Scavenger Receptor-A (CD204): A Two-Edged Sword in Health and Disease

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ABSTRACT: Scavenger receptor A (SR-A), also known as the macrophage scavenger receptor and cluster of differentiation 204 (CD204), plays roles in lipid metabolism, atherogenesis, and a number of metabolic processes. However, recent evidence points to important roles for SR-A in inflammation, innate immunity, host defense, sepsis, and ischemic injury. Herein, we review the role of SR-A in inflammation, innate immunity, host defense, sepsis, cardiac and cerebral ischemic injury, Alzheimer's disease, virus recognition and uptake, bone metabolism, and pulmonary injury. Interestingly, SR-A is reported to be host protective in some disease states, but there is also compelling evidence that SR-A plays a role in the pathophysiology of other diseases. These observations of both harmful and beneficial effects of SR-A are discussed here in the framework of inflammation, innate immunity, and endoplasmic reticulum stress.

KEY WORDS: Scavenger receptor-A, CD204, inflammation, sepsis, infection, innate immunity, atherosclerosis, brain and heart ischemia, reperfusion injury.

ABBREVIATIONS: AcLDL: acetyl low-density lipoprotein; AD: Alzheimer's disease; CD204: cluster of differentiation 204; CLP: cecal ligation and puncture; CSR: cellular stress response; EC: endothelial cells; ER: endoplasmic reticulum; LAD: left anterior descending coronary artery; LPS: lipopolysaccharide; LTA: lipoteichoic acid; MVP: major vault protein; MARCO: macrophage receptor with collagenous structure; MerTK: Mer receptor tyrosine kinase; mRNA: messenger ribonucleic acid; NFκB: nuclear factor kappa B; PI3K: phosphoinositol 3-OH kinase; SCARA 1, 2, 3, 4, 5: scavenger receptor A member 1, 2, 3, 4, 5; SR-A^{-/-}: SR-A knockout mice; SR-A: scavenger receptor AI/AII also named CD204; SR-AI/AII/AIII: scavenger receptor A type AI, AII, AIII; TLR 2, 3, 4, 9: toll like receptor 2, 3, 4, 9; TNFα: tumor necrosis factor alpha; WT: wild type

I. INTRODUCTION

Macrophage scavenger receptors were initially discovered by Goldstein and Brown^{1,2} and have subsequently been shown to participate in multiple macrophage metabolic processes, including adhesion,³ phagocytosis,^{4,5} production of reactive oxygen species⁶ and host defense.^{7–11} Scavenger receptors bind and internalize modified plasma low-density lipoproteins (LDL) and high-density lipoproteins leading to accumulation of cholesterol esters.^{1,2} However, scavenger receptors also recognize a diverse family of ligands that include oxidized and chemically modified plasma lipoproteins and proteins,^{1,2,12} apolipoproteins AI and E,¹³

advanced glycation end-product modified protein,¹⁴ collagen,¹⁵ beta-amyloid,¹⁶ crocidolite asbestos,¹⁷ silica,^{18–20} fucoidan,¹ dextran sulfate,² glucans,²¹ carrageenan,² polyvinyl sulfate,² lipopolysaccharide (LPS),²² lipoteichoic acid (LTA),²³ polyinosinic acid and polyguanylic acid,² heat-shock proteins,²⁴ major vault protein (MVP),²⁵ apoptotic cells,²⁶ human cytomegalovirus (HCMV),²⁷ and double-stranded ribonucleic acid^{28–30} (Table 1).

In 1997, Krieger et al. proposed a nomenclature for scavenger receptors based on their common structural characteristics (class A, B, C, etc.).⁸ Currently, five scavenger receptors are designated as class A, each encoded by distinct and unrelated

TABLE 1: SR-A ligands

Acetyl LDL ¹
Advanced glycation end product modified proteins ¹⁴
Apolipoproteins AI and E ¹³
Apoptotic cells ²⁶
Beta-amyloid ¹⁶
Carrageenan ²
Collagen ¹⁵
Crocidolite Asbestos ¹⁷
Cytomegalovirus-human ²⁷
Dextran sulfate ²
Fucoidin ^{1,2}
Glucan ²¹
Heat shock proteins ²⁴
Lipopolysaccharide ^{22,155}
Lipoteichoic acid ²³
Major vault protein ²⁵
Maleylated high density lipoprotein ²
Maleylated LDL ²
Oxidized LDL ¹⁵⁶
Poly I: Poly C ²
Polyguanylic acid ²
Polyinosinic acid ²
Polyvinyl sulfate ²
Polyxanthynic acid ²
Proteoglycans ¹⁵⁷
Ribonucleic acid, double-stranded ^{28,29,158}
Silica ^{18–20}
Sulfatides ²

genes.^{31–35} All class A scavenger receptors are trans-membrane proteins with homotrimeric structures (Fig. 1). The first class A scavenger receptor to be cloned was named macrophage scavenger receptor A (SR-A) SCARA1, cluster of differentiation 204 (CD204).^{8,31,36} This receptor was initially described as the acetylated low-density lipoprotein (AcLDL) receptor.^{1,31,36} SR-A exists as three naturally occurring types: SR-AI, SR-AII, and SR-AIII.^{37,38} SR-A type II and type III are alternatively spliced variants of the

same gene.^{37–39} The major isoforms in mammalian species are SR-AI and II (SR-AI/II), which are the focus of this review. SR-AI/II is typically referred to in the literature as SR-A,^{36,40,41} however, there are several other class A scavenger receptors. In this review, we use the same nomenclature and refer to SR-AI/II as SR-A. SR-AII has the same structure as SR-AI except that it does not contain the cysteine-rich C-terminus region.^{31,36,40} Lack of differences in binding of modified lipoproteins between SR-AI and SR-AII led to the discovery that the binding site for modified lipoproteins resides in the collagen-like region.³⁶ SR-AIII, which is found in human macrophages, has the same structure as SR-AI except that exon 8 is directly fused to exon 11.³⁸ SR-AIII is translated but is not inserted into the membrane and therefore is not functional in lipoprotein binding and uptake. *In vitro* studies indicate that SR-AIII may serve as a dominant negative regulator of SR-A I/II function.³⁸ SR-A is preferentially expressed on macrophages;^{1,2,8,41–43} however, SR-A has been described in vascular smooth muscle cells,^{44–46} endothelial cells (EC),^{47–51} human lung epithelial cells,²⁸ microglia,^{52,53} astrocytes,⁵⁴ and murine embryonic fibroblasts.²⁹ Bickel and Freeman showed that the gene for SR-A could be induced in cultured smooth muscle cells by stimulation with phorbol myristate acetate; however, they did not detect SR-A mRNA in rabbit venous EC or bovine aortic EC.⁴⁴ In contrast, Hashizume and Mihara showed induction of SR-A mRNA and protein in cultured human aortic EC after stimulation with tumor necrosis factor alpha (TNF α) or interleukin 6.⁵¹ Although SR-A is named the scavenger receptor and is predominately found on macrophages, the recent observations that an SR-A message is expressed in endothelial cells,⁵¹ lung epithelial cells,²⁸ microglia,^{52,53} astrocytes,⁵⁴ and primary murine fibroblasts,²⁹ broadens the scope of the pathophysiologic importance of SR-A.

As shown in Fig. 1, there are five members of the class A scavenger receptor family. Although this review is focused on SR-A (CD204), it is instructive to briefly comment on the other members of this class and how they relate to SR-A. The second class A scavenger receptor, named macrophage receptor with collagenous structure (MARCO) or SCARA2,

FIG. 1: The structure(s) of class A scavenger receptors. Scavenger receptors are classified as class A because of their similar structure. Specifically, they are all homo trimeric transmembrane proteins with an intracellular N-terminus, a short cytoplasmic tail, a transmembrane sequence, and a spacer sequence. Class A scavenger receptors differ in the presence of coiled-coil, collagen-like, and C-terminus structures. The C-terminus may have a scavenger receptor cysteine-rich (SRCR), a c-type lectin, or a truncated or absent SRCR structure. Abbreviations: Scavenger receptor A (SCARA), Scavenger receptor-A (SR-A, also named CD204), Macrophage receptor with collagenous structure (MARCO), Cellular stress response (CSR), Scavenger receptor with C-type lection (SRCL), Scavenger receptor class A, member 5 (SCARA5).

is similar in structure to SR-A except that MARCO has an elongated collagenous domain and lacks the alpha helical coiled-coil domain.⁵⁵ MARCO expression is principally found in macrophages of the marginal zone of the spleen⁵⁵ but has been observed on alveolar macrophages in mice^{56–58} and humans.^{58,59} The third class A scavenger receptor is described as cellular-response protein (CSR) or SCARA3.³³ CSR is a trimeric protein that resembles SR-A with an alpha-helical coiled-coil domain and a collagenous domain. CSR is expressed ubiquitously and is increased in cells exposed to oxidative stimuli. CSR is localized intracellularly near the Golgi apparatus and presumably protects cells from oxidative dam-

age.³³ CSR was recently shown to suppress prostate cancer progression by inducing tumor cell death.^{60,61} The fourth class A scavenger receptor is scavenger receptor with C-type lectin, SCARA4^{34,62} which resembles SR-A, except the C-terminal cysteine-rich domain is replaced by a C-type lectin binding domain.³⁴ SCARA4 is the same as collectin-12 and collectin placenta protein 1. Ohtani et al.⁶² described collectin protein 1 is a scavenger receptor enriched in placenta and expressed by vascular endothelial cells, but not in macrophages. In contrast, Nakamura et al. showed that collectin protein 1 is expressed in perivascular macrophages and in perivascular astrocytes associated with clearance of b amyloid in Alzheimer's

disease (AD).⁶³ The fifth class A scavenger receptor is SCARA5, which resembles SR-A but does not have a typical coiled-coil domain.³⁵ Expression of SCARA5 is localized to epithelial cells.³⁵

II. SR-A FUNCTIONS IN MULTIPLE DISEASES AND ORGAN SYSTEMS

In this review, we explore the role of SR-A in diverse systemic diseases, including atherosclerosis, endotoxemia, sepsis, and viral infections. In addition, SR-A participates in either beneficial or detrimental effects in organs, including brain stroke and Alzheimer's disease, lung injury, cardiac infarction and coronary artery disease, and bone metabolism (Fig. 2).

A. SR-A in Atherosclerosis

Since the early 1980s, atherosclerosis has been considered to be an inflammatory disease.⁶⁴ The

role of SR-A in atherosclerosis has been studied extensively and reviewed.^{1,2,7,10,40,65,66} The overall consensus is that macrophages in arterial plaques express SR-A that contributes to atherogenesis by binding modified lipoproteins and by participating in macrophage activation, resulting in secretion of chemotactic factors and inflammatory cytokines. The magnitude of SR-A's contribution to atherosclerosis is modulated in different animal models, depending on the genetic background and local inflammatory responses coupled with the contributions of other scavenger receptors, such as scavenger receptor B (also named CD36)^{67–70} and scavenger receptor E (also named LOX-1).^{71–73}

B. SR-A in Innate Immunity

The concept that SR-A is a pattern-recognition receptor in the innate immune system was promoted in a series of reviews by Krieger, Gordon, and colleagues.^{7,66,74–79} The observation that SR-A binds a

FIG. 2: SR-A functions in multiple diseases and organ systems. SR-A exerts systemic effects in a number of diseases, including atherosclerosis, endotoxemia, sepsis, and viral infections. In addition, SR-A mediates either beneficial or detrimental effects in stroke, Alzheimer's disease, lung injury, cardiac infarction, coronary artery disease, and bone metabolism.

broad spectrum of ligands, including key constituents of bacteria cell wall, supports the concept that SR-A is a pattern-recognition receptor and may play a role in host defense. In addition, the observation that SR-A is found primarily on macrophages, which are an important component of host defense and innate immunity, also supports a role for SR-A as a pattern-recognition receptor.^{66,74,77} An expanded view of the contribution of SR-A to host defense and innate immunity is explored in the following sections.

C. SR-A in Host Defense Against Pathogenic Bacteria

Because of its collagen-like domain and broad ligand specificity, Kodama et al. speculated that the macrophage SR-A could be involved in host defense, in particular, bacterial recognition and macrophage related immune responses.³¹ Shortly thereafter, bovine SR-A was purified⁸⁰ and cloned by the Kreiger laboratory.^{31,36} Hampton et al. demonstrated that bovine SR-A was responsible for binding and internalization of Gram-negative *E. coli* lipid A, lipid IV_A, and endotoxin by cultured macrophages and Chinese hamster ovary cells transfected with SR-AI and SR-AII.²² SR-A has been implicated as a receptor for both Gram-positive and Gram-negative bacteria, and its presence is generally considered host protective.^{23,81–83} For example, Dunne et al. showed that bovine SR-A-I binds to the gram-positive bacteria *Streptococcus pyogenes*, *S. aureus*, *Enterococcus hirae*, and *Listeria monocytogenes* via lipoteichoic acid (LTA).²³ They postulated that SRs may participate in host defense by clearing LTA and/or intact bacteria from tissues and the circulation during Gram-positive infections.

In 1990, Freeman et al. cloned mouse SR-A-I and -II, which led to the development of a murine model that did not express SR-A.³⁷ In 1997, Suzuki et al. first described the creation of SR-A knockout mice (SR-A^{-/-}) by disrupting exon 4 of the SR-A gene.¹⁰ Using this new model, they demonstrated that SR-A^{-/-} mice had a lower survival after a lethal challenge with *L. monocytogenes* or herpes simplex virus-1. They concluded that the lower survival after *L. monocytogenes* challenge may be related to a defect in the uptake and killing of bacteria by macrophages

and not due to the clearance of bacteria from the circulation. Peiser et al. observed that bone-marrow-derived macrophages from SR-A^{-/-} mice ingested fewer *E. coli in vitro* when compared to the wild type (WT).⁸² However, uptake of opsonized *E. coli* was unaffected, suggesting that SR-A binds and ingests bacteria directly and may play a role in host defense *in vivo*. These authors also showed that *E. coli* and *S. aureus* bind to Chinese hamster ovary cells transfected with human SR-AII.⁸²

Thomas et al. reported that SR-A protects mice from a lethal intraperitoneal challenge with *S. aureus*.⁸⁴ SR-A^{-/-} mice showed an impaired ability to clear bacteria from the peritoneum and blood. SR-A^{-/-} mice also showed decreased survival after *S. aureus* challenge. Thomas et al. concluded that opsonin-independent phagocytosis of Gram-positive bacteria was significantly decreased, indicating that SR-A-mediated phagocytosis is an important mechanism in *in vivo* host defense.⁸⁴

Peiser et al. showed that SR-A is responsible for recognition of *Neisseria meningitides*.⁸³ Using bone-marrow-derived macrophages from WT and SR-A^{-/-} mice, they determined that most of the non-opsonic phagocytosis of *N. meningitides* was due to binding by macrophage SR-A. Also, using a mutant strain of *N. meningitides* that did not contain LPS, Peiser et al. determined that LPS was not the ligand for binding to SR-A. SR-A^{-/-} mice bound and internalized fewer *N. meningitides* than WT controls.⁸³ Peiser et al. also demonstrated that SR-A-mediated uptake leads to killing and digestion of *N. meningitides* by macrophages.⁸³ SR-A ligation of *N. meningitides*, which were devoid of LPS, did not lead to cytokine production indicating that LPS is responsible for cytokine expression via a Toll-like receptor 4 (TLR4)-dependent mechanism.⁸³ Peiser et al. determined that the SR-A ligands present on *N. meningitides* include *N. meningitides* group B (NMB) proteins expressed on the surface of the bacterium, namely, NMB 1220, 0278, and 0667.⁸⁵

Arredouani et al. demonstrated that SR-A contributed to host defense against *S. pneumoniae in vivo* in mice.⁸⁶ SR-A^{-/-} mice showed decreased survival, diminished clearance of bacteria from the lung, increased TNF α and macrophage inflammatory

protein 2 production, and increased neutrophilia. Pierini et al. were the first to show that SR-A is responsible for opsonized uptake of a pathogenic Gram-negative bacteria *Francisella tularensis* in macrophages.⁸⁷ In contrast to other studies showing that the presence of SR-A is host protective, Sever-Chroneos et al. showed that SR-A^{-/-} mice survived longer after infection with *Mycobacterium tuberculosis*.⁸⁸ They concluded that the protection was due to the increased numbers of CD4⁺ lymphocytes during the chronic phase of the infection. Interestingly, Areschoug et al. demonstrated the first example of pathogenic bacteria (*S. agalactiae* and *S. pyogenes*) that have developed mechanisms to avoid recognition by SR-A (Table 2).⁸⁹

D. The Conflicting Role of SR-A in Endotoxemia

Endotoxin (also known as lipopolysaccharide or LPS) has been used for many years as a surrogate for sepsis and/or septic shock.^{90,91} However, there are significant differences in the pathophysiology of endotoxemia and clinical sepsis.^{92,93} The role of SR-A in endotoxemia appears to be very complex. The majority of studies indicate that the presence of SR-A is host protective in endotoxemia, both *in vivo* and *in vitro*.^{43,94–99} *In vivo* studies have shown that mice lacking SR-A (SR-A^{-/-}) had a lower survival rate after endotoxin treatment than did their WT counterparts.^{94,98,99} This decreased survival was correlated with an increased cytokine response in cultured macrophages and increased pro-inflammatory cytokines in the systemic circulation, in particular, increased levels of TNF α , interleukin 6, and interferon- γ .^{94,98,99} Yu et al. reported that the anti-inflammatory effect of SR-A was due to down-regulation of inflammatory gene expression via decreased TLR4-mediated NF κ B activation in dendritic cells.⁹⁹ Haworth et al. reported the direct involvement of TNF α in the increased susceptibility of mice lacking SR-A after endotoxemia.⁹⁴ In contrast to the studies listed above, Kobyashi et al. reported that the presence of SR-A was detrimental to mice after LPS treatment.¹⁰⁰ Their data supported the conclusion that SR-A played a role in the pathophysiology of endotoxemia.

Specifically, Kobyashi et al. observed that mice lacking SR-A had a better survival rate than their WT counterparts after endotoxin challenge.¹⁰⁰ Clearance of LPS was decreased in SR-A^{-/-} mice, and serum levels of interleukin-1 β were decreased, suggesting that macrophage activation was diminished in the absence of SR-A. Survival improved when WT mice were pretreated with an interleukin-1 antagonist, suggesting that interleukin-1 production is associated with mortality in this model. In support of the results of Kobyashi et al., Czerkies et al. used cultured J774 macrophages to show that high doses of LPS resulted in proinflammatory effects that required SR-A.¹⁰¹ They exposed the cells to 1000 ng ml⁻¹ LPS and measured the role of SR-A in LPS uptake and expression of inflammatory mediators. Czerkies et al. showed that simultaneous treatment with the SR-A ligand dextran sulfate and LPS resulted in an enhanced pro-inflammatory responses.¹⁰¹ Similarly, Yu et al. reported that the concomitant treatment of J774 macrophages with the SR-A ligand fucoidan and high levels of LPS resulted in an enhanced proinflammatory response.¹⁰² When considered as a whole, the data on the role of SR-A in endotoxemia present a conflicting and contradictory picture. Some studies report that SR-A is protective, while other studies provide evidence that SR-A contributes to the pathophysiology of endotoxemia.^{94–101} The precise causes for these disparate results are not readily apparent (Table 2).

E. SR-A Plays a Central Role in the Pathophysiology of Polymicrobial Sepsis and Septic Shock

As indicated in the previous section, the role of SR-A in endotoxemia is conflicting and controversial. However, endotoxemia does not mimic the clinical scenario of sepsis. The cecal ligation and puncture (CLP) model of sepsis is considered by many to be the “gold standard” for clinically relevant sepsis in that it incorporates several injury modalities that mimic human sepsis/septic shock, namely, the production of a non-healing defect in the wall of the gut through a combination of trauma, ischemia and/or necrosis, and polymicrobial infection due

TABLE 2: Role of SR-A in models of sepsis and endotoxemia

Authors	Sepsis/endotoxin model	SR-A ^{-/-} Mouse	Dose	Route	Time Course	Effect of SR-A
Bacterial inoculum						
Suzuki et al. ¹⁰	<i>Listeria monocytogenes</i>	129/SvJ/ICR	10 ⁵ CFU/mouse	iv	18 days	↑ survival
Arredouani et al. ⁸⁶	<i>Streptococcus pneumoniae</i> type 3	129/SvJ/ICR	10 ⁵ CFU/mouse	Lung instillation	4, 24 hours	↑ survival
Thomas et al. ⁸⁴	<i>Staphylococcus aureus</i>	129/SvJ/ICR	2 × 10 ⁵ – 10 ⁷ CFU/mouse	ip	72 hours	↑ survival
Endotoxemia						
Haworth et al. ⁹⁴	BCG primed, then treated with <i>Salmonella typhimurium</i> LPS	129/SvJ/ICR	0.1–500 µg/mouse	ip	5 days	↓ inflammation ↑ survival
Ohnishi et al. ⁹⁸	<i>Escherichia coli</i> 0111:B4 LPS	129/SvJ/ICR/ C57BL/6j	10 µg/g body weight	ip	3 days	↓ inflammation ↑ survival
Yu et al. ⁹⁹	Ultrapure LPS	129/SvJ/ICR/ C57BL/6j	10–30 µg/g body weight	ip	4 days	↓ inflammation ↑ survival
Kobayashi et al. ¹⁰⁰	<i>Escherichia coli</i> 0111:B4 LPS	129/SvJ/ICR	200–1000 µg/mouse	ip	3 days	↑ inflammation ↓ survival
Polymicrobial sepsis						
Ozment et al. ¹⁰⁶	Polymicrobial	129/SvJ/ICR/ C57BL/6j	CLP, 20-gauge needle	CLP	21 days	↑ inflammation ↓ survival
Drummond et al. ¹⁰⁷	Polymicrobial	129/SvJ/ICR/ C57BL/6j	CLP, 16- and 18-gauge needles	CLP	3–5 days	↑ inflammation ↓ survival

to the subsequent release of gut bacteria into the peritoneal cavity and bloodstream.^{103–105} These bacteria ultimately enter the bloodstream and activate a strong inflammatory response that leads to septic shock, organ failure, and death.¹⁰³ Two recent studies investigated the role of SR-A in the CLP sepsis model. In 2012, Ozment et al. reported that SR-A plays a role in the pathophysiology of CLP-induced polymicrobial sepsis.¹⁰⁶ In this study, SR-A^{-/-} mice had significantly improved survival after CLP compared with WT mice, and the improved survival outcome in SR-A^{-/-} mice strongly correlated with a decreased systemic inflammatory response. Nuclear factor kappa B (NFκB) activation was decreased, and the levels of inflammatory cytokines in the serum were also decreased in SR-A^{-/-} mice compared with WT mice. Ozment et al. provided insights into the mechanisms by which SR-A mediates septic sequelae.¹⁰⁶ Specifically, these authors showed that SR-A amplifies the pro-inflammatory response via increased physical association of SR-A with TLR4, but not TLR2. Thus, SR-A may act as a co-receptor for TLR4 in sepsis, thereby amplifying TLR4/myeloid differentiation primary response gene 88/NFκB-dependent signaling.¹⁰⁶ At approximately the same time, Drummond et al. reported that SR-A^{-/-} mice showed increased survival in response to CLP sepsis when compared with WT mice.¹⁰⁷ These two independent studies make a strong case that SR-A plays a detrimental role in the pathophysiology of sepsis and septic shock (Table 2).

F. SR-A in Myocardial Ischemia and Reperfusion Injury

The role of SR-A in myocardial ischemic injury has been studied using two different models of cardiac ischemia, that is, ischemic injury after permanent occlusion of the left anterior descending coronary artery (LAD)^{108,109} and transient occlusion of the LAD followed by a period of reperfusion.¹¹⁰ Two studies employed a murine model of ischemia due to permanent ligation of the LAD coronary artery, and both demonstrated that SR-A is cardioprotective.^{108,109} Tsujita et al. followed survival after permanent ligation of the LAD and observed that

SR-A^{-/-} mice had significantly decreased survival and death was due to cardiac rupture.¹⁰⁸ Tsujita et al. concluded that SR-A was important in infarct repair and long-term survival.¹⁰⁸ They also noted an increase in metalloproteinase 9 activity in the infarct tissue that was higher in SR-A^{-/-} mice than in WT controls, which would be consistent with increased tissue damage. In addition, tissue TNFα levels were increased, and the anti-inflammatory cytokine interleukin-10 was decreased in SR-A^{-/-} mice compared with WT mice. This was the first study to demonstrate that SR-A is essential for the healing of damaged myocardium.

In a separate study, Hu et al. examined the role of SR-A in myocardial injury using the permanent ligation of the LAD coronary artery model.¹⁰⁹ In this study, they examined survival, inflammation, and cardiac pathology over a period of 14 days post ligation of the LAD coronary artery in SR-A^{-/-} and WT mice. They observed that there was no difference in cardiac injury or function 1 day post ligation between SR-A^{-/-} and WT mice. However, cardiac injury and function in SR-A^{-/-} mice deteriorated over the next 13 days. Mortality due to heart failure and cardiac rupture were significantly greater in the SR-A^{-/-} mice than the WT mice. In animals that survived 14 days, cardiac function was lower in SR-A^{-/-} mice than WT mice. Hu et al. postulated that regulation of macrophage activation to the M2 type (inflammatory) versus the M1 type (anti-inflammatory) might explain the differences in response of the SR-A^{-/-} mice compared with the WT mice after permanent ligation of the LAD.¹⁰⁹ They observed preferential cardiac influx of the M1 phenotype of activated macrophages compared with the M2 phenotype. This study suggested that SR-A is anti-inflammatory; therefore, the overall effect would be to protect the heart from failure and rupture by facilitating repair mechanisms.

In a separate study, Ren et al. employed a murine model in which temporary ligation of the LAD coronary artery is followed by reperfusion.¹¹⁰ This model is perhaps more relevant to human myocardial infarction than the permanent ligation model used by Tsujita et al.¹⁰⁸ and Hu et al.¹⁰⁹ because this model more closely mimics the clinical scenario of transient

LAD coronary artery occlusion followed by reperfusion upon treatment. Thus, the Ren model has two major components: ischemia and reperfusion that create different magnitudes and modalities of injury. Ren et al. occluded the LAD for 45 minutes followed by 4 hours of reperfusion. In WT mice, this resulted in significant cardiac cellular and tissue damage.¹¹⁰ In striking contrast, they observed significantly less damage to hearts from SR-A^{-/-} mice when compared with the WT mice. Inflammatory cytokine levels and NFκB activity were also decreased in SR-A^{-/-} mice compared with WT mice. SR-A^{-/-} mice also had better cardiac functional recovery compared with the WT mice. These data clearly suggest that SR-A plays an important role in the pathophysiology of cardiac ischemia/reperfusion injury. These data also suggest that modulation of SR-A-mediated processes may provide a means of attenuating cardiac injury during ischemic and/or reperfusion injury. In addition, the investigations of Tsujita et al.,¹⁰⁸ Hu et al.,¹⁰⁹ and Ren et al.¹¹⁰ suggest that SR-A may contribute to cardiac repair in ischemia, but in the scenario of ischemia followed by reperfusion, SR-A contributes to a poor outcome (Table 3).

G. SR-A Contributes to the Pathophysiology of Cerebral Ischemic Injury

Cerebral ischemic injury (i.e., stroke) shares many of the features of myocardial infarction in that both involve ischemia, inflammation, necrosis, and reperfusion injury if blood flow is re-established.

Xu et al. used a permanent ligation of the middle cerebral artery in SR-A^{-/-} and WT mice.¹¹¹ They observed that SR-A was up-regulated in brain tissue (as early as 10 h) after 24 hours of occlusion. SR-A^{-/-} mice subjected to middle cerebral artery occlusion showed less brain damage compared with WT mice and attenuated microglia/macrophage M1 activation with preservation of M2 markers. Xu et al. concluded that SR-A promotes cerebral ischemic injury by preferentially activating microglia/macrophages to express the M1 inflammatory phenotype.¹¹¹

Lu et al. examined the role of SR-A in cerebral ischemia-reperfusion injury using a standard model of

focal cerebral injury induced by transient middle cerebral artery occlusion.¹¹² After 60 minutes of occlusion, the blockage was removed and reperfusion allowed for varying periods of time. SR-A^{-/-} mice showed less cerebral damage (smaller infarct size) after ischemia and decreased cerebral and systemic inflammatory response when compared with WT mice with cerebral ischemia/reperfusion. In addition, SR-A^{-/-} mice showed less cerebral apoptosis in the non-infarcted areas when compared with WT mice. The authors concluded that SR-A contributes to cerebral injury by increasing the systemic and cerebral inflammatory responses that led to increased tissue damage.

While there are differences in the experimental models employed by Xu¹¹¹ and Lu¹¹² both studies led to the same conclusion: SR-A contributes to brain injury after ischemia and/or reperfusion. In support of this concept, Murgas et al. used SR-A^{-/-} astrocytes *in vitro* to demonstrate that the presence of SR-A contributes to the neuro-inflammatory response (Table 3).⁵⁴

H. Role of SR-A in Alzheimer's Disease (AD)

Several observations indicate that SR-A may participate in AD. SR-A on microglial cells mediates the binding of β amyloid fibrils and is responsible for preventing the accumulation of amyloid in the brain.¹⁶ SR-A was elevated in activated microglia and in senile plaques in brains from human subjects diagnosed with AD.¹¹³ In a murine model of AD, Hickman et al. demonstrated that the levels of SR-A and other scavenger receptors decreased in latter stages of AD, while levels of inflammatory cytokines increased.¹¹⁴ The decrease in SR activity could contribute to the progression of neurodegeneration.^{114,115}

I. SR-A in Virus Recognition and Uptake

Haisma et al. first demonstrated that adenovirus type 5, a double-stranded DNA virus was specifically bound by SR-A and was internalized and degraded by macrophages.¹¹⁶ This knowledge could be used to increase the efficacy of gene therapy by blocking SR-A which would prolong the life time of adenovirus type in the circulation. Yew et al. showed

TABLE 3: Role of SR-A in ischemia reperfusion injury in heart and brain

Citation(s)	SR-A ^{-/-} mouse background	Ischemia Time	Reperfusion Time	Effect of SR-A
Heart Ischemia - Permanent Occlusion of LAD				
Tsujita et al. ¹⁰⁸	129/SvJ/ICR/C57BL/6J	31 days	0	↑ survival ↓ inflammation ↓ heart rupture
Hu et al. ¹⁰⁹	129/SvJ/ICR	21 days	0	↑ survival ↓ inflammation ↓ heart rupture
Heart Ischemia – Temporary Occlusion of LAD – Reperfusion				
Ren et al. ¹¹⁰	129/SvJ/ICR/C57BL/6J	45 min	4 hrs – 7 days	↑ heart injury ↑ inflammation ↑ apoptosis
Brain Ischemia - Permanent Occlusion of MCA				
Xu et al. ¹¹¹	129/SvJ/ICR and 129/SvJ/ICR/C57BL/6J	24 hr	0	↑ infarct size ↑ inflammation
Brain Ischemia - Temporary Occlusion of MCA - Reperfusion				
Lu et al. ¹¹²	129/SvJ/ICR/C57BL/6J	1 hr	24 hr	↑ infarct size ↑ inflammation ↑ neuronal injury ↑ apoptosis

for the first time that SR-A is required for sensing human cytomegalovirus (HCMV) by TLR3 and TLR9 in the human monocytic cell line THP-1 *in vitro*.²⁷ mRNA levels for SR-A and TLR2 increased within 10 minutes, while mRNA levels for TLR3 and TLR9 increased in less than 60 minutes after exposure to HCMV. Ligation of SR-A was required for TLR3- and TLR9-mediated signaling, which was independent of TLR2-dependent pro-inflammatory cytokine production. Induction of TLR3-dependent interferon β and TLR9-mediated induction of TNF α was dependent on ligation of SR-A. The interaction of TLR3 and TLR9 with SR-A was required to up-regulate pro-inflammatory cytokines following HCMV exposure.²⁷

J. Role of SR-A in Bone Metabolism

Several reports have shown a role of SR-A in bone remodeling and metabolism.^{117–119} Bone remodeling

is important in the maintenance of bone integrity.¹²⁰ Osteoclasts and osteoblasts play important roles in bone remodeling where osteoclasts, which are derived from a monocyte/macrophage lineage originating from hematopoietic stem cells, degrade bone matrix, whereas osteoblasts secrete bone matrix.¹²⁰ Lin et al. were the first to report a role of SR-A in bone growth and osteoclast differentiation.¹¹⁷ They observed that SR-A^{-/-} mice had 40% greater body weight compared with WT mice. The SR-A^{-/-} mice had increased bone mineral density due to significantly fewer osteoclasts, although increased bone density does not account for the substantial weight differences. Lin et al. concluded that SR-A plays an important role in normal osteoclast differentiation.¹¹⁷ Takemura et al.¹¹⁸ confirmed the observations of Lin et al.¹¹⁷ and determined the mechanism responsible for the decreased numbers of osteoclasts in SR-A^{-/-} mice. Takemura et al. determined that SR-A promotes osteoclast differentiation by stimulation of the recep-

tor for activation of NF κ B ligand and related osteoclastogenic molecules.¹¹⁸ Therefore, SR-A promotes osteoclastogenesis that provides a balance between bone formation and breakdown.

In another report, Herrmann et al. showed that SR-A mediated the clearance of fetuin A-containing calciprotein particles from the circulation.¹¹⁹ Fetuin-A is a liver-derived plasma protein that is involved in the regulation of calcified matrix metabolism and is essential for the formation of protein-mineral complexes designated calciprotein complexes. Calciprotein complexes must be cleared from the circulation to prevent local deposition in soft tissues leading to calcification, for example, calcified plaques in the aorta that are observed in advanced atherosclerosis. Herrmann et al. demonstrated for the first time that calciprotein complexes are removed from the systemic circulation of mice by SR-A on the Kupffer cells in liver and in the macrophages in the marginal zone of the spleen; therefore, SR-A is important in preventing calcific particle deposition in soft tissues.¹¹⁹

K. SR-A in Pulmonary Injury

Several studies have reported that pulmonary macrophages express SR-A,^{121,122} however, Kobayashi et al. were the first to demonstrate that SR-A protects the lung from hyperoxia-induced injury.¹²³ Using *in vivo* and *in vitro* models of lung hyperoxia and SR-A^{-/-} mice, they determined that the presence of SR-A protects the lung from hyperoxia injury by reducing oxidative stress. For example, expression of inducible nitric oxide synthase in alveolar macrophages was lower in WT mice compared with SR-A^{-/-} mice. After hyperoxia, levels of pulmonary expression of TNF α were lower in the WT mice than in SR-A^{-/-} mice, indicating that the presence of SR-A attenuated hyperoxic injury by decreasing the macrophage inflammatory response. Arrendouani et al. also showed that SR-A is protective to the lung using the ovalbumin-asthma model of lung injury.⁵⁷ They concluded that SR-A functions via a novel mechanism to down-regulate the migration of pulmonary dendritic cells to lymph nodes, thereby decreasing T-cell responses to specific inhaled aller-

gens. These data suggest that SR-A plays a protective role in pulmonary injury through two distinct mechanisms, namely decreasing oxidative injury and decreasing T-cell responses in the lung.

III. INTRACELLULAR SIGNALING

A. Intracellular Signaling after Ligand Binding by SR-A

Because SR-A does not possess typical signaling sequences in its cytoplasmic N-terminus,^{31,40,124} the mechanism(s) by which SR-A influences intracellular signaling events involves the association of SR-A with other membrane receptors that lead to the activation of both pro-survival and pro-death pathways (Fig. 3).

There have been several reports that ligands for SR-A activate cell signaling pathways presumably through engagement with SR-A.^{125–130} Miki et al. reported that incubation of AcLDL with human THP-1-derived macrophages resulted in rapid activation of the cytoplasmic tyrosine kinase Lyn. Lyn and SR-A co-precipitated with specific antibodies, indicating that they may be physically associated.¹²⁵ Falcone et al.¹²⁶ observed that incubation of AcLDL with RAW246.7 macrophages stimulated the secretion of urokinase-type plasminogen activator, a process which is regulated by protein kinase C and cyclic adenosine monophosphate-dependent pathways.^{131–134} In support of Falcone's observation, Hsu et al. showed that THP-1 macrophages incubated with AcLDL or fucoidan resulted in stimulation of tyrosine phosphorylation and increased protein kinase C.¹²⁷ Hsu et al. also observed that SR-A ligands led to activation of phospholipase C gamma 1 and phosphoinositol 3-OH kinase (PI3K).¹²⁷ In a follow-up manuscript, Hsu et al. showed that oxidized low-density lipoproteins and fucoidan up-regulated TNF α production in J774A.1 macrophages.¹²⁸ In addition, fucoidan induced interleukin-1 secretion by activating the PTK(src)/Rac1/PAK/Jnk pathway. This study suggested that macrophage SR ligands modulate specific protein kinase signaling pathways that lead to inflammatory cytokine production. Whitman et

FIG. 3: Schematic illustrating mechanisms of SR-A intracellular signaling. SR-A does not contain an intracellular activating signal sequence; therefore, SR-A interacts with other signaling and transport proteins to promote activation of cell signaling pathways. SR-A interacts with TLR4 to signal through activation of NFκB, which enters the nucleus, binds DNA, and results in the synthesis of inflammatory cytokines and a pro-death state. SR-A binds to human cytomegalovirus (HCMV) and is then transported to endosomes. There it associates with TLR3, which signals to interferon regulating factor 3 (IRF3), resulting in translocation of IRF3 to the nucleus. There, it binds to DNA and mediates interferon beta (IFNβ) synthesis, resulting in a pro-survival state. SR-A also associates with TLR9 and activates the NFκB pathway, similar to the SR-A-TLR4 association, leading to a pro-death state. After binding to the SR-A ligand fucoidan, the SR-A–fucoidan complex associates with major vault protein (MVP), which is internalized into the cell. There, it signals via the p38 and c-Jun N-terminal kinase (JNK) pathways, leading to a pro-death state. In the presence of sepsis and endoplasmic reticulum (ER) stress, the intracellular signaling shifts the balance from pro-survival to pro-death.

al. showed that the increased activation of cytosolic kinase and phospholipases after treatment of resident mouse peritoneal macrophages with AcLDL involved pertussis toxin-sensitive G proteins.¹²⁹ This finding suggested that pertussis toxin-sensitive G proteins can regulate SR-A function. Collier and Paulnock examined the effect of the SR-A ligands polyinosinic-

polycytidilic acid and LTA on TNFα secretion by RAW 264.7 macrophages.¹³⁰ They concluded that the cellular signaling response to these ligands was due to tyrosine phosphorylation and activation of the mitogen activated protein kinase pathway.

The studies cited above imply that the signaling effects of SR-A ligands are dependent on binding

and internalization of these ligands by SR-A. Kim et al. used SR-A^{-/-} mice to show that the effects of two SR-A ligands, fucoidan and LTA, on cellular activation pathways were independent of the presence of SR-A.¹³⁵ Furthermore, they showed that PI3K activation and TNF α production were due to the participation of CD14. The study by Kim et al. does not support a direct role of SR-A in intracellular signaling.¹³⁵ However, these data must be considered in light of the possible differential upregulation of other scavenger receptors in the absence of SR-A.

B. Intracellular Signaling During SR-A-Mediated Adhesion and after Uptake of Apoptotic Cells

SR-A-dependent adhesion could play a part in the pathophysiology of disease by increasing the numbers of macrophages at sites of injury and activation of intracellular signaling pathways. Post et al. showed that class A scavenger receptor-mediated cell adhesion activates pertussis-toxin-sensitive Gi/o proteins and formation of focal adhesion complexes by mouse peritoneal macrophages.¹³⁶ Nikolic et al.¹³⁷ confirmed the results of Post et al.¹³⁶ showing that SR-A-dependent adhesion was via activation of Gi/o protein. Nikolic et al. further showed that SR-A-mediated cell spreading required the sequential activation of the Src tyrosine kinase Lyn and PI3K.¹³⁷ Colewa et al. observed that PI3K regulated SR-A-mediated adhesion.¹²⁴ They suggested a mechanism in which SR-A binding to an immobilized ligand activates PI3K to recruit additional SR-A receptors to the cell surface membrane to enhance adhesion. Thus, PI3K appears to interact with SR-A to promote adhesion via the presence of a conserved motif EDAD located in the cytoplasmic N-terminus of SR-A.

SR-A is also known to participate in uptake of apoptotic cells. Todt et al. reported that SR-A signals by interacting with Mer receptor tyrosine kinase (Mertk) during uptake of apoptotic thymocytes by J774.A macrophages.²⁶ Binding of apoptotic thymocytes by macrophages resulted in a physical association between SR-A and Mertk that resulted in phosphorylation of Mertk and phospholipase C γ 2. Additional experiments using SR-A^{-/-} mice showed

that SR-A was required for optimal phosphorylation of Mertk and subsequent signaling required for apoptotic cell ingestion and clearance. Mertk is known to be essential for apoptotic cell uptake by murine macrophages, and Mertk possesses signaling capabilities via a multi-substrate docking site that can activate multiple downstream signaling intermediates.¹³⁸

Several studies have reported that SR-A may interact with other membrane components to modulate the inflammatory response (Fig. 3).^{25,27,102,106,139} For example, Seimon et al. presented evidence supporting a model in which SR-A cooperates with TLR4 following LPS treatment in endoplasmic reticulum (ER)-stressed macrophages.¹³⁹ Seimon et al. proposed that SR-A/TLR4 cooperation resulted in activation of the myeloid differentiation primary response gene 88/NF κ B-dependent signaling pathway leading to inflammatory cytokine production, while simultaneously inhibiting the pro-survival TLR4/Trif-Tram/interferon regulatory factor 3/interferon β signaling pathway.¹³⁹ In support of Seimon's model, Yu et al. showed that SR-A is required for TLR4-mediated NF κ B activation of J774.A macrophages.¹⁰² In addition, Yu et al. demonstrated a physical association between TLR4 and SR-A after LPS treatment supporting the hypothesis that TLR4 and SR-A may be co-receptors.¹⁰² In an *in vivo* model of infection, Ozment et al. demonstrated a co-association between SR-A and TLR4, but not TLR2, in lung tissue harvested from septic mice, indicating a role of SR-A as a co-receptor.¹⁰⁶ In contrast to these studies, Yu et al. provided evidence that SR-A decreases TLR4-mediated activation of NF κ B by inhibiting ubiquitination of TNF receptor-associated factor 6.⁹⁹ They showed a direct interaction between SR-A and TNF receptor-associated factor 6 in mouse bone-marrow-derived dendritic cells.

In a recent study, Ben et al. provided data to support a model in which SR-A interacts with caveolin and major vault protein to stimulate TNF α secretion via a caveolin-mediated endocytic pathway that was linked to the pro-apoptotic c-Jun N-terminal protein kinase signaling pathway.²⁵ Ben et al. demonstrated a direct interaction between SR-A and major vault protein that resulted in an increased inflammatory response to an SR-A ligand (Fig. 3).²⁵

Yew et al. showed that SR-A was required for the interaction of HCMV and subsequent intracellular signaling via endosomal TLR3 and TLR9.²⁷ These data suggested that the initial pro-inflammatory response of macrophages to HCMV was due to interaction of HCMV with TLR2 but a delayed response to HCMV was due to interaction with TLR3 and TLR9 in intracellular endosomes (Fig. 3). SR-A is endocytosed in caveoli and in clathrin-coated pits in the plasma membrane of cells followed by processing into endosomes.^{27,140,141} Therefore, it is reasonable to propose that while in the endosomes SR-A could interact with both endosomal TLR3 and TLR9 to promote intracellular activation of pro-survival and pro-death pathways.²⁷ For example, the pro-survival activation of the TLR3/IRF3 survival pathway and the TLR9/TRIF/NF κ B/TNF α pro-inflammatory pro-death pathway is illustrated in Fig. 3.

Because SR-A does not contain an intracellular activating signal sequence, SR-A interacts with other proteins to mediate intracellular signaling events (Fig. 3). Further studies are needed to explain the complex interactions of SR-A with its ligands and a host of cell signaling pathways that lead to both cell survival and cell death.

IV. SR-A: A TWO-EDGED SWORD

The published data have given rise to an intriguing dilemma. On the one hand, SR-A is clearly beneficial and/host protective in some models of disease.^{10,57,84,86,94,98,108,109,123} However, the data also indicate that SR-A contributes to the pathophysiology of other diseases and may even play a role in disease propagation.^{100,106,107,110–112} The question is what mechanism(s) might explain the conflicting role of SR-A in different disease states.

The endoplasmic reticulum (ER) stress response may provide important insights into the conflicting effects of SR-A.^{139,142–145} Seimon et al. have shown that ER-stressed macrophages treated with LPS, a TLR4 ligand, respond with inflammatory cytokine release and cell survival: However, when ER-stressed macrophages that have been concomitantly exposed to LPS and fucoidan, a SR-A ligand, result in blunt-

ing of the pro-survival interferon regulatory factor 3 pathway and activating the pro-apoptotic c-Jun N-terminal protein kinase, thereby shifting the balance from survival to cell death.¹³⁹

ER stress can be elicited by a number of stressors, i.e., alterations in cellular calcium homeostasis, accumulation of cellular lipids, alterations in cellular energy balance, ischemia, oxidative stress (redox imbalance), and increases in cellular protein synthesis.^{142–145} Macrophages accumulate cholesterol esters and express cellular markers of ER stress^{139,146} that could play a role in atherosclerosis.^{147–149} Lymphocytes from CLP-induced septic animals show ER-stress-related apoptosis.¹⁵⁰ ER stress has been shown to contribute to ischemia-induced cardiomyocyte apoptosis,¹⁵¹ and inhibition of ER stress protects the heart against ischemia/reperfusion injury.¹⁵² In the brain, ischemia activates the ER stress response.¹⁵³ Inhibition of ER stress ameliorated LPS-induced lung inflammation.¹⁵⁴ Thus, it is reasonable to conclude that prolonged ER stress and engagement of SR-A may shift the balance from cell survival to cell death. The mechanisms by which this shift takes place are likely to be complex and intricately regulated. A major goal of future studies should be to dissect these mechanisms and to discover new treatments, based on modulation of SR-A, that can shift the balance toward decreased morbidity and mortality.

V. CONCLUSION

This review highlights the pivotal role that SR-A plays in health and disease. Compelling literature indicates that SR-A contributes to the pathophysiology of inflammation, sepsis, and ischemic injury. However, published data also point to a role for SR-A as a host protective receptor, which attenuates disease progression. This dual nature of SR-A may be influenced, in part, by the experimental models that have been employed. Future studies should be focused on delineating the precise role of SR-A in specific disease entities and defining the mechanism(s)-of-action of SR-A. Of equal importance, future studies should focus on developing approaches to

modulate SR-A activity such that it can be utilized to prevent and/or treat important diseases.

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