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CONTEMPORARY REVIEW

Scavenger Receptors in Myocardial Infarction and Ischemia/Reperfusion Injury: The Potential for Disease Evaluation and Therapy

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ABSTRACT: Scavenger receptors (SRs) are a structurally heterogeneous superfamily of evolutionarily conserved receptors that are divided into classes A to J. SRs can recognize multiple ligands, such as modified lipoproteins, damage-associated molecular patterns, and pathogen-associated molecular patterns, and regulate lipid metabolism, immunity, and homeostasis. According to the literature, SRs may play a critical role in myocardial infarction and ischemia/reperfusion injury, and the soluble types of SRs may be a series of promising biomarkers for the diagnosis and prognosis of patients with acute coronary syndrome or acute myocardial infarction. In this review, we briefly summarize the structure and function of SRs and discuss the association between each SR and ischemic cardiac injury in patients and animal models in detail. A better understanding of the effect of SRs on ischemic cardiac injury will inspire novel ideas for therapeutic drug discovery and disease evaluation in patients with myocardial infarction.

Key Words: acute coronary syndrome ■ ischemia/reperfusion ■ myocardial infarction ■ scavenger receptor

Scavenger receptors (SRs) were first identified and defined by Goldstein and Brown in the 1970s because of their ability to recognize and internalize oxidized low-density lipoprotein (oxLDL), which belongs to damage-associated molecular patterns (DAMPs).[1] In recent years, additional members of the SR family have been gradually identified, and the range of ligands has also been expanded. At present, the definition of SRs has been extended to recognize a variety of endogenous and exogenous ligands, including DAMPs, pathogen-associated molecular patterns, lipoproteins, apoptotic cells, phospholipids, ferritin, advanced glycation end-products (AGEs), and advanced oxidation protein products.[2] Therefore, SRs have also been regarded as a subcategory of pattern recognition receptors. SRs are a structurally heterogeneous superfamily of evolutionarily conserved receptors. Based on structural and functional properties, SRs are divided into classes A to J, which have little or no structural resemblance.[3] However, the members within each class have a primary sequence similarity. SRs are usually defined as cell-surface receptors and are typically expressed on macrophages, regulating macrophage endocytosis and immune functions.[2] In addition, certain membrane SRs can be cleaved by exofacial proteases, which results in soluble forms of SRs that may be biomarkers for disease diagnosis and progression, such as soluble SR-A for rheumatoid arthritis.[4] Several SRs are also located inside the cell. A detailed description of the structures and classes of SRs has been summarized in several reviews,[2,5] and a brief introduction to these SRs is also

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Nonstandard Abbreviations and Acronyms

CXCL16	CXC chemokine ligand 16
DAMPs	damage-associated molecular patterns
ECs	endothelial cells
I/R	ischemia/reperfusion
LDLR	LDL receptor
LOX-1	lectin-like oxidized LDLR 1
oxLDL	oxidized low-density lipoprotein
RAGE	receptor for advanced glycation end-products
ROS	reactive oxygen species
SRs	scavenger receptors
STAT3	signal transducer and activator of transcription 3
UA	unstable angina

shown in Figure 1 (structure and location) and Table 1 (genetic locus and ligands).

Myocardial infarction (MI) and cardiac ischemia/reperfusion (I/R) injury remain leading causes of death worldwide, resulting in heavy economic burdens. After MI, tissue damage and necrosis initiate a series of pathological responses, including inflammation, oxidative stress, cardiomyocyte apoptosis, fibrosis, and angiogenesis. Although multiple drugs improve the outcomes of patients with MI, the disease burden from ischemic heart disease rose steadily from 1990 to 2019. Therefore, it is still imperative to develop novel medications for this condition. After MI or cardiac I/R injury, a mass of DAMPs, apoptotic cells, and debris accumulates in cardiac tissue, and a large number of immune cells, such as neutrophils and macrophages, infiltrate the ischemic heart. As described previously, SRs are usually located in macrophages and can bind to and recognize DAMPs and apoptotic cells. Therefore, SRs may play a critical role in the pathological process of cardiac ischemic injury. Previous studies have shown that several SRs, such as classes A, B, and E, exert significant effects on MI,[6–8] indicating the possible therapeutic potential of the SR family in patients with MI. In this review, the class of SRs will be briefly summarized, and the effects of SRs on MI and I/R injury will be discussed in detail, which may inspire novel ideas for treatments. Because SR class C does not exist in mammals,[2] our review mainly focuses on SR classes A, B, D, E, F, G, H, I, and J.

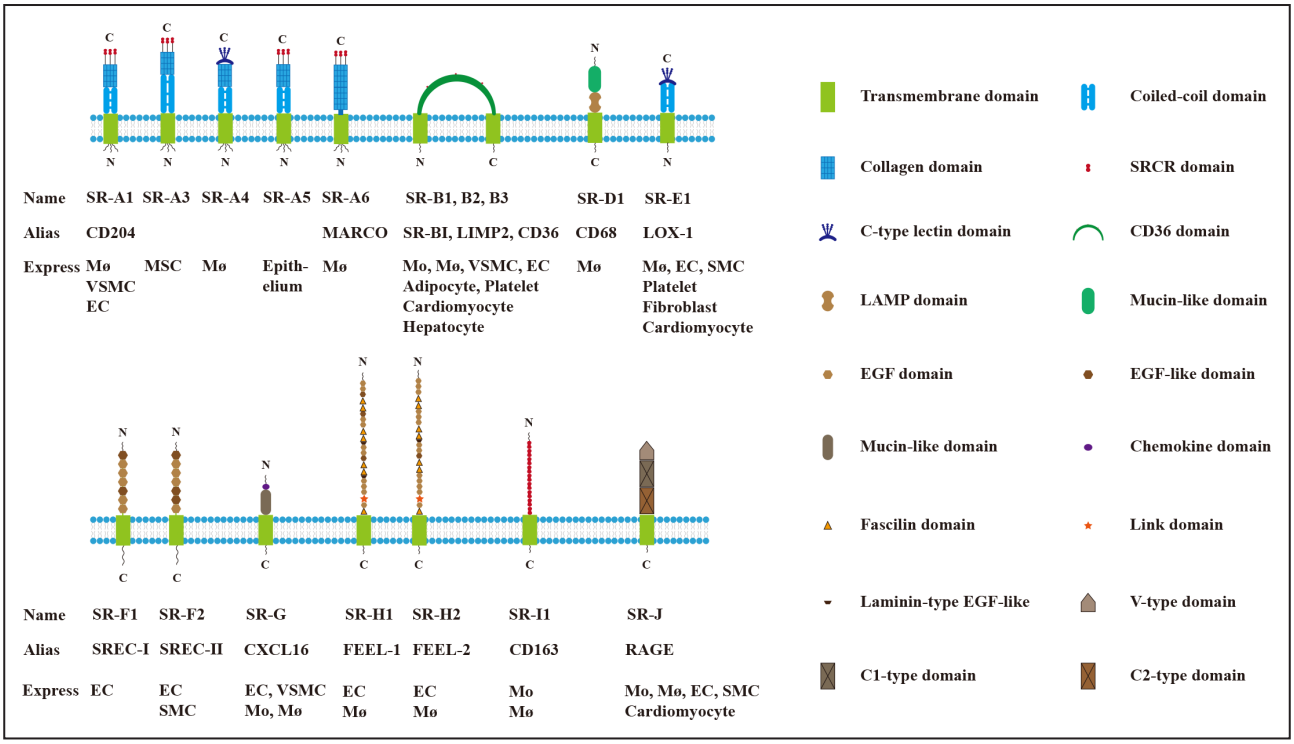

Figure 1. Schematic overview of SRs. SRs contain classes A, B, D, E, F, G, H, I, and J.
The structure and location cells of each SR are displayed in the figure. CXCL16 indicates CXC chemokine ligand 16; EC, endothelial cell; EGF, epidermal growth factor; FEEL-1, fasciclin, EGF-like, laminin-type EGF-like, and link domain-containing SR-1; FEEL-2, fasciclin, EGF-like, laminin-type EGF-like, and link domain-containing SR-2; LAMP, lysosome-associated membrane protein; LIMP2, lysosomal integral membrane protein-2; LOX-1, lectin-like oxidized LDLR 1; MARCO, macrophage receptor with collagenous structure; Mø, macrophage; Mo, monocyte; MSC, mesenchymal stem cell; RAGE, receptor for advanced glycation end-products; SMC, smooth muscle cell; SR, scavenger receptor; SRCR, scavenger receptor cysteine-rich domain; and VSMC, vascular smooth muscle cell.

Table 1. Genetic Locus and Ligands of Scavenger Receptors

Class of SRs	Receptors	Genetic locus in humans	Ligands
Class A	SR-A1	chromosome 8	oxLDL, acLDL, malondialdehyde LDL, maleylated LDL, phosphatidic acid, cholesterol, lysophosphatidylcholine, LPS, gram-positive and gram-negative bacteria, CRP
Class A	SR-A3	chromosome 8	No data available
Class A	SR-A4	chromosome 18	oxLDL, yeast, gram-positive and gram-negative bacteria
Class A	SR-A5	chromosome 8	Gram-positive and gram-negative bacteria, L-ferritin, haptoglobin-hemoglobin
Class A	SR-A6/MARCO	chromosome 1	oxLDL, acLDL, LPS, gram-positive and gram-negative bacteria
Class B	SR-BI/SR-B1	chromosome 12	acLDL, oxLDL, native LDL, very LDL, HDL, LPS, gram-negative bacteria and gram-positive bacteria, apoptotic cells
Class B	SR-B3/CD36	chromosome 7	acLDL, oxLDL, lipoteichoic acid and a diacylated lipopeptides, gram-negative bacteria, phosphatidylserine
Class B	SR-B2/lysosomal integral membrane protein-2	chromosome 4	Enterovirus 71, Coxsackie virus A7, A14 and A16, β-glucocerebrosidase
Class D	CD68	chromosome 17	oxLDL, phosphatidylserine-rich liposomes, intracellular adhesion molecule L
Class E	Lectin-like oxidized LDL receptor 1	chromosome 12	oxLDL, electronegative LDL, dysfunctional HDL, CRP, fibronectin, apoptotic cells, activated platelets, phosphatidylserine, phosphatidylinositol, polyanions, AGEs
Class F	SR-F1/SREC-I	chromosome 17	Gram-positive and gram-negative bacteria, hepatitis C virus, acLDL, oxLDL, carbamylated LDL, calreticulin
Class F	SR-F2/SREC-II	chromosome 22	Form heterodimers with SR-F1, suppressing the ligand-binding properties of SR-F1
Class G	CXC chemokine ligand 16	chromosome 17	oxLDL, phosphatidylserine, gram-positive and gram-negative bacteria, CXC chemokine receptor 6, eryptotic erythrocytes
Class H	SR-H1/FEEL-1	chromosome 3	acLDL, heat-shock protein 70, AGEs, gram-negative and gram-positive bacteria, phosphatidylserine
Class H	SR-H2/FEEL-2	chromosome 12	acLDL, AGEs, gram-negative and gram-positive bacteria
Class I	CD163	chromosome 12	Hemoglobin:haptoglobin complexes, tumor necrosis factor-like weak inducer of apoptosis, gram-positive and gram-negative bacteria
Class J	Receptor for advanced glycation end-product	chromosome 6	AGEs, high-mobility group protein 1, S100-proteins, DNA, lipopolysaccharide, microbial DNA

acLDL indicates acetylated LDL; AGEs, advanced glycation end product; CRP, C-reactive protein; FEEL, asciclin, EGF-like, laminin-type EGF-like, and link domain-containing SR;HDL, high density lipoprotein; LPS, lipopolysaccharide; oxLDL, oxidized low-density lipoproteins; and SRs, scavenger receptors.

ASSOCIATION BETWEEN EACH SR AND MI OR CARDIAC I/R INJURY

Effect of SR Class A on MI and I/R Injury

SR class A members, including SR-A1, SR-A3, SR-A4, SR-A5, and SR-A6 (also named MARCO [macrophage receptor with collagenous structure]), contain an N-terminal cytoplasmic domain, a single transmembrane region, and a large extracellular C-terminal domain that recognizes ligands. In the extracellular region, SR-A has a collagen domain, an α-helical coiled-coil domain (except for SR-A6), and a type-A SRCR (scavenger receptor cysteine-rich domain) or a CLEC (C-type lectin domain) (Figure 1).

The *SR-A1* (also named *CD204*) gene is located on chromosome 8 in both mice and humans and has been reported to be expressed on macrophages, vascular smooth muscle cells (SMCs), and endothelial cells (ECs).[2] The *SR-A3* gene is located on chromosome 8 in humans and can be expressed on mesenchymal stem cells.[9] Similarly, the *SR-A5* gene is located on chromosome 8 in humans and may be expressed on epithelial cells.[10] In addition, *SR-A5* is a receptor for ferritin-bound iron. *SR-A4* (a gene located on human chromosome 18) contains a CLEC domain instead of an SRCR domain in other SR-A members and can be expressed on macrophages and in the liver and spleen. *MARCO* (a gene located on human chromosome 1) is mainly expressed on macrophages and plays a critical role in macrophage phagocytosis (Figure 1; Table 1).

Previous studies have suggested that SR class A is not only involved in the recognition and clearance of modified lipids (such as oxLDL) but also participates in the regulation of inflammation in several diseases, such as atherosclerosis and chronic obstructive pulmonary disease.[11,12] To evaluate the association between SR-A$^+$ monocytes and vulnerable plaques, Emura et al established an SR-A index, in which the upper normal limit of

SR-A$^+$ monocytes in 10 high-power fields of peripheral blood smear samples was 30 cells. The researchers revealed that a high SR-A index (> or =30) was associated with an indication of disrupted, fissured, or eroded plaques in patients with acute coronary syndrome (ACS).[13] An increase in SR-A$^+$ cells may be a useful indicator of the presence of platelet thrombi that are associated with the presence of coronary artery stenosis.[14] These findings suggested that SR class A may have a critical regulatory effect on ischemic cardiac injury in patients. In an animal model of ischemic cardiac injury, Hu et al generated deficient mice (SR-A1$^{-/-}$) and found that SR-A1 deficiency could promote M1 macrophage polarization, increase proinflammatory cytokine production (including TNF-α [tumor necrosis factor-α], interleukin [IL]-1β, and IL-6), and exacerbate cardiac dysfunction in mice after MI. Interestingly, transplantation with bone marrow from wild-type mice reversed M1 polarization and improved cardiac function in SR-A1$^{-/-}$ mice after MI[7] (Figure 2A). In another experimental MI mouse model, SR-A1 deficiency exacerbated myocardial remodeling and increased the risk of cardiac rupture, and the mechanisms might involve a reduction in IL-10 production and an increase in TNF-α levels[15] (Figure 2A). Therefore, SR-A1 may have a positive effect on ischemic cardiac injury in patients. However, in a mouse model of myocardial I/R injury, Ren et al[16] concluded that SR-A1 deficiency reduced infarct size and improved I/R injury by targeting the p53-mediated apoptotic signaling pathway (Figure 2A). SR-A1 deficiency inhibited hypoxia/reoxygenation-induced nuclear factor-κB activation, MCP-1 (monocyte chemoattractant protein-1) production, and caspase-3/7 hyperactivity in macrophages, and miR-125b may play a critical role in this process, because miR-125b expression was significantly increased in SR-A1-deficient macrophages, and transfection of wild-type macrophages with miR-125b mimics reversed caspase-3/7 hyperactivity and the increase in p-53/bax expression in macrophages challenged with hypoxia/reoxygenation injury[16] (Figure 2A). In addition, a clear protective effect of miR-125b against MI and I/R injury through cell apoptotic pathways has been reported in several previous studies.[17,18] Therefore, SR-A1 deficiency in macrophages may result in the reversal of inflammation, contributing to the attenuation of cardiac I/R injury. However, the effect of SR-A1 on cardiac I/R injury is opposite to the effect of SR-A1 on MI, and the reason

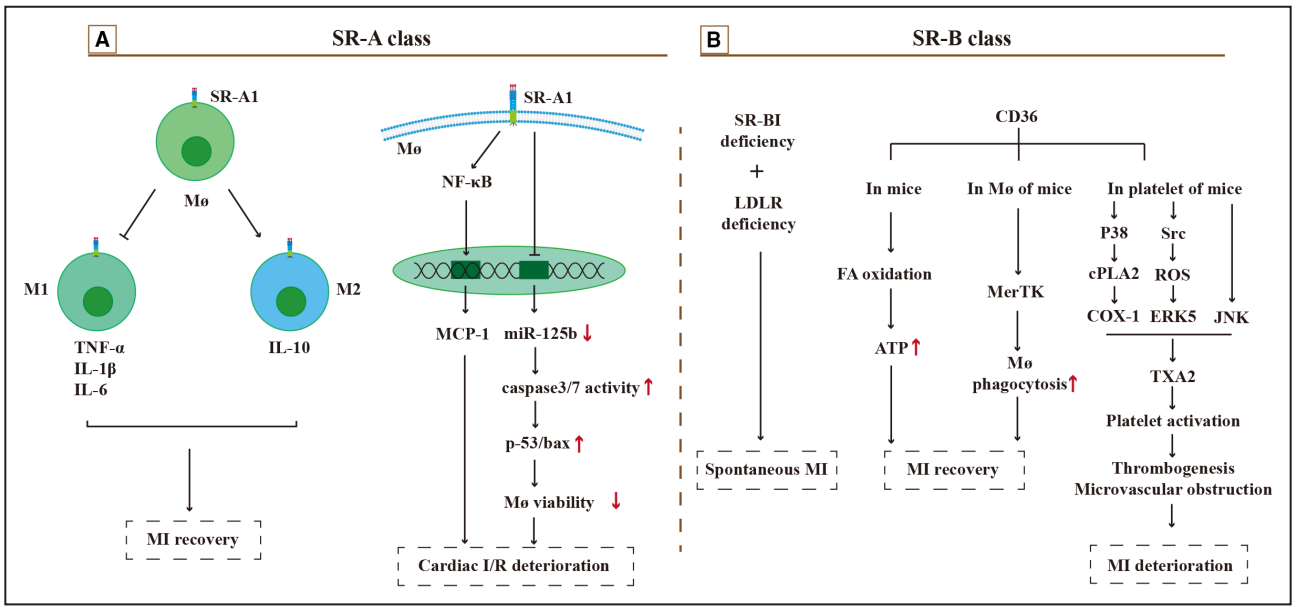

Figure 2. The effect of SR A class and B class in MI and cardiac I/R injury.
A, SR-A1 inhibits M1 polarization, reduces proinflammatory cytokine production (including TNF-α [tumor necrosis factor-α], IL-1 β, and IL-6), promotes M2 polarization, and increases IL-10 synthesis, contributing to the MI recovery; inversely, SR-A1 activates nuclear factor-κB/MCP-1 pathway and regulates miR-125b-caspase3/7-P53/bax apoptotic pathway in Mø, leading to the deterioration of cardiac I/R injury; therefore, SR-A1 has a complex effect on cardiac ischemic injury, and the effects of the other SR-A class members on cardiac ischemic injury still remain unknown. **B**, The double deficiency of SR-BI and LDLR leads to the occurrence of spontaneous MI, indicating that SR-BI may play a protective role in MI; in mice, CD36 is needed for maintaining FA oxidation and ATP production, which contributes to MI recovery; in addition, macrophage CD36 is needed for maintaining effective macrophage phagocytosis, which leads to the attenuation of MI; however, in platelet, CD36 activates TXA2 through P38/cPLA2/COX-1, Src/reactive oxygen species/ERK5, and JNK pathways, which lead to the activation of platelet, thrombogenesis, microvascular obstruction, and MI deterioration. COX-1 indicates cyclooxygenase 1; cPLA2, calcium-dependent cytosolic phospholipase A2; ERK5, extracellular-signal-regulated kinase 5; FA, fatty acid; IL, interleukin; I/R, ischemia/reperfusion; JNK, c-Jun N-terminal kinase; LDLR, low-density lipoprotein receptor; MCP-1, monocyte chemoattractant protein-1; MI, myocardial infarction; Mø, macrophages; SR, scavenger receptor; and TXA2, thromboxane A2.

may be associated with the different immune microenvironments in different animal models. In addition, differences in SR-A1 expression in cells may also alter the effect of SR-A1 on animal models, and identifying the main cells that express SR-A1 and subsequently using cell-specific SR-A1-knockout mice may be a promising strategy to clarify the effect of SR-A1 on MI and cardiac I/R injury. In addition, as research on SR class A is progressing, the effects of several other members of the SR class A family on MI and cardiac I/R injury are still unknown and need to be examined.

Effect of SR Class B on MI and I/R Injury

SR class B members are composed of a C-terminal cytoplasmic region, an N-terminal cytoplasmic region, 2 transmembrane domains, and a large highly glycosylated extracellular domain and include SR-BI (also named SR-B1), CD36 (SR-B3), and LIMP2 (lysosomal integral membrane protein-2, also named SR-B2)[2] (Figure 1). Typically, SR class B recognizes extracellular signals through the highly glycosylated extracellular domain and subsequently activates intracellular signaling pathways through the 2 cytoplasmic domains, playing a critical role in multiple physiological and pathological mechanisms, especially lipid metabolism.

In brief, *SR-BI* (a gene located on chromosome 12 in humans) is a high-affinity receptor for high-density lipoprotein (HDL) (Table 1), promotes the efflux of cholesterol from peripheral tissues to the liver, and plays a positive role in the uptake of HDL-associated cholesterol esters in hepatocytes.[19] In addition, SR-BI can also be expressed on macrophages, ECs, SMCs, keratinocytes, and adipocytes[19] (Figure 1) and mediates numerous biological processes. Along with the transport of HDL, SR-BI can promote the clearance of LDL, very LDL, and apolipoprotein A, contributing to the attenuation of atherosclerosis.[20] *CD36* (a gene located on chromosome 7 of humans) is expressed on macrophages, monocytes, ECs, SMCs, platelets, and cardiac myocytes (Figure 1; Table 1) and has been reported to play an important role in inflammation, angiogenesis, and atherosclerosis by binding different ligands.[21] In macrophages, oxLDL can increase CD36 expression, and CD36 recognizes and facilitates the endocytosis of oxLDL, resulting in the development of foam cells and the progression of atherosclerosis.[22] On the other hand, the interaction between CD36 and oxLDL can increase proinflammatory cytokine production and facilitate M1 polarization, which worsens atherosclerosis.[23] The *LIMP2* gene is located on human chromosome 4, and this receptor can be expressed in macrophages and hepatocytes (Figure 1; Table 1). *LIMP2* may regulate the export of cholesterol into the bile, contributing to reducing hepatocyte burden.

A previous study showed that *SR-BI* gene variants exhibited a specific distribution in patients with a history of early MI, suggesting that *SR-BI* may play an important role in MI and that the specific variants may be involved in dyslipidemia.[24] The soluble form of CD36 (sCD36) is found in plasma and is a predictor of several metabolic disorders, such as dyslipidemia, insulin resistance, and steatosis. Parra-Reyna et al[25] showed that sCD36 was significantly higher in patients with ST-segment–elevation MI (STEMI) than in patients with unstable angina (UA), indicating that sCD36 plasma levels may be associated with the clinical spectrum of patients with MI. However, in another study in which 1516 participants with chronic kidney disease were followed for 4 years, plasma concentrations of sCD36 were not associated with an increased risk of the defined or predefined composite cardiovascular end point and all-cause mortality.[20] However, increased plasma concentrations of CD5 L could be a predictor of an increased risk of cardiovascular events in these patients. Overall, sCD36 may be a predictive or diagnostic marker for patients with MI, although further clinical studies are necessary in the future (Table 2).

Because SR-BI was identified as a high-affinity receptor for HDL, the association between SR-BI and atherosclerosis has been well studied and reviewed. Typically, SR-BI plays a protective role in atherosclerosis and may be a promising therapeutic target. In addition to HDL metabolism, SR-BI also affects inflammation and immune disorders.[26] For example, in asthma, SR-BI could inhibit pulmonary neutrophilic inflammation and IL-17A production, possibly by maintaining adrenal function.[27] Wei et al[28] showed that cholesterol and HDL components could bind the S1 subunit of SARS-2-S, and subsequently, SR-BI could promote SARS-CoV-2 entry into angiotensin-converting enzyme 2-expressing cells and induce a series of inflammatory responses favoring HDL-SARS-CoV-2 binding. These reports suggested that SR-BI, which is a pattern recognition receptor, plays a critical role in lipid metabolism and inflammation, indicating its possible effect on MI or cardiac I/R injury. LDL receptor (LDLR) or apolipoprotein E deficiency is used to establish atherosclerosis animal models, and SR-BI ablation further significantly increases the progression of atherosclerosis.[29] After being fed a high-cholesterol diet for 12 weeks, some SR-BI/LDLR double-knockout mice experienced spontaneous MI, but MI was not detected in LDLR-knockout mice[29] (Figure 2B). Double-knockout-induced spontaneous MI in mice is consistent with the clinical mechanism of MI and may be a promising animal model for MI research in the future. This study also indicates that SR-BI plays a protective role in MI; however, the association between SR-BI and MI induced by ligation of the anterior descending branch or I/R in animal models remains unknown.

In 2003, Irie et al[30] first investigated the association between CD36 and MI. CD36 plays a critical role in

Table 2. The Soluble Types of Several SRs May Be a Series of Promising Biomarkers for the Diagnosis and Prognosis of Patients With ACS or AMI

Soluble SRs	Occurrence risk of ACS or AMI in population	Expression in patients with ACS or AMI	Possible biomarkers for patients with ACS or AMI	
			Diagnosis	Prognosis
Soluble CD36	N/A	Increase in plasma[25]	N/A, possible	N/A
Soluble lectin-like oxidized low-density lipoprotein receptor 1	N/A	Increase in plasma or serum[44–47]; Increase in coronary thrombi[47]	Yes, especially in the early stage[72–74]	Yes, higher levels indicate poor prognosis[48,49]
sCXCL16	Yes, higher levels indicate MI occurrence risk[62]	Increase in blood[60,61]	N/A, possible	Yes, admission levels of sCXCL16 indicate poor prognosis[63,64]
Soluble CD163	N/A	No change[73]	N/A	N/A
Soluble receptor for advanced glycation end-products	N/A	Decrease in blood[81–83]	N/A, possible	Yes, but complex: Higher levels in the early and late stage indicate poor prognosis and better outcome, respectively[85]; Lower levels indicate post-percutaneous coronary intervention restenosis[86]; Circulating levels inversely correlated with basal cardiac function after ST-segment–elevation myocardial infarction, had no relationship with 6 months prognosis.[87]

ACS indicates acute coronary syndrome; AMI, acute myocardial infarction; N/A, not available; PCI, sCXCL16, soluble CXC chemokine ligand 16; and SRs, scavenger receptors.

the transport and uptake of fatty acids that provide a large amount of cardiac energy. CD36 deficiency reduces fatty acid oxidation and the stores of glycogen, triglycerides, and ATP in the heart, reducing energy supply and dampening the recovery of MI in mice in the early stage. The administration of a medium-chain fatty acid (caprylic acid) that did not require CD36 could improve cardiac energy supply and cardiac function in CD36-deficient mice after MI[30] (Figure 2B). In addition, pretreatment with EP80317, a selective synthetic peptide ligand of CD36, reduced infarct size and attenuated cardiac dysfunction after I/R injury.[31] Considering the protective effect of EP80317 on atherosclerosis,[32] CD36 ligands such as EP80317 may be promising treatments for coronary heart disease. Lindsey et al[33] showed that CXCL4 administration through a mini-pump reduced the survival rate and exacerbated cardiac dysfunction in mice 5 to 7 days after MI, and the mechanism was associated with reducing macrophage phagocytosis. In macrophages, CXCL4 impaired phagocytosis by reducing the expression levels of the phagocytosis receptor CD36, which could be cleaved in an MMP9 (matrix metalloproteinase-9)-dependent manner, impairing inflammation resolution.[33] In another animal study,[8] CD36 was shown to be expressed on cardiac Ly6c^{-hi} monocytes. Cd36$^{+/+}$ mice were irradiated and then received bone marrow transplantation from CD36$^{+/+}$ and CD36$^{-/-}$ donors. The results showed that mice that received CD36$^{+/+}$ bone marrow had smaller infarct sizes and higher cardiac ejection fractions, suggesting that the myeloid receptor CD36 is necessary for cardiac repair after MI. CD36 is required to maintain the expression of macrophage MerTK (c-mer tyrosine kinase) and Nr4a1 in cardiac macrophages, both of which are critical for macrophage phagocytosis.[8] Therefore, the myeloid receptor CD36 can attenuate cardiac dysfunction after MI by maintaining effective macrophage phagocytosis and inflammation resolution (Figure 2B). PCSK9 (proprotein convertase subtilisin/kexin 9), a serine protease in the plasma, can increase plasma LDL cholesterol levels by degrading LDLR and has been reported to play a critical role in thrombosis and MI.[34] Plasma PCSK9 recognizes platelet CD36 and activates downstream signaling pathways, including the P38/cPLA2 (calcium-dependent cytosolic phospholipase A2)/COX1 (cyclooxygenase 1) pathway, Src/reactive oxygen species/ERK5 (extracellular-signal-regulated kinase 5) pathway, and JNK (c-Jun N-terminal kinase) pathway, all of which subsequently activate TXA2 (thromboxane A2), leading to platelet activation and thrombogenesis. In addition, plasma PCSK9 can also induce reactive oxygen species production and P38 MAPK (mitogen-activated protein kinase) pathway activation in platelets by binding to the receptor CD36, resulting in platelet activation, microvascular obstruction, and subsequent MI deterioration. The depletion of CD36 could reverse PCSK9-mediated exacerbation of cardiac dysfunction after MI[34] (Figure 2B). This study suggested that the platelet receptor CD36 may contribute to MI exacerbation, which is opposite to the effect of the myeloid receptor CD36. Therefore, CD36 in different cells may play distinct roles in MI and cardiac I/R injury.

Effect of SR Class D on MI and I/R Injury

The *SR-D1* gene (also named CD68) is located on human chromosome 17 (Table 1). It is composed of an extracellular region (including an N-proximal mucin-like region), a proline-rich hinge region and a LAMP (lysosome-associated membrane glycoprotein) domain, a single transmembrane region and a short cytoplasmic region and can be expressed on monocytes, macrophages, dendritic cells, and osteoclasts[35] (Figure 1). CD68 is regarded as a specific marker of macrophages and plays a critical role in the regulation of inflammation. The association between $CD68^+$ monocytes/macrophages and MI has been well investigated,[36] but the functional role of CD68 in MI has remained unclear. During the early stage of MI, a large number of $CD68^+$ monocytes/macrophages infiltrate the infarct tissue, and depleting these cells ameliorates MI or I/R injury. However, during the late stage of MI, macrophages are indispensable for the reparative process in the heart.

Effect of SR Class E on MI and I/R Injury

SR class E 1 (SR-E1) is also known as LOX-1 (lectin-like oxidized LDLR 1) and was first identified by Sawamura et al[37] in 1997. In this study, the authors successfully identified a cDNA encoding an endothelial receptor for oxLDL and designated it LOX-1. LOX-1 is a 50-kDa transmembrane glycoprotein composed of a short N-terminal cytoplasmic region, a single transmembrane region, and an extracellular domain that contains a coiled-coil "neck" region and a C-type lectin-like domain (Figure 1). The *LOX-1* gene is located on human chromosome 12 within a region that is enriched for genes involved in the innate immune response (Table 1). LOX-1 can be expressed on macrophages, ECs, SMCs, platelets, fibroblasts, and cardiomyocytes (Figure 1). Except for oxLDL, the ligands of LOX-1 still include other modified lipoproteins (electronegative LDL, dysfunctional HDL), proteins (CRP [C-reactive protein], fibronectin), cells (apoptotic cells, activated platelets), phospholipids (phosphatidylserine, phosphatidylinositol), polyanions, and advanced glycation end products[38] (Table 1). By binding to LOX-1, oxLDL can not only be internalized but also induce intracellular oxidative stress, the inflammatory response, and cell apoptosis. In endothelial cells, oxLDL induces cell apoptosis by promoting endoplasmic reticulum stress, which is abolished by the administration of an anti-LOX-1 antibody.[39] In addition, oxLDL/LOX-1 can enhance the activation of arginase II and subsequently reduce the expression of nitric oxide synthase, which leads to a reduction in nitric oxide synthesis and endothelial dysfunction.[40] Besler et al[41] revealed that disease-modified dysfunctional HDL recognizing LOX-1 could promote the macrophage inflammatory response and induce endothelial dysfunction. CRP not only increases LOX-1 expression in endothelial cells but also engages LOX-1, inducing monocyte-endothelial cell adhesion and increasing vascular permeability in vivo.[42] For apoptotic cells, LOX-1 located in the membrane of endothelial cells has been reported to play a critical role in mediating the phagocytosis of apoptotic cells.[43] In summary, by binding different ligands, LOX-1 plays an important role in vascular dysfunction, oxidative stress, and inflammation, suggesting the possible regulatory effect of LOX-1 on cardiac ischemic injury.

In recent years, the association between LOX-1 and myocardial ischemic disease has been gradually investigated. sLOX-1 (soluble LOX-1) is derived from the proteolytic degradation of the extracellular domain of cell-bound LOX-1 and can be detected in serum or plasma. Several clinical studies have shown that high blood levels of sLOX-1 are associated with acute MI (AMI) or ACS.[44–47] Hayashida et al[46] showed that plasma sLOX-1 levels were significantly increased in patients with ACS, and at a cutoff value of 1.0 ng/mL, plasma sLOX-1 could indicate ACS in other groups with a sensitivity of 81% and specificity of 75%. sLOX-1 could also differentiate ACS without ST elevation and ACS without troponin-T elevation from patients without ACS with a sensitivity of 91% and specificity of 83%, respectively. In addition, in ACS, the peak values of plasma sLOX-1 occurred earlier than those of troponin-T. In another study, plasma sLOX-1 levels were significantly higher in patients with STEMI (median [25th, 75th] percentiles: 241.0 [132.3, 472.2] pg/mL) and in patients with non-STEMI (NSTEMI) (47.3 [92.9, 262.4] pg/mL) than in patients with nonacute MI (non-AMI) (64.3 [54.4, 84.3] pg/mL).[44] At the optimal cutoff value of 91.0 pg/mL, plasma sLOX-1 could identify STEMI with 89.6% sensitivity and 82.4% specificity and identify NSTEMI with 79.5% sensitivity and 82.4% specificity. Importantly, the diagnostic sensitivity of plasma sLOX-1 for STEMI on admission (89 minutes after onset) was significantly higher than that of plasma H-FABP (heart-type fatty acid binding protein), myoglobin, troponin-T, or CK-MB (creatine kinase-MB; 93% versus 78% versus 70% versus 56% versus 33%, respectively), indicating that compared with myoglobin, troponin-T, and CK-MB, sLOX-1 was a more reliable biomarker for AMI diagnosis in the early stage. In addition, compared with that in healthy donors, the sLOX-1/oxLDL ratio (median, 64.6 versus 25.29) was significantly increased in patients with AMI within the first 6 hours of chest pain.[45] The area under the curve of the sLOX-1/oxLDL ratio for MI diagnosis was 0.714 (95% CI, 0.583–0.846, P=0.004), and the sensitivity and specificity were 70% and 67%, respectively, at a cutoff value of 42.46. Except for plasma sLOX-1, the expression levels of sLOX-1 and LOX-1 were also measured in coronary thrombi from patients with MI. Compared

with those in patients with NSTEMI, sLOX-1 levels and the sLOX-1/membrane LOX-1 ratio were significantly increased in patients with STEMI,[47] indicating that LOX-1 was associated with the severity of thrombosis in coronary arteries. Based on these studies, we hypothesize that sLOX-1 may be a promising biomarker for the diagnosis of ACS and AMI and that targeting LOX-1 may be useful for regulating thrombi formation and progression. However, clinical studies with larger sample sizes are needed to confirm this hypothesis (Table 2).

In a prospective cross-sectional study, 320 patients with ACS were selected, and the results showed that sLOX-1 cutoff values of 1.75 and 1.35 ng/mL could be used to predict major adverse cardiac events in hospitals in patients with STEMI and in patients with unstable angina/NSTEMI, respectively, indicating that blood sLOX-1 levels could be used as a novel biomarker for prognosis in patients with ACS.[48] Another prospective cohort study recruited 153 consecutive patients with STEMI who were admitted within 24 hours of disease onset. Of these patients, 144 accepted primary percutaneous coronary intervention (PCI) and were divided into 2 groups according to the median value (71 pg/mL) of plasma sLOX-1 levels. After patients were followed for a median of 1156 days, cardiovascular mortality and the recurrent MI rate were observed. The results showed that cardiovascular mortality and the recurrent MI rate were significantly higher in the group with sLOX-1 values higher than the median, and plasma sLOX-1 values above the median might be an independent predictor for all-cause mortality in patients with STEMI.[49] To evaluate the association between sLOX-1 and PCI-related periprocedural MI, 214 stable patients undergoing elective native single-vessel PCI were enrolled in a study and divided into 2 groups according to whether PCI-related periprocedural MI occurred. The results revealed that serum sLOX-1 levels were higher in patients with PCI-related periprocedural MI than in patients without PCI-related periprocedural MI, suggesting that circulating sLOX-1 levels may be a predictive marker of the perioperative prognosis of stable patients undergoing live native single-vessel PCI.[50] In summary, sLOX-1 may have good application prospects in the prognostic assessment of MI in patients (Table 2).

Because of the important association between LOX-1 and MI, animal studies have been performed to verify the effect and examine the underlying mechanisms. Ishino et al[51] revealed that the expression levels of LOX-1, MMP9, and MCP-1 were increased in the atherosclerotic plaques of rabbits and that LOX-1 expression was positively associated with MM9 expression and the plaque instability index. Therefore, the authors indicated that LOX-1 may be associated with the presence of unstable plaques and contribute to the occurrence of AMI. Li et al[52] showed that LOX-1 expression was significantly increased in the myocardial tissue of rats after cardiac I/R injury and that inhibiting LOX-1 with a neutralizing antibody could reduce the production of MMP-1 and adhesion molecules through P38 MAPK (mitogen-activated protein kinase) signaling, leading to improvements in cardiac I/R injury (Figure 3A). As described previously,[53] LOX-1 SNPs were associated with MI in patients. In an animal study, Mango et al[54] detected intronic SNPs linked to MI and found a novel functional splicing isoform of the *LOX-1* gene known as LOXIN (lacking exon 5). In vitro, LOXIN dose-dependently reversed LOX-1-induced apoptosis, which may provide a therapeutic approach for preventing atherosclerotic plaque rupture and MI injury. In addition, LOX-1 ablation in mice confirmed the negative effect of LOX-1 on ischemic cardiac injury.[55] LOX-1 ablation could attenuate cardiac injury and dysfunction in mice with MI, inhibit the renal inflammatory response, and improve MI-induced renal function[55] (Figure 3A). Previous studies indicated that LOX-1 depletion could attenuate myocardial fibrosis in aged hypertensive mice and inhibit proinflammatory M1 macrophage polarization in vitro.[6] Because fibrosis and the inflammatory response play important roles in myocardial remodeling after MI or I/R injury, LOX-1 inhibition may improve myocardial remodeling after ischemic cardiac injury.

In summary, circulating sLOX-1 may be a promising biomarker for the diagnosis of early AMI and the short-term and long-term prognosis of patients with AMI. Inhibiting LOX-1 through different approaches can attenuate cardiac injury and myocardial remodeling after MI or I/R injury.

Effect of SR Class F on MI and I/R Injury

SR class F includes SR-F1 (also named SREC-I) and SR-F2 (also named SREC-II). *SREC-I* is located on human chromosome 17, whereas *SREC-II* is located on human chromosome 22 (Table 1). Both SREC-I and SREC-II contain an extracellular region that is composed of several EGF (epidermal growth factor)-like cysteine-rich motifs, a single transmembrane region and a large cytoplasmic domain[35] (Figure 1). SREC-I is typically expressed on ECs and macrophages, whereas SREC-II is mainly expressed on ECs and SMCs (Figure 1). Previous studies revealed that SREC-I in ECs could recognize modified LDL, such as oxLDL and acetylated LDL, and play a critical role in atherosclerosis.[56] In addition, SREC-I could be increased after *Aspergillus fumigatus* stimulation, and SREC-I inhibition mitigated proinflammatory factor production in ECs, suggesting that SREC-I may regulate inflammation.[57] In contrast to SREC-I, SREC-II has little ability to take up modified LDL but can interact with SREC-I in a strong heterophilic manner through its extracellular

EGF-like repeat domains. However, the association between SR-F and ischemic cardiac injury remains unknown.

Effect of SR Class G on MI and I/R Injury

SR class G (SR that binds phosphatidylserine and oxidized lipoprotein) is also known as CXCL16 (CXC chemokine ligand 16). The *CXCL16* gene is located on chromosome 17 in humans and can be expressed in monocytes, macrophages, ECs, and vascular SMCs[58] (Figure 1; Table 1). CXCL16 is composed of an N-terminal extracellular domain (containing a chemokine-related motif and a mucin-like stalk part), a single transmembrane region, and a short cytoplasmic domain. The membrane-bound form CXCL16 can be cleaved by disintegrin-like metalloproteases to produce a soluble form known as sCXCL16. CXCL16 mediates the recognition and engulfment of oxLDL and plays a critical role in lipid metabolism and atherosclerosis.[59] In recent years, the effect of CXCL16 on MI or I/R injury has been studied.

In a clinical study, 20 patients with AMI, 20 patients with UA, and 20 healthy donors were recruited, and the expression levels of CXCL16 in monocytes in the peripheral blood in each group were examined. The results showed that sCXCL16 levels were significantly higher in patients with AMI and UA than in controls.[60] In the PENN-CATH case–control study (a study from the University of Pennsylvania Medical Center which studies the association of biochemical and genetic factors with coronary artery disease in subjects undergoing cardiac catheterization), 196 patients with ACS and 235 control patients were enrolled, and the results showed that circulating sCXCL16 was obviously higher in patients with ACS.[61] These studies indicate the close association between sCXCL16 and ACS. To evaluate the predictive effect of sCXCL16 on the risk of MI, a case–control study nested within a population-based HUNT2 cohort study in Norway was performed. A total of 58 761 participants without cardiovascular disease were followed for a first MI occurrence, and during the 11.3 years of follow-up, a total of 1587 patients with MI were registered. Interestingly, circulating sCXCL16 levels were significantly higher in patients with MI occurrence (median [25th, 75th]: 9.9 [7.2, 12.6] ng/mL) than in participants without MI occurrence (9.6 [6.9, 12.3] ng/mL). After adjusting for multiple risk factors, compared with participants in the lowest quartile of circulating sCXCL16 levels, MI risk (odds ratio [OR], 1.46 [95% CI, 1.19–1.79]) was significantly increased among participants in the highest quartile.[62] Therefore, circulating sCXCL16 may be a reliable indicator for assessing clinical cardiovascular risk, but other prospective cohort studies are needed to confirm this conclusion. To evaluate the prognostic value of sCXCL16 in patients with ACS or AMI, 3 clinical studies were performed. Jansson et al[63] conducted a study in which 1351 patients with a diagnosis of UA, NSTEMI, or STEMI were recruited, and circulating levels of sCXCL16 in blood samples were measured within 24 hours of admission. After 80 months of follow-up, a total of 377 dead patients were examined. After adjusting for multiple cardiovascular risk factors, sCXCL16 levels within 24 hours of admission provided a strong independent predictor of long-term mortality in patients with ACS. In another clinical study, 5142 patients with ACS from the PLATO (A Comparison of Ticagrelor (AZD6140) and Clopidogrel in Patients With Acute Coronary Syndrome) trial were recruited, and composite end points, including cardiovascular death, spontaneous MI, or stroke,

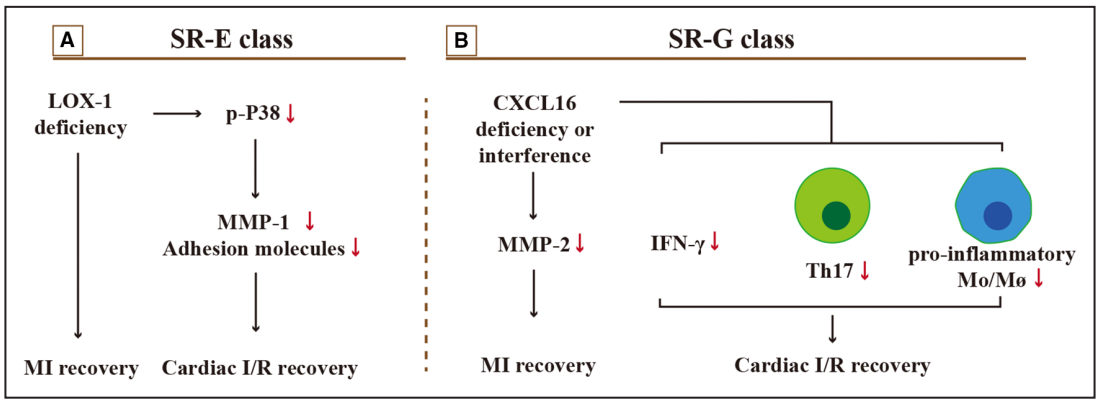

Figure 3. The effect of SR E class and G class in MI and cardiac I/R injury.
A, The deficiency of SR-E1, also named lectin-like oxidized LOX-1 (low-density lipoprotein receptor 1), protects from MI injury and attenuates cardiac I/R injury through inhibiting P38 phosphorylation and reducing the production of MMP-1 and adhesion molecules. **B**, The deficiency or interference of CXCL16 contributes to MI recovery through inhibiting MMP-2 production; in addition, the deficiency or interference of CXCL16 can reduce IFN-γ production, inhibit Th17 cells, and reduce proinflammatory Mo/Mø, leading to cardiac I/R recovery. CXCL16 indicates CXC chemokine ligand 16; IFN, interferon; I/R, ischemia/reperfusion; MI, myocardial infarction; MMP-1, matrix metalloproteinase-1; Mo, monocytes; Mø, macrophages; and SR, scavenger receptor.

and the individual components, were examined during 12 months of follow-up. The results showed that after adjusting for multiple cardiovascular risk factors, circulating levels at admission were independently associated with cardiovascular death (hazard ratio, 1.50 [95% CI, 1.17–1.92]; *P*=0.0014) but not with ischemic events alone. However, there was an association between adverse clinical outcomes and circulating sCXCL16 at 1 month after ACS occurrence and a change in sCXCL16 from admission to 1 month.[64] Therefore, the admission levels of sCXCL16 may provide more information for patient stratification at admission and the prognosis of patients with ACS. In addition, increased plasma sCXCL16 levels were observed in patients with intermediate coronary artery lesions. After 2 years of follow-up, the upper plasma sCXCL16 quartile was also independently associated with adverse outcomes (including all-cause death, MI, and revascularization) in these patients.[65] Based on these studies, circulating sCXCL16 may have strong promising potential as a clinical biomarker for predicting MI occurrence and for the diagnosis and prognosis of MI (Table 2).

In animal studies, several reports have revealed the regulatory effect of CXCL16 on ischemic cardiac injuries.[66–68] CXCL16 expression was significantly increased in cardiac tissue after MI in mice,[67] inhibiting CXCL16 attenuated cardiomyocyte apoptosis and inflammation in vitro. CXCL16 interference also mitigated myocardial remodeling by mediating MMP-2 expression levels after MI in vivo (Figure 3B). In addition, CXCL16 expression was elevated in the heart after cardiac I/R injury. Inhibiting CXCL16 or depleting CXCR6, which is the receptor of CXCL16, could attenuate cardiomyocyte apoptosis, reduce infarct size, and improve cardiac function after cardiac I/R injury, and the mechanism was associated with preventing the infiltration of IL-17A-producing T lymphocytes[68] (Figure 3B). Zhao et al showed that CXCR6 depletion prevented the cardiac infiltration of CD11b+ monocytes and inhibited interferon (IFN)-γ production and IFN-γ-mediated cardiac autophagy, leading to improvements in cardiac I/R injury[66] (Figure 3B). In ECs, IL-18 promoted the phosphorylation of STAT3 (signal transducer and activator of transcription 3), which interacted with FOXP3 (forkhead box P3) and enhanced CXCL16 transcription induced by FOXP3. Subsequently, CXCL16 promoted the cardiac infiltration of $CD11b^{+}Ly6C^{+}$ monocytes/macrophages and exacerbated myocardial injury and cardiac dysfunction after I/R injury[69] (Figure 3B). Therefore, inhibiting CXCL16/CXCR6 signaling may be a promising treatment strategy in ischemic cardiac injury.

In summary, circulating CXCL16 could be a promising biomarker for the diagnosis and prognosis of MI in patients. Because inhibiting CXCL16/CXCR6 signaling has a protective effect against ischemic cardiac injury, developing specific drugs that target CXCL16/CXCR6 signaling in various manners, such as inhibitors, antagonists, and siRNA therapy with nanomaterial carriers, may be useful for improving the prognosis of patients with MI.

Effect of SR Class H on MI and I/R Injury

SR class H includes SR-H1 (also named FEEL-1 [fasciclin, EGF-like, laminin-type EGF-like, and link domain-containing SR-1] and stabilin-1) and SR-H2 (FEEL-2). *SR-H1* and *SR-H2* are located on chromosomes 3 and 12 in humans (Table 1), respectively, and are mainly expressed in the spleen, lymph nodes, macrophages, and ECs[2] (Figure 1). SR-Hs can recognize modified LDL and bacteria, suggesting their effects on cholesterol metabolism and pathogen recognition. A previous study suggested that stabilin-1 could be used as a surface marker of M2 macrophages, and stabilin-1+ macrophages were significantly increased in the infarct and peri-infarct areas during the reparative phase of MI.[70] However, the functional effect of SR-Hs on ischemic cardiac injury has not been investigated.

Effect of SR Class I on MI and I/R Injury

The *SR-I1* gene (also named CD163) is located on human chromosome 12p13 (Table 1). SR-I1 is composed of an extracellular domain that contains 9 tandem SRCR domains, a transmembrane region and a short C-terminal intracellular cytoplasmic tail and is mainly expressed on monocytes and macrophages[71] (Figure 1). In general, proinflammatory signals/mediators can inhibit CD163 expression, whereas anti-inflammatory signals can increase CD163 expression. CD163 can recognize and bind Hb-Hp (hemoglobin-haptoglobin) complexes, tumor necrosis factor-like weak inducers of apoptosis and patterns of multiple viruses and bacteria (Table 1), indicating that CD163 may play an important role in the clearance of hemoglobin and pathogenic microorganisms. In addition to recognition and receptor-mediated endocytosis, CD163 can also perform biological functions and activate intracellular signaling pathways. During macrophage polarization, CD163 is regarded as a specific marker of M2 or anti-inflammatory macrophages. In addition, CD163 can be shed to produce a soluble type (sCD163), which may be a biomarker of macrophage activation and a risk factor for the prognosis of inflammatory diseases.[72]

In a clinical study, 526 patients with chest pain were recruited and divided into 3 groups: patients with non-cardiac chest pain, patients without STEMI, and patients with STEMI. The results showed that circulating sCD163 levels were not significantly different among the 3 groups[73] (Table 2). However, in another clinical study, CD163 expression and $CD163^{+}$ macrophages were significantly decreased in diabetes plaques. The

percentage of CD163+ peripheral blood monocytes was lower and plasma sCD163 was higher in patients with diabetes than in controls.[74] Diabetes is a risk factor for vulnerable plaques, and patients with diabetes easily suffer from plaque rupture and MI, suggesting that CD163 may be closely associated with MI occurrence. Sato et al[75] recruited 40 patients with AMI in a clinical study, and coronary atherothrombotic debris was retrieved from all patients during PCI. According to the percentage of CD163+ cells in atherothrombotic debris, patients were divided into 2 groups: CD163-high and CD163-low. The CD163-high group had higher expression levels of IL-10, which was associated with improvements in patient cardiac function. Therefore, CD163 may have a regulatory effect on ischemic cardiac injury.

Diabetes could impair heme clearance and contribute to adverse cardiac remodeling after MI. Compared with those of wild-type mice, plasma-free hemoglobin levels were significantly elevated in mice with diabetes after MI. Plasma-free hemoglobin was positively associated with infarct size.[76] IL-10 could inhibit inflammation, reduce apoptosis, improve capillary density, and attenuate MI-induced cardiac dysfunction by increasing CD163 and heme oxygenase-1 expression in macrophages, because CD163 and heme oxygenase-1 promote the clearance of hemoglobin.[76,77] Therefore, we hypothesized that CD163 overexpression may play a protective role in MI and cardiac I/R injury.

Effect of SR Class J on MI and I/R Injury

RAGE (receptor for advanced glycation end-products) is the only member of SR class J and belongs to the immunoglobulin superfamily. The *RAGE* gene is located on human chromosome 6 (Table 1). It is composed of 3 extracellular immunoglobulin domains (a V-type, a C1-type, and a C2-type domain), a transmembrane region and a short C-terminal cytosolic domain[78] (Figure 1). Membrane RAGE is mainly expressed on ECs, SMCs, cardiomyocytes, monocytes, and macrophages[79] (Figure 1) and can be shed as a soluble form (sRAGE), which may be a marker that is inversely associated with inflammation. RAGE, which is a pattern recognition receptor implicated in diverse inflammatory diseases, can recognize or be activated by multiple ligands, including DAMPs (including AGEs, HMGB1 [high-mobility group protein 1], S100-proteins, and DNA) and pathogen-associated molecular patterns (such as lipopolysaccharide and microbial DNA),[80] resulting in the activation of intracellular signal cascades.

In a clinical study, 36 patients with NSTEMI and 30 control donors were recruited, and circulating sRAGE levels were measured. The results showed that circulating sRAGE was lower and troponin-I was higher in patients with NSTEMI than in controls. Circulating sRAGE was negatively correlated with troponin-I levels.[81] Similarly, circulating sRAGE was also decreased in patients with NSTEMI in another clinical study, and both sRAGE and the AGE/sRAGE ratio may be biomarkers for NSTEMI diagnosis.[82] In addition, compared with those of patients with stable angina, plasma sRAGE levels were significantly decreased in patients with MI and UA.[83] Therefore, circulating sRAGE may be a marker in the diagnosis of MI. In addition, several studies have evaluated its potential prognostic value for patients with cardiovascular disease, especially those with ACS. In a 3-year longitudinal cohort study, 1002 individuals with cardiovascular disease were recruited, and circulating sRAGE levels were measured. The results showed that high levels of sRAGE (fourth quartile) were associated with the highest incidence of combined outcome events (including MI, stroke, and cardiovascular death), and after adjusting for risk factors, high levels of sRAGE (fourth quartile) had an independent ability to predict adverse outcome events in patients with cardiovascular disease (HR, 1.616 [95% CI, 1.027–2.544]; P=0.038).[84] In another clinical cohort, circulating sRAGE was measured in 524 patients with ACS within 24 hours of onset and again 6 weeks later in a subgroup of 114 individuals with ACS. Patients were followed up for an average of 25.7 months, and the end point was defined as recurrent major adverse cardiovascular events, including cardiovascular death and recurrent ACS. After adjusting for multiple cardiovascular risk factors, high sRAGE levels were independently positively associated with the incidence of recurrent major adverse cardiovascular events. However, the incidence of recurrent ACS was lower in patients with increased circulating sRAGE levels at week 6 of ACS than at baseline.[85] Therefore, high levels of circulating sRAGE at admission or in the early stage of ACS may be an independent predictor for the risk of adverse outcomes in patients with ACS, but in the late stage, sRAGE may be associated with a better outcome. McNair et al[86] recruited 46 patients with NSTEMI with PCI intervention and found that 19 of these patients developed post-PCI restenosis after follow-up. Circulating sRAGE levels were lower in patients with restenosis, and lower sRAGE levels may provide a predictive value for post-PCI restenosis. In addition, in a pilot study that recruited 67 consecutive patients with STEMI, Redondo et al[87] found that circulating sRAGE levels within 24 hours of MI occurrence were inversely correlated with basal cardiac function after STEMI stimulation but were not associated with left ventricular remodeling after 6 months of follow-up. Therefore, the association between circulating sRAGE levels and the prognosis of patients with ACS is complex and even contradictory, and the exact prognostic

value of sRAGE needs to be confirmed by clinical studies with large sample sizes (Table 2).

In animal studies, the effect of RAGE on ischemic cardiac injury has been well investigated. The expression of RAGE in ischemic hearts was significantly enhanced in mice and rats after I/R injury.[88,89] RAGE deficiency could attenuate I/R-induced cardiac injury, and the mechanisms were associated with improvements in myocardial energy metabolism and the alleviation of cardiomyocyte apoptosis[88,89] (Figure 4). sRAGE, which is the soluble form of membrane RAGE, is a ligand-binding decoy that blocks RAGE function. Therefore, treatment with sRAGE could attenuate I/R-induced cardiac injury and improve myocardial function. The mechanisms may involve promoting angiogenesis,[90] attenuating cardiomyocyte apoptosis,[91–93] ameliorating cardiac fibrosis, regulating autophagy,[94,95] mitigating mitochondrial damage,[96,97] reducing inflammation, and inhibiting pyroptosis[98] (Figure 4). In brief, sRAGE could increase STAT3 phosphorylation and subsequently promote angiogenesis.[90] sRAGE inhibited p53-mediated cardiomyocyte apoptosis by promoting the IFN-γ/β5i signaling pathway.[91] sRAGE could also attenuate apoptosis by mediating the STAT3/β1i/β5i pathway or JAK2/STAT3 pathway.[92,93] In addition, sRAGE attenuated cardiomyocyte apoptosis and autophagy by activating the integrinβ3/AKT (protein kinase B)/STAT3 pathway or STAT3 pathway.[94,95] sRAGE mitigated mitochondrial damage by inhibiting the FoxO3a-Bnip3 pathway.[96] sRAGE attenuated cardiomyocyte injury by inhibiting JNK phosphorylation and activating the AKT/GSK-3β (glycogen synthase kinase-3 beta) pathway.[99] sRAGE protected the heart against pyroptosis through the nuclear factor-κB/NLRP3 (NLR family pyrin domain containing 3)/GSDMD (gasdermin D)/IL-1β/IL-18 signaling pathway.[98] Considering the protective role of sRAGE or RAGE inhibition in cardiac I/R injury, RAGE can be a promising target for developing therapeutic drugs for patients with MI. Ku et al[100] made a preliminary attempt to use deoxycholic acid-modified polyethyleneimine-based nanocarriers for RAGE siRNA therapy to treat cardiac I/R injury in animals, which provided satisfactory results.

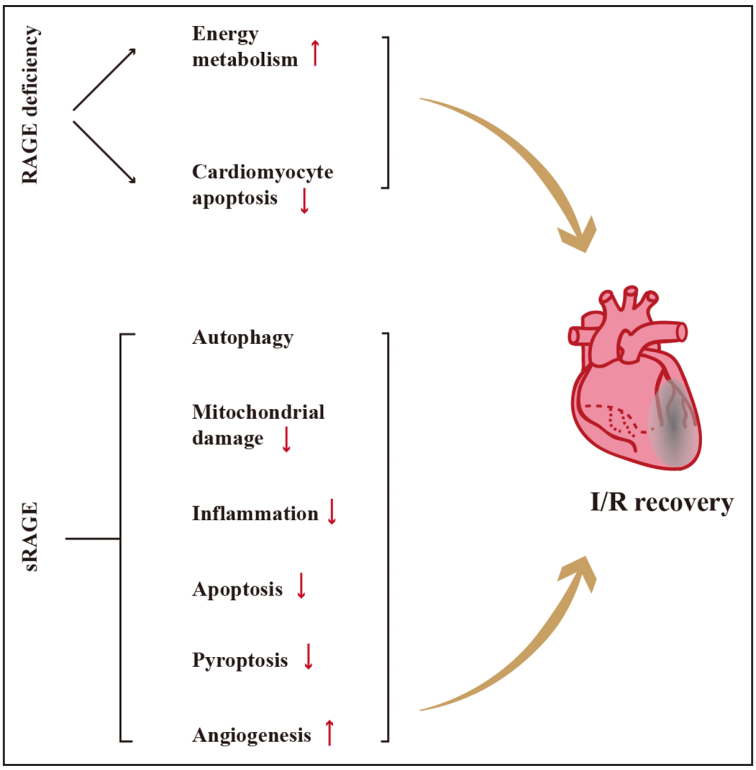

Figure 4. The effect of SR J class (RAGE) in cardiac I/R injury.
RAGE deficiency attenuates cardiac I/R injury through mediating energy metabolism and inhibiting cardiomyocyte apoptosis; sRAGE, which is the soluble form of membrane RAGE, is a ligand-binding decoy that blocks RAGE function. The administration of sRAGE can also attenuate cardiac I/R injury, and the mechanisms are associated with autophagy, mitochondrial damage, inflammation, cardiomyocyte apoptosis and pyroptosis, and angiogenesis. I/R, ischemia/reperfusion; RAGE, receptor for advanced glycation end-products; and SR, scavenger receptor.

In summary, circulating sRAGE not only has the potential to be a biomarker for ACS or AMI diagnosis but also provides possible predictive value for prognosis in patients with MI. However, clinical studies with larger samples are needed to confirm this conclusion. The administration of sRAGE, or suppression of RAGE, may play a protective role in ischemic cardiac injury in patients, which provides a clear target for drug discovery.

CONCLUSIONS

SRs, which are a series of pattern recognition receptors, can recognize multiple ligands, such as modified lipoprotein, DAMPs, andpathogen-associated molecular patterns, and regulate lipid metabolism, immunity, and homeostasis. In addition, our review indicated that SRs play critical roles in MI or cardiac I/R injury, including the confusing role of SR-A1; the possible protective role of SR-BI and CD163; the bidirectional regulatory effect of CD36; and the protective role of LOX-1, CXCL16, and RAGE inhibition, although the association between other SR members and ischemic cardiac injury remains unknown. In addition, several circulating soluble types of SRs, such as sCD36, sLOX-1, sCXCL16, and sRAGE, may be promising biomarkers for the diagnosis and prognosis of patients with AMI, but prospective clinical studies with larger sample sizes are needed to confirm these conclusions. Therefore, it is necessary to deeply clarify the association between SRs and ischemic cardiac injury, which may inspire novel ideas to discover specific drugs targeting SRs.

ARTICLE INFORMATION

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Disclosures

None.

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