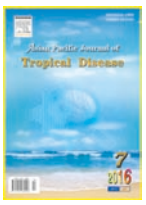
HOSTED BY
ELSEVIER

Contents lists available at ScienceDirect

Asian Pacific Journal of Tropical Disease

journal homepage: www.elsevier.com/locate/apjtd



Mini review doi: 10.1016/S2222-1808(16)61088-5

Scavenger receptor class-A plays diverse role in innate immunity, cell signaling and different pathologies

Aamir Rana[1*], Syed Sajjad Sattar[2], Afshann Shahzad[3], Ghulam Muhammad Ali[1], Yasir Waheed[4]

[1]*National Institute for Genomics and Advanced Biotechnology (NIGAB), NARC, Park Road, 45500, Islamabad, Pakistan*

[2]*Research Center of Modelling and Simulation, National University of Science and Technology, Sector H-12, Islamabad, Pakistan*

[3]*Atta-ur-Rahman School of Applied Biosciences, National University of Sciences and Technology, Sector H-12, Islamabad, Pakistan*

[4]*Foundation University Medical College, Foundation University, Islamabad, DHA Phase I, Islamabad, Pakistan*

ARTICLE INFO

Article history:
Received 4 Apr 2016
Received in revised form 18 Apr, 2nd revised form 3 May, 3rd revised form 4 May 2016
Accepted 5 Jun 2016
Available online 29 Jun 2016

Keywords:
Scavenger receptors
Innate immunity
Interleukins
Cell signaling
Apoptosis

ABSTRACT

Evidences have been increasingly provided to comfirm that lipid accumulation in cells contributes to the progression of pathogeneses. The receptor-mediated lipid uptake is the crucial step for lipid retention as scavenger receptors class-A (SR-A) is not controlled via negative feedback by cytoplasmic cholesterol and therefore it plays a fundamental role in the formation of foam cells. Along with participation in apoptosis, SR-A presents very deceitful characteristics to control immune responses during age-related degenerative pathologies such as atherosclerosis and Alzheimer's disease. It is henceforth undeniable that targeted inhibition of these receptors will be helpful in getting a step closer to individualized medicine. This review unfolds current understanding of SR-A signaling with a focus on its role in apoptosis and immune regulation during different pathologies.

1. Introduction

Scavenger receptors class-A (SR-A), also known as CD204, is a class of receptors responsible for modified appearances of lipoproteins including acetylated and oxidized low-density lipoproteins (oxLDL)[1]. SR-A shares its binding affinity with multiple ligands, such as Gram-positive and Gram-negative bacteria, lipopolysaccharides (LPS), and advanced glycation end products. Scavenger receptors (SR) family is divided into eight different subclasses (A–H) and the majority of them express on the surface of antigen-presenting cells[1,2]. SR-A expresses primarily on macrophages, dendritic cells (DCs) and smooth muscle cells[3]. Macrophage SR-A type I and II (SR-AI and II) belong to the family of transmembrane glycoprotein receptors, which favor the binding of numerous negatively charged polyanionic macromolecules[4,5]. The internalization of LDLs by macrophage SR-A and lipoprotein lipase is indispensable to encourage atherosclerosis and foam cell formation[6,7]. Subsequently, SR-A recognizes modified host components, apoptotic cells, exogenous pathogens associated molecular patterns and endogenous ligands to initiates innate and inflammatory responses[8-12]. Lack of signaling motif in intracellular domain of SR-A restricts its straight signaling into the cell, while phosphorylated intracellular domains facilitate the interaction of transmembrane domain with intracellular signaling components[13-15]. SR-A, as a co-receptor for toll-like receptors (TLRs), facilitates innate immune recognition and responses by eliciting an over exuberant response[16]. TLRs ligands synergize with SR-A to intercede bacterial phagocytosis, induce SR-A expression and promote SR-A binding to the TLR4 ligands[17,18]. SR-A interacts with TLR4 to endorse a pro-inflammatory apoptotic phenotype in lipopolysaccharide exposed macrophages. In addition, SR-A curbs for survival signaling pathways, such as interferon regulatory factor-3 mediated interferon-β (IFN-β) production[16]. In contrast, SR-A ligands trigger apoptosis in the endoplasmic reticulum

*Corresponding author: Aamir Rana, National Institute for Genomics and Advanced Biotechnology, NARC, Park Road, 45500, Islamabad, Pakistan.
Tel: +923324977542
E-mail: aamirrana_grg@yahoo.com
The journal implements double-blind peer review practiced by specially invited international editorial board members.

harassed macrophages by cooperating with TLR4 and serve as a negative regulator of TLR4 in mediating immune responses[3,16]. Collectively, SR-A contributes the activation of innate immune and inflammatory responses by acting as a co-receptor to TLR4.

2. An overview

Isoforms of SR-A (SR-AI and SR-AII) are highly conserved molecules holding over 60% homology in mice, humans and rabbits[19-21]. SR-AI and SR-AII are alternative splice variants of the same gene presenting on chromosome 8p22 in humans[20], while macrophage receptor with collagenous structure (MARCO), the third member of the subclass, is expressed by another gene on chromosome that shares analogous structural motifs with SR-AI and II, thus it is classified as a SR-A[22]. SR-A and MARCO with six and five distinct domains, respectively, belong to type II trimeric transmembrane glycoproteins[20]. The first 50N-terminal amino acids (aa) of SR-AI and SR-AII make the cytoplasmic domain and the followings: 25-aa transmembrane region, 75-aa N-glycosylated spacer domain, 121-aa-helical coiled-coil domain, 69-aa collagenous region and the C-terminus. The α-helical coiled-coil domain of SR-AI and II is most significant in receptor trimerization and their dissociation from the ligand in endosomes[23]. SR-AI, SR-AII and SR-AIII vary in their C-terminus. SR-AI holds a conserved 110-aa scavenger receptor cysteine-rich domain[24], while SR-AII and SR-AIII have a short or truncated C-terminal region, respectively (Figure 1). The cytoplasmic amino acids proximal to the membrane are essential for SR-A post-transcriptional processing and play a decisive role in SR-A trafficking to the cell surface. Furthermore, these amino acids are sufficient for SR-A-mediated adhesion[25]. MARCO with longer collagenous domain does not hold any α-helical coiled-coil domain and depends on the scavenger receptor cysteine-rich domain domain for ligands binding[22].

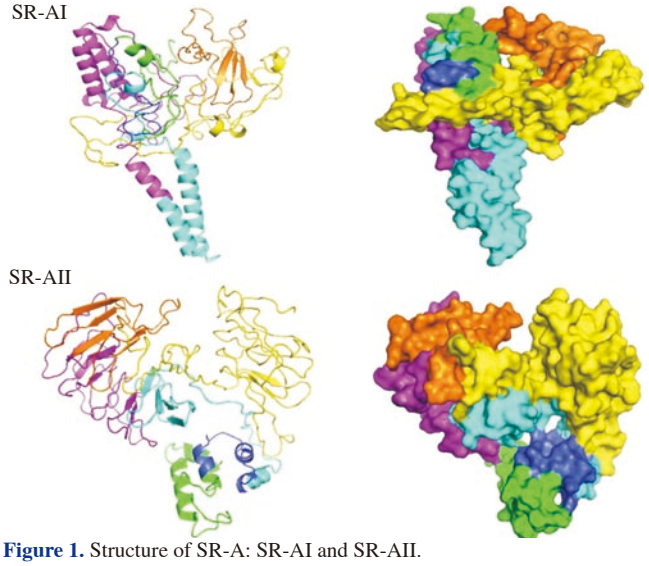


Figure 1. Structure of SR-A: SR-AI and SR-AII.
Green: Cytoplasmic domain; TV blue: Transmembrane domain; Cyan: Spacer domain; Purple: α-helical coiled-coil domain; Orange: collagenous domain; Yellow: C-terminus. The models were designed by using Modeller 9.14.

3. Cellular errands

SR-A, CD36 (a member of scavenger receptor class B family) and scavenger receptor class BI are multifunctional receptors to elucidate large complex molecules. Most functional studies demonstrate the involvement of SRs in the accumulation of modified lipids within macrophages that leads toward atherosclerosis and atherogenesis. SR-mediated endocytosis of targeted ligands such as maleylated native proteins follows the presentation of modified-specific antigens to T cells[26]. The regulation of SR-A during inflammation is indistinct as most of the ligands are common to all SRs. Although the mouse and human SR-A proteins are highly conserved but their control of expression is quite different[27]. In murine macrophages, SR-A expression augments LPS challenge *in vitro* but is down-regulated in human macrophages. It is unclear that SR-A protects against endotoxic shock in humans, but it is hasty to suggest that SR-A does not have a role. SR-A regulates the complex relationship between immune responses to LPS such as cytokine release. For example, SR-A dampens the expression of both transcriptionally and post-transcriptionally inflammatory cytokines such as tumor necrosis factor-α (TNF-α) and IFN-γ[28]. SR-AIII is not functional and displays dominant negative control on post-translational mechanism for SR-AI and SR-AII[29]. Further investigations are needed to find specific ligands that various receptors recognize on the dying cells and the signaling events after the binding of apoptotic cells with SR binding and how the cells regulate the induction of inflammation. The expression of SR-A on bone marrow dendrictic cells helps in DCs-mediated phagocytosis of apoptotic cells infected with influenza virus and the following uptake of viral antigens are presented to T cells via major histocompatibility complex-I (MHC-I). In comparison, this cross-priming ability is not exhibited by macrophages[30]. It shows that the chief immunological consequences of SR-A serve as an anti-inflammatory molecule for the removal of potentially damaging altered host proteins by macrophages and its inflammatory role in DCs.

4. SR-A and apoptosis

SR-A can recognize apoptotic cells. Platt *et al.*[31] reported that macrophages from knockout mice have a very less *in vitro*, but high *in vivo* ability to remove apoptotic cells despite the induction of enormous apoptosis by sub-lethal irradiation. Although the role of SR-A in pro-apoptotic mechanisms is not fully understood, SR-A involves in triggering JNK-dependent apoptosis in macrophages with stressed endoplasmic reticulum (ER). In macrophages under stressed ER, fucoidan agonist SR-A causes the inhibition of microtubule-associated protein light chain 3-phospholipid conjugates (LC3-II) and a number of autophagosomes, which promotes the activation of mammalian target of rapamycin (mTOR), JNK and p38 signaling. Further activation of TNF-α encourages apoptosis[32]. During myocardial ischemia/reperfusion (I/R) injury the low expression of SR-A leads to the up-regulated expression of miRNA 125b (pro-apoptotic), but in hypoxia/re-oxygenation (H/R)-induced cell damage

SR-A inhibits the activation of caspase 3, 7 and 8 to reduce the chances of apoptosis[33]. On one side SR-A augments the expression of LPS, but on the other it may causes the inhibition of caspase 3, 7 and 8, the key players of apoptosis (Figure 2).

5. Cell signaling and antigen presentation

To control foam cell formation, the signaling mechanisms of SR-A are not fully understood. Some studies are conducted to find the role of cellular signaling mediated by SR-A which leads towards foam cell formation. Recently, Michael *et al.*[7] investigated that phosphoinositide 3-kinase promotes foam cell formation by up-regulating SR-A expression. In myocardial infarction knockout SR-A leads to the increased expressions of apoptosis signal-regulating kinase 1, p38, mitogen-activated protein kinases and nuclear factor-κB (NF-κB). During the attenuated expression of SR-A, it not only exacerbates the expressions of apoptosis signal-regulating kinase 1, p38, and NF-κB, but also dampens the expressions of interleukin (IL)-6, IL-1β, and TNF-α[34]. Nifedipine, an anti-hypersensitive drug, protects against atherosclerosis and inhibits the expression of SR-A, which results in the less expression of protein kinase C theta (PKC-θ)[35]. SR-A by its microbial ligands effectively encourages the production of a wide range of inflammatory cytokines, including TNF-α, IL-1β and IL-6. SR-A also mediates the activation of TNF-α using biochemical inhibitors like polyinosinic: polycytidylic acid and lipoteichoic acid[36].

SRs direct the loading of Ag in antigen-presenting cells by MHC-I restricted presentation. SR-A internalizes heat shock proteins gp96/grp94 and calreticulin that are further presented by MHC-I[37]. Similarly, recognition of heat shock proteins 70 by lysyl oxidase-1 is implicated in cross-presentation[38]. SR-A and CD36 present the antigen of live and apoptotic cells by MHC-I restricted fashion[39]. Conversely, the expression of MARCO directs the maturation of DCs and may affect its Ag presentation ability[40].

6. SR-A as a pattern recognition receptor

SR-A absence extensively attenuates the cooperation of TLR4 and TLR4-mediated activation of NF-κB during cerebral I/R[3,17]. SR-A is now considered to be a pattern recognition receptor which have the affinity to recognize several ligands such as double-stranded RNA[11], CpG DNA, DCs and some unknown endogenous ligands which are released from stressed or damaged cells during I/R[10]. SR-A also have an abilty to mediate self-complementary adeno-associated virus serotype 8 endocytosis[41].

7. SR-A in disease

SR-A promotes oxLDL uptake capacity of DCs in hyperinsulinaemia leading to atherogenesis[42]. Despite the role of SR-A in atherosclerosis by foam cell formation, it is a key mediator of cell adhesion, endocytosis, phygocytosis and the regulation of cellular immunity[43]. It is recently investigated that SR-A promotes the internalization of Aβ oligomer in Alzheimer's disease[44]. SR-A with gluc-collagen collectively helps in stimulating the enhanced expression of prostaglandin in atherosclerosis and diabetes[45], whereas visfatin induced the modulated expression of SR-A leading to the accumulation of cholesterol in microphages during atherosclerosis[46]. In ovarian (OVA) and pancreatic cancer, it inhibits cell invasion[47], while the dysregulated expression of SR-A in prostate cancer directs the elevated cross-presentation of OVA antigen in DCs[48]. When inflammation SR-A put an impact on the LDL receptor-mediated macrophages derived foam cells formation[49], TLR4 regulated the up-regulation of NFκB and TNF receptor-associated factor 6 inhibition[50] (Table 1). High expressions of SR-A, NFκB, monocyte chemoattractant protein, matrix metalloproteinases

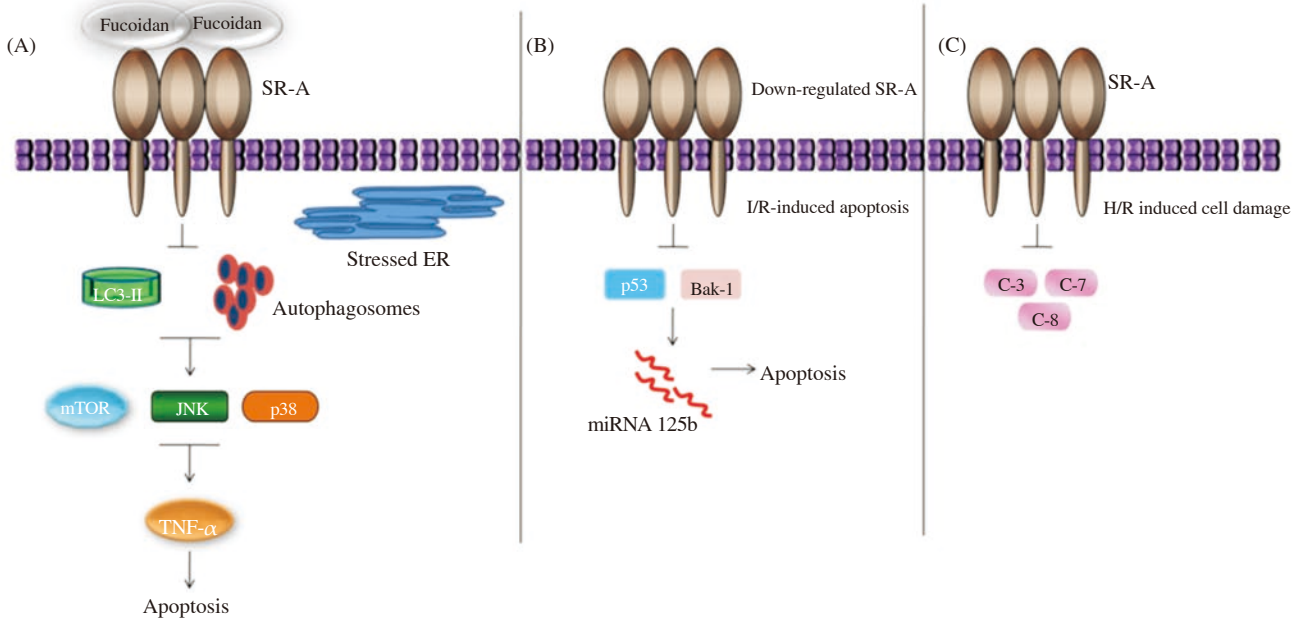


Figure 2. SR-A and apoptosis.

A: SR-A with fucoidan inhibits LC3-II and autophagosomes that leads to the up-regulation of mTOR, JNK and p38 signaling. Higher expressions of mTOR, JNK and p38 activate TNF-α to promote apoptosis; B: Down-regulated expression of SR-A dampens the activation of p53 and Bak-1 but uplifts the presence of miRNA 125b which takes part in I/R induced apoptosis; C: During H/R induced cell damage, SR-A inhibits the activation of caspase 3, 7 and 8.

Table 1

Roles of SR-A in diseases and cellular signaling.

Cell/cell lines/animal models	Diseases/disease models	Output/role in cellular immunity	References
Macrophages isolated from SR-A$^{+/+}$ and SR-A$^{-/-}$ mice	Atherosclerosis and diabetes	Gluc-collagen binding to SR-A stimulates prostaglandins production	[45]
i. Apolipoprotein E (ApoE)$^{-/-}$ mice ii. RAW264.7 cells	Atherosclerosis	Visfatin induces modulated expression SR-A leading cholesterol accumulation in macrophages	[46]
i. Chinese hamster ovary cells ii. ApoE$^{-/-}$ mice iii.ApoE$^{-/-}$ SR-A$^{-/-}$ mice	Atherogenesis	Recombinant heat shock protein 27 leads to the down-regulation of SR-A expression, resulting in attenuated foam cell formation SR-A is required for heat shock protein 27-mediated atheroprotection *in vivo*	[51]
i. SR-A$^{-/-}$ mice ii. Chinese hamster ovary cells with the SR-A gene	Inflammation	Altered TLR4 signaling pathway and high levels of HDL in circulation	[52]
LPS-stimulated macrophage-like RAW264.7 cell line	Inflammatory stress	Up-regulated SR-A and dysregulated LDL receptor contribute to macrophage-derived foam cell formation	[49]
i. Wild type (WT)-C57BL/6J mice ii. SRA$^{-/-}$ mice iii. Phoenix cells human embryonic kidney293-TLR4/MD2-CD14 cells	Inflammation	SR-A down-regulates inflammatory gene expression in DCs by suppressing TLR4 induced the activation of NF-κB SR-A resulting in inhibition of TNF receptor-associated factor 6 dimerization and ubiquitination	[50]
i. Macrophages (J774/a) treated with Pam2CSK4, (TLR2 ligand) ii. Murine macrophage cell line J774 A.1 iii. Peritoneal macrophages from SR-A$^{-/-}$ mice (C57BL/10ScCr) iv. TLR4$^{-/-}$ and WT mice (C57BL/10ScCr)	Endotoxin-induced inflammatory responses	Up-regulation of TNF-α and IL-1β production in WT macrophages have no effect in either TLR4$^{-/-}$ or SR-A$^{-/-}$ macrophages in the presence of fucoidan Similarly, in the presence of fucoidan, LPS-induced NF-kappa-B inhibitor alpha phosphorylation, NF-κB binding activity and association between TLR4 and SR-A are significantly increase in WT macrophages compared with LPS stimulation alone It suggests that SR-A is needed for LPS-induced inflammatory responses in macrophages	[51]
Microglia and astrocytes	Alzheimer's disease	Promote glial phagocytosis of Aβ oligomer in Alzheimer's disease	[44]
i. Bone marrow-derived macrophages ii. Human embryonic kidney293 cell line	Diabetic retinopathy	Antagonism between SR-A and the receptor for advanced glycated end-product leads to the pathogenesis of diabetic retinopathy by nurturing a disease-prone macrophage phenotype	[53]
SR-A$^{-/-}$ nonobese diabetic mice	Human type 1 diabetes	Suppression of diabetes progression in SR-A$^{-/-}$ nonobese diabetic mice	[54]
i. WT-SR-A ii. SR-A$^{-/-}$ iii. WT-macro iv. Macro$^{-/-}$ v. SR-A and macro double knockout	Laser-induced choroidal neovascularization	SR-A contributes to choroidal neovascularization formation and inflammation in age-related macular degeneration	[55]
TGF-β1/SR-A$^{(-/-)}$ mice	Cerebrovascular amyloid	TGF-β1/SR-A$^{-/-}$ leads to cerebrovascular pathology at an earlier age (3 months) as compared with TGF-β1 mice	[56]
WT *vs.* SR-A$^{-/-}$ mice	Autoimmune encephalomyelitis, multiple sclerosis	SR-A deficiency leads to the reduction of pro-inflammatory cytokines such as IL-2, IFN-γ, IL-17 and IL-6 that play a major role in experimental autoimmune encephalomyelitis progression	[57]
SR-A$^{-/-}$ mice in two *in vivo* models of OVA and pancreatic cancer	Ovarian and pancreatic cancer	Inhibition of tumor cell invasion	[47]
i. SR-A$^{-/-}$ mice ii. OVA-expressing RM1 prostate tumor line	Prostate cancer	SR-A absence greatly enhances DCs-mediated cross-presentation of OVA antigen DCs deficiency in SR-A displays a increased expression of inflammatory cytokines and chemokines	[48]

are consistent with the hyperlipidemia-induced atherosclerosis[58]. Recently, PKC has been implicated as a regulator of oxLDL uptake and foam cell formation via the down-regulation of PKC-β while SR-A expression re-evaluates the role of PKC in oxLDL uptake and foam cell formation[59]. High glucose also increased IL-6 and IL-12 secretion and decreased IL-10 secretion. High glucose level increases the expression of SR-A, CD36 and lysyl oxidase-1, which in response enhances the oxLDL-uptake capacity of DCs[60].

8. Conclusion

Multifunctional traits of SR-A to regulate immune responses need further investigations to standardize high throughput approaches to overcome different pathologies. The overview of the data suggests that reuptake of lipid occurs because of the over expression of SR. It is important to dissect various regulators of endocytic pathway which influence increasing cell surface appearance of these receptors. Additionally, lesser internalization of the receptor and escape from degradation add another layer of complication that needs detailed investigation.

Conflict of interest statement

We declare that we have no conflict of interest.

Acknowledgments

The corresponding author sincerely thank Prof. Leticia Moreno-Fierros (Inmunidad en Mucosas, UBIMED, FES-Iztacala, Universidad Nacional Autonoma de Mexico) for her helpful suggestions during the structuring of the review.

References

[1] Wang JG, Aikawa M. Toll-like receptors and Src-family kinases in atherosclerosis-focus on macrophages. *Circ J* 2015; **79**(11): 2332-4.

[2] Adachi H, Tsujimoto M. Endothelial scavenger receptors. *Prog Lipid Res* 2006; **45**(5): 379-404.

[3] Yi H, Yu X, Gao P, Wang Y, Baek SH, Chen X, et al. Pattern recognition scavenger receptor SRA/CD204 down-regulates Toll-like receptor 4 signaling-dependent CD8 T-cell activation. *Blood* 2009; **113**(23): 5819-

28.

[4] Peiser L, Gordon S. The function of scavenger receptors expressed by macrophages and their role in the regulation of inflammation. *Microbes Infect* 2001; **3**(2): 149-59.

[5] Husemann J, Loike JD, Anankov R, Febbraio M, Silverstein SC. Scavenger receptors in neurobiology and neuropathology: their role on microglia and other cells of the nervous system. *Glia* 2002; **40**(2): 195-205.

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

[7] Michael DR, Davies TS, Laubertová L, Gallagher H, Ramji DP. The phosphoinositide 3-kinase signaling pathway is involved in the control of modified low-density lipoprotein uptake by human macrophages. *Lipids* 2015; **50**(3): 253-60.

[8] Platt N, Gordon S. Is the class A macrophage scavenger receptor (SR-A) multifunctional? -the mouse's tale. *J Clin Invest* 2001; **108**(5): 649-54.

[9] Greaves DR, Gordon S. The macrophage scavenger receptor at 30 years of age: current knowledge and future challenges. *J Lipid Res* 2009; **50**(S): S282-6.

[10] Zhu FG, Reich CF, Pisetsky DS. The role of the macrophage scavenger receptor in immune stimulation by bacterial DNA and synthetic oligonucleotides. *Immunology* 2001; **103**(2): 226-34.

[11] Hollifield M, Bou Ghanem E, de Villiers WJ, Garvy BA. Scavenger receptor A dampens induction of inflammation in response to the fungal pathogen *Pneumocystis carinii*. *Infect Immun* 2007; **75**(8): 3999-4005.

[12] Limmon GV, Arredouani M, McCann KL, Corn Minor RA, Kobzik L, Imani F. Scavenger receptor class-A is a novel cell surface receptor for double-stranded RNA. *FASEB J* 2008; **22**(1): 159-67.

[13] Bowdish DME, Gordon S. Conserved domains of the class A scavenger receptors: evolution and function. *Immunol Rev* 2009; **227**(1): 19-31.

[14] Nikolic DM, Cholewa J, Gass C, Gong MC, Post SR. Class A scavenger receptor-mediated cell adhesion requires the sequential activation of Lyn and PI3-kinase. *Am J Physiol Cell Physiol* 2007; **292**(4): 1450-8.

[15] Todt JC, Hu B, Curtis JL. The scavenger receptor SR-A I/II (CD204) signals via the receptor tyrosine kinase Mertk during apoptotic cell uptake by murine macrophages. *J Leukoc Biol* 2008; **84**(2): 510-8.

[16] Seimon TA, Obstfeld A, Moore KJ, Golenbock DT, Tabas I. Combinatorial pattern recognition receptor signaling alters the balance of life and death in macrophages. *Proc Natl Acad Sci USA* 2006; **103**(52): 19794-9.

[17] Amiel E, Alonso A, Uematsu S, Akira S, Poynter ME, Berwin B. Pivotal advance: toll-like receptor regulation of scavenger receptor-A-mediated phagocytosis. *J Leukoc Biol* 2009; **85**(4): 595-605.

[18] Xu WY, Wang L, Wang HM, Wang YQ, Liang YF, Zhao TT, et al. TLR2 and TLR4 agonists synergistically up-regulate SR-A in RAW264.7 through p38. *Mol Immunol* 2007; **44**(9): 2315-23.

[19] Ashkenas J, Penman M, Vasile E, Acton S, Freeman M, Krieger M. Structures and high and low affinity ligand binding properties of murine type I and type II macrophage scavenger receptors. *J Lipid Res* 1993; **34**(6): 983-1000.

[20] Matsumoto A, Naito M, Itakura H, Ikemoto S, Asaoka H, Hayakawa I, et al. Human macrophage scavenger receptors: primary structure, expression, and localization in atherosclerotic lesions. *Proc Natl Acad Sci USA* 1990; **87**(23): 9133-7.

[21] Bickel PE, Freeman MW. Rabbit aortic smooth muscle cells express inducible macrophage scavenger receptor messenger RNA that is absent from endothelial cells. *J Clin Invest* 1992; **90**(4): 1450-7.

[22] Elomaa O, Kangas M, Sahlberg C, Tuukkanen J, Sormunen R, Liakka A, et al. Cloning of a novel bacteria-binding receptor structurally related to scavenger receptors and expressed in a subset of macrophages. *Cell* 1995; **80**(4): 603-9.

[23] Andersson L, Freeman MW. Functional changes in scavenger receptor binding conformation are induced by charge mutants spanning the entire collagen domain. *J Biol Chem* 1998; **273**(31): 19592-601.

[24] Hohenester E, Sasaki T, Timpl R. Crystal structure of a scavenger receptor cysteine-rich domain sheds light on an ancient superfamily. *Nat Struct Biol* 1999; **6**(3): 228-32.

[25] Kosswig N, Rice S, Daugherty A, Post SR. Class A scavenger receptor-mediated adhesion and internalization require distinct cytoplasmic domains. *J Biol Chem* 2003; **278**(36): 34219-25.

[26] Singh N, Bhatia S, Abraham R, Basu SK, George A, Bal V, et al. Modulation of T cell cytokine profiles and peptide-MHC complex availability *in vivo* by delivery to scavenger receptors via antigen maleylation. *J Immunol* 1998; **160**(10): 4869-80.

[27] Fitzgerald ML, Moore KJ, Freeman MW, Reed GL. Lipopolysaccharide induces scavenger receptor A expression in mouse macrophages: a divergent response relative to human THP-1 monocyte/macrophages. *J Immunol* 2000; **164**(5): 2692-700.

[28] Hsu HY, Nicholson AC, Hajjar DP. Inhibition of macrophage scavenger receptor activity by tumor necrosis factor-alpha is transcriptionally and post-transcriptionally regulated. *J Biol Chem* 1996; **271**(13): 7767-73.

[29] Gough PJ, Greaves DR, Gordon S. A naturally occurring isoform of the human macrophage scavenger receptor (SR-A) gene generated by alternative splicing blocks modified LDL uptake. *J Lipid Res* 1998; **39**(3): 531-43.

[30] Albert ML, Sauter B, Bhardwaj N. Dendritic cells acquire antigen from apoptotic cells and induce class I-restricted CTLs. *Nature* 1998; **392**(6671): 39286-9.

[31] Platt N, Suzuki H, Kodama T, Gordon S. Apoptotic thymocyte clearance in scavenger receptor class A-deficient mice is apparently normal. *J Immunol* 2000; **164**(9): 4861-7.

[32] Huang H, Li X, Zhuang Y, Li N, Zhu X, Hu J, et al. Class A scavenger receptor activation inhibits endoplasmic reticulum stress-induced autophagy in macrophage. *J Biomed Res* 2014; **28**(3): 213-21.

[33] Ren D, Wang X, Ha T, Liu L, Kalbfleisch J, Gao X, et al. SR-A deficiency reduces myocardial ischemia/reperfusion injury; involvement of increased microRNA-125b expression in macrophages. *Biochim*

Biophys Acta 2013; **1832**(2): 336-46.

[34] Hu Y, Zhang H, Lu Y, Bai H, Xu Y, Zhu X, et al. Class A scavenger receptor attenuates myocardial infarction-induced cardiomyocyte necrosis through suppressing M1 macrophage subset polarization. B*asic Res Cardiol* 2011; **106**(6): 1311-28.

[35] Ma AZ, Zhang Q, Song ZY. TNFa alter cholesterol metabolism in human macrophages via PKC-θ-dependent pathway. *BMC Biochem* 2013; **14**: 20.

[36] Coller SP, Paulnock DM. Signaling pathways initiated in macrophages after engagement of type A scavenger receptors. *J Leukoc Biol* 2001; **70**(1): 142-8.

[37] Berwin B, Hart JP, Rice S, Gass C, Pizzo SV, Post SR, et al. Scavenger receptor-a mediates gp96/GRP94 and calreticulin internalization by antigen-presenting cells. *EMBO J* 2003; **22**(22): 6127-36.

[38] Delneste Y, Magistrelli G, Gauchat J, Haeuw J, Aubry J, Nakamura K, et al. Involvement of LOX-1 in dendritic cell-mediated antigen cross-presentation. *Immunity* 2002; **17**(3): 353-62.

[39] Harshyne LA, Zimmer MI, Watkins SC, Barratt-Boyes SM. A role for class A scavenger receptor in dendritic cell nibbling from live cells. *J Immunol* 2003; **170**(5): 2302-9.

[40] Granucci F, Petralia F, Urbano M, Citterio S, Di Tota F, Santambrogio L, et al. The scavenger receptor MARCO mediates cytoskeleton rearrangements in dendritic cells and microglia. *Blood* 2003; **102**(8): 2940-7.

[41] van Dijk R, Montenegro-Miranda PS, Riviere C, Schilderink R, ten Bloemendaal L, van Gorp J, et al. Polyinosinic acid blocks adeno-associated virus macrophage endocytosis *in vitro* and enhances adeno-associated virus liver-directed gene therapy *in vivo*. *Hum Gene Ther* 2013; **24**(9): 807-13.

[42] Lu H, Huang D, Yao K, Li C, Chang S, Dai Y, et al. Insulin enhances dendritic cell maturation and scavenger receptor-mediated uptake of oxidised low-density lipoprotein. *J Diabetes Complications* 2015; **29**(4): 465-71.

[43] Gordon S. Macrophage-restricted molecules: role in differentiation and activation. *Immunol Lett* 1999; **65**(1-2): 5-8.

[44] von Bernhardi R, Cornejo F, Parada GE, Eugenín J. Role of TGFβ signaling in the pathogenesis of Alzheimer's disease. *Front Cell Neurosci* 2015; **9**: 426.

[45] Nikolic DM, Vadali S, He B, Ware J, Kelly T, Post SR. Prostaglandins produced during class A scavenger receptor-mediated macrophage adhesion differentially regulate cytokine production. *J Leukoc Biol* 2015; doi: 10.1189/jlb.2A1014-471RR.

[46] Zhou FH, Pan YY, Huang ZY, Jia YH, Zhao XS, Chen YY, et al. Visfatin induces cholesterol accumulation in macrophages through up-regulation of scavenger receptor-A and CD36. *Cell Stress Chaperones* 2013; **18**(5): 643-52.

[47] Neyen C, Plüddemann A, Mukhopadhyay S, Maniati E, Bossard M, Gordon S, et al. Macrophage scavenger receptor a promotes tumor progression in murine models of ovarian and pancreatic cancer. *J Immunol* 2013; **190**(7): 3798-805.

[48] Guo C, Yi H, Yu X, Hu F, Zuo D, Subjeck JR, et al. Absence of scavenger receptor A promotes dendritic cell-mediated cross-presentation of cell-associated antigen and antitumor immune response. *Immunol Cell Biol* 2012; **90**(1): 101-8.

[49] Su T, Zhao L, Ruan X, Zuo G, Gong J. Synergistic effect of scavenger receptor A and low-density lipoprotein receptor on macrophage foam cell formation under inflammatory stress. *Mol Med Rep* 2013; **7**(1): 37-42.

[50] Yu X, Yi H, Guo C, Zuo D, Wang Y, Kim HL, et al. 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* 2011; **286**(21): 18795-806.

[51] Yu H, Ha T, Liu L, Wang X, Gao M, Kelley J, et al. Scavenger receptor A (SR-A) is required for LPS-induced TLR4 mediated NF-κB activation in macrophages. *Biochim Biophys Acta* 2012; **1823**(7): 1192-8.

[52] Drummond R, Cauvi DM, Hawisher D, Song D, Niño DF, Coimbra R, et al. Deletion of scavenger receptor A gene in mice resulted in protection from septic shock and modulation of TLR4 signaling in isolated peritoneal macrophages. *Innate Immun* 2013; **19**(1): 30-41.

[53] Ma K, Xu Y, Wang C, Li N, Li K, Zhang Y, at al. A cross talk between class a scavenger receptor and receptor for advanced glycation end-products contributes to diabetic retinopathy. *Am J Physiol Endocrinol Metab* 2014; **307**(12): E1153-65.

[54] Shimizu M, Yasuda H, Hara K, Takahashi K, Nagata M, Yokono K. The dual role of scavenger receptor Class A in development of diabetes in autoimmune NOD Mice. *PLoS One* 2014; **9**(10): e109531.

[55] Jawad S, Liu B, Li Z, Katamay R, Campos M, Wei L, et al. The role of macrophage class a scavenger receptors in a laser-induced murine choroidal neovascularization model. *Invest Ophthalmol Vis Sci* 2013; **54**(9): 5959-70.

[56] Lifshitz V, Weiss R, Levy H, Frenkel D. Scavenger receptor A deficiency accelerates cerebrovascular amyloidosis in an animal model. *J Mol Neurosci* 2013; **50**(1): 198-203.

[57] Levy-Barazany H, Frenkel D. Expression of scavenger receptor A on antigen presenting cells is important for CD_4^+ T-cells proliferation in EAE mouse model. *J Neuroinflammation* 2012; **9**: 120.

[58] Yamada S, Wang KY, Tanimoto A, Sasaguri Y. Novel function of histamine signaling in hyperlipidemia-induced atherosclerosis: histamine H1 receptors protect and H2 receptors accelerate atherosclerosis. *Pathol Int* 2015; **65**(2): 67-80.

[59] Kooij G, Braster R, Koning JJ, Laan LC, van Vliet SJ, Los T, et al. *Trichuris suis* induces human non-classical patrolling monocytes via the mannose receptor and PKC: implications for multiple sclerosis. *Acta Neuropathol Commun* 2015; **3**: 45.

[60] Lu H, Yao K, Huang D, Sun A, Zou Y, Qian J, et al. High glucose induces upregulation of scavenger receptors and promotes maturation of dendritic cells. *Cardiovasc Diabetol* 2013; **12**: 80.