British Journal of Pharmacology

DOI:10.1111/bph.13105
www.brjpharmacol.org

Themed Section: Chinese Innovation in Cardiovascular Drug Discovery

REVIEW

Class A1 scavenger receptors in cardiovascular diseases

Jingjing Ben, Xudong Zhu, Hanwen Zhang and Qi Chen

Atherosclerosis Research Center, Key Laboratory of Cardiovascular Disease and Molecular Intervention, Nanjing Medical University, Nanjing 210029, China

Correspondence
Professor Qi Chen, Atherosclerosis Research Center, Key Laboratory of Cardiovascular Disease and Molecular Intervention, Nanjing Medical University, Nanjing 210029, China. E-mail: qichen@njmu.edu.cn

Received
16 June 2014
Revised
15 January 2015
Accepted
2 February 2015

Class A1 scavenger receptors (SR-A1) are membrane glycoproteins that can form homotrimers. This receptor was originally defined by its ability to mediate the accumulation of lipids in macrophages. Subsequent studies reveal that SR-A1 plays critical roles in innate immunity, cell apoptosis and proliferation. This review highlights recent advances in understanding the structure, receptor pathway and regulation of SR-A1. Although its role in atherosclerosis is disputable, recent discoveries suggest that SR-A1 function in anti-inflammatory responses by promoting an M2 macrophage phenotype in cardiovascular diseases. Therefore, SR-A1 may be a potential target for therapeutic intervention of cardiovascular diseases.

LINKED ARTICLES

This article is part of a themed section on Chinese Innovation in Cardiovascular Drug Discovery. To view the other articles in this section visit http://dx.doi.org/10.1111/bph.2015.172.issue-23

Abbreviations

acLDL, acetylated low-density lipoprotein; ER, endoplasmic reticulum; I/R, ischaemia/reperfusion; LTA, lipoteichoic acid; MI, myocardial infarction; mLDL, modified low-density lipoprotein; oxLDL, oxidized low-density lipoprotein; PRR, pattern recognition receptor; RAGE, receptor for advanced glycated end-products; SR-A1, class A1 scavenger receptor; TLR4, Toll-like receptor 4; TRAF6, TNF receptor-associated factor 6

Tables of Links

TARGETS
Catalytic receptors[a]
Mer receptor tyrosine kinase
TLR4
Enzymes[b]
Caspase 3
ERK
JNK
Mitogen-activated protein kinase kinase 7 (MKK7)
p38
PI3K
PKC
PLC-γ1

LIGANDS
Amyloid β
IFN-γ
IL-1
IL-10
LPS
Lysophosphatidylcholine
Macrophage colony-stimulating factor (M-CSF)
MMP-9
Phorbol ester (PMA)
Phosphatidylserine
TGF-β1
TNF-α

These Tables list key protein targets and ligands in this article which are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY (Pawson *et al.*, 2014) and are permanently archived in the Concise Guide to PHARMACOLOGY 2013/14 ([a,b]Alexander *et al.*, 2013a,b).

Scavenger receptors are cell surface receptors that are structurally diverse but they typically recognize many different ligands to participate in diverse biological functions. The functional mechanisms of scavenger receptors include endocytosis, phagocytosis, adhesion and signalling, which ultimately leads to the removal of non-self- or altered self-targets. There are 10 classes of scavenger receptors according to a unified nomenclature system for scavenger receptors (Prabhudas *et al.*, 2014). Class A scavenger receptors have several structural features in common, including a cytoplasmic tail, a transmembrane domain, a spacer region, a helical coiled coil domain, a collagenous domain and a C-terminal cysteine-rich domain (Figure 1). Class A1 scavenger receptor (SR-A1), also known as SCARA1, CD204 or macrophage scavenger receptor 1, is the prototypical SR-A molecule and was the first scavenger receptor to be identified (Goldstein *et al.*, 1979; Kodama *et al.*, 1990; Rohrer *et al.*, 1990)

SR-A1 was initially identified by its ability to mediate the formation of foam cells, a characteristic component of atherosclerotic lesions (Goldstein *et al.*, 1979; Kodama *et al.*, 1990; Krieger and Herz, 1994; Bowdish and Gordon, 2009). However, observations from various SR-A1 gene knockout mouse models have yielded discrepant results concerning its role in the occurrence and development of atherosclerotic lesions (Suzuki *et al.*, 1997; Kuchibhotla *et al.*, 2008; Manning-Tobin *et al.*, 2009). A role beyond the handling of cholesterol is emerging for SR-A1 in the pathogenesis of cardiovascular diseases. It not only functions as a phagocytic receptor and an innate immune recognition receptor but also plays an important role in cell apoptosis and cell proliferation. An overview of the recent progress of SR-A1 structure, signal transduction and its roles in cardiovascular diseases will be provided in this review.

Structure and expression of SR-A1

SR-A1 is a type II membrane glycoprotein that forms homotrimers. The *SR-A1* gene is located on human chromosome 8 and there are three protein isoforms generated by alternative RNA splicing, including SR-A1, SR-A1.1 and SR-A1.2 (Matsumoto *et al.*, 1990; Kzhyshkowska *et al.*, 2012; Prabhudas *et al.*, 2014). The human SR-A1 is composed of 451 amino acid residues with six domains: the N-terminal cytoplasmic domain, the transmembrane domain, the extracellular domain comprising α-helical coiled coils, multiple collagen-like repeats and a cysteine-rich C-terminal region. SR-A1.1 has a shorter cysteine-rich C terminus than SR-A1. It can still bind the ligands as the positively charged residues within the collagen-like repeats, which are critical for ligand recognition, are retained. The SR-A1.2 isoform contains a truncated C terminus composed of only four of the six SR-A1 C-proximal cysteine residues. It remains trapped in the endo-

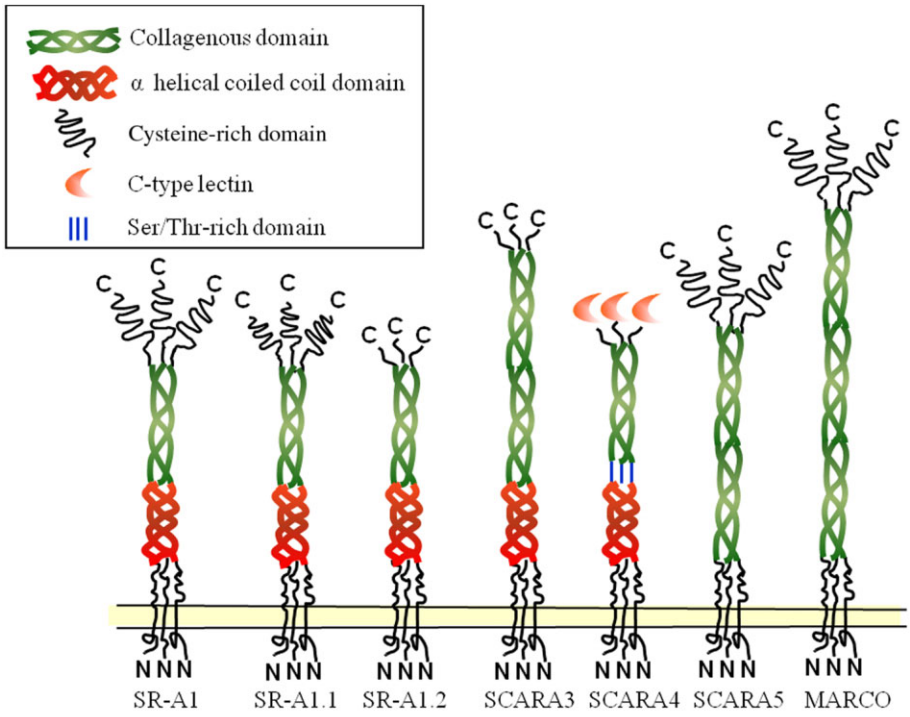

Figure 1

Members of class A scavenger receptor family. The members of class A scavenger receptor family have a similar structure that is composed of a cytoplasmic tail, a transmembrane domain, a spacer region, a helical coiled coil domain, a collagenous domain and a C-terminal cysteine-rich domain.

plasmic reticulum (ER) and hence cannot bind with extracellular ligands (Emi *et al.*, 1993; Gough *et al.*, 1998; Murphy *et al.*, 2005).

Among the six domains of SR-A1, the cysteine-rich domain is the most highly conserved, although its function is not fully elucidated (Hohenester *et al.*, 1999). The α-helical coiled coil domain is involved in the adhesion function of the receptor with its high flexibility (Fraser *et al.*, 1993; Hughes *et al.*, 1994). The collagen-like domain of SR-A1 is responsible for the binding of its ligands. The lysine residues cluster throughout this domain, so these residues required for binding (Andersson and Freeman, 1998) are found not only at the C terminus. The cytoplasmic domain of SR-A1 consists of 40–55 amino acid residues, which depends on the species. This domain functions in membrane trafficking and recycling, internalization and adhesion. Deletion of the cytoplasmic domain of SR-A1 significantly reduced the number of receptors and decreased internalization of the receptor into cells. The six amino acids proximal to the membrane seem to be important for expression of the receptor, as the mutant SR-AΔ1–49 can restore receptor protein abundance but not the internalization of acetylated low-density lipoprotein (acLDL) into the cell. The spreading and adhesion are also increased after restoration of the six amino acids. Thus, the membrane-proximal amino acids of SR-A1 may also be associated with the receptor-mediated cell adhesion (Fong and Le, 1999; Kosswig *et al.*, 2003). The di-leucine motif in the cytoplasmic domain seems to mediate the uptake of SR-A1 into the cell. Cells expressing mutants of the di-leucine motif exhibit a decreased internalization of SR-A1 into cells but unchanged ability to bind acLDL (Chen *et al.*, 2006).

The ligands of SR-A1 include a broad spectrum of macromolecules, generally polyanionic. They are (a) modified low-density lipoprotein (mLDL) such as acLDL and oxidized low-density lipoprotein (oxLDL) but not native LDL, maleylated or glycated BSA, β-amyloid, heat shock proteins and hepatitis C virus (Pluddemann *et al.*, 2007); (b) polyribonucleotides (poly G and poly I but not poly A, T or C); (c) polysaccharides, including LPS and lipoteichoic acid (LTA), which are both surface molecules of Gram-positive and Gram-negative bacteria, and dextran sulfate; and (d) anionic phospholipids, such as phosphatidylserine (Table 1). SR-A1 is primarily expressed in macrophages, monocytes, mast cells and dendritic cells (Ingersoll *et al.*, 2010). It is also expressed in vascular endothelial cells (Loboda *et al.*, 2006) and in smooth muscle cells within atherosclerotic plaques, in which oxLDL induces an up-regulation of SR-A1 and increased uptake of acLDL by cells (Mietus-Snyder *et al.*, 2000). Macrophage colony-stimulating factor and phorbol ester up-regulate SR-A1 in cells, whereas TNF-α, N-acetylcysteine, IFN-γ and TGF-β1 down-regulate this receptor (Bottalico *et al.*, 1991; Geng and Hansson, 1992; Hsu *et al.*, 1996).

Table 1

Ligands of class A1 scavenger receptor

Modified proteins	oxLDL, acLDL, malondialdehyde-LDL, maleylated LDL, modified albumin, AGE-BSA, β-amyloid fibrils, glycated type IV collagen, modified collagen type I, III and IV
Native proteins	Calreticulin, gp96, HSP70 family members, apoA-I, apo E
Lipids	Lysophosphatidylcholine, phosphatidic acid, cholesterol
Polysaccharides	Dextran sulfate, fucoidin, biglycan, decorin
Nucleic acids	poly G, poly I, poly G : I
Others	Gram-positive and Gram-negative bacteria, hepatitis C virus, lipopolysaccharide, lipoteichoic acid, the apoptotic cell

SR-A1 functions and regulation

SR-A1 regulates macrophage activities but the underlying mechanisms are not yet fully elucidated. The SR-A1 pathway consists of at least the receptor, the coupling signal molecules and the modulating molecules. SR-A1 is found in both coated pits and lipid rafts of cell membranes, binding with clathrin or caveolin-1 separately. SR-A1-mediated internalization of acLDL into cell is primarily via the process of coated pit-related endocytosis (Chen *et al.*, 2006; Zhu *et al.*, 2011). Meanwhile, macropinocytosis also contributes to the uptake of acLDL at a low level (Jones *et al.*, 2000). The SR-A1 in coated pits is linked to ERK signalling, which is presumably responsible for the SR-A1-mediated uptake of lipids into the cell (Zhu *et al.*, 2011).

Endocytosis of the VirB-dependent bacteria by macrophages induces localization of SR-A1 into the detergent-resistant membrane lipid rafts, which are sterol- and sphingolipid-enriched (Mommaas-Kienhuis *et al.*, 1985; Jones *et al.*, 2000; Kim *et al.*, 2004). Cell apoptosis and TNF-α synthesis triggered by internalization of SR-A1–fucoidan complexes also follow caveolae-dependent endocytosis. The caveolae-related SR-A1 endocytic route is linked to p38 and JNK signalling pathways (Zhu *et al.*, 2011). Different endocytic routes of SR-A1 may provide a molecular basis for the many functions of SR-A1 and the corresponding signalling pathways, although detailed mechanisms are not yet fully known.

Binding of SR-A1 with its ligands activates signalling pathways involving PKC, heterotrimeric $G_{i/o}$ proteins and MAPKs. It causes tyrosine phosphorylation of PLC-γ1 and PI3K. There are two fucoidan-mediated SR-A1 signalling pathways: PTK (Src)/Rac1/PAK/JNK and PTK(Src)/Rac1/PAK/p38. Both play critical roles in pro-interleukin-1 (IL-1)/IL-1 production in macrophages (Hsu *et al.*, 1998; 2001; Kim *et al.*, 2003). SR-A1 binding with polyinosinic-polycytidylic acid (poly I : C) and LTA leads to a tyrosine phosphorylation and activation of the MAPK pathway. Selective inhibition of this pathway can blunt SR-A1-dependent TNF-α release (Coller and Paulnock, 2001). Fucoidan-induced NO production in macrophages is also required for SR-A1, which is linked to both the p38 MAPK and the NF-κB signalling (Nakamura *et al.*, 2006). MEK-ERK signalling also participates in SR-A1-mediated TNF-α production in macrophages (Gao *et al.*, 2009). An interaction between SR-A1 and Mer receptor tyrosine kinase can activate downstream signalling pathways of

SR-A1. However, deletion of SR-A1 in mice does not influence fucoidan and LTA-evoked signalling in macrophages, which may be attributable to the presence of CD14 (Kim *et al.*, 2003). Presumably, the cytoplasmic tail of SR-A1 plays a key role in activation of SR-A1 signalling by a protein–protein interaction mechanism. For example, Hook3 has been identified as a binding partner of cytoplasmic domain of SR-A1 to positively regulate the degradation but negatively regulate the expression of SR-A1 (Sano *et al.*, 2007). Ben *et al.* (2013) found that major vault protein, a scaffolding protein, is also a binding partner for SR-A1 in lipid rafts to increase SR-A1-mediated TNF-α synthesis and apoptosis in macrophages. In terms of the SR-A1-mediated uptake of lipids into cells, an ER resident molecular chaperone, glucose-regulated protein 78, seems to play an important role. It negatively regulated the acLDL–SR-A1 complex into macrophages by binding directly with the cytoplasmic domain of SR-A1 (Ben *et al.*, 2009), although the biological significance of this regulatory mechanism *in vivo* is unknown. However, it is clear that the SR-A1 pathway is very precisely regulated in macrophages, in response to a range of stimuli.

As a subclass of the membrane-bound pattern recognition receptors (PRRs), SR-A1 has a synergistic coordination with other PRRs. For example, SR-A1 is considered as a physiological negative regulator of Toll-like receptor 4 (TLR4)-mediated immune consequences, which has important clinical implications for the development of PRR-targeted immunotherapeutic intervention. SR-A1 down-regulates inflammatory gene expression in dendritic cells by suppressing TLR4-induced activation of the transcription factor NF-κB. The potential mechanism is that SR-A1 directly interacts with the TRAF-C domain of TNF receptor-associated factor 6 (TRAF6), resulting in inhibition of TRAF6 dimerization and ubiquitination (Yi *et al.*, 2009; Chen *et al.*, 2010; Yu *et al.*, 2011). Recently, we found that SR-A1 interacts with the receptor for advanced glycated end-products (RAGE), a member of the PRR family, by inhibiting the phosphorylation of mitogen-activated protein kinase kinase 7, the major kinase in the RAGE–MAPK–NF-κB signalling pathway. By this mechanism, SR-A1 may antagonize RAGE-associated diabetic retinopathy (Ma *et al.*, 2014).

Roles of SR-A1 in cardiovascular diseases

SR-A1 and atherosclerosis

The first SR-A1-deficient mouse model was used to identify the role of SR-A1 in atherosclerosis by Suzuki *et al.* (1997). They found that SR-A1$^{-/-}$ApoE$^{-/-}$ mice exhibited an increased plasma cholesterol but a reduced atherosclerotic plaque area, compared with ApoE$^{-/-}$ mice. Meanwhile, degradation of acLDL and oxLDL by SR-A1$^{-/-}$ macrophages was reduced by 80 and 50%, respectively, indicating a major role of SR-A1 in clearance of mLDL by macrophages. Subsequent studies using SR-A1$^{-/-}$LDL-R$^{-/-}$ mice confirmed a positive role of SR-A1 in the development of atherosclerotic lesions in mice (Babaev *et al.*, 2000). These *in vivo* observations plus many *in vitro* results showed that SR-A1 seems to be pro-atherogenic (Lougheed *et al.*, 1997; Sugano *et al.*, 2001; Kunjathoor *et al.*, 2002; Zhao *et al.*, 2005). Consequently, loss function of SR-A1 may prevent or decrease the development of atherosclerosis, by inhibiting the accumulation of lipids in macrophages.

However, Such allocation of pro-atherogenic activity to SR-A1 is challenged by other observations. For example, SR-A1 gene deletion leads to increased atherosclerotic lesions and the deterioration of local atherosclerotic lesions in the ApoE3Leiden transgenic mouse model (with the human mutation ApoE gene) (de Winther *et al.*, 1999). Overexpression of the human SR-A1 in either ApoE$^{-/-}$ or LDL-R$^{-/-}$ mice did not change the atherosclerotic lesions (Herijgers *et al.*, 2000; Van Eck *et al.*, 2000). Moreover, overexpression of bovine SR-A1 in mice diminished the atherosclerotic lesions (Whitman *et al.*, 2002). The discrepant observations on the role of SR-A1 in the pathogenesis of atherosclerosis may be caused by differences in atherosclerotic lesion stages, genetic backgrounds of mouse model and the high-fat diets used.

Since 2005, a new set of studies have been carried out, using new approaches in experimental technology to identify the exact role of SR-A1 in atherosclerosis. Moore *et al.* conducted comparative studies and demonstrated that neither SR-A1 nor CD36 ablation significantly influenced the atherosclerotic plaque area in mice. The atherosclerotic lesions in the aortic sinus were actually made worse but the foam cell formation in the lesion was not changed (Moore *et al.*, 2005). Kuchibhotla *et al.* (2008) found that SR-A1 deficiency reduced atherosclerotic lesion area by 32% only in female mice, not in male mice. Thus, the role of SR-A1 in atherogenesis is still a matter of debate. Tobin *et al.* showed that deficiency in both SR-A1 and CD36 did not alter atherosclerotic plaque area and foam cell formation, although it did reduce necrosis of lesions, inflammation and macrophage apoptosis (Manning-Tobin *et al.*, 2009). As a TLR4 co-receptor, SR-A1 is involved in ER stress and macrophage apoptosis (Devries-Seimon *et al.*, 2005; Seimon *et al.*, 2006). Recently, Robbins *et al.* (2013) found that the accumulating macrophage foam cells in the established atherosclerotic lesions primarily originated from SR-A1-mediated proliferation. Therefore, SR-A1 may contribute to atherogenesis primarily by mediation of macrophage proliferation, apoptosis and inflammatory responses.

SR-A1 and cardiovascular remodelling

Chronic inflammation plays an important role in myocardial infarction (MI)-induced ventricular remodelling. The mortality of SR-A1-deficient mice with experimental MI is dramatically increased. Increased risk of cardiac rupture in SR-A1-deficient mice is associated with insufficient production of IL-10 and increased levels of TNF-α and MMP-9 (Tsujita *et al.*, 2007). Hu *et al.* (2011) showed that the protective effect of SR-A1 against MI-induced cardiomyocyte necrosis may be through suppressing the polarization of macrophages towards the M1 subtype. The promotion of M2 macrophage polarization by SR-A1 has also been found in angiotensin II-induced vascular remodelling and in obese adipose tissue in mice (Zhu *et al.*, 2014). It seems that SR-A1 may exert an anti-inflammatory role in ischaemia-induced cardiovascular remodelling by shifting macrophages towards an M2 subtype (Figure 2).

However, the role of SR-A1 in myocardial ischaemia/reperfusion (I/R) injury seems to be opposite to that in ischae-

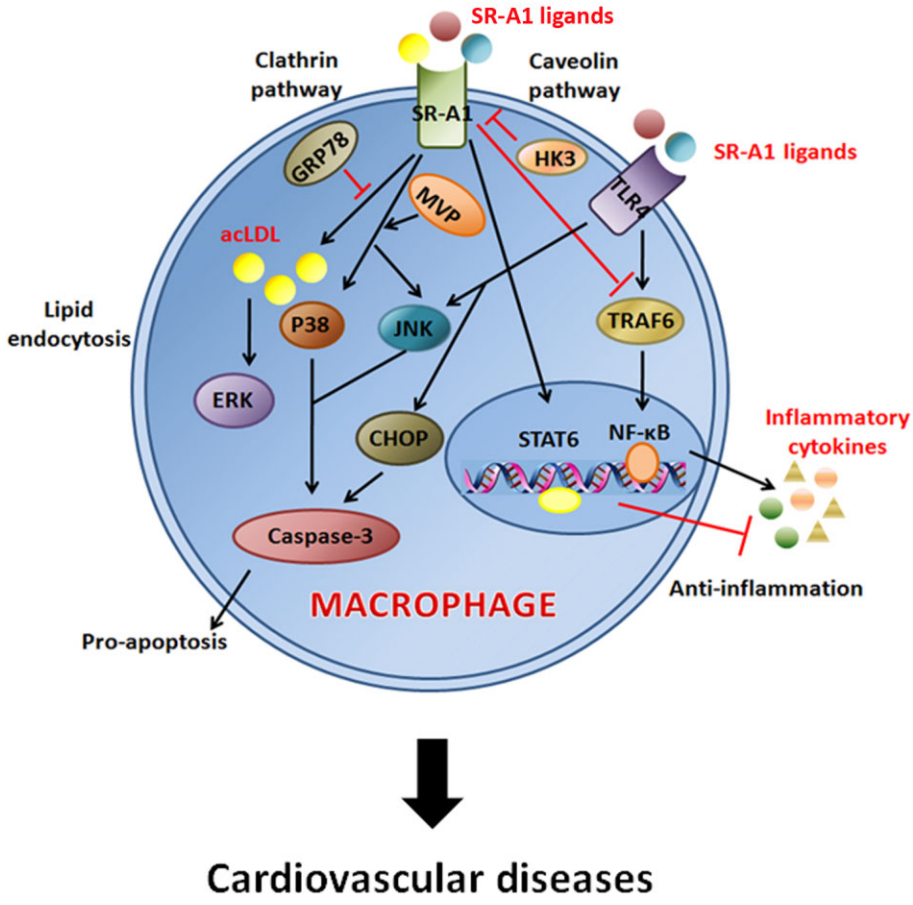

Figure 2
SR-A1-regulated macrophage activities in cardiovascular diseases.

mic injury model. SR-A1$^{-/-}$ mice have a smaller myocardial infarct size and better cardiac function than wild-type (WT) mice. This is associated with an attenuated I/R-induced myocardial apoptosis by preventing p53-mediated Bak-1 apoptotic signalling. The levels of microRNA-125b in heart and macrophages from SR-A1$^{-/-}$ mice are also significantly higher than those in WT tissues (Ren *et al.*, 2013).

SR-A1 and cerebrovascular diseases

In an experimental brain I/R injury model, SR-A1 deficiency decreased infarct area with mitigation of hippocampal neuronal damage, associated with a reduced NF-κB activity and cell apoptosis in the brain (Lu *et al.*, 2010). Xu *et al.* demonstrated that SR-A1 was up-regulated in mice brains with permanent occlusion of middle cerebral artery. SR-A1-deficient mice displayed a reduced infarct size and improved neurological function, compared with WT mice. This was accompanied by a decrease in M1 macrophages and an increase in M2 macrophages (Xu *et al.*, 2012). These observations from the brain are opposite to those from the peripheral tissues. As microglia play a key role in pathogenesis of brain ischaemia, the effects of SR-A1 on cell polarized differentiation between microglia and macrophage is worth investigating. Moreover, the microenvironment may be an important determinant of SR-A1 function. This hypothesis is consistent with a recent discovery from cerebrovascular amyloidosis, which can lead to haemorrhagic stroke. Lifshitz *et al.* demonstrated that SR-A1-deficient mice show a cerebrovascular pathology at an earlier age. Furthermore, SR-A1 deficiency in macrophages leads to impaired clearing of cerebrovascular amyloid and inhibited phagocytosis of both soluble and insoluble Aβ *in vivo* (Lifshitz *et al.*, 2013). Therefore, SR-A1 in macrophages may be a useful target in the prevention of cerebral amyloid angiopathy.

Therapeutic application of SR-A1 regulation to cardiovascular diseases

Although there are contradictory reports on the role of SR-A1 in cardiovascular diseases, attempts to use SR-A1 as a target for the prevention and treatment of cardiovascular diseases are continuing. Tsubamoto *et al.* showed that treatment with dextran sulfate, a ligand for SR-A1, resulted in a 40% reduction in atherosclerotic plaque area in hyperlipidaemic Watanabe rabbits, with no changes in blood lipids (Tsubamoto *et al.*, 1994). A low MW antagonist of SR-A1 has been identified and inhibited mLDL endocytosis by SR-A1 but did not

affect binding and degradation of mLDL by macrophages (Lysko *et al.*, 1999). Wang *et al.* generated a peptide H11 that specifically binds with the cytoplasmic domain of SR-A1, which can inhibit the expression and endocytosis of SR-A1 in macrophages (Wang *et al.*, 2009). Segers *et al.* also generated a SR-A1-binding peptide PP1. This peptide is taken up by endocytosis into macrophages via SR-A1 and accumulates in atherosclerotic lesions in mice (Segers *et al.*, 2012). The ultrasmall super-paramagnetic iron oxide particle-conjugated PP1 has been used to detect *in situ* inflammatory plaques in atherosclerosis (Segers *et al.*, 2013). The SR-A1-binding peptides seem to be useful tools not only for positioning SR-A1 *in vivo* but also for the regulation of SR-A1 function. As a protective role of SR-A1 against cardiovascular diseases has been identified recently, more agonists of SR-A1 are expected to be tested in the future.

Prospects

Although SR-A1 was identified more than 30 years ago, its role in cardiovascular diseases is still a matter for debate. Recent findings revealed that SR-A1 may function in anti-inflammatory responses by promoting an M2 macrophage phenotype in cardiovascular diseases. New and further studies should focus on (i) elucidation of its definite role in different types of cell and microenvironment; (ii) endogenous ligands of SR-A1 and their pathophysiological significance; and (iii) signalling pathways linking to SR-A1. We believe that, with the continuing development of new techniques and methods, clear biological functions and detailed mechanisms of SR-A1 in cardiovascular diseases will be revealed, which will be of benefit to the prevention and treatment of cardiovascular diseases.

Acknowledgements

This work was supported by the project of National Natural Science Foundation of China (Nos. 81230070 and 91339202) and National Basic Research Program (973) (Grant Nos. 2012CB517503 and 2011CB503903) to Q. C., the project of National Natural Science Foundation of China Grant (No. 81370005) to J. B., and the project of National Natural Science Foundation of China (Grant No. 81300211) to X. Z.

Conflict of interest

No conflicts of interest exist.

References

Alexander SPH, Benson HE, Faccenda E, Pawson AJ, Sharman JL, Spedding M *et al.* (2013a). The Concise Guide to PHARMACOLOGY 2013/14: Catalytic Receptors. Br J Pharmacol 170: 1676–1705.

Alexander SPH, Benson HE, Faccenda E, Pawson AJ, Sharman JL, Spedding M *et al.* (2013b). The Concise Guide to PHARMACOLOGY 2013/14: Enzymes. Br J Pharmacol 170: 1797–1867.

Andersson L, Freeman MW (1998). Functional changes in scavenger receptor binding conformation are induced by charge mutants spanning the entire collagen domain. J Biol Chem 273: 19592–19601.

Babaev VR, Gleaves LA, Carter KJ, Suzuki H, Kodama T, Fazio S *et al.* (2000). Reduced atherosclerotic lesions in mice deficient for total or macrophage-specific expression of scavenger receptor-A. Arterioscler Thromb Vasc Biol 20: 2593–2599.

Ben J, Gao S, Zhu X, Zheng Y, Zhuang Y, Bai H *et al.* (2009). Glucose-regulated protein 78 inhibits scavenger receptor A-mediated internalization of acetylated low density lipoprotein. J Mol Cell Cardiol 47: 646–655.

Ben J, Zhang Y, Zhou R, Zhang H, Zhu X, Li X *et al.* (2013). Major vault protein regulates class A scavenger receptor-mediated tumor necrosis factor-α synthesis and apoptosis in macrophages. J Biol Chem 288: 20076–20084.

Bottalico LA, Wager RE, Agellon LB, Assoian RK, Tabas I (1991). Transforming growth factor-beta 1 inhibits scavenger receptor activity in THP-1 human macrophages. J Biol Chem 266: 22866–22871.

Bowdish DM, Gordon S (2009). Conserved domains of the class A scavenger receptors: evolution and function. Immunol Rev 227: 19–31.

Chen Y, Wang X, Ben J, Yue S, Bai H, Guan X *et al.* (2006). The di-leucine motif contributes to class a scavenger receptor-mediated internalization of acetylated lipoproteins. Arterioscler Thromb Vasc Biol 26: 1317–1322.

Chen Y, Wermeling F, Sundqvist J, Jonsson AB, Tryggvason K, Pikkarainen T *et al.* (2010). A regulatory role for macrophage class A scavenger receptors in TLR4-mediated LPS responses. Eur J Immunol 40: 1451–1460.

Coller SP, Paulnock DM (2001). Signaling pathways initiated in macrophages after engagement of type A scavenger receptors. J Leukoc Biol 70: 142–148.

Devries-Seimon T, Li Y, Yao PM, Stone E, Wang Y, Davis RJ *et al.* (2005). Cholesterol-induced macrophage apoptosis requires ER stress pathways and engagement of the type A scavenger receptor. J Cell Biol 171: 61–73.

Emi M, Asaoka H, Matsumoto A, Itakura H, Kurihara Y, Wada Y *et al.* (1993). Structure, organization, and chromosomal mapping of the human macrophage scavenger receptor gene. J Biol Chem 268: 2120–2125.

Fong LG, Le D (1999). The processing of ligands by the class A scavenger receptor is dependent on signal information located in the cytoplasmic domain. J Biol Chem 274: 36808–36816.

Fraser I, Hughes D, Gordon S (1993). Divalent cation-independent macrophage adhesion inhibited by monoclonal antibody to murine scavenger receptor. Nature 364: 343–346.

Gao S, Zhong X, Ben J, Zhu X, Zheng Y, Zhuang Y *et al.* (2009). Glucose regulated protein 78 prompts scavenger receptor A-mediated secretion of tumor necrosis factor-alpha by RAW 264.7 cells. Clin Exp Pharmacol Physiol 36: 940–944.

Geng YJ, Hansson GK (1992). Interferon-gamma inhibits scavenger receptor expression and foam cell formation in human monocyte-derived macrophages. J Clin Invest 89: 1322–1330.

Goldstein JL, Ho YK, Basu SK, Brown MS (1979). Binding site on macrophages that mediates uptake and degradation of acetylated

low density lipoprotein, producing massive cholesterol deposition. Proc Natl Acad Sci U S A 76: 333–337.

Gough PJ, Greaves DR, Gordon S (1998). A naturally occurring isoform of the human macrophage scavenger receptor (SR-A) gene generated by alternative splicing blocks modified LDL uptake. J Lipid Res 39: 531–543.

Herijgers N, de Winther MP, Van Eck M, Havekes LM, Hofker MH, Hoogerbrugge PM *et al.* (2000). Effect of human scavenger receptor class A overexpression in bone marrow-derived cells on lipoprotein metabolism and atherosclerosis in low density lipoprotein receptor knockout mice. J Lipid Res 41: 1402–1409.

Hohenester E, Sasaki T, Timpl R (1999). Crystal structure of a scavenger receptor cysteine-rich domain sheds light on an ancient superfamily. Nat Struct Biol 6: 228–232.

Hsu HY, Nicholson AC, Hajjar DP (1996). Inhibition of macrophage scavenger receptor activity by tumor necrosis factor-alpha is transcriptionally and post-transcriptionally regulated. J Biol Chem 271: 7767–7773.

Hsu HY, Hajjar DP, Khan KM, Falcone DJ (1998). Ligand binding to macrophage scavenger receptor-A induces urokinase-type plasminogen activator expression by a protein kinase-dependent signaling pathway. J Biol Chem 273: 1240–1246.

Hsu HY, Chiu SL, Wen MH, Chen KY, Hua KF (2001). Ligands of macrophage scavenger receptor induce cytokine expression via differential modulation of protein kinase signaling pathways. J Biol Chem 276: 28719–28730.

Hu Y, Zhang H, Lu Y, Bai H, Xu Y, Zhu X *et al.* (2011). Class A scavenger receptor attenuates myocardial infarction-induced cardiomyocyte necrosis through suppressing M1 macrophage subset polarization. Basic Res Cardiol 106: 1311–1328.

Hughes DA, Fraser IP, Gordon S (1994). Murine M phi scavenger receptor: adhesion function and expression. Immunol Lett 43: 7–14.

Ingersoll MA, Spanbroek R, Lottaz C, Gautier EL, Frankenberger M, Hoffmann R *et al.* (2010). Comparison of gene expression profiles between human and mouse monocyte subsets. Blood 115: e10–e19.

Jones NL, Reagan JW, Willingham MC (2000). The pathogenesis of foam cell formation: modified LDL stimulates uptake of co-incubated LDL via macropinocytosis. Arterioscler Thromb Vasc Biol 20: 773–781.

Kim S, Watarai M, Suzuki H, Makino S, Kodama T, Shirahata T (2004). Lipid raft microdomains mediate class A scavenger receptor-dependent infection of Brucella abortus. Microb Pathog 37: 11–19.

Kim WS, Ordija CM, Freeman MW (2003). Activation of signaling pathways by putative scavenger receptor class A (SR-A) ligands requires CD14 but not SR-A. Biochem Biophys Res Commun 310: 542–549.

Kodama T, Freeman M, Rohrer L, Zabrecky J, Matsudaira P, Krieger M (1990). Type I macrophage scavenger receptor contains alpha-helical and collagen-like coiled coils. Nature 343: 531–535.

Kosswig N, Rice S, Daugherty A, Post SR (2003). Class A scavenger receptor-mediated adhesion and internalization require distinct cytoplasmic domains. J Biol Chem 278: 34219–34225.

Krieger M, Herz J (1994). Structures and functions of multiligand lipoprotein receptors: macrophage scavenger receptors and LDL receptor-related protein (LRP). Annu Rev Biochem 63: 601–637.

Kuchibhotla S, Vanegas D, Kennedy DJ, Guy E, Nimako G, Morton RE *et al.* (2008). Absence of CD36 protects against atherosclerosis in ApoE knock-out mice with no additional protection provided by absence of scavenger receptor A I/II. Cardiovasc Res 78: 185–196.

Kunjathoor VV, Febbraio M, Podrez EA, Moore KJ, Andersson L, Koehn S *et al.* (2002). Scavenger receptors class A-I/II and CD36 are the principal receptors responsible for the uptake of modified low density lipoprotein leading to lipid loading in macrophages. J Biol Chem 277: 49982–49988.

Kzhyshkowska J, Neyen C, Gordon S (2012). Role of macrophage scavenger receptors in atherosclerosis. Immunobiology 217: 492–502.

Lifshitz V, Weiss R, Levy H, Frenkel D (2013). Scavenger receptor A deficiency accelerates cerebrovascular amyloidosis in an animal model. J Mol Neurosci 50: 198–203.

Loboda A, Jazwa A, Jozkowicz A, Molema G, Dulak J (2006). Angiogenic transcriptome of human microvascular endothelial cells: effect of hypoxia, modulation by atorvastatin. Vascul Pharmacol 44: 206–214.

Lougheed M, Lum CM, Ling W, Suzuki H, Kodama T, Steinbrecher U (1997). High affinity saturable uptake of oxidized low density lipoprotein by macrophages from mice lacking the scavenger receptor class A type I/II. J Biol Chem 272: 12938–12944.

Lu C, Hua F, Liu L, Ha T, Kalbfleisch J, Schweitzer J *et al.* (2010). Scavenger receptor class-A has a central role in cerebral ischemia-reperfusion injury. J Cereb Blood Flow Metab 30: 1972–1981.

Lysko PG, Weinstock J, Webb CL, Brawner ME, Elshourbagy NA (1999). Identification of a small-molecule, nonpeptide macrophage scavenger receptor antagonist. J Pharmacol Exp Ther 289: 1277–1285.

Ma K, Xu Y, Wang C, Li N, Li K, Zhang Y *et al.* (2014). A crosstalk between class A scavenger receptor and receptor for advanced glycation end-products contributes to diabetic retinopathy. Am J Physiol Endocrinol Metab 307: E1153–E1165.

Manning-Tobin JJ, Moore KJ, Seimon TA, Bell SA, Sharuk M, Alvarez-Leite JI *et al.* (2009). Loss of SR-A and CD36 activity reduces atherosclerotic lesion complexity without abrogating foam cell formation in hyperlipidemic mice. Arterioscler Thromb Vasc Biol 29: 19–26.

Matsumoto A, Naito M, Itakura H, Ikemoto S, Asaoka H, Hayakawa I *et al.* (1990). Human macrophage scavenger receptors: primary structure, expression, and localization in atherosclerotic lesions. Proc Natl Acad Sci U S A 87: 9133–9137.

Mietus-Snyder M, Gowri MS, Pitas RE (2000). Class A scavenger receptor up-regulation in smooth muscle cells by oxidized low density lipoprotein. Enhancement by calcium flux and concurrent cyclooxygenase-2 up-regulation. J Biol Chem 275: 17661–17670.

Mommaas-Kienhuis AM, van der Schroeff JG, Wijsman MC, Daems WT, Vermeer BJ (1985). Conjugates of colloidal gold with native and acetylated low density lipoproteins for ultrastructural investigations on receptor-mediated endocytosis by cultured human monocyte-derived macrophages. Histochemistry 83: 29–35.

Moore KJ, Kunjathoor VV, Koehn SL, Manning JJ, Tseng AA, Silver JM *et al.* (2005). Loss of receptor-mediated lipid uptake via scavenger receptor A or CD36 pathways does not ameliorate atherosclerosis in hyperlipidemic mice. J Clin Invest 115: 2192–2201.

Murphy JE, Tedbury PR, Homer-Vanniasinkam S, Walker JH, Ponnambalam S (2005). Biochemistry and cell biology of mammalian scavenger receptors. Atherosclerosis 182: 1–15.

Nakamura T, Suzuki H, Wada Y, Kodama T, Doi T (2006). Fucoidan induces nitric oxide production via p38 mitogen-activated protein kinase and NF-kappaB-dependent signaling pathways through macrophage scavenger receptors. Biochem Biophys Res Commun 343: 286–294.

Pawson AJ, Sharman JL, Benson HE, Faccenda E, Alexander SP, Buneman OP *et al.*; NC-IUPHAR (2014). The IUPHAR/BPS Guide to PHARMACOLOGY: an expert-driven knowledge base of drug targets and their ligands. Nucl Acids Res 42 (Database Issue): D1098–D1106.

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

Prabhudas M, Bowdish D, Drickamer K, Febbraio M, Herz J, Kobzik L *et al.* (2014). Standardizing scavenger receptor nomenclature. J Immunol 192: 1997–2006.

Ren D, Wang X, Ha T, Liu L, Kalbfleisch J, Gao X *et al.* (2013). SR-A deficiency reduces myocardial ischemia/reperfusion injury; involvement of increased microRNA-125b expression in macrophages. Biochim Biophys Acta 1832: 336–346.

Robbins CS, Hilgendorf I, Weber GF, Theurl I, Iwamoto Y, Figueiredo JL *et al.* (2013). Local proliferation dominates lesional macrophage accumulation in atherosclerosis. Nat Med 19: 1166–1172.

Rohrer L, Freeman M, Kodama T, Penman M, Krieger M (1990). Coiled-coil fibrous domains mediate ligand binding by macrophage scavenger receptor type II. Nature 343: 570–572.

Sano H, Ishino M, Kramer H, Shimizu T, Mitsuzawa H, Nishitani C *et al.* (2007). The microtubule-binding protein Hook3 interacts with a cytoplasmic domain of scavenger receptor A. J Biol Chem 282: 7973–7981.

Segers FM, Yu H, Molenaar TJ, Prince P, Tanaka T, van Berkel TJ *et al.* (2012). Design and validation of a specific scavenger receptor class AI binding peptide for targeting the inflammatory atherosclerotic plaque. Arterioscler Thromb Vasc Biol 32: 971–978.

Segers FM, den Adel B, Bot I, van der Graaf LM, van der Veer EP, Gonzalez W *et al.* (2013). Scavenger receptor-AI-targeted iron oxide nanoparticles for in vivo MRI detection of atherosclerotic lesions. Arterioscler Thromb Vasc Biol 33: 1812–1819.

Seimon TA, Obstfeld A, Moore KJ, Golenbock DT, Tabas I (2006). Combinatorial pattern recognition receptor signaling alters the balance of life and death in macrophages. Proc Natl Acad Sci U S A 103: 19794–19799.

Sugano R, Yamamura T, Harada-Shiba M, Miyake Y, Yamamoto A (2001). Uptake of oxidized low-density lipoprotein in a THP-1 cell line lacking scavenger receptor A. Atherosclerosis 158: 351–357.

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

Tsubamoto Y, Yamada N, Watanabe Y, Inaba T, Shiomi M, Shimano H *et al.* (1994). Dextran sulfate, a competitive inhibitor for scavenger receptor, prevents the progression of atherosclerosis in Watanabe heritable hyperlipidemic rabbits. Atherosclerosis 106: 43–50.

Tsujita K, Kaikita K, Hayasaki T, Honda T, Kobayashi H, Sakashita N *et al.* (2007). Targeted deletion of class A macrophage scavenger receptor increases the risk of cardiac rupture after experimental myocardial infarction. Circulation 115: 1904–1911.

Van Eck M, De Winther MP, Herijgers N, Havekes LM, Hofker MH, Groot PH *et al.* (2000). Effect of human scavenger receptor class A overexpression in bone marrow-derived cells on cholesterol levels and atherosclerosis in ApoE-deficient mice. Arterioscler Thromb Vasc Biol 20: 2600–2606.

Wang X, Zheng Y, Xu Y, Ben J, Gao S, Zhu X *et al.* (2009). A novel peptide binding to the cytoplasmic domain of class A scavenger receptor reduces lipid uptake in THP-1 macrophages. Biochim Biophys Acta 1791: 76–83.

Whitman SC, Rateri DL, Szilvassy SJ, Cornicelli JA, Daugherty A (2002). Macrophage-specific expression of class A scavenger receptors in LDL receptor(-/-) mice decreases atherosclerosis and changes spleen morphology. J Lipid Res 43: 1201–1208.

de Winther MP, Gijbels MJ, van Dijk KW, van Gorp PJ, Suzuki H, Kodama T *et al.* (1999). Scavenger receptor deficiency leads to more complex atherosclerotic lesions in APOE3Leiden transgenic mice. Atherosclerosis 144: 315–321.

Xu Y, Qian L, Zong G, Ma K, Zhu X, Zhang H *et al.* (2012). Class A scavenger receptor promotes cerebral ischemic injury by pivoting microglia/macrophage polarization. Neuroscience 218: 35–48.

Yi H, Yu X, Gao P, Wang Y, Baek SH, Chen X *et al.* (2009). Pattern recognition scavenger receptor SRA/CD204 down-regulates Toll-like receptor 4 signaling-dependent CD8 T-cell activation. Blood 113: 5819–5828.

Yu X, Yi H, Guo C, Zuo D, Wang Y, Kim HL *et al.* (2011). Pattern recognition scavenger receptor CD204 attenuates Toll-like receptor 4-induced NF-kappaB activation by directly inhibiting ubiquitination of tumor necrosis factor (TNF) receptor-associated factor 6. J Biol Chem 286: 18795–18806.

Zhao Z, de Beer MC, Cai L, Asmis R, de Beer FC, de Villiers WJ *et al.* (2005). Low-density lipoprotein from apolipoprotein E-deficient mice induces macrophage lipid accumulation in a CD36 and scavenger receptor class A-dependent manner. Arterioscler Thromb Vasc Biol 25: 168–173.

Zhu X, Zong G, Zhu L, Jiang Y, Ma K, Zhang H *et al.* (2014). Deletion of class A scavenger receptor deteriorates obesity-induced insulin resistance in adipose tissue. Diabetes 63: 562–577.

Zhu XD, Zhuang Y, Ben JJ, Qian LL, Huang HP, Bai H *et al.* (2011). Caveolae-dependent endocytosis is required for class A macrophage scavenger receptor-mediated apoptosis in macrophages. J Biol Chem 286: 8231–8239.