

# Macrophage Scavenger Receptor Class A

## A Multifunctional Receptor in Atherosclerosis

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**Abstract**—In atherogenesis, elevated plasma levels of low density lipoprotein (LDL) lead to the chronic presence of LDL in the arterial wall. There, LDL is modified (eg, oxidized), and these modified lipoproteins activate endothelial cells, which attract circulating monocytes. These monocytes enter the vessel wall, differentiate into macrophages, and subject the modified lipoproteins to endocytosis through scavenger receptor pathways. This unrestricted uptake, which is not limited by intracellular cholesterol levels, eventually leads to the formation of lipid-filled foam cells, the initial step in atherosclerosis. Macrophage scavenger receptor class A (SRA) is thought to be one of the main receptors involved in foam cell formation, mediating the influx of lipids into the macrophages. In addition to this role in modified lipoprotein uptake by macrophages, the SRA has been shown to be important in the inflammatory response in host defense, cellular activation, adhesion, and cell-cell interaction. Given the importance of these processes in atherogenesis, these latter functions may prove to make the SRA a multifunctional player in the atherosclerotic process. (*Arterioscler Thromb Vasc Biol.* 2000;20:290-297.)

**Key Words:** inflammation ■ cardiovascular disease ■ modified lipoprotein ■ transgenic mouse

### SRA Structure, Function, and Expression

In 1979, Goldstein et al<sup>1</sup> first described a binding site on macrophages that mediated the uptake and degradation of acetylated LDL (acLDL) and produced massive intracellular cholesterol deposition. This binding site was initially referred to as the acLDL receptor and later became the macrophage scavenger receptor. Currently, it is known that this receptor belongs to a large family of scavenger receptors consisting of at least 6 classes (Table 1),<sup>2</sup> all mediating the uptake of modified LDL. This article will focus on macrophage scavenger receptor class A (SRA) types I and II. This multifunctional receptor has been shown to bind a broad variety of ligands. Binding and competition studies have shown that these ligands are generally polyanionic macromolecules, including (1) acLDL, oxidized LDL (oxLDL), and maleylated or glycated BSA; (2) polyribonucleotides (poly G and poly I but not poly A, T, or C); (3) polysaccharides, including lipopolysaccharide (LPS) and lipoteichoic acid (LTA), which are both surface components of bacteria, and dextran sulfate; and (4) anionic phospholipids, such as phosphatidylserine.<sup>3-8</sup>

The molecular characterization of the SRA began with the cloning of bovine SRA in 1990.<sup>9,10</sup> It was shown that SRA is a trimeric transmembrane glycoprotein consisting of 6 distinct domains (Figure 1). The collagen-like domain has been shown to be the site for receptor interaction with modified lipoproteins.<sup>11-14</sup> This collagen-like domain contains a lysine cluster, which forms a positively charged groove that specifically interacts with the negatively charged ligands. The gene

coding for the 6 different domains contains 11 exons and spans ≈80 kb in humans.<sup>15</sup> Two variants of SRA (types I and II) are generated by alternative splicing of the same gene. Type I SRA is encoded by exons 1 to 8 and 10 to 11 and contains a 110-amino acid C-terminal cysteine-rich domain. Type II SRA is encoded by exons 1 to 9 and lacks the cysteine-rich domain (Figure 1). Recently, a third transcript, which acts in a dominant-negative manner, was described. This variant resembles type I SRA but skips exon 10, thereby deleting part of the cysteine domain.<sup>16</sup> The exact function of the cysteine-rich domain has not yet been elucidated. However, specific regulation of the type I and II isoforms has been described.<sup>17-19</sup> Freshly isolated human monocytes express low amounts of SRA mRNA, but it is highly upregulated during differentiation to macrophages. This increase in expression is mainly observed for type I SRA. However, both types have been shown to be present in atherosclerotic lesions.<sup>20</sup> Because SRA type I has been described as a receptor containing a cysteine-rich domain, a new family of genes has emerged, all containing a scavenger receptor cysteine-rich domain. A function has been proposed for only 1 of these genes. CD6, containing 3 scavenger receptor cysteine-rich domains, has been shown to be the ligand for the leukocyte adhesion molecule CD166,<sup>21</sup> indicating the involvement of the scavenger receptor cysteine-rich domain in cell-cell interaction. For SRA types I and II, no differences have been shown in ligand interaction between both isoforms. Recently, we have generated a mouse model specifically

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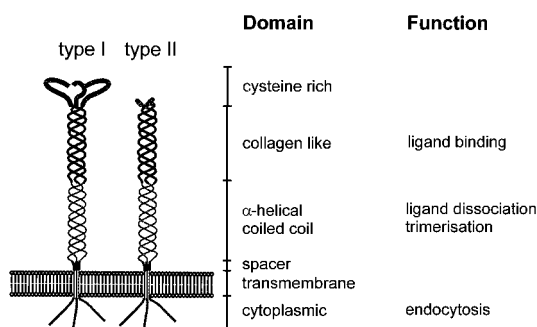
**TABLE 1. Members of Scavenger Receptor Family, Their Cell Types of Expression, Putative Functions, and Ligands**

Class/Name	Cell Type	Function	Major Ligands
<b>Class A</b>			
SRA I/II/III	Macrophages	Uptake of modified LDL, innate immunity, adhesion	AcLDL, oxLDL, AGE, LPS, LTA, apoptotic thymocytes
MARCO	Spleen macrophages	Innate immunity?	AcLDL, bacteria
<b>Class B</b>			
CD36	Platelets, monocytes, macrophages	Fatty acid transporter, uptake of apoptotic cells	OxLDL, apoptotic cells
SR-BI (CLA-I)	Adrenals, liver, gonads	Cholesterol transport	HDL, oxLDL
<b>Other</b>			
CD68 (macrosialin)	Macrophages	Unknown	OxLDL, apoptotic cells
SR-C	Embryonic insect macrophages	Uptake of apoptotic cells	AcLDL
SREC	Endothelial cells	Unknown	AcLDL, oxLDL
LOX-1	Endothelial cells	Unknown	OxLDL

lacking type I SRA. This mouse may give new insight into the *in vivo* function of the cysteine-rich domain of type I SRA.

The expression of SRA is mainly confined to macrophages, including Kupffer cells and alveolar, splenic, thymic, and many other tissue macrophages.<sup>20,22,23</sup> SRA is also expressed on endothelial cells lining the liver and adrenal sinusoids<sup>20,22</sup> and on the high endothelial cells of postcapillary venules in the lymph nodes.<sup>24</sup> Immunohistochemical studies could not detect SRA expression in the aortic endothelium of cows,<sup>23</sup> mice,<sup>22</sup> and humans.<sup>25</sup> Therefore, it is likely that aortic endothelium does not express SRA. Different reports have shown the presence of SRA on smooth muscle cells, *in vitro* and *in vivo*, in atherosclerotic lesions,<sup>26–28</sup> although other reports did not find SRA expression on smooth muscle cells and found it to be restricted to the macrophage foam cells in the lesions.<sup>29,30</sup>

Several different motifs in the promoter of SRA are required for the expression of SRA in macrophages. Positive transcriptional control of SRA has shown to be mediated by a domain for PU.1/Spi-1, a macrophage-specific and B-cell-specific transcription factor belonging to the *ets* domain

**Figure 1.** Structure of SRA types I and II with the 6 domains and their functions.**TABLE 2. Effects of Different Cytokines and Growth Factors on Macrophage SRA Expression**

Cytokine/Growth Factor	Effect on Macrophage SRA Expression
TNF- $\alpha$	↓
IFN- $\gamma$	↓
M-CSF	↑
GM-CSF	↑/↓
TGF- $\beta$	↓
PDGF	↑

TNF- $\alpha$  indicates tumor necrosis factor- $\alpha$ ; IFN- $\gamma$ , interferon- $\gamma$ ; TGF- $\beta$ , transforming growth factor- $\beta$ ; PDGF, platelet-derived growth factor; ↓, downregulation; and ↑, upregulation.

family, and by domain-binding activator protein-1 (AP-1) family members and a distinct subset of *ets* family members, which include c-Jun, JunB, and *ets2*.<sup>31</sup> In particular, the AP-1 domain has been shown to be of great importance because several AP-1 sites have been found in the SRA promoter area. These elements induce SRA transcription in monocytes in response to macrophage colony-stimulating factor (M-CSF),<sup>31–34</sup> probably through protein kinase C activity.<sup>26,33</sup> The elevated expression in atherosclerotic lesions and foam cells is also attributed to these transcriptional elements, as was shown in transgenic mice by use of a reporter gene driven by different SRA promoter elements.<sup>35</sup>

The expression levels of SRA in macrophages are influenced by several different cytokines (Table 2). Both tumor necrosis factor- $\alpha$  and interferon- $\gamma$  are produced locally in atherosclerotic lesions and inhibit SRA activity on macrophages by transcriptional and posttranscriptional regulation.<sup>36,37</sup> M-CSF and granulocyte M-CSF (GM-CSF) are upregulators of murine SRA expression.<sup>34,38,39</sup> However, another group reported a downregulation of SRA expression by GM-CSF<sup>18</sup> in human monocyte-derived macrophages, so the effect of this factor is not completely clear and may depend on the differentiation state of the macrophages studied. Two growth factors that are expressed in lesions, platelet-derived growth factor and transforming growth factor- $\beta$ , were shown to increase and decrease, respectively, SRA expression in monocyte-derived macrophages.<sup>40–42</sup> Recently, it was shown that peroxisome proliferator-activated receptor- $\gamma$  (PPAR- $\gamma$ ), a regulator of macrophage activation, inhibits the expression of SRA.<sup>43</sup>

### SRA in Adhesion and Cell-Cell Contact

In 1993, Fraser et al<sup>44</sup> isolated a monoclonal antibody (2F8) that inhibited the calcium-independent adhesion of RAW264 macrophages to tissue culture plastic. They showed that this monoclonal antibody was directed against murine SRA, and this was the first evidence that SRA could mediate cellular adhesion and thereby function in the recruitment and retention of mononuclear phagocytes to tissues, such as atherosclerotic lesions. The adhesion observed was dependent on the presence of serum, indicating that SRA adhesion activity needs a serum component to function. In more elaborate studies, it was shown that 2F8 could also block the adherence of macrophages to tissue sections. RAW264 macrophages adhere in an EDTA-resistant fashion to spleen, lymph node, liver, thymus, gut, skin, and lung tissue sections. This

adhesion could be completely blocked by 2F8 in all tissues except liver and gut.<sup>22,44–46</sup> Again, this shows that the SRA may be important for the recruitment and retention of macrophages to tissues, although it has not been possible to demonstrate by use of 2F8 antibodies that SRA can mediate macrophage migration in vivo. This problem may be attributable to the very rapid clearance of 2F8 from the circulation, which prohibits these in vivo experiments. Recently, Robbins and Horlick<sup>47</sup> transfected HEK293 cells with human SRA. Although this cell line poorly adheres to tissue culture plastic, after these cells are transfected with human SRA, adherence to plastic and glass is largely improved.

In the thymus, immature thymocytes often undergo apoptosis during selection and are removed by phagocytosis by thymic macrophages. SRA was shown to be an important macrophage receptor involved in the recognition and uptake of these apoptotic thymocytes. In vitro, thymic macrophages from SRA-deficient mice showed an  $\approx 50\%$  reduction in the uptake of apoptotic thymocytes.<sup>48–50</sup> The phagocytotic uptake of normal thymocytes was not changed.<sup>50</sup> In addition, Yokota et al<sup>51</sup> demonstrated the cell adhesion properties of the SRA by showing that the SRA could mediate the adhesion of activated B cells to Chinese hamster ovary cells stably expressing SRA type I or type II.

Nonenzymatic glycation of arterial basement membrane proteins occurs during normal aging and at an accelerated rate in diabetic patients. With time, these glucose adducts form advanced glycation end (AGE) products. These AGEs are taken up by cells through SRA pathways.<sup>52–56</sup> El Khoury et al<sup>57</sup> showed that macrophages can adhere to surfaces coated with glucose-modified basement membrane collagen IV through their SRAs. These findings indicate a potential role of SRA in the accelerated atherogenesis found in diabetes; ie, SRA promotes the adhesion of macrophages to glucose-modified basement membrane proteins in the arterial wall. Furthermore, it has been shown that ligation of AGEs to SRA stimulates macrophages to secrete proinflammatory cytokines and growth factors and could thereby enhance the attraction of monocytes and inflammation at the lesion site.<sup>58–62</sup>

### SRA in Host Defense, Innate Immunity, and Cellular Activation

In the course of the characterization of the binding specificity of the SRA, many different ligands, in addition to the modified lipoproteins, have been discovered. These include maleylated BSA, polyribonucleotides such as poly I and poly G (but not poly A, T, or C), polysaccharides (eg, dextran sulfate), anionic phospholipids such as phosphatidylserine, and other negatively charged molecules such as polyvinyl sulfate.<sup>1,3–6</sup> All these ligands are polyanionic, but not all polyanionic molecules are ligands for SRA. Extension of the search for new ligands for SRA resulted in the identification of lipid A and its precursor, lipid IVA, as molecules that can bind to the SRA.<sup>7</sup> Lipid A is a constituent of LPS that is present on the surface of Gram-negative bacteria and stimulates macrophage activation and causes endotoxic shock. Binding and uptake of LPS by the macrophage cell line RAW264 is mediated by the SRA. In vivo, the liver uptake of LPS could be blocked by SRA ligands. More recently, it was shown that SRA can also bind to Gram-positive bacteria,

including *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Streptococcus aureus*, *Enterococcus hirae*, and *Listeria monocytogenes*.<sup>8</sup> Competition studies that used LTA, a surface molecule of these Gram-positive bacteria, showed that this was recognized by the SRA. With the establishment of SRA knockout mice, the in vivo role of SRA on LPS and infection has been investigated. Suzuki et al<sup>63</sup> have found that SRA-deficient mice show an increased susceptibility to infection with *Listeria monocytogenes* or herpes simplex virus type 1. Haworth et al<sup>64</sup> extended these investigations to a model with acquired immunity by using a viable bacillus Calmette-Guérin infection model. They showed that after infection with bacillus Calmette-Guérin, SRA knockout mice are much more susceptible to LPS-induced endotoxic shock. These mice produce more tumor necrosis factor- $\alpha$  and interleukin-6 and show an increased mortality in response to LPS. This increased mortality could be blocked by administration of anti-tumor necrosis factor- $\alpha$  antibodies before the LPS challenge. An explanation for this increased sensitivity to LPS-induced endotoxic shock might be a changed balance between LPS receptors that do trigger the release of cytokines (eg, CD14) and receptors that mediate the binding and uptake of LPS but do not directly mediate an inflammatory response (eg, SRA). The exact nature of the increased susceptibility of SRA knockout mice to completely different pathogens, such as bacteria and viruses, remains unclear but may indicate an even broader involvement of the SRA than just the binding of LPS and LTA.

OxLDL and lysophosphatidylcholine are able to induce the growth of macrophages. It has been shown that oxLDL, but not acLDL, has this mitogenic effect. Treating acLDL with phospholipase A<sub>2</sub>, however, markedly increased its mitogenic activity, concomitant with a 75% conversion of its phospholipids to lysophosphatidylcholine.<sup>65</sup> The mitogenic effect of lysophosphatidylcholine containing modified LDL was shown to be mediated by uptake through the SRA, because macrophages from SRA-deficient mice showed a strong decrease in cell growth in response to oxLDL.<sup>66</sup> More recently, it was shown that macrophage growth induced by oxLDL is mediated through uptake via the SRA, followed by protein kinase C activation and subsequent secretion of GM-CSF. This GM-CSF secretion was strongly reduced in SRA-deficient macrophages.<sup>67</sup> In the atherosclerotic lesion, this GM-CSF production in response to oxLDL may play a very important role in priming macrophage growth, in conjunction with other cytokines. In addition to this proliferative role for the SRA, more recently, SRA expression was shown to confer resistance of macrophages to apoptosis.<sup>68</sup> In differentiated THP-1 monocytes and Chinese hamster ovary cells, expression of SRA increased the resistance to G-protein-coupled apoptosis. This antiapoptotic effect of the SRA can greatly affect apoptosis in atherosclerotic lesions.

Other activation markers are also affected by oxLDL. Recently, it was shown that PPAR- $\gamma$ , a modifier of macrophage activation, is regulated by both colony stimulating factors (M-CSF and GM-CSF) and oxLDL.<sup>43,69,70</sup> These 2 factors, both present in atherosclerotic lesions, were shown to stimulate PPAR- $\gamma$  expression in primary macrophages and monocytic cell lines. The activation of PPAR- $\gamma$  was shown to inhibit NF- $\kappa$ B activation and thereby reduce the inflammatory response. SRA expression is affected by PPAR- $\gamma$ , and

oxLDL uptake through SRA modifies GM-CSF production by macrophages.<sup>67</sup> Some studies have also reported a modifying effect of the activation response to LPS by oxLDL through SRA.<sup>71,72</sup> How these processes are exactly intertwined is not yet clear.

In conclusion, it can be said that different SRA ligands, including oxLDL, modify macrophage activation through as-yet-unknown pathways, thereby greatly affecting the atherosclerotic process in the vessel wall.

### SRA in Foam Cell Formation and Atherosclerosis

Atherogenesis is induced by elevated levels of atherogenic lipoproteins, such as LDL and VLDL, in the blood. This leads to the accumulation of LDL in the intima, where it becomes modified. This modified LDL activates the endothelial cells lining the vessel wall, attracting monocytes from the circulation, which subsequently will adhere to the endothelial cells, cross the endothelial layer to enter the media, differentiate into macrophages, and eventually become foam cells. These foam cells are characterized by a massive accumulation of cholesterol esters,<sup>73</sup> resulting from the unrestricted uptake of modified lipoproteins, such as oxLDL, through scavenger receptor pathways. The SRA was first identified as a binding site specific for acLDL on macrophages that mediates the formation of foam cells.<sup>1</sup> Overexpression of SRA in Chinese hamster ovary cells results in foam cell formation after incubation with acLDL.<sup>74</sup> We have found that isolated peritoneal macrophages from a recently generated mouse model overexpressing the human SRA gene also show an increased foam cell formation and cholesterol ester accumulation after incubation with acLDL.<sup>75</sup> Furthermore, the SRA has been shown to be highly expressed in atherosclerotic lesions,<sup>76,77</sup> whereas the SRA ligand, oxLDL, is present in plaques.<sup>77–79</sup> On the basis of these results, SRA has been assigned an important role in atherogenesis.<sup>80–82</sup>

The relevance of the SRA in atherosclerosis was first studied in vivo when SRA knockout mice were generated.<sup>63</sup> Resident peritoneal macrophages from SRA-deficient mice show an 80% reduction in acLDL degradation and a 30% reduction in oxLDL degradation. However, the in vivo clearance by the liver of both forms of modified LDL was not changed.<sup>63,83,84</sup> This observation is in line with the results of Van Berkel et al,<sup>85</sup> who showed that 70% of the injected dose of acLDL was cleared by the liver endothelial cells in SRA-deficient and wild-type mice, indicative of the fact that for this process other receptors are the main players. Future research into these receptors is needed to elucidate the main endothelial receptors involved in modified LDL clearance. It should be noted, however, that uptake of modified LDL by the liver for clearance and uptake of modified LDL by macrophages in the subintimal space in the process of atherosclerosis are 2 completely different processes that do not necessarily share any receptor pathways.

To study the effect of SRA deficiency on atherosclerosis, SRA knockout mice were crossed with different mouse strains susceptible to atherosclerosis. On an apoE-deficient background, SRA deficiency resulted in a moderate increase in plasma cholesterol levels coinciding with a strong decrease (60%) in lesion area development.<sup>63</sup> However, on an LDL

**TABLE 3. Different Atherosclerosis Experiments Performed With Different SRA Mouse Models**

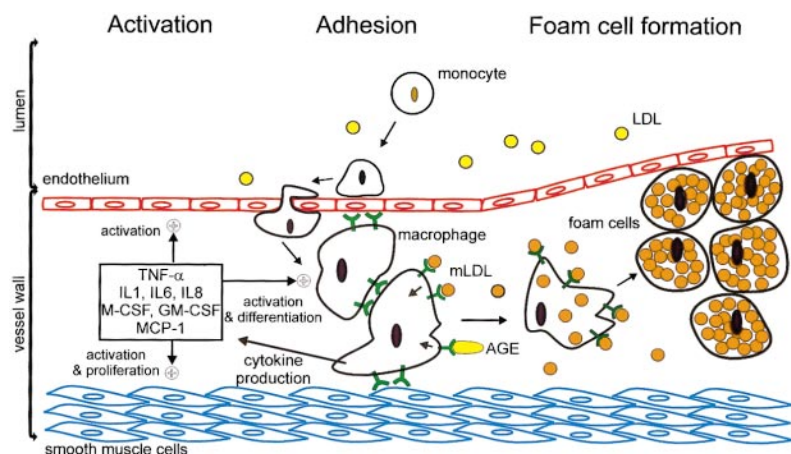
SRA Genotype	Atherosclerotic Model	Effect on Cholesterol	Effect on Atherosclerosis
SRA <sup>-/-</sup>	ApoE <sup>-/-</sup>	↑	↓ ↓
SRA <sup>-/-</sup>	LDLR <sup>-/-</sup>	↓	↓
SRA <sup>-/-</sup>	APOE3Leiden	...	↑
MSR1 transgene	LDLR <sup>-/-</sup>	...	↓

Shown are the SRA model, the atherosclerotic background, and the effects of SRA on cholesterol levels and atherosclerosis compared with those of SRA wild-type mice.

receptor (LDLR)-deficient background, SRA deficiency resulted in a 20% lower plasma cholesterol level and only a 20% reduction in atherosclerosis.<sup>86</sup> We have bred the SRA knockout mice on an APOE3Leiden transgenic background. These mice carry a dominant variant of the human apoE gene, resulting in hypercholesterolemia and sensitivity to diet-induced atherosclerosis.<sup>87,88</sup> In these mice, absence of SRA resulted in the development of more severe lesions, as judged by their cellular composition.<sup>89</sup> This means that in the APOE3Leiden mice, SRA deficiency actually enhanced atherosclerosis.

To extend the in vivo studies on SRA, additional models have been generated. Wölle et al<sup>90</sup> generated a mouse model with hepatic overexpression of SRA. Bovine SRA type I cDNA was cloned behind the mouse transferrin promoter, which resulted in overexpression of SRA in hepatocytes. They showed that SRA can prevent diet-induced hyperlipidemia through a reduction in apoB-containing lipoproteins. In addition, high levels of SRA overexpression increased HDL cholesterol levels, decreased cholesteryl esters in the liver, and increased the fecal bile acid flux, all in the presence of a high-fat diet. This shows that the SRA can affect lipid levels in the blood, although the hepatocytes are not the natural site of SRA expression in the liver. Overexpression of SRA in the liver Kupffer cells, its natural site of expression, will have more subtle effects. Recently, we generated a mouse carrying the human SRA gene region as a 180-kb transgene.<sup>75</sup> Macrophages from these humane SRA transgenic mice (MSR1 mice) show a high expression of human SRA. This results in an increased degradation of acLDL and oxLDL in vitro. Moreover, these macrophages show an enhanced foam cell phenotype after incubation with acLDL. However, when crossed on an LDLR-deficient background, the MSR1 transgenic mice showed a decrease in atherosclerosis. Similar results were obtained by Teupser, Thierry, and colleagues.<sup>91,92</sup> They used a completely different approach by generating 2 rabbit strains, from 1 parental strain, by selecting for a high and a low susceptibility to diet-induced atherosclerosis. This strategy was maintained during >10 generations of breeding. They showed that the rabbits with a low susceptibility to atherosclerosis have elevated SRA expression levels compared with levels in rabbits that have a high susceptibility to atherosclerosis.

Thus, several different atherosclerosis experiments are not in agreement. The results are outlined in Table 3. Between the different mouse models with an absence of SRA, opposing effects of SRA on the development of atherosclerosis have been observed. In addition, these models do not all confirm



**Figure 2.** Atherosclerotic lesion formation with the different processes in which the SRA may play an important role. Indicated are adhesion and cell-cell interaction of macrophages in the lesion, activation of the lesion through macrophage-derived cytokines modulated by the SRA, and foam cell formation in which the SRA mediates the unrestricted uptake of modified LDL (mLDL) by macrophages. Endothelial cells are red, smooth muscle cells are blue, and SRA is depicted in green. TNF- $\alpha$  indicates tumor necrosis factor- $\alpha$ ; IL, interleukin; and MCP-1, monocyte chemoattractant protein-1.

the results found in studies of animals overexpressing SRA. This shows that in addition to the uptake of modified lipoproteins, other functional properties of SRA probably affect atherogenesis. Some research is focusing on the use of SRA agonists or antagonists as possible drugs against atherosclerosis.<sup>93</sup> However, the broad range of the functional properties of SRA should be taken into account when considering this. Blocking the SRA with antagonists will not just simply block lipid uptake and thereby reduce atherosclerosis, as is clear from our results with the SRA-deficient mice on an APOE3Leiden background.<sup>89</sup>

### Conclusion

Figure 2 outlines the atherosclerotic process and the many steps in which the macrophage SRA participates. SRA may be a player in 3 processes.

First, the invasion of monocyte-derived macrophages into the lesion area is the first process in which the SRA may play a role. In response to the activation of the endothelium, circulating monocytes adhere to the vessel wall and enter the lesion area. There, they differentiate into macrophages. The adherence and interaction of these macrophages with other cells in the plaque, such as endothelial cells, smooth muscle cells, or other macrophages, may be mediated through the SRA, as is strongly suggested by *in vitro* data. Furthermore, uptake or removal of apoptotic cells from the atherosclerotic lesion may also be mediated by the SRA. In addition to this direct cell-cell interaction, the SRA may also mediate binding of macrophages to (AGE-modified) extracellular membrane molecules, which have also been shown to be present in the plaque. Whether this adhesive function of the SRA in atherogenesis will turn out to be proatherogenic or antiatherogenic is not clear.

Second, the SRA may modulate the activation of macrophages in the plaque. In response to this activation, macrophages secrete a repertoire of cytokines that will act on the endothelial cells, smooth muscle cells, and macrophages themselves that are present in the lesion. Binding and uptake of modified LDL and AGE-modified proteins have been shown to modulate the activation of macrophages, which may also be the case in atherosclerotic lesions. The different SRA ligands present in the plaque can modify the activation of macrophages, thereby changing the cytokines produced in the plaque. This will result in a change in activation and inflammation profile of such a lesion. The antiapoptotic effect of

SRA expression may modulate the rate of apoptosis in the lesion, affecting the development of the plaque. Again, these modifications of macrophage activation through SRA pathways can turn out positive or negative for atherogenesis. In addition to this modification of macrophage activation through SRA ligands, changing the cytokines produced in a lesion can also affect SRA expression itself, as a sort of feedback loop.

Third, the SRA does play an important role in the foam cell formation itself. The modified LDL present in the plaques is taken up through the SRA, resulting in an accumulation of lipid droplets in macrophages, leading to foam cell formation. Modification of SRA will influence this process and change lesion formation. Most of the *in vitro* data suggest that overexpression of the SRA enhances the accumulation of fat in the cells; thus, the SRA should be a proatherogenic factor. However, one can also envision, very early in the process of atherogenesis, removal of modified lipoproteins from the vessel wall to be beneficial because this may reduce inflammation at the lesion area.

The multifunctional nature of the SRA is clearly illustrated by its involvement in cell adherence, activation, and foam cell formation. All these processes are involved in the development and progression of atherosclerosis. This likely explains the divergent outcomes of experiments involving atherosclerosis in different animal models. SRA-deficient mice showed a reduction in lesion area when crossed on an apoE or LDLR-deficient background but showed an enhancement of lesion development when crossed on an APOE3Leiden transgenic background. Mice overexpressing the human SRA showed a reduction in lesion area when crossed on an LDLR-deficient background. An antiatherogenic effect of the SRA was also found in rabbit strains expressing a high level of SRA.

In conclusion, we propose the SRA to play an important role in many processes in atherogenesis (some are proatherogenic, and others are antiatherogenic), depending on the local factors mediating atherosclerosis. The net result of the balance between these proatherogenic and antiatherogenic properties of the SRA will be determined by the dominance of these processes that drive atherogenesis in a specific situation. It is clear that additional investigation is necessary to fully appreciate the role of the SRA in the different processes underlying atherogenesis.

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