Serum Amyloid A and Lipoprotein Retention in Murine Models of Atherosclerosis


Objective—Elevated serum amyloid A (SAA) levels are associated with increased cardiovascular risk in humans. Because SAA associates primarily with lipoproteins in plasma and has proteoglycan binding domains, we postulated that SAA might mediate lipoprotein retention on atherosclerotic extracellular matrix.

Methods and Results—Immunohistochemistry was performed for SAA, apolipoprotein A-I (apoA-I), apolipoprotein B (apoB), and perlecan on proximal aortic lesions from chow-fed low-density lipoprotein receptor (LDLR)−/− and apoE−/− mice euthanized at 10, 50, and 70 weeks. SAA was detected on atherosclerotic lesion extracellular matrix at all time points in both strains. SAA area correlated highly with lesion areas (apoE−/−, r=0.76; LDLR−/−, r=0.86), apoA-I areas (apoE−/−, r=0.88; LDLR−/−, r=0.80), apoB areas (apoE−/−, r=0.74; LDLR−/−, r=0.89), and perlecan areas (apoE−/−, r=0.83; LDLR−/−, r=0.79) (all P<0.0001). In vitro, SAA enrichment increased high-density lipoprotein (HDL) binding to heparan sulfate proteoglycans, and immunoprecipitation experiments using plasma from apoE−/− and LDLR−/− mice demonstrated that SAA was present on both apoA-I–containing and apoB-containing lipoproteins.

Conclusions—In chow-fed apoE−/− and LDLR−/− mice, SAA is deposited in murine atherosclerosis at all stages of lesion development, and SAA immunoreactive area correlates highly with lesion area, apoA-I area, apoB area, and perlecan area. These findings are consistent with a possible role for SAA-mediated lipoprotein retention in atherosclerosis.


Key Words: atherosclerosis ■ lipoproteins ■ perlecan ■ proteoglycans ■ serum amyloid A

Lipid accumulation and inflammation have been recognized as prominent features of atherosclerotic lesions.1 Recent studies have demonstrated an association between increased levels of plasma markers of inflammation, such as C-reactive protein and serum amyloid A (SAA), and increased cardiovascular risk.2–5 In vitro studies have suggested mechanisms through which C-reactive protein might participate in atherogenesis, such as increasing endothelial monocyte chemoattractant protein-1 expression6 and decreasing endothelial production of endothelial nitric oxide synthase,7,8 and prostacyclin.9 In contrast, little attention has been paid to the possibility that SAA might participate in atherogenesis.

See cover

SAA is a family of homologous proteins that include SAA1 and SAA2, which are major acute phase reactants,10 and SAA4, which is constitutively expressed in humans11 but not in mice.10,12 In humans and mice, plasma SAA1 and SAA2 levels can increase by several hundred-fold in response to an acute inflammatory stimulus.10,12 The majority of plasma SAA is associated with lipoproteins, primarily high-density lipoproteins (HDL), but also with very-low-density lipoproteins (VLDL).12 Both HDL13,14 and VLDL remnants15,16 accumulate in human atherosclerotic lesions. In the case of HDL, in vitro studies have demonstrated that proteins that may associate with HDL, including apolipoprotein E (apoE)14,17 and phospholipid transfer protein,18 dramatically increase the binding of HDL to extracellular matrix proteoglycans. However, apolipoprotein A-I (apoA-I), the major apolipoprotein of HDL, also is present in lesions of apoE-deficient (apoE−/−) mice,19 implying that molecules other than apoE must also mediate HDL retention on atherosclerotic extracellular matrix. SAA contains proteoglycan-binding domains,12,20 raising the possibility that SAA might mediate HDL retention on vascular extracellular matrix.

The present study was undertaken to determine whether SAA is present in lesions of apoE−/− and low-density lipoprotein receptor-deficient (LDLR−/−) mice and, if so, whether

Original received June 29, 2003; final version accepted January 26, 2005.
From the Divisions of Cardiology (K.D.O., T.O.M., K.E., E.A.K., R.L.) and Metabolism, Endocrinology, and Nutrition (K.L., A.C.), Department of Medicine and Department of Pathobiology (E.A.K., R.C.L.), University of Washington, Seattle; Massachusetts General Hospital (V.K.), Boston, Mass; and Hope Heart Program at the Benaroya Research Institute (T.N.W.), Seattle, Wash; and Department of Medicine (F.C.d.B.), University of Kentucky, Lexington.
Correspondence to Kevin D. O’Brien, MD, Division of Cardiology, Box 356422, University of Washington, Seattle, WA 98195-6422. E-mail cardiac@u.washington.edu
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Arterioscler Thromb Vasc Biol. is available at http://www.atvbaha.org

DOI: 10.1161/01.ATV.0000158383.65277.2b

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SAA colocalizes with apoA-I and/or apoB, as well as with perlecán, a heparan sulfate proteoglycan that is the major extracellular proteoglycan in murine atherosclerotic lesions. In addition, in vitro binding studies were performed to determine whether higher SAA content was associated with increased HDL binding to heparan sulfate proteoglycans. Also, immunoprecipitation studies were performed to determine whether SAA-containing lipoproteins from the plasma of apoE−/− or LDLR−/− mice also contained either apoA-I or apoB.

**Methods**

**Animals**

Sections of proximal aortic tissue were available from the majority of (though not all) mice used in a previous study evaluating the proteoglycan and apolipoprotein composition of murine atherosclerotic lesions. Briefly, LDLR−/− and apoE−/− mice (both strains back-crossed for at least 8 generations onto the C57BL/6 genetic background) were obtained either from the Jackson Laboratory (Bar Harbor, Me) or from colonies at the University of Washington (Seattle, Wash). The mice were fed rodent chow (Wayne Rodent BLOX 8604; Teklad Test Diets, Madison, Wis). This diet contains 5.063 to 1.21 g/mL) by density gradient for HDL isolation. Plasma from each of these groups was pooled for retro-orbital sinus into tubes containing 1 mmol/L EDTA and used (n=10 mice) or from colonies at the University of Washington (Seattle, Wash). The mice were fed rodent chow (Wayne Rodent BLOX 8604; Teklad Test Diets, Madison, Wis). This diet contains 4.4% fat and no added cholesterol. Mice had ad libitum access to chow and water and were housed in a temperature-controlled (25°C), modified, specific pathogen–free facility. After euthanization by intraperitoneal injection of pentobarbital (80 mg/kg) at age 10 to 11 weeks (LDLR−/−, n=9 [female=4, male=5]; apoE−/−, n=8 [female=5, male=3]), age 50 to 54 weeks (LDLR−/−, n=10 [female=5, male=5]; apoE−/−, n=7 [female=5, male=2]), or age 70 to 73 weeks (LDLR−/−, n=10 [female=5, male=5]; apoE−/−, n=8 [female=6, male=2]), blood was collected from the retro-orbital sinus, anticoagulated with 1 mmol/L EDTA, and stored at −70°C before lipoprotein analysis. Hearts were perfusion-fixed with 10% neutral-buffered formalin and embedded in paraffin wax. Sections of 6-μm thickness were obtained from the aortic sinuses and mounted on glass slides.

To obtain HDL with increased SAA content for in vitro proteoglycan binding assays, additional apoE−/− mice (10 weeks of age) were given intraperitoneal injections of 100 μg lipopolysaccharide (LPS) (Sigma) in 100 μL saline (n=10 mice) or 100 μL sterile saline (n=10 mice), then euthanized 48 hours later by intraperitoneal injection of pentobarbital (80 mg/kg). Blood was collected from the retro-orbital sinus into tubes containing 1 mmol/L EDTA and used for HDL isolation. Plasma from each of these groups was pooled for the isolation of HDL (density 1.063 to 1.21 g/mL) by density gradient ultracentrifugation as described previously. Further, increased SAA content of HDL from LPS-injected as compared with saline-injected animals was confirmed by immunoblotting.

**Antisera**

SAA was detected using a rabbit polyclonal antiserum raised at the University of Kentucky against recombinant human SAA1 (titer 1:500). This antiserum also recognizes SAA in immunoblots of murine plasma, HDL, and purified murine SAA (data not shown), but is not specific for any individual SAA isoform. ApoA-I was detected using a goat polyclonal antiserum raised against human apoA-I (titer 1:7500; a kind gift from Dr John Oram, University of Washington); this antiserum has been shown previously to identify mouse apoA-I in immunohistochemistry. ApoB was detected using a rabbit polyclonal antiserum (titer 1:1000; a kind gift from Dr Thomas Innerarity, Gladstone Institute, San Francisco, Calif) and had been shown previously to recognize murine, but not human, apoB in Western blots. Perlecán was detected using a rabbit polyclonal antiserum EY9, which had been raised against murine Engelbreth-Holm-Swarm sarcoma (titer 1:200; a kind gift from Dr John Hassell, Shriner’s Hospital for Children, Tampa, Fla). Macrophages were detected using Mac-2 antibody (titer 1:10 000, Cedarlane Laboratories, Hornby, Ontario, Canada).

**Plasma Cholesterol Measurements**

Total plasma cholesterol levels were measured by an enzymatic assay (Liberty Scientific, #225 to 26) using cholesterol standards (Preciset 12552; Roche Molecular Biochemicals, Inc, Indianapolis, Ind) as described previously. After plasma cholesterol levels had been obtained, no remaining plasma samples were saved. Therefore, it was not possible to perform plasma SAA levels on these animals.

**Single-Label Immunohistochemistry**

Single-label immunohistochemistry was performed as described previously. Briefly, 6-μm-thick tissue sections were deparaffinized with xylene and dehydrated with graded alcohols. Endogenous peroxidase activity was blocked by treatment with 3% H2O2. Sections then were washed with phosphate-buffered saline and incubated with the primary antiserum. A biotinylated secondary antibody (anti-goat or anti-rabbit, as appropriate) then was applied for 30 minutes, followed by avidin-biotin-peroxidase conjugate (ABC Elite; Vector Laboratories, Burlingame, Calif) for 30 minutes. 3,3′-diaminobenzidine with nickel chloride was used as the chromagen. Sections were counterstained with methyl green. Antisera to apoA-I, SAA, and apoB were applied, in that order, to consecutive tissue sections. The perlecán antiserum was applied to a tissue section that was separated from the apoB section by 3 intervening tissue sections. Negative controls included omission of the primary antiserum and use of normal rabbit serum as the primary antiserum.

**Heparan Sulfate Proteoglycan Isolation**

Heparan sulfate proteoglycans were isolated from cultured human arterial smooth muscle cells that had been metabolically labeled with 100 μCi/mL Na[35]S-sulfate. Conditioned medium was concentrated and purified by ion exchange chromatography and applied to a Sepharose CL-2B molecular sieve column. Fractions, including Kav 0.30 to 0.44, were taken for preparation of heparan sulfate proteoglycans (HSPGs). These pools were concentrated by ion exchange chromatography on DEAE Sephadex in 8 mol/L urea buffer, washed with 8 mol/L urea buffer lacking detergent, eluted with 4 mol/L guanidine buffer without detergent, and changed into Tris acetate buffer. Eluted material was incubated with chondroitin ABC lyase (Sigma, St Louis, Mo). The digestion product was applied to DEAE Sephadex, washed with 8 mol/L urea buffer to remove disaccharides resulting from digestion of chondroitin sulfate/dermatan sulfate, and eluted again with guanidine buffer. Eluted fractions were then dialyzed into association buffer for the gel-shift assay.

**Gel-Mobility Shift Assay**

Before the assay, the 35S-labeled HSPG and HDL preparations were dialyzed extensively at 4°C against 10 mmol/L Hepes, 150 mmol/L NaCl, 5 mmol/L CaCl2, and 2 mmol/L MgCl2 (pH 7.4; Buffer A), and the protein concentrations were determined (BioRad Laboratories, Hercules, Calif) using bovine gamma globulin as the standard. Increasing concentrations of lipoprotein were incubated with ~2000 dpm of 35S-labeled HSPG (~0.4 μg glycosaminoglycan) for 1 hour at 37°C in a total volume of 20 μL of buffer A. Electrophoretic gel-shift mobility assays then were performed as described previous-
ly. Gels were fixed in 0.1% cetyl pyridium chloride in 70% ethanol for 90 minutes, air-dried, and the radioactive label detected by gel exposure to a PhosphorImager screen (Packard, Meriden, Conn). The amounts of HDL-bound and free HSPG in each lane were quantified using the OptiQuant computer program (Packard).

**Immunoprecipitation Experiments**

SAA-containing lipoproteins were isolated from 50 μL of plasma from each of 6 mice using 5 μL of rabbit anti-mouse SAA antiserum (kind gift from Dr. Godfrey Getz, University of Chicago) coupled to 100 μL of protein-G Dynal beads, according to manufacturer’s instructions (Dynal Biotech, Brown Deer, Wis); 20 μL of immunoprecipitation elutant from each mouse then was used in each subsequent immunoblotting experiment.

**Statistical Analyses**

All experimental data are expressed as mean±SEM. Mean values were compared using Student t test or ANOVA. Pearson correlation coefficients were calculated to examine relationships between lesion SAA immunostained areas and either total aortic sinus lesion areas or immunostained areas for apoA-I, apoB, or perlecan. P<0.05 was considered statistically significant. Statistical analyses were performed using the GraphPad Prism Program (Version 3.02, GraphPad Software, Inc, San Diego, Calif).

**Results**

**Plasma Total Cholesterol Levels, Aortic Sinus Lesion Areas, and Presence of SAA in Plasma of LDLR−/− and ApoE−/− Mice**

Plasma total cholesterol levels (mean±SEM) were slightly higher at all time points in apoE−/− as compared with LDLR−/− mice (Table). Aortic sinus lesion areas (mean±SEM) were substantially greater in apoE−/− mice, especially at the later time points (Table). At the 10-week time point in chow-fed LDLR−/− mice, only 2 of 9 animals had any detectable lesions. Lesion size was substantially higher at 70 weeks than at 50 weeks in the LDLR−/− mice. The reason for the apparent dramatic increase in lesion size between 50 and 70 weeks seen in this strain is not known; it may prove to be a reproducible finding or may be caused by chance, because the number of animals in each group is relatively low.

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<th>10 Wk</th>
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<td>Plasma cholesterol, mg/dL</td>
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<td>381±37</td>
<td>330±23</td>
<td>549±70</td>
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<td>LDLR−/−</td>
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<td>440±39</td>
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<td>4570±879</td>
<td>362 821±67 702</td>
<td>505 184±69 199</td>
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<tr>
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<td>125±93</td>
<td>42 082±10 541</td>
<td>180 809±23 935</td>
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All values are mean±SEM.

**Early Lesions: Colocalization of SAA With ApoA-I and ApoB**

In both apoE−/− and LDLR−/− strains, the earliest detectable atherosclerotic lesions consisted of subendothelial, extracellular accumulation of SAA, apo A-I, and apoB, with or without macrophages. SAA colocalized with both apoA-I (Figure 1, comparison of left and center) and apoB (Figure 1, right).

**Intermediate Lesions: Colocalization of SAA With ApoA-I and ApoB**

In addition, SAA and apoA-I colocalized in intermediate lesions of both apoE−/− and LDLR−/− mice (Figure 2, left and middle). As with the early lesions, apoB also was colocalized with SAA.

**SAA Areas in Murine Atherosclerotic Lesions and Correlations With Apolipoprotein and Lesion Areas**

In apoE−/− mice (n=23), SAA immunostained areas correlated strongly with lesion areas (r=0.76), apoA-I areas (r=0.88), and apoB areas (r=0.74) (all P<0.0001). Similarly, in LDLR−/− mice (n=29), SAA immunostained areas correlated strongly with lesion areas (r=0.79), apoA-I areas (r=0.88), and apoB areas (r=0.75) (all P<0.0001).
correlated strongly with lesion areas ($r=0.86$), apoA-I areas ($r=0.80$), and apoB areas ($r=0.89$) (all $P<0.0001$).

**Localization of SAA, ApoA-I, and ApoB With the HSPG, Perlecan, in Murine Atherosclerotic Lesions**

It has been demonstrated previously that the HSPG, perlecan, colocalized with apoA-I in atherosclerotic lesions of apoE−/− mice,19 a surprising finding, because it also has been shown previously that only apoE-containing, but not apoE-free, HDL binds to proteoglycans in vitro.14 SAA immunostained areas correlated strongly with immunostained areas for the HSPG, perlecan, in both apoE−/− mice ($n=16$, $r=.83$) and in LDLR−/− mice ($n=21$, $r=.79$) (both $P<0.0001$) (Figure 3).

**Increased SAA Content Is Associated With Increased HDL Binding to HSPGs**

To determine whether HDL with an increased SAA content had increased ability to bind to HSPGs, HDL was isolated from mice that had been injected with LPS to increase HDL

![Figure 2. Intermediate (50-week) apoE−/− and LDLR−/− mouse lesions. Colocalization of SAA with apoA-I and apoB. Shown are photomicrographs of directly adjacent aortic sinus sections demonstrating colocalization of SAA with apoA-I and apoB in intermediate lesions of both strains. (original magnification = 40×; methyl green counterstain).](image)

![Figure 3. Late (70-week) LDLR−/− lesion. Colocalization of perlecan with SAA, apoA-I, and apoB. Shown are directly adjacent aortic sinus sections stained for SAA, apoA-I, and apoB (lower panels), as well as neighboring, but not adjacent, sections stained with the Gomori stain or for perlecan (upper panels). SAA, apoA-I, and apoB are present in the regions with intense perlecan staining (black arrows) (original magnification = 40×; Gomori stain (upper left panel) or methyl green counterstain).](image)

![Figure 4. Effect of SAA content on apoE−/− mouse HDL binding to heparan sulfate proteoglycans. Autoradiographs of gel from a gel-mobility shift assay in which 35S-labeled heparan sulfate proteoglycans (HSPGs) had been incubated with pooled HDL isolated from LPS-injected (A) or saline-injected (B) apoE−/− mice. Radiolabeled HSPGs bound to HDL are retained at the origin, whereas free HSPGs migrate into the gel. Greater amounts of radiolabeled HSPGs are retained at the origin for HDL from LPS-injected mice (A) as compared with saline-injected mice (B). Relative binding of LPS–HDL and saline–HDL to HSPGs is shown graphically (C). By immunoblotting, SAA content was dramatically increased in HDL from LPS-injected as compared with saline injected mice (D).](image)

SAA content and from control saline-injected mice. HDL was isolated from apoE−/− mice, HDL was isolated from apoE−/− mice to remove any potential contribution of apoE to HDL binding. In the gel-mobility shift assay, HDL isolated from LPS-injected mice had increased binding to HSPGs as compared with HDL isolated from control mice (Figure 4). By immunoblotting, the SAA content was dramatically increased in HDL from LPS-injected, as compared with saline-injected apoE−/− mice (Figure 4D).

**SAA Is Present on Both ApoA-I–Containing and ApoB-Containing Lipoproteins in apoE−/− and LDLR−/− Mouse Plasma**

SAA-containing lipoproteins were isolated by immunoprecipitation from plasma of chow-fed apoE−/− and LDLR−/− mice as described in Methods. Immunoblots then were performed using antisera to apoA-I or to mouse apoB-48 (kind gift from Dr Stephen Young, Gladstone Institute, San Francisco, Calif).28 As shown in Figure 5, SAA-containing lipoproteins from each strain include both apoA-I–containing (Figure 5A) and apoB-48–containing (Figure 5B) lipoproteins.

**Discussion**

The present study demonstrates that SAA accumulates in atherosclerotic lesions of apoE−/− and LDLR−/− mice. SAA was detected at all time points studied, consistent with the possibility that SAA might play a role at each of these stages of lesion development. In addition, lesion SAA areas correlated strongly with both lesion apoA-I areas and lesion apoB areas. There were strong correlations between lesion SAA area and total lesion area. Moreover, HDL in which SAA...
content was increased because of intraperitoneal LPS injection had increased in vitro binding to heparan sulfate proteoglycans as compared to HDL isolated from control saline-injected mice. Finally, immunoprecipitation demonstrated that SAA-containing lipoproteins included both apoA-I-containing lipoproteins and apoB-containing lipoproteins. These observations are consistent with a potential role for SAA in lipoprotein retention in atherosclerotic lesions. However, these observations cannot determine whether the effect of SAA-mediated lipoprotein retention on atherogenesis might be positive, negative, or neutral.

Several recent clinical studies have demonstrated an association between elevated levels of SAA and increased risk of cardiovascular events. Epidemiologically, elevated SAA levels are associated with a number of atherosclerotic risk factors, including obesity and insulin resistance, which are features of the metabolic syndrome. However, it is unknown whether SAA is simply a marker for increased cardiac risk or actually participates in the pathogenesis of atherosclerosis. SAA are acute phase proteins synthesized by the liver. They are secreted into plasma, where they associate primarily with HDL particles but also with VLDL particles. SAA has been shown to mediate binding of HDL to differentiated macrophages and endothelial cells and to impair the ability of HDL to promote cholesterol efflux from macrophages. Free SAA also has been shown to promote monocyte chemotaxis and adhesion. Thus, SAA could have multiple cellular, pro-atherogenic effects. However, SAA also may have antiatherogenic effects, because one recent study has demonstrated that the SAA isoform, SAA 2.1, can promote macrophage cholesterol efflux. This study has focused on a potential role for SAA in mediating lipoprotein retention on extracellular matrix. Recent work has suggested that in addition to inflammation, lipoprotein retention on extracellular matrix is an early and key event in the pathogenesis of atherosclerosis. Most work in this area has focused on mechanisms involved in LDL retention on matrix. In addition to a direct interaction of LDL with matrix, molecules with the capacity to bind both lipoproteins and extracellular matrix, such as lipoprotein lipase and sphyngomyelin, can act as “bridging” molecules that further promote retention of LDL on vascular extracellular matrix. We previously have shown that apoE and phospholipid transfer protein (PLTP) also can act as bridging molecules that facilitate the retention of HDL on extracellular matrix. HDL is retained in both human and murine atherosclerotic lesions, possibly via the “bridging” roles of apoE and/or PLTP. The results of this study are consistent with a similar role in lesion HDL retention for SAA, which not only associates with HDL in plasma but also contains proteoglycan-binding domains.

SAA also may associate with plasma VLDL, particularly in inflammatory states, VLDL, which contains apoB, is retained in human atherosclerotic lesions. In the present study, there also were strong correlations between lesion SAA areas and lesion apoB areas in both strains of mice, consistent with the possibility that SAA might also enhance lesion retention of VLDL. Thus, the results of the present study suggest that SAA may be playing a role in lesion retention of both HDL and VLDL.

Retention of either VLDL or of HDL might be expected to stimulate atherosclerotic lesion formation because both would result in increased cholesterol deposition in plaques. Also, in the case of HDL, the effect might be particularly deleterious, because retained HDL would not be able to remove excess cholesterol from lesions. However, it also is possible that retained SAA might itself be antiatherogenic, for example, by promoting macrophage cholesterol efflux.

Further, it is interesting to note that as in our previous study with apoB, no SAA deposition was detected in nonlesioned areas that lacked proteoglycan accumulations. This observation is most consistent with the hypothesis that retention of lipoproteins is preceded by cellular secretion of proteoglycans, like perlecan, that have the capacity to bind lipoproteins. However, it does not exclude the possibility that, in addition to retention on proteoglycans, additional mechanisms might also contribute to lipoprotein retention in atherosclerotic plaques.

Because plasma was not available for measurement of circulating SAA levels, it was not possible to study whether plasma SAA levels correlate with atherosclerotic lesion size. However, a correlation between plasma SAA levels and lesion size would represent only indirect evidence of a role for SAA in lesion pathogenesis. In contrast, the present study demonstrates that SAA is present in atherosclerotic lesions. Further, this study has the advantage of evaluating SAA content of lesions obtained from 2 different atherosclerotic strains at three different points in time and finds that SAA is present even in the earliest detectable lesions. Therefore, the results suggest that lesion SAA is a common feature of all stages of lesion development in mouse models of atherosclerosis. However, it cannot determine whether the overall effect of SAA is to promote or to retard atherogenesis.
In summary, SAA was detected in early through late stages of lesion development in 2 mouse models of atherosclerosis. Lesion SAA area correlated strongly with lesion size and with lesion apoA-I area in both mouse models, and increased SAA content was associated with increased HDL binding to heparan sulfate proteoglycans. The results are consistent with a role for SAA in lipoprotein retention in atherogenesis and suggest one potential mechanism by which this plasma inflammatory “marker” may participate in atherosclerosis.

Acknowledgments

Supported in part by grants HL30086, HL02788, and HL52848 from the National Institutes of Health, Bethesda, Md. The authors thank Shari Wang for expert technical assistance and Karen Fowler for assistance with manuscript preparation.

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6. Bedossa P, Lemaigre G, Martin E. The authors thank the National Institutes of Health, Bethesda, Md. The authors thank Shari Wang for expert technical assistance and Karen Fowler for assistance with manuscript preparation.
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Arterioscler Thromb Vasc Biol. 2005;25:785-790; originally published online February 3, 2005; doi: 10.1161/01.ATV.0000158383.65277.2b

Arteriosclerosis, Thrombosis, and Vascular Biology is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1079-5642. Online ISSN: 1524-4636

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