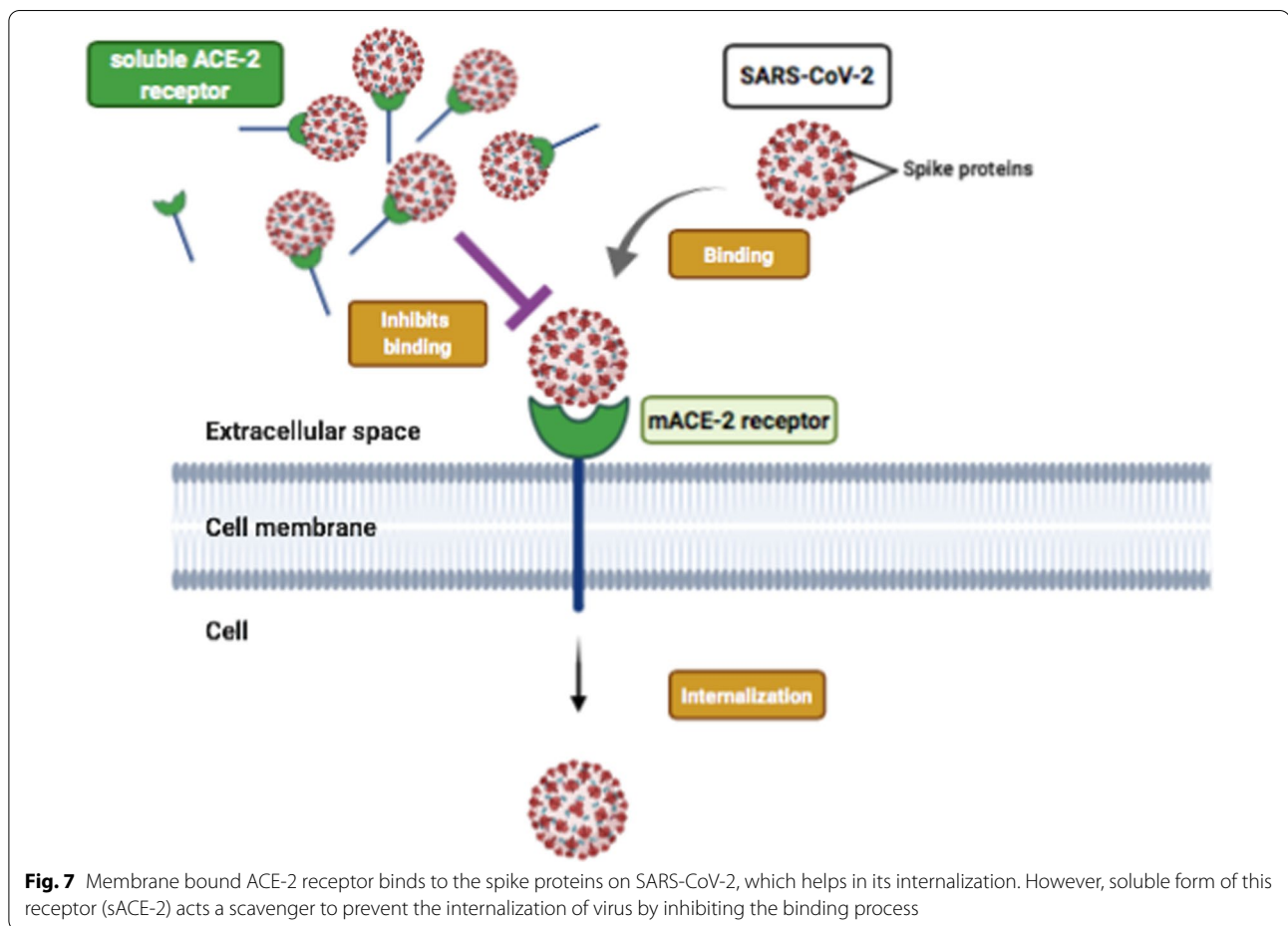
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Fig. 7 Membrane bound ACE-2 receptor binds to the spike proteins on SARS-CoV-2, which helps in its internalization. However, soluble form of this receptor (sACE-2) acts a scavenger to prevent the internalization of virus by inhibiting the binding process

with CD5 ectodomain. Both CD5 and CD6 are lymphocytic receptors found on T and B cells. CD6 is differentially expressed on CD56 NK cell subpopulation and trigger cytokines (INF-γ and TNF-α) and chemokines such as IP-10 and CXCL1 [101]. In Sjögren's syndrome, CD166 is highly expressed on epithelial cells. Unlike CD5, both soluble and membrane-bound forms of CD6 bind to gram-negative and positive bacteria while its soluble form shows less affinity to fungal species (binds to saprophytic but not pathogenic). CD6 binds to both LPS and LTA components in presence of calcium and activate the MAPK signalling cascade [102].

Class J
RAGE (receptor for advanced glycation end-products) is the only member of class J of scavenger receptors belonging to the Ig superfamily of cell surface molecules (Fig. 6). The ectodomain of this receptor is known to show various ligand interactions with amyloid-β-protein, HMGB1, and microbial PAMPs and DAMPs [103]. As a PRR it is involved in chronic inflammation and immunity, share common ligands and pathways with TLRs thus

cooperating synergistically. RAGE interacts with TLR4/2 associated adaptor proteins (TIRAP and MyD88) to activate downstream signalling pathways [104]. HMGB1, a ligand of RAGE works in cooperation with LPS in triggering the macrophages through phosphorylation of MAPK p38 and activation of NF-kB as seen in experimentally induced arthritis in mice [105]. While HMGB1-LPS complexes use TLR4, the HMGB1-Pam$_3$CSK$_4$ complexes use TLR2. RAGE-HMGB1 interactions are stabilized by heparin sulfate that readily forms a complex with RAGE at the cell surface before binding to HMGB1 [106]. S100 protein family members also interact with RAGE triggering immune responses in cooperation with TLR4 and activation of p38 MAPK, NF-κB and downstream signalling molecules [107]. Despite evidence that S100A8/A9 complex also interacts with TLR4 directly via MD2, [108] it is yet to be investigated if glycans expressed on TLR4 also mediate binding between the S100A8/A9 and TLR4. Also, in vitro analysis indicates that RAGE has a higher affinity with S100A8/A9 than TLR4, whereby the former interaction is linked with inflammation-mediated carcinogenesis and the latter with autoimmune disorders

and infection [109]. Direct interaction of RAGE with LPS molecule was also determined through competition assay with another RAGE ligand, AGE-BSA [110] and produced comparable immune reactions as that seen with TLR4 binding in the in vitro and in vivo. Unlike, HMGB1–RAGE interactions in synergy with LPS and TLR4 has been demonstrated, the RAGE-TLR4 interactions in response to LPS or whole bacteria are still ambiguous. Like membrane-bound forms, the soluble form of RAGE called sRAGE also functions in various processes and disease pathogenesis [111].

Class K
The only receptor of class K is CD44 and is a hyaluronan (HA) receptor that shows ligand binding with proteoglycans, growth factors, cytokines, and matrix metalloproteinase through its extracellular domains. ADAM10, ADAM17, and MMP14 act as sheddase of membrane bound CD44 in various tumour cells lines. The external ectodomain cleavage product of this receptor is biologically active [112] and it participates in intracellular signalling through the Src family of kinases such as Src, Lck, Fyn and Lyn and activates small Rho GTPases. CD44 has a wide ligand spectrum and interactions with a diverse range of receptors thereby activating multiple signalling pathways. The most important interactions in the context of immunity are with TLRs. In acute pulmonary infection, CD44 prevents overstated inflammatory responses to LPS. Intratracheal LPS treatment in CD44-/- mice show a marked increase in NF-κB, inflammatory cell recruitment, raised chemokine expression in lung tissue in vivo and reduced induction of the negative regulators of TLR4 signalling pathways [113]. A direct association between CD44 and TLR2 was shown in a study that demonstrates, on stimulation with TLR2 ligand, zymosan, CD44 promoted NF-κB deactivation, suppression of proinflammatory cytokine and that CD44 and TLR2 function together in diminishing TLR-mediated inflammation in CD44+/+ macrophages derived from mice as compared to CD44-/-macrophages [114]. CD44 also functions in response with hyaluronan and LPS in association with TLR4 against the septic response to LPS and show-decreased serum IL-6 and TNFα in CD+/+ mice [115]. However, in osteoarthritis, activation of TLR2 and TLR4 induce IL-1β and TNF-α release that notably increased CD44 gene expression and protein concentrations in human macrophages, whereas blocking CD44 with anti-CD44 Ab or HA show opposite results [116]. CD44 also aids in host defence against Group A *Streptococcus* (GAS) through the interaction of CD44 to capsular HA polysaccharide of the bacteria. In transgenic mice expressing a CD44-antisense transgene, no bacteria were internalized by macrophages, thus adding to the fact that CD44 functions as a phagocytic receptor via HA signalling. In macrophages, the molecular mass of HA also determines if the bacteria undergo phagocytosis or not. While degradation of HA with protease, hyaluronidase augmented internalization of GAS by macrophages [117]. CD44-HA interactions are also responsible for progression towards gastric cancer after *Helicobacter pylori* infection whereby a cascade is triggered, which leads to degeneration of parietal cells followed by neoplasia [118]. Similarly in pneumonia, CD44 plays a positive but opposite role in the advancement of infection instigated by *Escherichia coli* and Streptococcus species. Unlike E.*coli* based pneumonia, S. *pneumonia* and *Klebsiella pneumonia* induced pneumonia shows decreased CD44–HA-mediated signalling and downstream activation of inflammatory pathways [119]. Overall these reports indicate CD44 prolong bacterial infections by decreasing lung inflammations and increasing bacterial diffusion to other locations. In viral diseases such as HIV and hepatitis C, CD44 plays the opposite role in infection. In HIV, the virus acquires the CD44 molecules from the host and decreases the activation of blood mononuclear cells, CD4 (+) T cells (by not triggering protein kinase C-α release), and M7-Lue cells in presence of endogenous HA which shows a defensive role in HIV by interfering with CD44-HA interactions [120]. While as in hepatitis C, the CD44 expression is amplified in infected cells with HCV when induced with HA that increases IP-10 (gamma interferon-inducible protein 10) expression via CD44–TLR2–MyD88 interactions [121].

Class L
Class L has two receptors named: SR-L1 (also called LDLR-related protein 1 (LRP1)) or CD91 and SR-L2 (LRP2 or Megalin). They belong to the LDLR gene family and SR-L1 is the one most studied so far. SR-L1 functions uniquely as a scavenger receptor thus scavenging the extracellular ligands or bioactive compounds (cross-presentation) that come in its contact as well as an extracellular sensor that senses the same ligands and transfer the signal to the cell's interior for activation of classical signal transduction pathways (costimulation). While doing so it is known to bind over 100 diverse ligands whose functions and interactions with other co-receptors and signal transducers mainly remain unknown. One of the important ligands is defensins that are endogenous peptides with antimicrobial action alongside a broad spectrum of pathogens including bacteria, fungi, viruses, and many parasites. SR-L1 expressed on dendritic cells is upregulated by human defensins, HNP-1 alpha defensin or HBD-1 and thus show the existence of an autocrine loop [122]. SR-L1 act as a receptor for heat shock proteins such as gp96, hsp90, hsp70, and calreticulin on

APCs (Macrophages, T cells and DCs) and is one of the potential receptors that mediate APC- HSP interactions. It conducts signal to APCs for their activation in presence of immunogenic HSPs followed by stimulation of NF-κB and p38 MAPK and release of TNF-α, IL-1β, IL-6, IL-12, and GM-CSF [123] and costimulatory and maturation markers like CD80, CD86, CD40, and MHC II [124]. The release of proinflammatory cytokines triggers chronic inflammation during increased levels of hsp70 in synovial fluid from swollen joints of rheumatoid arthritis patients that triggers autoimmunity [125]. However, whether CD91 functions along with TLRs on immune cells in inflammatory processes needs more validation.

Megalin or SR-L2 is another endocytic receptor that belongs to this class, which is expressed on various cells. Megalin is expressed at the blood–brain barrier and lack of this receptor leads to neuroinflammatory processes and impaired neurogenesis by triggering the discharge of pro-inflammatory cytokines such as IL-1β, IL-6 and TNF-α on activation of microglial and astroglial cells and attenuating the suppressor of cytokine signalling-3 (SOCS3) in cortical and hippocampal regions [126].

Angiotensin-converting Enzyme 2 (ACE-2): a scavenger receptor?

Many receptors that participate in the entry of viruses in cells, rather than evoking an immune response against the viral particles that happens in the case of SRs, facilitate the replication and dissemination of the pathogen. One of such receptors is Angiotensin-converting Enzyme 2 ACE-2. It is a transmembrane metallopeptidase that functions as a monocarboxypeptidase to cleave diverse regulatory peptides such at the carboxyl-terminal of Angiotensins II and I, bradykinin, kinetensin, and neurotensin [127, 128]. It functions as a vasodilator, unlike ACE-1. ACE-2 was first isolated from Vero E6 (African green monkey kidney cell line) that interact with the S1 domain of the SARS-CoV (Coronavirus) S protein through S1-Ig interaction. ACE-2 permits the cell–cell fusion and then replication of the virus that was confirmed when the soluble form of ACE-2 inhibited the S1-Ig interactions with Vero E6 cells and ACE2-transfected 293 T cells shows signs of cytopathicity on infection respectively. ACE-2 is a principal receptor for SARS-CoV was also confirmed *in vivo* on established mouse animal models [129, 130]. A novel virus, SARS-CoV-2 originated from bats and pangolins as possible intermediate hosts showed structural homology, 76.5% identity in amino acid sequences of spike proteins with SARS-CoV [131]. Also, the spike proteins of SARS-CoV-2 recognize and bind to human ACE-2 with high affinity than SARS-CoV thus contributing to a higher rate of transmission

[132]. Overexpression of membrane-bound ACE-2 on HeLa cells from diverse species like humans, civets, pigs, other than mouse show SARS-Cov-2 uses only ACE-2 receptor for entry and not other receptors like aminopeptidase N and dipeptidyl peptidase 4 [133]. Of note, however, most of the scavenger receptors discussed above have both membrane-bound forms and soluble forms that participate in scavenging. But ACE-2 only in its soluble form might participate in preventing the viral entry and replication unlike its membrane form, which is one of the properties of scavenger receptors (Fig. 7). It is suggested that free ACE-2 competitively binds to the spike proteins of CoV-2 thus preventing the virus to bind ACE-2 found excessively on alveolar epithelial type II and hence the viral spread. Also, it prevents lung injury by negatively regulating the Renin-Angiotensin pathway (RAS) by increasing the ratio of ACE/ACE-2 [134]. Thus, classifying ACE-2 as a prospective scavenger receptor will be assessed if additional information becomes available.

Conclusions

Initially, the role of scavenger receptors was confined to their involvement in lipoprotein binding. With time it was clear just like other PPRs, SRs have dynamically complex interactions with an extraordinary repertoire of ligands like PAMPs, DAPMs, modified self-molecules etc. This versatility is because this family of receptors is classified in various classes each with diverse functional roles in host–pathogen interactions, innate immunity, adaptive immune response, inflammation signaling, ligand delivery and antigen presentation etc. Also, different SRs can bind to the same type of ligands and a single SR can show interaction with a variety of pathogenic ligands. Another important property that enables these receptors to have a dynamic behaviour is to have a reversible interaction with various co-receptors in response to ligands thus taking part in homeostasis and in combatting infections. Interestingly, each receptor type can induce inflammation to control infection under some conditions while having an anti-inflammatory response in some other conditions. But mostly SRs are capable to contribute to pathogen elimination by controlling the recruitment and the activation of phagocytic cells and regulating inflammatory response through proinflammatory cytokine production. Differential responses generated by a single receptor against different ligands and with various co-receptors need to be comprehensively studied. In our study, we conclude SCARB1 (Class B receptor) to play a vital role in the *E.coli*-induced activation of TLR4 signaling cascades thus providing a deeper insight into host pathogen interactions. Therapeutic tools involving

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functional manipulation of these receptors through various approaches are attractive prospects to explore their role as therapeutic targets in inflammatory diseases and present an opportunity for the development of clinical therapies to target autoimmunity. Also, sophisticated techniques like proteomics, transcriptomic approaches, biophysical methods and super-resolution techniques are required to understand the signalling complexes and clusters in inflammation signalling pathways and the biology of scavenger receptors overall.

Abbreviations
LDLs: Low-density lipoproteins; DAMPS: Damage-associated molecular patterns; PAMPs: Pathogen-associated molecular patterns; LPS: Lipopolysaccharide and; LTA: Lipoteichoic acid; PRRs: Pattern recognition receptors; TLRs: Toll like receptors; CLEC: C-type lectin domain; HSV-1: Herpes simplex virus type 1; CDE: Clathrin-dependent endocytosis; CIE: Clathrin-independent endocytosis; ROS: Reactive oxygen species; HFMD: Hand Foot and Mouth Disease; STST3: Signal transducer and activator of transcription 3; SRCL: Scavenger receptor with C-type lectin; MAPKs: Mitogen-activated protein kinases; HCV: Hepatitis C virus; DCs: Dendritic cells; BECs: Bronchial epithelial cells; PGMECs: Primary goat mammary epithelial cells; LIMP-2: Lysosome membrane protein 2; EV71: Enterovirus 71; LAMP: Lysosome-associated membrane glycoprotein; LOX-1: Low-density lipoprotein receptor; CHO-K1: Chinese hamster ovary-K1; ASGPR1: Asialoglycoprotein receptor 1; EGF: Epidermal growth factor; CXCL16: Chemokine 16; SR-PSOX: Scavenger receptor for phosphatidylserine and oxidized LDL; CXCR6: CXC-chemokine receptor 6; ADAM10: A Disintegrin and metalloproteinase domain-containing protein 10; FAS1: Fasciclin 1; TWEAK: TNF-related weak inducer of apoptosis; RAGE: Receptor for advanced glycation end products; HA: Hyaluronan; GAS: Group A *Streptococcus*; LRP1: LDLR-related protein 1; ACE-2: Angiotensin-converting Enzyme 2; SARS-CoV: Severe acute respiratory syndrome coronavirus; RAS: Renin Angiotensin pathway.

Authors' contributions
QM conceived the review, wrote, and edited the manuscript. PTM, KM, EH and SMA helped in writing and collection of information. All authors read and approved the final manuscript.

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Declarations

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None.

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Competing interests
The authors declare that they have no competing interests.

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