Brief Review

S100A8 and S100A9 in Cardiovascular Biology and Disease

Michelle M. Averill, Claus Kerkhoff, Karin E. Bornfeldt

Abstract—There is recent and widespread interest in the damage-associated molecular pattern molecules S100A8 and S100A9 in cardiovascular science. These proteins have a number of interesting features and functions. For example, S100A8 and S100A9 (S100A8/A9) have both intracellular and extracellular actions, they are abundantly expressed in inflammatory and autoimmune states, primarily by myeloid cells but also by other vascular cells, and they modulate inflammatory processes, in part through Toll-like receptor 4 and the receptor for advanced glycation end products. S100A8/A9 also have anti-inflammatory and immune regulatory actions. Furthermore, increased plasma levels of S100A8/A9 predict cardiovascular events in humans, and deletion of these proteins partly protects Apoe<sup>−/−</sup> mice from atherosclerosis. Understanding the roles of S100A8 and S100A9 in vascular cell types and the mechanisms whereby these proteins mediate their biological effects may offer new therapeutic strategies to prevent, treat, and predict cardiovascular diseases. (Arterioscler Thromb Vasc Biol. 2012;32:223-229.)

Key Words: atherosclerosis ■ immune system ■ macrophages ■ S100A8 ■ S100A9

S100A8 (calgranulin A or migration inhibitory factor-related protein 8; MRP-8) and its binding partner S100A9 (calgranulin B, or MRP-14) are members of the S100 calcium-binding family of proteins, which exhibit increased levels in a number of inflammatory and autoimmune states.1 S100A8 and S100A9 form a heterocomplex, termed S100A8/A9 or calprotectin, but the 2 proteins may also have distinct functions and are regulated in part by different mechanisms.2 The role of S100A8 and S100A9 in biology and disease is complex.3–7 S100A8 and S100A9 (S100A8/A9) are generally viewed as inflammatory, but further studies have revealed both anti-inflammatory and immune regulatory actions.2,6–7 The ability of S100A8/A9 to modulate inflammatory processes appears to be both context and cell type specific, suggesting an intricate network of regulation. Another layer of complexity surrounding the actions of S100A8/A9 is that these proteins have both intracellular and extracellular functions. The intracellular functions include calcium and arachidonic acid binding, and regulation of microtubuli.8,9 Released S100A8/A9 exert extracellular functions, some of which are mediated by Toll-like receptor 4 (TLR4),10 the receptor for advanced glycation end products (RAGE),11 or other receptors.12 S100A8/A9 are released from damaged and dying cells or activated cells through an atypical pathway that appears to require protein kinase C13 and RAGE,14 and S100A8 and S100A9 are therefore included in the group of proteins termed damage-associated molecular pattern (DAMP) molecules.6

Recently, S100A8/A9 were found to be of significance in cardiovascular disease in both humans and mice. In this review, we discuss S100A8/A9 as mediators of biological effects in the cardiovascular system, with a special focus on atherosclerosis and cardiac dysfunction, and S100A8/A9 as markers of cardiovascular events.

What Cardiovascular Cell Types Express and Release S100A8/A9?

Many cell types influence cardiovascular disease progression. Understanding which cells express and release S100A8/A9 is one of the first steps in elucidating the cardiovascular effects of S100A8/A9. Constitutive S100A8/A9 expression is believed to be limited to neutrophils and monocytes. This expression is tightly regulated throughout hematopoietic development and is lost during macrophage maturation. However, recent reports have highlighted the maintained expression of S100A8/A9 in some mature myeloid cell populations and the induction of S100A8/A9 expression in nonmyeloid cardiovascular cell types, as discussed below. These cell populations play distinct roles in cardiovascular biology and disease and are affected by S100A8/A9 in different ways (Figure 1).

Expression of S100A8/A9 in Hematopoietic Development, Neutrophils, and Monocytes

S100A8 and S100A9 are predominantly expressed in, and released from, myeloid cells on cellular activation.1,15,16 An early study of S100A9 gene expression in human cells demonstrated the tight regulation of S100A9 gene expression in a differentiation- and lineage-specific manner within the hematopoietic system.17 Primitive, uncommitted CD34+
S100A9 is detectable only in CD15 of CD11b and CD14. Within the neutrophilic pathway, upregulation of S100A9 correlates with the expression of vascular smooth muscle cells, which might contribute to fibrous cap formation. Thus, S100A8/A9 affect the major cell types involved in atherosclerosis, and these proteins have cell type-selective effects. The relative contribution of these cell types during different stages of lesion progression is likely to govern the overall effect of S100A8/A9 inhibition.

CD38⁺CD33⁻ and early myeloid CD34⁺CD33⁺ progenitor cells lack expression of S100A9. During monocyte maturation, upregulation of S100A9 correlates with the expression of CD11b and CD14. Within the neutrophilic pathway, S100A9 is detectable only in CD15⁺ cells, in which it slightly precedes and then correlates with CD11b expression. Mature CD15⁻CD16⁻CD33⁻ neutrophils express S100A9, indicating that S100A9 expression is initiated during maturation of promyelocytes toward myelocytes and then maintained up to the level of mature neutrophils. Similar patterns of expression are observed in murine myeloid development. Other lineage hematopoietic cells, including the CD19⁺B-lineage, CD3⁺T-lineage, and GlyA-positive erythroid cells, are S100A9 negative, although recent reports describe S100A8 and S100A9 gene expression in a highly purified B-cell population and in platelets. S100A8 and S100A9 constitute approximately 40% of the cytosolic protein fraction in circulating human blood neutrophils and 1% in monocytes. Although expression is down-regulated during maturation of peripheral blood monocytes to tissue macrophages, expression can be found in macrophages in inflamed tissues.

Expression of S100A8/A9 in Other Myeloid-Derived Cell Populations
S100A8/A9 are expressed in dendritic cells (DCs) and myeloid-derived suppressor cells. Although S100A8/A9 expression diminishes during differentiation into DCs, some expression is maintained in DCs. Moreover, gene expression of S100A8 and S100A9 is significantly upregulated in mature human DCs after interleukin-10 treatment. In contrast to macrophages, DCs constitutively release S100A8/A9. Myeloid-derived suppressor cells also synthesize and secrete S100A8/A9, which in turn activate RAGE and promote myeloid-derived suppressor cell migration. These cells accumulate in tumor-bearing hosts and in response to inflammation, where they inhibit T and natural killer cell activation and DC differentiation. Another myeloid-derived cell population, termed fibrocytes, expresses S100A8/A9. Human fibrocytes are believed to be derived from circulating CD14⁺ monocytes, to express typical macrophage markers, and to play a role in tissue repair and fibrosis. The roles of myeloid-derived suppressor cells and fibrocytes in cardiovascular disease are unknown.

Expression of S100A8/A9 in Nonmyeloid Cells
The hallmark of S100A8 and S100A9 expression in nonmyeloid cells is their gene induction to inflammatory mediators. There is little S100A8/A9 in endothelial cells and vascular smooth muscle cells (VSMCs) under normal conditions. Expression in endothelial cells can be induced after activation with lipopolysaccharide (LPS), interleukin-1β, or tumor necrosis factor-α, or after exposure to elevated glucose levels in vitro or diabetes in vivo. No detectable release of S100A8/A9 has been found from cultured endothelial cells. In VSMCs, S100A9 expression is induced by the Gram-negative bacterium Porphyromonas gingivalis, and S100A8/A9 expression is stimulated by LPS in cardiomyocytes. Together, these studies show that S100A8/A9 expression can be induced in nonmyeloid cardiovascular cells through inflammatory stimuli likely to be present in atherosclerotic lesions and other cardiovascular pathologies.

S100A8/A9 release from intact nonmyeloid cells is significantly lower than that from myeloid cells, suggesting that the biological effects of S100A8/A9 expressed by these cells might be largely intracellular, unless membrane integrity is compromised. Accordingly, Croce et al demonstrated that the effects of S100A8/A9 on VSMC proliferation are mediated by intracellular actions.

S100A8/A9 Play Important Roles in Atherosclerosis and Vascular Injury

**Human Studies**
Monocytes play important roles in all stages of atherosclerosis in humans and mice. It was recently shown that the human CD14⁺CD16⁻ monocyte population expresses more S100A8 than does the CD14⁺CD16⁺ monocyte population, similar to the elevated expression of S100A8 in mouse Ly-6C⁺ monocytes, as compared with Ly-6C⁻ monocytes. In mice, the Ly-6C⁺ monocyte population preferentially infiltrates lesions of atherosclerosis, but the role of different monocyte populations in human atherosclerosis is not well understood. Within human lesions, S100A9 immunoreactivity is associated with macrophages, microvessels, and calcified areas. A subsequent study demonstrated that the percentage of S100A8/A9-positive macrophages is higher in rupture-prone lesions as compared with stable ones. Furthermore, increased serum levels and expression of...
S100A8/A9 were observed in infiltrated neutrophils in atherosclerotic plaques of patients with unstable angina.40

The interest in S100A8/A9 in relation to cardiovascular disease increased markedly when Healy et al.21 demonstrated that plasma levels of S100A9 among apparently healthy women predict the risk of future nonfatal myocardial infarction, nonfatal stroke, and cardiovascular death. S100A8/A9 were subsequently found to be an early marker for detection of acute coronary syndromes,41 and the risk of a recurrent cardiovascular event was increased with each increasing quartile of S100A8/A9 in the Pravastatin or Atorvastatin Evaluation and Infection Therapy: Thrombolysis in Myocardial Infarction (PROVE IT-TIMI 22) trial.42 Together, these studies demonstrate that plasma levels of S100A8/A9 appear to be a marker of cardiovascular risk in humans.

**Mouse Studies**

Monocyte populations that infiltrate atherosclerotic lesions in Apoe<sup>−/−</sup> mice express S100A9.43 Studies in mice have also demonstrated that S100A8/A9 are upregulated in macrophages overexpressing urokinase plasminogen activator concomitant with increased plaque rupture in low-density lipoprotein receptor–deficient (Ldlr<sup>−/−</sup>) mice44 and that S100A8 gene expression is reduced in macrophages from regressing lesions.45 Together, these studies suggest that S100A8/A9 are upregulated in activated macrophages in vivo. Interestingly, a connection to diabetic vascular disease was established with the findings that macrophages from diabetic Ldlr<sup>−/−</sup> mice express and secrete higher levels of S100A8 as compared with macrophages from nondiabetic mice46 and that elevated glucose levels result in increased expression of S100A8 in isolated macrophages.47 These results are corroborated by findings of increased S100A9 immunoreactivity in macrophage-rich lesions in these diabetic mice46 and in diabetic Apoe<sup>−/−</sup> mice.47

Mouse models have been used to investigate whether S100A8/A9 play causative roles in atherosclerosis. An interesting study on S100a9<sup>−/−</sup>; Apoe<sup>−/−</sup> mice demonstrates that this is indeed the case.33 These double knockout mice had an approximate 30% reduction in en face aortic lesion area in response to a high-fat diet, as compared with Apoe<sup>−/−</sup> controls. This reduction was not due to differences in plasma lipids but to a reduced accumulation of lesion macrophages.33 The same study showed that both neointimal thickening following femoral artery injury, and lesions in a model of thrombohemorrhagic vasculitis are reduced in S100a9<sup>−/−</sup> mice.33 Interestingly, accumulation of both monocytes and neutrophils was reduced in S100a9<sup>−/−</sup> mice, suggesting that S100A8/A9 promote accumulation of both cell types at sites of vascular injury and atherosclerosis.

Based on these findings and the concept that a majority of S100A8/A9 is derived from myeloid cells, we hypothesized that the protective effects of S100A9 deficiency on atherosclerosis would be mimicked by S100A9 deficiency specifically in bone marrow-derived cells. We therefore undertook a study in which Ldlr<sup>−/−</sup> mice were transplanted with bone marrow from S100a9<sup>−/−</sup> mice or wild-type littermate controls and then fed a high-fat diet for 20 weeks.26 Surprisingly, neither atherosclerosis nor macrophage accumulation in lesions was affected by bone marrow S100A9 deficiency. Lesion neutrophils were not abundant in this study.26 The lack of effect of bone marrow S100A9 deficiency on atherosclerosis might be due to the production and secretion of S100A8/A9 at sufficiently high levels from nonbone marrow-derived, compensation by other DAMPs or their receptors for the loss of bone marrow-derived S100A8/A9, or to intracellular levels S100A8/A9 levels in nonmyeloid cell types, which might play a more important role than previously recognized. The latter possibility is supported by data describing inducible S100A8/A9 expression in both VSMCs and endothelial cells and “proatherosclerotic” effects of S100A8/A9 in these cell types.32,33,48 However, we cannot exclude the possibility that S100A8/A9 might be relatively more important mediators in atherosclerosis in Apoe<sup>−/−</sup> mice as compared with Ldlr<sup>−/−</sup> mice.

A more significant question is whether S100A8/A9 promote atherosclerosis and cardiovascular disease in humans. New tools, such as S100A8/A9-neutralizing antibodies or specific inhibitors of S100A8/A9 secretion, will have to be developed and proved safe before this important question can be addressed. S100A8 and S100A9 polymorphism studies49 might shed additional light onto the roles of these proteins in cardiovascular disease in humans.

**S100A8/A9 and Cardiac Dysfunction**

S100A8/A9 have important functions in the injured heart, especially in contributing to cardiovascular dysfunction as a result of sepsis. S100a9<sup>−/−</sup> mice are largely protected from endotoxin-induced cardiomyocyte dysfunction, measured as reduced ejection fraction.41 The effects of S100A8/A9 appear to be mediated by altered calcium flux following RAGE activation, because both cardiac S100A8 and S100A9 are found to coimmunoprecipitate with RAGE following LPS injection, and RAGE blockade abolishes the decreased calcium flux by S100A8 or S100A9.11 On the other hand, in a rat model of experimental autoimmune myocarditis, treatment with recombinant human S100A8/A9 results in improved left ventricular ejection fraction, reduces infiltration of immune cells, and reduces levels of cytokines as compared with saline-injected controls.50 Thus, the role of S100A8/A9 in the heart might depend on the stimuli and the contribution of RAGE or other receptors. The role of S100A8/A9 in the human heart is unknown.

**Are S100A8/A9 Pro- or Anti-Inflammatory in Cells Contributing to Cardiovascular Disease?**

As discussed above, S100A8/A9 can result in activation of TLR4 and RAGE, indicating a proinflammatory role for extracellular S100A8/A9. However, anti-inflammatory effects of these S100A proteins have also been described, which might be mediated by oxidation or S-nitrosylation of the S100A proteins,7 arachidonic acid binding,5 or other effects. Furthermore, it is becoming increasingly clear that S100A8/A9 have different functions in different cell types involved in atherosclerosis (Figure 1). For example, S100A8/A9 promote an inflammatory phenotype in neutrophils but suppress an inflammatory phenotype in DCs.26 We thus proposed that the overall function of S100A8/A9 on atherosclerosis depends on the relative levels of cell types involved in the disease process.26 What evidence supports cell type–specific effects of S100A8/A9 in vascular cells?
inflammatory cytokine production by human monocytes,56 both extracellular and intracellular pathways. S100A8/A9 mediate phagocytosis and inflammatory effects by advanced glycation end products; NF-kB, extracellular signal regulated kinase; RAGE, receptor for transtactant protein; TNF, tumor necrosis factor; TLR, Toll-like receptor, myeloid-derived cells. E indicates extracellular effects of S100A8/A9 on processes involved in inflammation, and the proposed signaling pathways are shown for different myeloid-derived cells. E indicates extracellular effects of S100A8/A9; I, intracellular effects of S100A8/A9; MCP, monocyte chemotactrant protein; TNF, tumor necrosis factor; TLR, Toll-like receptor, ERK, extracellular signal regulated kinase; RAGE, receptor for advanced glycation end products; NF-κB, nuclear factor-κB; MAPK, mitogen-activated protein kinase; ROS, reactive oxygen species; IL, interleukin; iNOS, inducible nitric oxide synthase.

Neutrophils

Neutrophils are present in lesions of atherosclerosis, although at levels lower than those of monocytes/macrophages.26,51,52 S100A8/A9 are abundant in neutrophils, and not surprisingly, many of the effects of S100A8/A9 have been described in neutrophils, in which S100A8/A9 are proinflammatory, at least in part through extracellular activation of TLR4 (Figure 2).10,26 The ability of S100A9 to promote phagocytosis in neutrophils has also been attributed to extracellular activation of TLR4, RAGE, or another receptor.53 Accordingly, neutrophils from S100a9−/− mice show decreased activation of NADPH oxidase, an enzyme involved in pathogen killing following phagocytosis, as compared with wild-type mice.54 This effect, however, appears to be mediated by intracellular S100A8/A9 activating NADPH oxidase through their intracellular arachidonic acid–binding activity (Figure 2).54 Furthermore, intracellular S100A8/A9 contribute to neutrophil CD11b surface expression, and neutrophil adhesion and migration into inflamed tissues through calcium and microtubule regulation.55 Thus, neutrophil S100A8/A9 mediate phagocytosis and inflammatory effects by both extracellular and intracellular pathways.

Monocytes/Macrophages

S100A8/A9 levels in monocytes are ∼40-fold lower than those of neutrophils.16 Extracellular S100A8/A9 enhance the inflammatory cytokine production by human monocytes,56 and monocytes from S100a9−/− mice exhibit a reduced ability to migrate toward chemokines.53 Furthermore, mouse S100a9−/− peritoneal macrophages isolated 48 hours after thioglycollate injection have an impaired ability to release cytokines following LPS stimulation.53 However, in mature peritoneal macrophages isolated 5 days after thioglycollate injection, S100A9 deficiency does not affect cytokine release in response to LPS.26 It is well known that as monocytes differentiate into macrophages, S100A8/A9 expression is markedly downregulated.23,24,57 Therefore, it is possible that the distinct responses to loss of endogenous S100A8/A9 between monocyte/early macrophages and mature macrophages are due to differences in S100A8/A9 expression. Another interesting possibility, based on forced S100A9 overexpression studies, is that S100A9 might delay myeloid differentiation,58 possibly explaining the different effects of S100A8/A9 deficiency in monocytes and different states of macrophage differentiation. The mechanisms whereby S100A8/A9 promote an inflammatory phenotype of monocytes/macrophages involve activation of the nuclear factor-κB and p38 mitogen-activated protein kinase pathways.56 It is tempting to speculate that this is due, at least in part, to activation of TLR4, RAGE, or both. S100A8/A9-mediated stimulation of monocyte adhesion has also been attributed to extracellular effects.59 On the other hand, S100A9 released in macrophages from phagocytosed apoptotic neutrophils has been proposed to inhibit macrophage activation through S100A9’s calcium-binding activity.60 These findings suggest that, as in neutrophils, S100A8/A9 have both extracellular and intracellular effects in monocytes/macrophages (Figure 2) and that the significance of endogenous S100A8/A9 depends on the expression levels in different monocyte/macrophage maturation and activation states.

DCs

DCs contribute significantly to atherosclerosis, at least in mice.61,62 DC differentiation is blocked by S100A9 overexpression, and it has been shown that S100A8/A9-overexpressing DCs have a lower ability to stimulate the proliferation of allogeneic T cells than do control DCs.58 The same study58 showed that overexpression of S100A9 in hematopoietic cells in mice results in accumulation of myeloid progenitors at the expense of DC and macrophage differentiation, and it suggested that the effects of S100A9 were due to increased reactive oxygen species. Consistent with these results, S100a9−/− DCs promote a higher T-cell proliferation compared with wild-type DC in mixed lymphocyte reactions.26 In addition, S100a9−/− DCs exhibit increased release of cytokines following stimulation with TLR2 or TLR4 ligands, as compared with DCs from wild-type littermates,26 and express more DC cell surface markers, (CD205, IA) and costimulatory molecules (CD40, CD86) compared with wild-type cells (Scholzen TW, Kerkhoff C, unpublished data, 2011). Because TLR4 and RAGE activation is thought to promote DC maturation,63,64 S100A8/A9 might act through mechanisms distinct from TLR4 and RAGE to suppress inflammatory effects in DCs, perhaps indirectly by suppressing DC differentiation.

Endothelial Cells

Exogenous S100A8/A9 increase expression of adhesion molecules, such as vascular cell adhesion molecule-1 and intercellular adhesion molecule-1, and chemokines, in endothelial cells, as well as increased permeability of endothelial cell monolayers.48 Together, these effects could promote infiltration of immune cells into inflamed tissues.
**S100A8/A9 Are Part of a Larger Network of Proteins With Cardiovascular Effects**

S100A8 and S100A9 belong to a multigenic family of S100 proteins that are differentially expressed in a wide variety of cell types. The functional diversity of S100 proteins is achieved by their specific cell- and tissue-expression patterns, structural variations, and different metal ion binding properties, as well as their ability to form homo-, hetero- and oligomeric assemblies. Some S100 proteins, in particular S100A8, S100A9, and S100A12, are released from cells as a result of cellular activation. In the extracellular milieu, they are believed to function as ligands of pattern-recognition receptors, such as TLR4 and RAGE, and possibly other receptors, as discussed above. Both TLR4 and RAGE have been found to promote atherosclerosis in mice, although the effect of TLR4 deficiency is not consistently observed.

Beside S100A8 and S100A9, S100A12, S100B, and S100A4 are implicated in the pathogenesis of atherosclerosis. S100A12 has been described as an endogenous RAGE ligand with proinflammatory functions in humans, but it is not expressed in the mouse. S100A12 is found in coronary artery plaques in association with macrophages, and elevated levels of S100A12 are found in sera from patients with coronary artery disease. The latter study did not detect increased cytokine production in human monocytes or macrophages stimulated with human S100A12, suggesting that S100A12 actions on inflammation might be as complex as those of S100A8/A9. However, a recent study demonstrated that expression of human S100A12 in VSMCs results in increased atherosclerosis and more calcification of lesions in ApoE−/− mice. The S100A12 transgene also elicited the expression of genes involved in osteogenesis by cellular pathways that were dependent on RAGE and oxidative stress signaling. These findings suggest a causative involvement of S100A12 in atherosclerosis and vascular calcification.

Another S100 protein, S100A4, exerts growth-promoting effects in VSMCs and therefore might play a role in atherogenesis. In humans, S100A4 is barely detectable in coronary artery media but is markedly expressed in VSMCs of atheromatous and restenotic coronary artery lesions. There is no direct evidence available for S100A4/RAGE interaction.

Besides its abundance in astrocytes, S100B is expressed in cells outside the brain, including in DCs and VSMCs. S100B exerts effects on both endothelial cells and VSMCs that might have an impact on atherosclerosis. These effects are mainly RAGE-dependent. In human endothelial cells, S100B upregulates the gene expression of monocyte chemotactrant protein-1, and RAGE. In VSMCs, S100B has been found to stimulate interleukin-6 and monocyte chemotactrant protein-1 production and cell migration.

Very recently, elevated serum levels of S100B, S100A6, and S100P were found to be associated with the acute coronary syndrome, and serum levels and myocardial expression of these proteins were related to infarct size. Thus, the group of S100 protein family members with potential roles in cardiovascular biology and disease is rapidly expanding.

Importantl, these S100 proteins, other DAMPs, and their receptors are likely to affect each other and to synergize in vivo. As an example, activation of RAGE results in increased expression and release of S100A8 and S100A9, and advanced glycation end products exacerbate the proinflammatory effects of S100A8/A9, contributing to a likely positive feedback loop in states of inflammation. Similarly, in the setting of diabetes, DAMPs, RAGE, and TLR4 are all upregulated in monocytes/macrophages, potentially contributing to a “perfect storm” of activation of this network of proteins.

**Many Questions Remain Unanswered**

We have reviewed the evidence that S100A8/A9 are both biomarkers and mediators of cardiovascular disease. However, more research is needed to elucidate the complex effects of S100A8 and S100A9. For example, to what extent are the biological effects of S100A8/A9 mediated by intracellular versus extracellular actions? Why and how do S100A8/A9 mediate proinflammatory and anti-inflammatory effects in different cell types and disease states? What is the relative contribution of S100A8/A9 versus other DAMPs? Which are the cell types that contribute to S100A8/A9 expression and secretion in different disease states? To what extent do S100A8 and S100A9 contribute to cardiovascular disease in humans? Answers to these questions are needed before S100A8/A9 can be considered as therapeutic targets.

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**Disclosures**

None.

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