Scavenger receptors in homeostasis and immunity

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Abstract | Scavenger receptors were originally identified by their ability to recognize and to remove modified lipoproteins; however, it is now appreciated that they carry out a striking range of functions, including pathogen clearance, lipid transport, the transport of cargo within the cell and even functioning as taste receptors. The large repertoire of ligands recognized by scavenger receptors and their broad range of functions are not only due to the wide range of receptors that constitute this family but also to their ability to partner with various co-receptors. The ability of individual scavenger receptors to associate with different co-receptors makes their responsiveness extremely versatile. This Review highlights recent insights into the structural features that determine the function of scavenger receptors and the emerging role that these receptors have in immune responses, notably in macrophage polarization and in the pathogenesis of diseases such as atherosclerosis and Alzheimer's disease.

Scavenger receptors were first defined by Goldstein and Brown in 1979 (REFS 1,2). Scavenger activity was associated with the ability of certain membrane receptors to bind to and to internalize oxidized low-density lipoprotein (oxLDL). Scavenger receptors were thought to recognize specific epitopes generated by oxidation of native LDL, hence enabling the differentiation between unaltered endogenous self molecules and modified self molecules[3]. Altered lipoproteins challenge normal homeostasis; indeed, oxLDL has been convincingly implicated in the pathogenesis of atherosclerosis[4–7]. For this reason, modified lipids and proteins are identified as danger-associated molecular patterns (DAMPs)[8,9].

In recent years additional members of the scavenger receptor family have been identified and more has been learned about their properties[10–14]. It is now appreciated that the range of ligands that they recognize is extremely diverse and includes unmodified endogenous proteins and lipoproteins, as well as a number of conserved microbial structures, such as bacterial lipopolysaccharide (LPS) and lipoteichoic acid (LTA)[15–17]. To account for this wide range of scavenger receptor ligands, Witztum[9] suggested that epitopes generated by peroxidation of endogenous proteins or lipoproteins resemble microbial structures. In view of the expanding number of cognate ligands, the definition of a scavenger receptor has been broadened to include not only the recognition of modified self molecules (which are a subset of DAMPs) but also the recognition of several exogenous (that is, non-self) pathogen-associated molecular patterns (PAMPs). As such, scavenger receptors are considered to be a subclass of the membrane-bound pattern recognition receptors (PRRs)[15,18–20].

The scavenger receptors are structurally very heterogeneous. They are subdivided into classes and, although members of each class share structural features, there is little or no homology among classes (FIG. 1). The amalgamation of the scavenger receptors into a superfamily is mostly due to their shared functional properties. Overall, scavenger receptors identify and remove unwanted entities, through the recognition of modified self molecules (for example, apoptotic cells, mineral-laden debris or damaged proteins) or through the recognition of non-self molecules (for example, microorganisms or foreign particles)[16,20–27]. Removal is often carried out by simple endocytosis but might entail more complex processes, such as macropinocytosis or phagocytosis, which both require elaborate signal transduction. Other emerging roles of these multifunctional receptors include cellular adhesion[28–30] and antigen presentation[31].

In light of their functional versatility and their selectivity for a wide range of ligands (FIG. 2; see Supplementary information S1,S2 (table, figure)), it is not surprising that scavenger receptors are involved in both the maintenance of homeostasis and in the pathogenesis of various diseases. Similarly to other PRRs[15], scavenger receptors have

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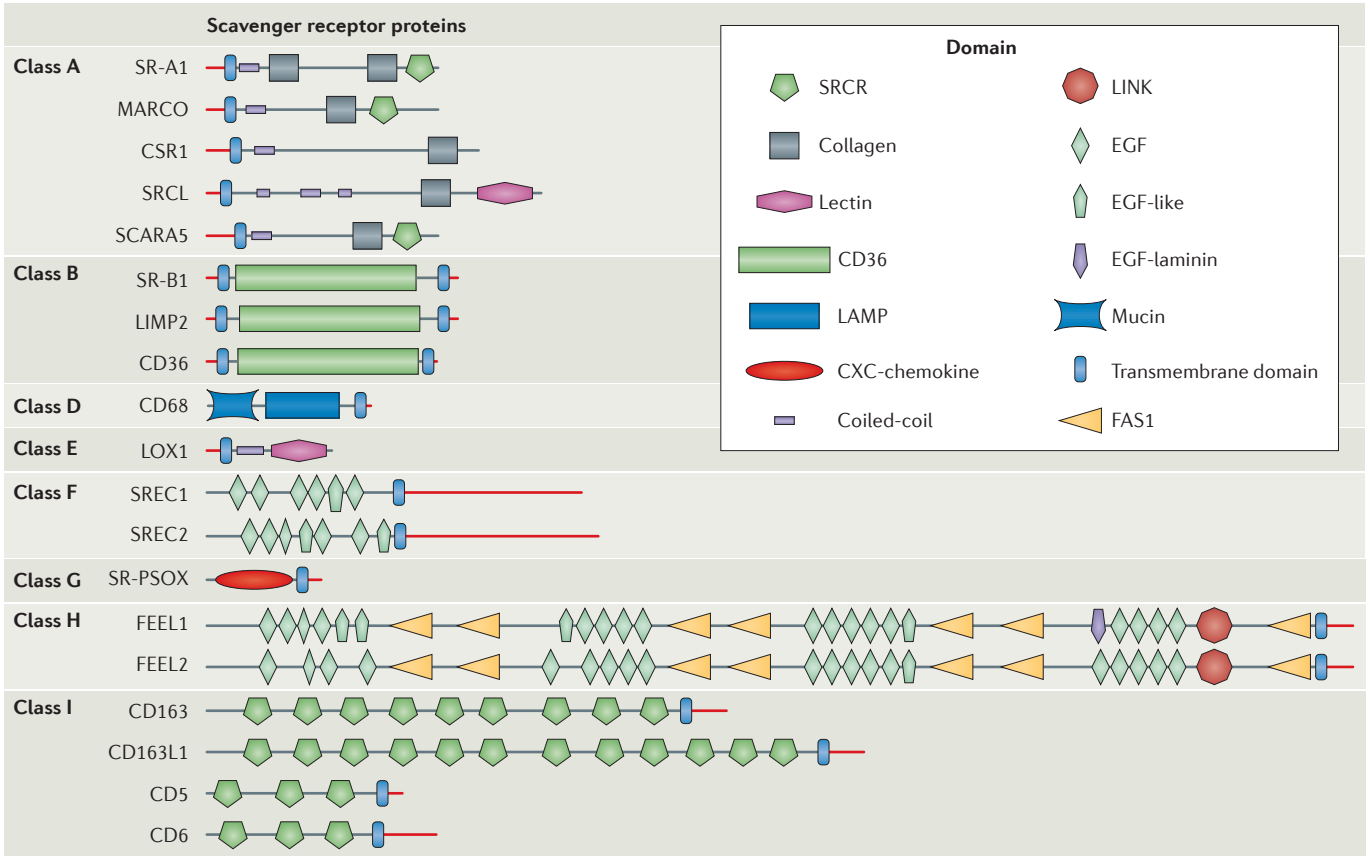

Figure 1 | **Domain architecture of scavenger receptors.** Mammalian membrane-associated scavenger receptors are multidomain proteins that are separated into eight classes. Scavenger receptors show more than 14 different characteristic protein domains that are identified in the figure inset. The combinations and permutations of domains give rise to a considerable diversity among classes. Note that although the majority of scavenger receptors are single-span membrane proteins, members of class B (including CD36, SR-B1 and lysosomal integral membrane protein 2 (LIMP2)) have two transmembrane domains. Despite the diversity in protein domain architecture it is striking that, with the exception of scavenger receptor expressed by endothelial cells 1 (SREC1; (also known as SCARF1) and SREC2, all other groups have very short cytoplasmic tails (shown in red). Furthermore, the cytoplasmic tails do not possess any identifiable protein domains or motifs. For descriptions of domain abbreviations and functions, see the SMART website. The class C scavenger receptor is not listed as it is only present in *Drosophila melanogaster*. CLEC, C-type lectin; CSR1, cellular stress response protein (also known as SCARA3); EGF, epidermal growth factor; EGF-laminin, laminin-type EGF-like; FAS1, fasciclin 1; FEEL1, fasciclin EGF-like laminin-type EGF-like and link domain-containing scavenger receptor 1 (also known as stabilin 1 and CLEVER1); LAMP, lysosome-associated membrane glycoprotein; LOX1, lectin-like oxidized LDL receptor 1; MARCO, macrophage receptor with collagenous structure (also known as SCARA2 and SR-A2); SR-PSOX, scavenger receptor for phosphatidylserine and oxidized low-density lipoprotein (also known as CXCL16); SCARA5, scavenger receptor class A member 5; SRCL, scavenger receptor with C-type lectin (also known as SCARA4 and CLP1); SRCR, scavenger receptor cysteine-rich domain.

Danger-associated molecular patterns
(DAMPs). Molecules that are released in association with tissue damage or injury; they promote inflammation and tissue repair by triggering pattern-recognition receptors. DAMPs can be released from the degraded stroma (for example, hyaluronan), from the cell nucleus (for example, high-mobility group box 1 protein) and from the cell cytosol (for example, ATP, uric acid, S100 molecules and heat-shock proteins).

Pathogen-associated molecular patterns
(PAMPs). Conserved microbial structures that are recognized by innate receptors, including Toll-like receptors.

Pattern recognition receptors
(PRRs). Host receptors (such as Toll-like receptors) that are able to sense pathogen-associated molecular patterns and to initiate signalling cascades (often involving the activation of nuclear factor-κB) that lead to an innate immune response.

a central role in innate immunity, and their promiscuous affinity for modified lipids and pathogens might be the link between altered metabolism and inflammation[20,32–37]. These recent findings and the rapid, continuing growth in the identification of members of the scavenger receptor family, provided the motivation for this Review. In this Review we restrict the discussion to the mammalian scavenger receptors (for invertebrate scavenger receptors the reader is referred to other reviews[38–40]).

Structural features of scavenger receptors

Scavenger receptor classes. On the basis of sequence alignments and protein domain architecture, Krieger[18] proposed in 1997 that scavenger receptors should be subdivided into six classes, designated A to F[18]. However, because functional considerations — such as the types of modified LDL that were recognized by the receptors — considerably influenced this classification, the resulting groups often include a range of structural determinants. Thus, as depicted in FIG. 1, class A scavenger receptors contain a collagen domain, and might also have a type A scavenger receptor cysteine-rich (SRCR) domain or a C-type lectin (CLEC) domain; class B scavenger receptors contain a CD36 domain; class D scavenger receptors contain mucin-like and lysosome-associated membrane glycoprotein (LAMP) domains[41]; class E scavenger receptors only have a CLEC domain; and class F scavenger receptors are rich in epidermal growth factor (EGF) and EGF-like domains.

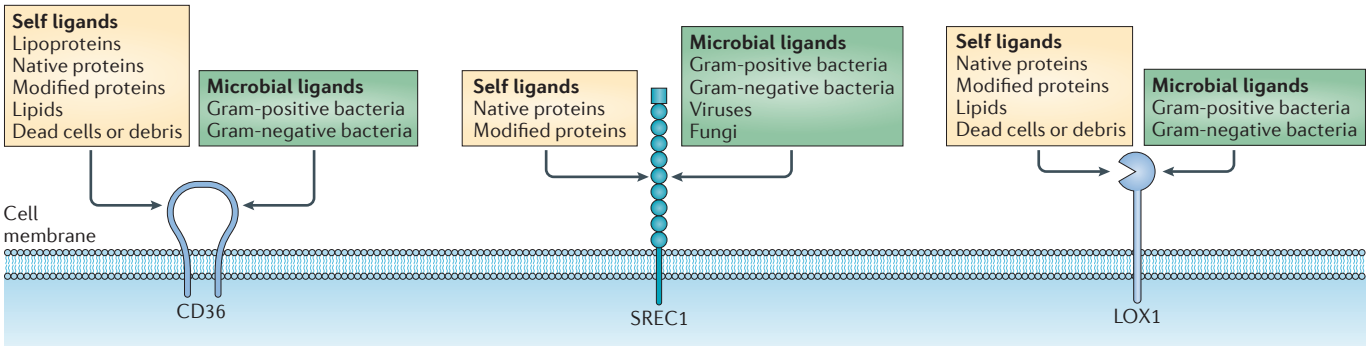

Figure 2 | **Scavenger receptors and their ligands: functional overlap.** Diagrammatic representation of the binding specificity of scavenger receptors for self or altered-self ligands (yellow boxes), and for non-self ligands (green boxes). This figure simplifies the information listed in Supplementary information S1,S2 (table, figure). The figure highlights the broad ligand specificity and the functional overlap of three representative scavenger receptors: CD36, scavenger receptor expressed by endothelial cells 1 (SREC1) and lectin-like oxidized LDL receptor 1 (LOX1).

The subsequent realization that scavenger receptors also participate in pathogen binding and clearance made it necessary to revise and to expand the original classification. As a result, proteins such as CD163 that lack the ability to bind to modified LDL are now classified as scavenger receptors[14,42]. In 2005, two additional classes, G and H, were added to the scavenger receptor family to accommodate the new members[43]. The only receptor in class G has a CXC-chemokine domain[44]. Class H scavenger receptors, like class F receptors, have multiple EGF and EGF-like domains, but they can also have fasciclin 1 (FAS1) and LINK (hyaluronan-binding) domains. Moreover, recent publications suggest the existence of three additional classes of scavenger receptors, which are characterized by hepatitis A virus cellular receptor 1 (HAVCR1; also known as KIM1 and TIM1)[13], the P2X purinoceptor 7 (REF. 12) and CD163 (REFS 14,42) (together with CD6 (REF. 45) and CD5 (REF. 46)). Unlike the well-established scavenger receptors, which are abundant in myeloid cells, HAVCR1 is highly expressed in the proximal tubular epithelium, particularly in response to kidney injury[47]. The ectodomain of HAVCR1, which belongs to the immunoglobulin superfamily[13], binds to and mediates the internalization of oxLDL[47]. P2X7, which has been recognized as a purinoceptor for a long time, was recently described to also function as a phagocytic receptor, facilitating the uptake of non-opsonized particles and bacteria[48,49], as well as apoptotic cells[12]. So far, no consensus has been reached as to whether CD5, CD6, CD163, HAVCR1 and P2X7 merit inclusion in the scavenger receptor family. If these receptors were to eventually be included, their unique structural features would require the creation of three novel classes of scavenger receptor, potentially designated I, J and K. Class I receptors would contain a type B SRCR domain, class J receptors would contain a mucin-like and an immunoglobulin domain, and class K receptors would contain a purinergic receptor domain.

Structure determines function of scavenger receptors. The domain architecture of scavenger receptors raises two puzzling questions. Firstly, how is the remarkable functional overlap of the different types of scavenger receptors (see Supplementary information S1,S2 (table, figure)) achieved, despite their lack of structural commonality? Secondly, what confers scavenger properties to these receptors, considering that most of their constituent domains are not unique but are in fact shared by a multitude of other proteins with divergent activities? For instance, EGF domains can be found in 488 different human proteins and CLEC domains in 169 others, but only a handful of these proteins have scavenger properties. In all likelihood, subtle differences in the sequence of each domain and in their arrangement in the three-dimensional structure of the protein (and possibly in multimolecular complexes) will determine their functional selectivity. Detailed structural information will clearly be required to unravel the basis of scavenger receptor selectivity and function.

Information regarding scavenger receptor structure is currently fairly scant. To our knowledge no single scavenger receptor has been fully characterized and only the X-ray or nuclear magnetic resonance (NMR) structures of a few isolated domains from selected receptors have been obtained. The domains that have been characterized include type A and type B SRCRs[50,51], CLEC [52–54], EGF, lysosome membrane protein 2 (LIMP2), LAMP[55], FAS1, LINK and P2X4 domains. Nevertheless a pattern is beginning to emerge. FIGURE 3 shows both cartoon and surface representations of the ligand-binding domains of macrophage receptor with collagenous structure (MARCO; also known as SCARA2 and SR-A2)[50] and lectin-like oxidized lectin-like oxidized LDL receptor 1 (LOX1; also known as OLR1 and SCARE1)[52], which highlights their electrostatic potential. Although structurally unrelated, the surfaces that are engaged in ligand binding share a high degree of similarity in terms of shape and charge distribution, displaying clusters of cationic residues that are generally centrally located, bounded by anionic patches. This singular electrostatic profile might explain the preference of scavenger receptors for polyanionic ligands, which accounts for the functional overlap of ostensibly dissimilar domains. Accordingly, mutating the arginine residues that form the cationic patch on the surface of the SRCR domain of

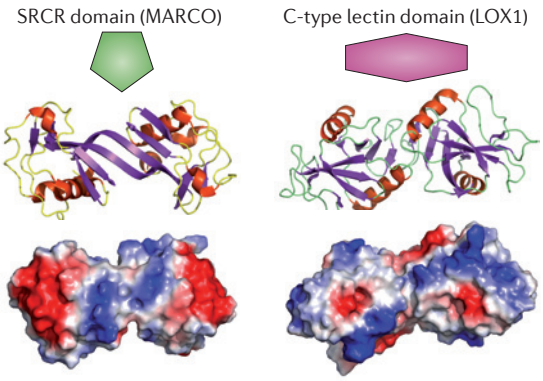

Figure 3 | **Structural features of the ligand-binding site of scavenger receptors.** Scavenger receptor domains of known structure are compared (the same symbols are used as in FIG. 1). Shown are the cartoon representation (middle) and the electrostatic potential (bottom) of the putative ligand-binding surface of the dimeric scavenger receptor cysteine-rich (SRCR) domain of macrophage receptor with collagenous structure (MARCO) and the C-type lectin (CLEC) domain of lectin-like oxidized LDL receptor 1 (LOX1). The red patches indicate the regions of most negative electrostatic potential, whereas the blue patches show the regions of most positive electrostatic potential. Notice the shape and the charge similarity of the receptors shown, despite their differences in primary sequence.

MARCO (R431A, R433A, R466A or R468A) impaired the ability of this protein to bind to acetylated LDL (acLDL)[50]. Similarly, mutations that reduced the positive charge on the surface of LOX1 (R208N, R229N or R248N) inhibited acLDL binding and uptake[52], and the residues K164 and K166 were shown to be important for oxLDL binding by CD36 (also known as platelet glycoprotein 4)[56]. These residues are predicted to be part of a cationic patch on the surface of CD36, as deduced by structural homology modelling (D.N., S.G., R. Collins, S. Dhe-Paganon, P. Loppnau, J. Peters, J. C. Pizarro, J. Plumb, M. Ravichandran, P. Saftig, M. Schwake, A. Seitova, W. S. Trimble and F. Zunke, unpublished observations). Extending this hypothesis further, we suggest that a set of conserved arginine residues in the chemokine domain of scavenger receptor for phosphatidylserine and oxidized low-density lipoprotein (SR-PSOX; also known as CXCL16 — a class G scavenger receptor) are exposed on its ligand-binding surface. This comes from the observation that charge-neutralizing mutations of these residues (R59A, R67A and R73A) preclude the binding of oxLDL and bacteria to SR-PSOX[57].

What seem to be paradoxical observations in the field can also be explained when considered in the context of this electrostatic patch model. A striking example is provided by the SRCR domain, which was shown to mediate binding of bacteria, LPS and modified LDL by MARCO[50,58,59] (FIG. 3). By contrast, the related SRCR domain of SR-A1 (also known as SCARA1 and MSR1) is not involved in ligand recognition, but instead mediates interactions with other membrane proteins. In SR-A1 it is the collagen domain that is responsible for ligand binding. This conundrum can be resolved when comparing the electrostatic map of the SRCR domain of MARCO with the homology model inferred for the SRCR of SR-A1. The positive arginine patch that is present on the surface of MARCO (FIG. 3) is absent in the case of SR-A1 (REF. 50).

The electrostatic patch model helps to explain the preference of scavenger receptors for polyanionic ligands; however, the precise structural determinants of the ligands themselves are less clear. This is probably due to the large scavenger receptor ligand repertoire and the scarcity of structural information about ligand–receptor complexes. One exception is the oxLDL–CD36 interaction. Oxidized lipids (which are a major constituent in oxLDL) are the moieties that are recognized by CD36 (REFS 60–64). Oxidation of the acyl chain of phosphatidylcholine generates a terminal γ-hydroxy-α,β-unsaturated carbonyl group that adopts a unique conformation, protruding into the aqueous phase where it becomes accessible to the receptor[27,65,66]. Phosphatidylserine has been reported to become oxidized in a similar way, functioning as an effective ligand for CD36 on the surface of apoptotic cells[67].

Two other structural features of the scavenger receptor family deserve mentioning. Firstly, with few exceptions (for example, scavenger receptor expressed by endothelial cells 1 (SREC1; also known as SCARF1) and SREC2 (also known SCARF2,)[10], the scavenger receptors have only short cytosolic tails that lack discernible signalling motifs. This feature is discussed in more detail below in the context of scavenger receptor function. Secondly, the propensity of scavenger receptors to oligomerize is also noteworthy[43,50,52,58,68–70]. This increases the avidity of binding, thus oligomerization of scavenger receptors might favour the binding of large, multivalent ligands such as modified lipoproteins and bacteria[50,69].

Functional features of scavenger receptors

Scavenger receptors have been attributed an impressively broad range of functions and are thought to be involved in complex events such as phagocytosis, antigen presentation and the clearance of apoptotic cells. Therefore, it is not surprising that scavenger receptors have been shown to activate a range of diverse signalling pathways.

The exact mechanisms by which scavenger receptors convey signals following ligand binding remain unclear, not least because few — if any — of the receptors have discernible signalling motifs or domains. A typical case is that of CD36. Similarly to other class B scavenger receptors, CD36 has two transmembrane domains and both its amino terminus and its carboxyl terminus are cytoplasmic. As the N terminus is particularly short (only seven residues in length), the C-terminal tail is thought to be the site of signal transduction[71]. Indeed, this region has been shown to associate with SRC family kinases, including FYN, YES and LYN[71–74]. Of note, the C-terminal region of CD36 contains a $CXCX_5K$ motif, which is also found in the cytosolic tails of the T cell co-receptors CD4

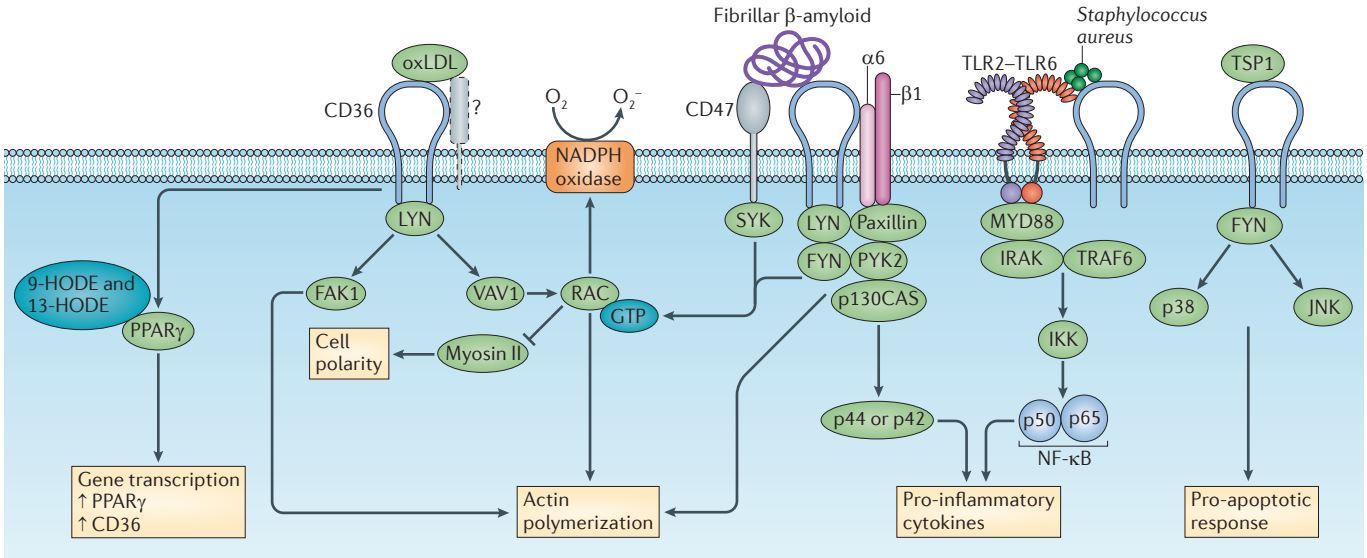

Figure 4 | **Scavenger receptors engage multiple intracellular signalling pathways.** Scavenger receptor signalling can result in very different outcomes depending on the ligand that is engaged and the cellular context. This is exemplified by CD36, which has been studied in some detail. CD36 can form complexes with integrins (for example, α6β1 and other β1 and β2 integrins), Toll-like receptors (TLRs) and other molecules, including the tetraspanins CD9 and CD81. The presence of specific ligands probably determines the nature of the complex formed. In most instances, the engagement of CD36 causes the activation of SRC family tyrosine kinases, such as FYN and/or LYN. Following oxidized low-density lipoprotein oxLDL binding, prolonged activation of focal adhesion kinase 1 (FAK1), together with the VAV1-mediated activation of RAC and the inhibition of non-muscle myosin II, result in actin polymerization, increased cell spreading and loss of cell polarity. RAC also stimulates the NADPH oxidase. Activating ligands for peroxisome proliferator-activated receptor-γ (PPARγ), such as 9-hydroxyoctadecadienoic acid (9-HODE) and 13-HODE, are also delivered to the cell following oxLDL binding to CD36, which results in the stimulation of PPARγ, increasing the expression CD36. In response to other ligands, including β-amyloid and thrombospondin 1, CD36 activates mitogen-activated protein kinase (MAPK) family serine/threonine kinases, such as p44, p42, p38, Jun N-terminal kinase (JNK) and the tyrosine kinase proline-rich tyrosine kinase 2 (PYK2), and recruits the adaptor proteins p130CAS (also known as BCAR1) and paxillin. These ligands induce actin rearrangement and stimulate the production of pro-inflammatory cytokines and of pro-apoptotic signals. CD36 can also partner with TLR complexes in response to pathogen ligands, which signal the production of pro-inflammatory cytokines through a myeloid differentiation primary-response protein 88 (MYD88)- and nuclear factor-κB (NF-κB)-dependent pathway. The question mark indicates an as yet uncharacterised co-receptor that has been proposed to cooperate with CD36 to mediate oxLDL binding. IKK, IκB kinase; IRAK, IL-1 receptor-associated kinase; SYK, spleen tyrosine kinase; TRAF6, TNF receptor-associated factor 6; TSP1, testis-specific protein 1.

and CD8, and which functions as a docking site for SRC family kinases[75,76]. However, it was convincingly shown that in CD36 the $CXCX_5K$ motif is not a major docking site for FYN and LYN[71]. Therefore, to the best of our knowledge, the exact nature of the interaction between CD36 — one of the most extensively studied scavenger receptors — and the SRC family kinases remains unclear. The signalling function of CD36 has also been linked to the activation of mitogen-activated protein kinases (MAPKs). The specific MAPKs that are engaged by CD36 vary depending on the cellular context and on the nature of the ligand; for example, in cells derived from the vascular endothelium, the p38 MAPKs are activated by CD36 following binding of thrombospondin 1 (REF. 75); MAPK/ERK kinase kinase 2 (MEKK2; also known as MAP3K2), Jun N-terminal kinase 1 (JNK1; also known as MAPK8) and JNK2 (also known as MAPK9) are activated in macrophages in response to oxLDL[71]; and MAPK p44 and p42 are activated in response to β-amyloid binding in both microglia and macrophages[77,78] (FIG. 4).

The failure to identify bona fide signalling domains and the context-dependent variability of the downstream effectors activated by CD36 can both be reconciled by a single model. It seems probable that CD36 — and in all probability most scavenger receptors — function as components of heteromultimeric signalling complexes known as signalosomes (FIG. 4). Indeed, CD36 has been shown to form complexes not only with SRC family kinases but also with a striking range of transmembrane proteins that include Toll-like receptor 2 (TLR2), TLR4 and TLR6, β1 integrin, β2 integrin, β5 integrin and tetraspanins, such as CD9 and CD81 (REFS 79–82). The promiscuity that has been reported for CD36 might be typical of the entire scavenger receptor family. We suggest that at least some of these associated proteins function as co-receptors, which renders the scavenger receptors necessary but not sufficient to initiate signal transduction. It is currently unclear if the association of scavenger receptors with the ancillary molecules is constitutive and stable, or whether this occurs only in response to exogenous ligands. The idea

that the association only forms in response to exogenous ligands would confer flexibility to the system, allowing cells endowed with a finite number of scavenger receptors to tune and to maximize their responses to a range of ligands.

A particular receptor may form various types of complexes with different co-receptors, not only in different cell types but also in a single cell type. This is best exemplified by the class A scavenger receptor SR-A1, which partners with tyrosine protein kinase MER (MERTK) to form a functional complex that enables apoptotic cell uptake[83] (FIG. 5). The association with SR-A1 was shown to be essential for optimal phosphorylation of MERTK and for the subsequent signalling events — such as phospholipase Cγ2 phosphorylation and activation — that are required for apoptotic cell clearance[83]. On the other hand, SR-A1 interacts with TLR4 in the presence of LPS[84]. In macrophages, this association is

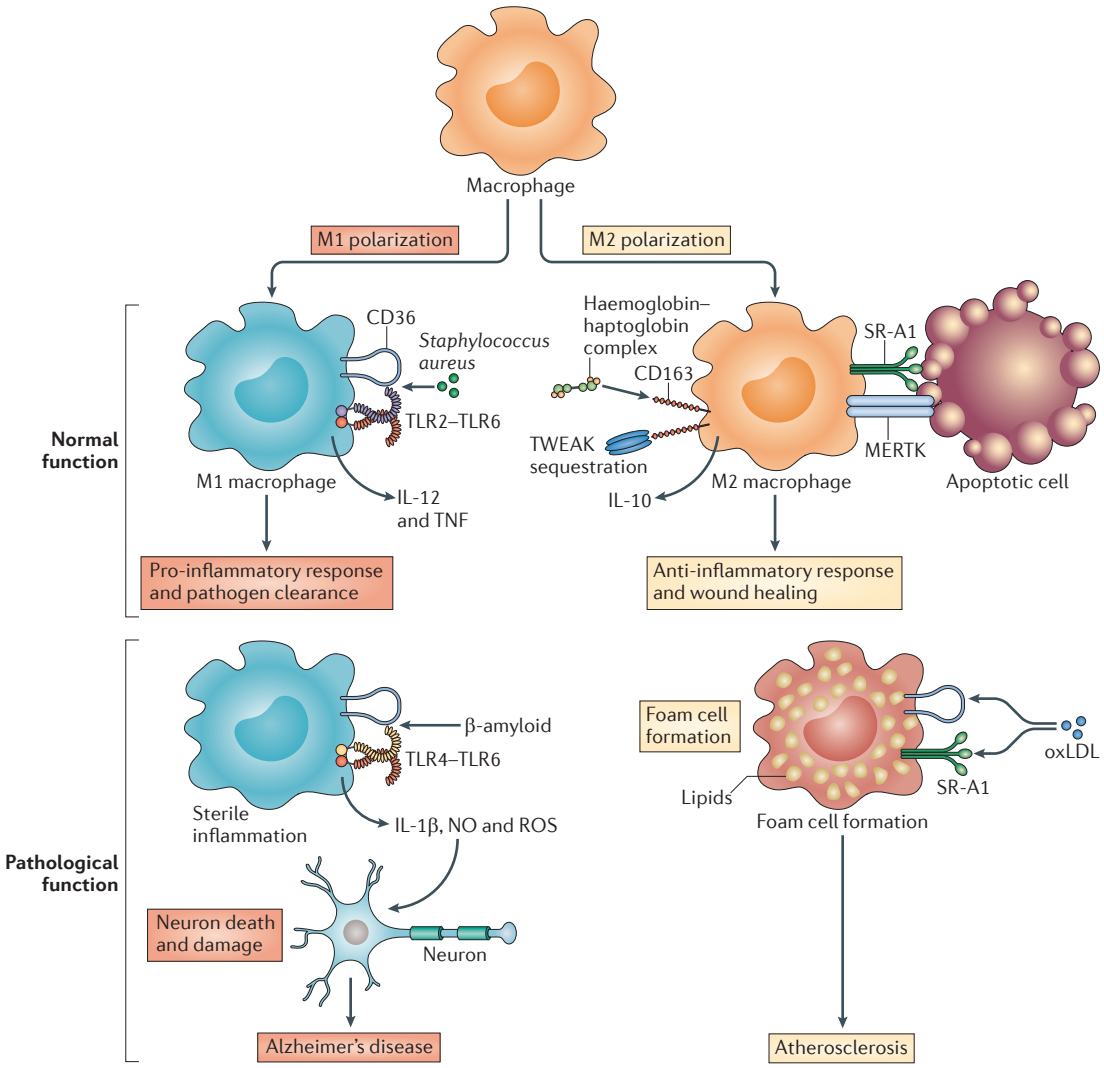

Figure 5 | **Scavenger receptors contribute to the functional phenotype of polarized macrophages.** Macrophages can polarize into M1 (also known as classically activated) and M2 (also known as alternatively activated) macrophages that have distinct functional phenotypes. The expression of several scavenger receptors, including SR-A1 and CD163, is increased in M2 macrophages. The increased expression of SR-A1 and CD163 contributes to the prototypical M2 functions: apoptotic cell clearance, sequestration of the inflammatory cytokine TNF-related weak inducer of apoptosis (TWEAK), clearance of haemoglobin–haptoglobin complexes at sites of tissue damage and the subsequent production of anti-inflammatory cytokines. By contrast, the expression of CD36 in M1 macrophages contributes to their characteristic phenotype by complexing with Toll-like receptors (TLRs) to potentiate the production of inflammatory cytokines. The differential expression of scavenger receptors in polarized cells contributes to various pathologies, including Alzheimer's disease and atherosclerosis. The increased expression of CD36 and SR-A1 on M2 macrophages can result in the accelerated uptake of modified low-density lipoprotein (LDL) and in the intracellular accumulation of cholesterol, thus contributing to the formation of foam cells. Conversely, engagement of CD36–TLR4–TLR6 receptor complexes in M1 macrophages (or microglia) results in sterile inflammation and consequent damage to local tissues at sites of β-amyloid accumulation. IL, interleukin; MERTK, tyrosine protein kinase MER; NO, nitric oxide; ROS, reactive oxygen species; TNF, tumour necrosis factor-α.

required for efficient activation of the nuclear factor-κB (NF-κB) pathway by LPS[84] (see REF. 85 for a conflicting perspective). Strikingly, the engagement of SR-A1 can therefore produce either a pro- or anti-inflammatory response depending on the nature of the co-receptor. A similar dichotomous behaviour has been described for CD36. This receptor induces inflammatory reactions in response to LTA or diacylated lipoproteins when in a complex with the TLR2–TLR6 heterodimer, and also in response to oxLDL or fibrillar β-amyloid when in a complex with the TLR4–TLR6 heterodimer[79,86] (FIG. 5). By contrast, the CD36-mediated internalization of *Plasmodium falciparum*-infected erythrocytes does not induce the production of pro-inflammatory cytokines[87] and this is also likely to be the case for CD36-mediated ingestion of apoptotic bodies. Although this behaviour has been shown for the class A and B receptors, it remains to be determined whether this is a general feature of the scavenger receptor family.

Scavenger receptors also rely on the formation of multimolecular complexes to achieve their ligand-internalization function[82]. It was recently shown that CD36 is bridged to the immunoreceptor tyrosine-based activation motif (ITAM)-containing high-affinity immunoglobulin-ε receptor subunit-γ (FcRγ) by a complex consisting of β1 integrins and/or β2 integrins, CD9 and CD81 (REF. 82). By incorporating FcRγ this multimolecular signalling complex can engage spleen tyrosine kinase (SYK), which possesses tandem SRC homology 2 (SH2) domains ideally spaced to engage the phosphorylated tyrosines of the ITAM motif, thereby mediating the internalization of CD36-bound ligands. Importantly, the ability to internalize ligands is not limited to CD36 but extends to other scavenger receptors, including SR-A1 and MARCO. Internalization can alter the mode of signalling or terminate it, and can also have metabolic functions, for instance by delivering modified lipoproteins to lysosomes. As in the case of CD36, receptors lacking identifiable endocytosis determinants might depend on their association with ancillary signalosome molecules for their internalization.

A scavenger receptor as a 'Jack-of-all-trades'

Despite their name, scavenger receptors are involved in more than just scavenging. They have been shown to carry out several functions, including functioning as lipid transporters, as chaperones that transport other cellular proteins to their destination and even as chemokines[44,57,88]. Various types of lipids have been reported to be transported by scavenger receptors: cholesterol esters are delivered to steroidogenic tissues and to liver cells by SR-B1, which is a non-endocytic high-density lipoprotein (HDL) receptor[89–93], whereas fatty acids are taken up by a variety of cells via CD36 (REFS 36,93,94). In both instances, lipid transfer may occur via a hollow section or tunnel connecting the ligand-binding surface of class B scavenger receptors to the exofacial leaflet of the membrane bilayer. This tunnel, recently uncovered by crystallographic determinations of the structure of these receptors, might be equivalent to the fatty acid-binding pocket that was previously proposed to exist on the exofacial domain of CD36 (REF. 36). Interestingly, the same pocket or tunnel may have a role in the gustatory perception of fatty acids. CD36, which is abundant in the lingual papillae, has been implicated in the ability to taste fats; indeed, individuals carrying the single nucleotide polymorphism rs1761667 G allele, which is a common *CD36* variant, show greater oral sensitivity to fat than individuals carrying the A allele, which causes lower expression of CD36 (REFS 95–97). Thus the same protein might be responsible for promoting excessive lipid ingestion, for clearing the modified species that are generated when lipoproteins circulate in excess and for the formation of foam cells and atherosclerotic plaques (see below).

CD36 has also been implicated in the formation of cytokine-induced multinucleated giant cells[98]. Multinucleated giant cells are present in granulomatous conditions such as tuberculosis and the foreign-body reaction to implanted materials, in which they restrict intercellular spreading of mycobacteria and might be involved in implant rejection, respectively[99,100]. Although the detailed mechanism responsible for these effects remains unclear, it has been suggested that multinucleated cells arise from the interaction of CD36 with phosphatidylserine on the surface of neighbouring cells[98].

Several scavenger receptors, particularly those of class B, have well-documented roles as chaperones. LIMP2, which is a member of the class B scavenger receptors, is essential for the delivery of β-glucocerebrosidase from the endoplasmic reticulum (ER) to the lysosomes[101]. Mutations that impair the association between LIMP2 and its cargo cause several neurodegenerative and renal diseases, such as myoclonic epilepsy and nephrotic syndrome[101–103]. Similarly, the class G scavenger receptor fasciclin EGF-like laminin-type EGF-like and link domain-containing scavenger receptor 1 (FEEL1; also known as stabilin 1) has been implicated in the intracellular sorting and lysosomal delivery of chitinase-like protein[11]; macrophages release FEEL1 by lysosomal secretion, thereby affecting inflammation and regulating apoptosis.

Certain scavenger receptors are susceptible to cleavage by exofacial proteases, which results in the shedding of soluble products to the circulation. Soluble forms of SR-PSOX and of the class I receptors CD163, CD5 and CD6 have been detected in the plasma[46,104,105]. Remarkably, the proteolytic fragments released from the membrane carry out functions that markedly differ from those of the precursor receptor. For instance, the soluble form of SR-PSOX is an interferon-regulated chemokine that stimulates CXC-chemokine receptor 6 (CXCR6), which is expressed by activated T cells and natural killer T cells[88,106]. CD163, which functions as an endocytic receptor for haptoglobin–haemoglobin complexes in its membrane-associated form[107–109], is also a substrate of proteases[14]. Its soluble extracellular domain retains the ability to associate with iron and can thereby inhibit the growth of bacterial pathogens. Moreover, soluble CD163, as well as fragments released from CD5

Immunoreceptor tyrosine-based activation motif (ITAM). A structural motif containing a tyrosine residue that is found in the cytoplasmic tails of several signalling molecules. The consensus sequence consists of Tyr–X–X–Leu or Tyr–X–X–Ile. The tyrosine is a target for phosphorylation by SRC tyrosine kinases and for the subsequent binding of proteins containing SRC homology 2 domains.

and CD6, are elevated in inflammation and in autoimmune disease. Even though their specific function is unknown, the soluble forms of class I receptors have been suggested to be potentially useful biomarkers for various clinical conditions[104,107,110].

SR-A1 was recently shown to prevent calcification of the vasculature and soft tissue. The formation of protein–mineral complexes, referred to as calciprotein particles, is a physiological mechanism that facilitates the clearance of calcium phosphate nanocrystals from the extracellular milieu in order to prevent their deposition and potentially pathological calcification. SR-A1-deficient macrophages have an impaired ability to bind and to internalize calciprotein particles[26]. Moreover, prolonged exposure of macrophages to calciprotein particles results in significant upregulation of SR-A1 (REF. 111). Taken together, these observations suggest a key role for this receptor in calciprotein particle clearance.

Scavenger receptors, specifically SR-A1 and MARCO, also have a role in the maintenance of the microarchitecture and functionality of the marginal zone of the spleen. The depletion of these receptors results in aberrant distribution of splenic macrophages[112], which, in turn, are required for B cell retention in the marginal zone[113].

In summary, scavenger receptors have important physiological roles inside cells, on their surface and in the circulation. This range of disparate functions emphasizes the rather arbitrary consolidation of the scavenger receptors into a single family.

Receptors and macrophage polarization

In the physiological setting, macrophages respond to environmental stimuli, such as TLR agonists and signals from activated lymphocytes, by assuming distinct functional phenotypes. It is generally accepted that there is a great deal of plasticity between their phenotypes and, depending on the combination of stimuli that they receive, macrophages can exist in various 'shades' of activation[114]. That said, a useful paradigm for understanding macrophage polarization has been to study the extremes of the activation range: that is, classically activated macrophages and alternatively activated macrophages (referred to as M1 and M2 macrophages, respectively). M1 macrophages are generally characterized as having an interleukin-12 (IL-12)^{hi} IL-23^{hi}IL-10^{low} phenotype and are efficient producers of reactive oxygen species, nitrogen intermediates and inflammatory cytokines, such as tumour necrosis factor-α (TNF) and IL-6 (REF. 115). M1 macrophages are considered to be essential participants in T helper 1 (T_H1) cell responses and to have a potent microbicidal and tumoricidal capacity[116]. Conversely, M2 macrophages have an IL-12^{low}IL-23^{low}IL-10^{hi} phenotype and a variable capacity to produce pro-inflammatory cytokines[115]. M2 macrophages are considered to have a central role in tissue repair and remodelling, in the resolution of inflammation, in apoptotic cell clearance and in the control of extracellular parasites[116].

In recent years, increasing attention has been paid to the contribution of scavenger receptors to macrophage polarization. The expression of several scavenger receptors, such as CD163, SR-A1 and CD36 is markedly increased in M2 macrophages[14,117–121]. Indeed, CD163 is a well-accepted marker of the M2 macrophage phenotype. Not only are some scavenger receptors more highly expressed in M2 cells than in M1 cells but also the presence of some receptors contributes to the polarization programme of these cells. Signals delivered by CD36 and SR-A1 to the ER stress, JNK and peroxisome proliferator-activated receptor-γ (PPARγ) pathways are seemingly necessary for the generation of the M2 phenotype[117]. The elevated expression of scavenger receptors is congruent with the function of M2 cells in apoptotic cell clearance and in the suppression of inflammation. For instance, by increasing the surface expression of SR-A1, along with its co-receptor MERTK (FIG. 5), M2 macrophages are better able to engulf apoptotic bodies[83,122–124]; CD36 also contributes to this function[125]. Conversely, CD163 is instrumental in promoting an anti-inflammatory phenotype in M2 macrophages. It can sequester and thus inactivate pro-inflammatory molecules such as TNF-related weak inducer of apoptosis (TWEAK)[126], and attenuates haemoglobin-associated damage that is a source of inflammation[127,128]. SR-A1 has similar anti-inflammatory effects in macrophages[129,130] (FIG. 5).

The preceding observations have led to the misconception that the entire family of scavenger receptors is upregulated in M2 macrophages and that scavenger receptors are anti-inflammatory in all cases. Neither of these conclusions is warranted. Although M2-polarizing factors, such as IL-4 and macrophage colony-stimulating factor (M-CSF), increase SR-A1 expression, they concomitantly decrease the expression of another class A scavenger receptor, MARCO[130]. Conversely, M1-polarizing factors such as LPS and granulocyte/macrophage colony-stimulating factor (GM-CSF) increase the expression of MARCO, but decrease SR-A1 levels[130]. Moreover, recent studies indicate that the differential expression of scavenger receptors helps to define the functional phenotype of M1 and M2 macrophages. Accordingly, MARCO positively regulates pro-inflammatory cytokine production, whereas SR-A1 has the opposite effect[130].

It is also worth noting that, because they function as part of complex signalling platforms, the context in which scavenger receptors are present is as important as their absolute level of expression. This is well illustrated by CD36: the net amount of this receptor increases in M2 macrophages, which suggests that it has an anti-inflammatory function; however, CD36 is also present in M1 cells in which it can interact with TLRs to produce pro-inflammatory cytokines in response to microbial ligands (FIG. 5)[86,131,132]. Thus, the predominant function of CD36 may be determined by the type and the extent of expression of co-receptors. In this regard, it is relevant that TLR2 and TLR4 are preferentially expressed by M1 macrophages[133].

In summary, although scavenger receptors are more prominently expressed by M2 macrophages, they are not exclusive to this macrophage population and can contribute to pro-inflammatory macrophage responses in certain contexts.

Scavenger receptors and innate immunity

It is now abundantly clear that, in addition to scavenging modified lipoproteins, many of the scavenger receptors have the ability to recognize conserved PAMPs on microbial surfaces. The role that scavenger receptors have in innate immunity, including the phagocytosis and the clearance of various microbial species, has been extensively reviewed in recent years[16,17,134]; therefore, in this section we will focus on some of the more recent advances concerning ligand specificity, on the interplay between scavenger receptors and other PRRs, and on the subversion of scavenger receptor function by pathogens.

As new information accumulates, the range of ligands recognized by scavenger receptors is becoming apparent. SR-A1, for example, has been shown to bind to the lipid A moiety of LPS (which is a feature of Gram-positive bacteria), LTA (which is expressed by Gram-negative bacteria) and bacterial CpG DNA[134] (FIG. 1; Supplementary information S1 (table)). As a result, SR-A1 can mediate the non-opsonic uptake of *Neisseria meningitides*, *Listeria monocytogenes* and *Staphylococcus aureus*[24,135–138]. MARCO shares with SR-A1 the ability to recognize LPS, LTA and CpG DNA, and can also bind *N. meningitides*[16]. The shared structural features (FIG. 2) and ligand specificities (FIG. 1; Supplementary information S1 (table)) of SR-A1 and MARCO seem to suggest that these receptors are functionally redundant. However, a recent study showed that SR-A1 and MARCO recognize overlapping but distinct sets of endogenous and microbial ligands, including several *N. meningitides* surface proteins, which highlights the distinct specificities of these two related scavenger receptors[139]. Such small differences in selectivity might have evolved to increase the repertoire of innate immune recognition[139]. As we learn more about the specificity of other receptors, this idea may be applied to the entire scavenger receptor family.

Another general feature that is shared by several members of the scavenger receptor family is the ability to interact with and to influence signalling through other PRRs. Several recent studies have provided interesting examples of the interplay between scavenger receptors and TLRs. In some instances, a synergistic relationship exists between the two types of PRRs. A recent analysis showed that SR-A1 interacts with TLR4 to promote the phagocytosis of the Gram-negative bacterium *Escherichia coli*, whereas SR-A1 and TLR2 cooperate in the phagocytosis of the Gram-positive bacterium *S. aureus*[140]. In addition, SR-A1 potentiates the responsiveness of PRRs that are located in endomembranes: by mediating pathogen internalization, SR-A1 enhances the inflammatory response mediated by TLR3 (REF. 85). The functional cooperation between scavenger receptors and TLRs is not unique to SR-A1 and has been shown to occur for several other scavenger receptors. MARCO, for example, partners with TLR2 and CD14 in the recognition of the *Mycobacterium tuberculosis* glycolipid trehalose 6,6′-dymycolate and is required for the optimal production of pro-inflammatory cytokines in response to this bacterial product[141]. Similarly, as discussed above, the class B scavenger receptor CD36 can form a functional complex with TLR2 and TLR6, which augments cytokine responses to *S. aureus*-derived LTA and which enhances the internalization of *P. falciparum*-infected erythrocytes[79,86]. Thus, a pattern is emerging: inflammatory ligands are recognized by both a scavenger receptor and another sensor PRR, such as a TLR. In this paradigm that was first appreciated by Mukhopadhyay *et al.*[85], the scavenger receptors potentiate the function of the sensor PRRs, thereby augmenting the inflammatory response.

As is often the case with innate immune receptors, scavenger receptors can be co-opted by pathogens to function in their infectious cycle. One well-studied example is the subversion of SR-B1 by hepatitis C virus, which uses this scavenger receptor as a co-receptor for entry into host cells. Functional complementation assays and the inhibitory effect of other SR-B1 ligands, such as oxLDL, showed that the lipid transfer activity of the receptor is essential for viral entry[142–145]. In addition, SR-B1 is used by the intracellular pathogen *Chlamydia trachomatis* for survival in host cells. *C. trachomatis*, which resides in a membrane-bound intracellular compartment termed the inclusion, has long been recognized to depend on the acquisition of host-derived factors (including lipids) for survival in its intracellular niche. One mechanism by which it acquires host-derived lipids is through the recruitment of SR-B1 to the inclusion membrane, where the lipid transfer activity of the scavenger receptor mediates the delivery of phosphatidylcholine to the lumen of the inclusion. This role is crucial to the progression of infection: inhibition of SR-B1-mediated lipid transfer impairs the intracellular replication of *C. trachomatis*[146].

Another class B receptor, LIMP2, has been identified as the cellular receptor for enterovirus 71 (EV71), coxsackievirus 7 (CVA7), CVA14 and CVA16 entry into host cells[147,148]. In the case of EV71, LIMP2 not only functions as a receptor but also as a determinant of viral uncoating and therefore of infection efficiency[149]. Intriguingly, CD36 — which has been implicated in the clearance of several bacterial and protozoan pathogens — is co-opted by mycobacteria[150–152]. The *Drosophila melanogaster* CD36 homologue Peste has been identified as an important determinant of uptake of mycobacteria into host cells[153]. In addition, CD36 deficiency results in reduced susceptibility to mycobacterial infection both *in vivo* and *in vitro*[154]; the mechanisms whereby CD36 improves mycobacterial survival are yet to be elucidated. The finding that pathogens have evolved mechanisms to subvert scavenger receptor function emphasizes the need for a clearer understanding of the roles that scavenger receptors have at the front line of host–pathogen interactions.

Scavenger receptors and disease

Considering the number of receptors that constitute the scavenger receptor family and the wide range of functions they carry out, the involvement of scavenger receptors in the pathogenesis of multiple diseases was anticipated. However, the extent and the mechanism of this involvement have not yet been fully appreciated because the

study of most scavenger receptors is in its infancy. Nevertheless, by participating in the recognition and the internalization of oxLDL[23] and β-amyloid[155,156], and in the transport of fatty acids[93], scavenger receptors have been implicated in diseases as diverse as atherosclerosis[4,5,157–160], type 2 diabetes mellitus[94,161,162] and Alzheimer's disease[34,155,163,164]. A brief overview of the involvement of scavenger receptors in these disorders, with a particular focus on CD36, is discussed below.

Scavenger receptors in atherosclerosis. Atherosclerosis is a chronic inflammatory disease characterized by a complex interplay between metabolic and immune processes, which may lead to the formation of vulnerable plaques[165,166]. The structural disruption of these plaques can cause atherothrombotic vascular disease, which is the most frequent cause of death in the industrialized world[166]. The pathogenesis of atherosclerosis is not yet fully understood, but a key event in the development of primary atherosclerotic plaques is the inability of macrophages to properly process modified lipoproteins, which results in the formation of foam cells. As SR-A1, MARCO, CD36, SR-B1, LOX1 and SR-PSOX can all recognize oxidation-specific epitopes of oxLDL, their role in atherosclerosis has been extensively investigated [4,44,158,167–170]. It has been unambiguously shown in *in vitro* studies that these receptors function as a major conduit for intracellular cholesterol accumulation[171]. However, when assessed *in vivo* using gene-knockout strategies in hyperlipidaemic apolipoprotein E $(ApoE)^{-/-}$ mice, the contribution of individual receptors (for example, of SR-A1) to atherosclerosis is much less clear[3], probably as a result of functional redundancy. Nevertheless the pro-atherogenic role of CD36 has been convincingly shown[172]: by coupling to TLR4 and TLR6, CD36 can trigger a sterile inflammatory response, which induces NF-κB activation when exposed to modified LDL[173,174]. Accordingly, genetic deletion of TLR4 or of the TLR signalling adaptor myeloid differentiation primary-response protein 88 (MYD88) attenuates atherosclerosis[175,176].

Conversely, oxidized components of oxLDL, such as 9-hydroxyoctadecadienoic acid (9-HODE) and 13-HODE, are potent activators and ligands for PPARγ, which is a transcription factor that is important in lipid metabolism[177]. Following activation, PPARγ heterodimerizes with the retinoid X receptor and the newly formed complex binds directly to PPARγ-response elements[178,179]. One such response element is found in the CD36 promoter, which causes increased CD36 expression. Thus, oxLDL has synergistic effects that might lead to ER stress[180] and foam cell formation, which are early steps in atherogenesis. In addition, by stimulating CD36 on the surface of platelets[181], oxLDL increases platelet reactivity and fosters a prothrombotic state[182,183], which increases the risk of a cardiovascular episode[31,184–187]. Furthermore, phosphatidylserine exposed on the surface of microparticles released by shedding cells can bind to CD36, which renders the platelets more sensitive to activation and to aggregation[188]. Microparticles are often generated at sites of vascular injury and inflammation, which are areas of elevated risk for thrombus formation. The class E scavenger receptor LOX1 is also expressed on platelets[189], but in an activation-dependent manner. The inhibition of LOX1 results in a dose-dependent reduction in agonist-induced platelet aggregation and activation[190].

In contrast to CD36, SR-B1 was shown to have not only an anti-atherogenic effect[191–194] but also to inhibit platelet aggregation and thrombosis[195,196]. These effects occur in the liver, where SR-B1 mediates the transport of cholesterol from HDL to the hepatocyte[89,197]. In cholesterol-laden macrophages, HDL is loaded with cholesterol by reverse transport down its concentration gradient. The protective role of SR-B1 is thought to reflect the net discharge of cholesterol from HDL to hepatocytes, which ultimately process the cholesterol for biliary excretion[198,199]. By indirectly removing cholesterol from macrophages and foam cells, SR-B1 reduces atherosclerosis[90,200–202,183]. Accordingly, several recent reports have identified a strong association of SR-B1 polymorphisms with atherosclerosis and cardiovascular disease[203–205].

Other scavenger receptors also contribute to atherosclerosis: the deletion of SR-PSOX exacerbates atherosclerosis[206] and MARCO expression is induced in mouse plaques[207]. However, at this stage their precise role and mode of action are unclear.

Scavenger receptors in type 2 diabetes. Type 2 diabetes mellitus is a metabolic disorder characterized by the accumulation of fatty acids and lipid metabolites that lead to alterations in insulin signalling, which causes the development of insulin resistance[94,208]. Scavenger receptors also have a role in this disease. CD36 is known to mediate fatty acid uptake in insulin-sensitive tissues such as adipocytes, skeletal muscle and cardiac muscle[209–211]. Pharmacological experiments using transport inhibitors, as well as *CD36* gene deletion studies, showed that nearly 70% of fatty acids are taken up by the heart via this transporter protein[212]. In animal models of insulin resistance, the increased rate of fatty acid transport into muscle correlated with an increase in levels of plasmalemmal CD36. Although fatty acid oxidation increases in these muscles, the primary fate of the fatty acids that have been taken up by CD36 is esterification[209]. The consequent accumulation of lipids is the primary cause of insulin resistance[209,210]. Similarly, fatty acid transport is markedly increased in skeletal muscles of obese humans and those with type 2 diabetes, even though CD36 mRNA and protein are not altered[211,213]. The transport activity of CD36 could be regulated and such regulation might go awry in obesity and diabetes. Along these lines, common *CD36* gene variants — including the rs3211867, rs3211883, rs3211908 and rs1527483 polymorphisms — associate with measures of obesity[214] and adiposity[215]. Nevertheless, the literature regarding the association between common *CD36* polymorphisms and insulin sensitivity remains controversial[215–220]. It is also interesting that CD36-containing microparticles correlate with the development of diabetes, which potentially provides a biomarker for the disease[221].

Platelet CD36 also enhances the risk of arterial thrombosis in individuals with diabetes. Advanced glycation end-products generated under the chronic hyperglycaemic conditions associated with diabetes can bind to and activate platelet CD36, which accounts for at least some of the vascular complications associated with diabetes[222]. These associations are an explanation for why polymorphisms that affect the expression of CD36 correlate with risk of developing thrombosis[223]. The class E scavenger receptor LOX1, which is expressed on platelets in an activation-dependent manner[189], also influences the state of platelet activation[190].

Scavenger receptors in Alzheimer's disease. Alzheimer's disease is characterized by a protracted inflammatory response driven by microglia, which are the central nervous system macrophages. The lesions found in the brains of patients with Alzheimer's disease consist of senile plaques that contain β-amyloid fibrils, microglia and astrocytes[163,224]. Microglia bind to β-amyloid fibrils via SR-A1 (REF. 225) and CD36 (REF. 226). Although SR-A1 is the primary phagocytic receptor for β-amyloid (SR-A1-deficient microglial cells show a 60% decrease in their ability to take up β-amyloid)[225], CD36 nevertheless markedly contributes to the process [163,226]. Indeed, the role of CD36 in the inflammatory response is well documented. In the presence of β-amyloid, CD36 forms a complex with TLR4 and TLR6, which stimulates the production of IL-1β and of reactive oxygen species; together with other inflammatory products, these molecules cause the neuronal death that is characteristic of the disease[173]. The role of CD36 in the pathogenesis of Alzheimer's disease was shown using Tg2576 mice, which are a useful model in which to study this disease. Deletion of the *CD36* gene in these animals had beneficial effects on vascular regulation and on cognitive performance[34]. Similarly, the disruption of TLR4–TLR6 signalling in microglia abrogated the production of IL-1β, nitric oxide and reactive oxygen species, and protected neurons from β-amyloid-induced death[78,173]. Scavenger receptors, together with TLRs, clearly have a determining role in the development of Alzheimer's disease.

Conclusions

As with other PRRs, scavenger receptors recognize both PAMPs and DAMPs, but they also recognize several non-modified self molecules. The capacity of scavenger receptors to interact with such an unprecedented repertoire of ligands is due to the wide range of receptors that constitute this family, as well as to their ability to partner with assorted co-receptors. The versatility of the scavenger receptors extends to their functional responsiveness, as they partake in homeostasis and also in combatting infections. By forming diverse complexes with different co-receptors, an individual receptor type can induce inflammation to control infection under some conditions, and it can have an anti-inflammatory response in others. How this adaptable behaviour is accomplished remains unclear, but there is evidence that suggests that coupling to co-receptors might be a reversible and inducible response that is induced by the presence of defined ligands. The nature and the stability of the signalosomes generated in every instance requires detailed study, as it will affect the design of therapeutic interventions. The complex and reversible nature of the signalling heteromultimers will require dynamic and sophisticated techniques of analysis. In our opinion, a combination of proteomic methods, spectroscopic biophysical methods and super-resolution approaches, including cryo-electron tomography, should be applied in the future to better understand the biology of scavenger receptors. Only then will we be able to establish whether rational approaches that target scavenger receptors can be applied to the prevention or to the treatment of atherosclerosis, Alzheimer's disease and other inflammatory diseases.

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Competing interests statement
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