Increased Expression of Serum Amyloid A in Glaucoma and Its Effect on Intraocular Pressure

Wan-Heng Wang,1 Loretta G. McNatt,1 Iok-Hou Pang,1 Peggy E. Hellberg,1 John H. Fingert,2 Mitchell D. McCartney,1 and Abbot F. Clark1

PURPOSE. To search for and validate potential molecular pathogenic mechanisms in the trabecular meshwork (TM) responsible for the elevated intraocular pressure (IOP) associated with glaucoma.

METHODS. Gene chip arrays were used to identify differential gene expression in glaucomatous TM tissues. Serum amyloid A (SAA) upregulation was subsequently confirmed with quantitative PCR (QPCR) and ELISA. The effect of SAA on gene expression of cultured human TM cells was tested with gene chip arrays and verified with ELISA, and its effect on IOP was evaluated in the human ocular perfusion organ culture.

RESULTS. Microarray analysis showed that the expression of SAA2 was increased in TM tissues from donors with glaucoma. This finding was subsequently confirmed by QPCR. The SAA mRNA levels were increased in glaucoma TM tissues by more than 5-fold (P < 0.05) and in cultured TM cells derived from donors with glaucoma by 25-fold (P < 0.05) compared with controls. SAA protein levels in the TM of glaucoma patients were also significantly (P < 0.05) elevated by 2.9-fold. Treatment of cultured human TM cells with recombinant SAA affected gene expression, including a 22-fold up-regulation of interleukin-8 (P < 0.001). SAA increased IOP by approximately 40% (P < 0.05) in the human ocular perfusion organ culture without any observable changes in the morphology of the tissues involved in aqueous outflow.

CONCLUSIONS. These findings indicate that SAA, which is an acute-phase apolipoprotein that plays important roles in infection, inflammation, and tissue repair, may contribute to the pathogenic changes to the TM in glaucoma. (Invest Ophthalmol Vis Sci. 2008;49:1916–1923) DOI:10.1167/iovs.07-1104

Glaucoma is a leading cause of blindness in the world.1 One major risk factor for glaucoma is elevated intraocular pressure (IOP).2,3 In primary open-angle glaucoma (POAG), the most prevalent form of glaucoma, this IOP increase occurs as a consequence of the reduction in aqueous humor outflow at the trabecular meshwork (TM).4 Various morphologic, biophysical, and biochemical methods have been used to reveal the pathogenesis of this disease, but little is known about the relevant molecular mechanisms affecting glaucomatous outflow resistance.

During the past decade, molecular biology and gene studies have provided important breakthroughs in the identification of genetic contributions and molecular understanding of this disorder. For example, linkage analysis of heritable forms of glaucoma has identified more than 17 glaucoma loci.5 The first glaucoma gene identified was myocilin (MYOC).6 Approximately 3% to 5% of patients with adult-onset glaucoma were shown to have myocilin mutations.6,7 Some of these mutations disrupt protein secretion, compromise TM cell functions, and affect IOP.8–10 In addition, several differentially expressed genes and gene products in glaucoma TM cells have been discovered using traditional methods, such as Western blotting and reverse-transcription–polymerase chain reaction (RT-PCR).11–13 Recently, microarray analysis has been applied to determine genomewide gene expression profiles of human TM cells and tissues.14,15 This exciting technology has enabled the evaluation of thousands of genes in a single RNA sample.

To identify differentially expressed genes in glaucomatous TM cells and tissues and to determine the possible contributions of these genes in the pathogenesis of glaucoma, we compared genomewide gene expression profiles in TM tissues from healthy donors and glaucoma patients using gene chip arrays. We report the identification and characterization of the human serum amyloid A protein (SAA) as a novel pathogenic factor. Most important, we further conducted characterization of the in vitro and ex vivo functions of SAA and demonstrated the involvement of this gene product in the aberrant biological structure of the TM leading to elevated IOP.

MATERIALS AND METHODS

Human Ocular Tissues and Serum Samples

All donor tissues used in this study were obtained and managed according to the tenets of the Declaration of Helsinki for research involving human tissues. Human donor eyes were obtained from the Central Florida Lions Eye and Tissue Bank. For protein extraction, donor eyes less than 5.5 hours (mean, 4.7 hours for both groups) after death were enucleated and stored in moist chambers. TM tissues were subsequently dissected under a microscope and stored at −80°C until use. Mean time from death to dissection was 22.9 hours for the healthy group and 22.3 hours for the glaucoma group (no statistical difference; P = 0.85). For RNA isolation, eyes less than 5 hours after death were bisected equatorially and submerged in tissue storage reagent (RNA-later, Ambion, Austin, TX) at the eye bank before shipment. TM tissues were carefully dissected later. We have previously shown that this RNA preservation method yielded high-quality, undegraded RNA.16

Human serum samples were collected from patients enrolled in an institutional review board-approved biomarker study. Written informed consent was obtained before blood was drawn. Patients were age matched (range, 48–86 years) in two groups of 51 each, healthy and glaucoma. There was no significant difference between patient...
groups in terms of sex or age. Whole blood was allowed to clot, and the serum was removed and stored at −80°C until assayed.

Throughout this study, the glaucoma group consisted exclusively of patients with a clinical diagnosis of POAG. POAG was defined as the presence of an IOP of more than 21 mm Hg and evidence of glaucomatous cupping of the optic disc. Visible damage to the optic disc alone was accepted as evidence if there was documented enlargement of the optic disc cup. Otherwise, both an enlarged cup with a thin neural rim and a characteristic visual field loss corresponding to the optic nerves were required. Patients were excluded if they had a history of eye surgery before the diagnosis of glaucoma or evidence of secondary glaucoma, such as pseudoxefoliation or pigment dispersion. Patients assigned to the healthy group had no clinical signs of POAG or other forms of glaucoma.

RNA and cDNA Preparation
Total RNA was extracted from cultured TM cells using reagent (TRIZOL; Invitrogen, San Diego, CA) or from tissue storage reagent (RNAlater; Ambion)-preserved TM tissues using a PCR isolation kit (RNAqueous-4PCR; Ambion) according to the manufacturer’s instructions. RNA quality was assessed by agarose gel electrophoresis or by use of a bioanalyzer (2100 Bioanalyzer; Agilent, Foster City, CA), cDNA was synthesized with reverse transcriptase and random hexamers (MultiScribe; PE Applied Biosystems, Foster City, CA). PCR was performed with GAPDH primers to evaluate cDNA quality.

Microarray Experiment
Gene expression in pooled RNA (10 μg total RNA) of TM tissue from 13 healthy donors (average age, 81.7 years; range, 70–92 years) and 9 glaucomatous donors (average age, 83.9 years; range, 76–89 years) was compared using Affymetrix gene chips (U133A/B; Affymetrix Inc., Santa Clara, CA). Synthesis of cDNA and biotin-labeled antisense cRNA, target hybridization, washing, staining, and scanning probe arrays were conducted at the University of Iowa DNA Facility, as described in the technical manual (Affymetrix Genechip Expression Analysis Technical Manual). Microarray gene expression was analyzed with the Affymetrix software (Microarray Suite and Significance Analysis of Microarrays).17

Real-Time Quantitative PCR
Real-time quantitative PCR (QPCR) was performed using a sequence detection system (ABPl prism 7700; PE Applied Biosystems, Foster City, CA) according to the manufacturer’s instructions. A typical multiplex QPCR reaction mixture consisted of 1× PCR master mix (TaqMan Universal PCR Master Mix; PE Biosystems), cDNA from 2.5 ng total RNA, and the specified primer (200 nM) and probe (100 nM) and ribosomal RNA control (18S rRNA; PE Applied Biosystems) in a final volume of 25 μL. Thermal cycling conditions were 50°C for 2 minutes and 95°C for 10 minutes, followed by 40 cycles at 95°C for 15 seconds and 60°C for 1 minute Relative mRNA expression was determined by comparison to a standard curve generated by different dilutions of TM cell cDNA and normalized against 18S internal control (PE glaucoma). PCR primers and probes specific for SAA1/2 (forward, 5'-CTGTGGAGAGCCTACTC-3'; reverse, 5'-CTGGACATAGACCTCACTAACTTTGTATC-3'; probe, FAM-AGAGAAGGAGCAATCAGGGCTCAGACAATA-TAMRA), SAA1 (forward, 5'-GCTTCCTCTCCTACCTGGCTCCTCA-3'; reverse, 5'-ACCTCTCTCCGGGCTTGGTA-3'; probe, FAM-AGATCTGCGTGAGGCCCTCATT C- TAMRA), SAA2 (forward, 5'-GGCTCTCTCCTACCTGGCTCCTCA-3'; reverse, 5'-GTCGGGATACAGATAGACCTCACTAACTTTGTATC-3'; probe, FAMAGACTGGCATATGGGCCCCTGCTG- TAMRA), and SAA4 (forward, 5'-GGGTGCTGGGCTGCTCTCAAC-3'; reverse, 5'-GTGGTCTGCTCTCTCCAAATGAAT- TAGTCG-3'; probe, FAM-ATCCGGCTTGAGGCTGCTCATT C- TAMRA) were designed with software (Primer Express; PE Biosystems) and synthesized (MWBiotech, High Point, NC). Primer and probe sets for interleukin-8 (IL-8; assay ID, hs00174103-m1) were purchased from Applied Biosystems (TaqMan).

Recombinant Human SAA
Because of the multiple SAA gene products and their posttranslational modifications, SAA preparations isolated from plasma are heterogeneous. In addition, SAA isoforms, which likely contain variable and undefined amounts of bound lipids, are difficult to purify. Therefore, a recombinant synthetic human apo-SAA (rhSAA; PeproTech, Rocky Hill, NJ) was used in the following specified studies. This protein is a consensus human SAA1 peptide except for the presence of an Nterminal methionine and a substitution of asparagine for aspartic acid and arginine for histidine at positions 60 and 71, respectively. Because the latter two substituted residues are present in human SAA2β, the molecule can be regarded as a hybrid of the closely related SAA1 and SAA2 isoforms.

Protein Preparation and ELISA
SAA protein levels were determined using ELISA kits (BioSource International, Camarillo, CA) with rhSAA as the standard. IL-8 ELISA kits were purchased from R&D Systems (Minneapolis, MN). The manufacturer’s instructions were followed for measurements of SAA and IL-8 in cell culture medium, TM tissues, and perfusate samples from human ocular perfusion organ culture. For analysis of cultured cells or ocular tissues, protein extracts were prepared by homogenizing briefly in a lysis buffer consisting of PBS with 0.05% Triton X-100 and protease inhibitors (Complete Mini, EDTA free; Roche Diagnostics, Mannheim, Germany). The supernatant obtained after centrifugation for 10 minutes at 10,000 g was used in the assay. Protein content was determined in cultured cells and TM tissues with reagents (BCA Protein Reagents; Pierce, Rockford, IL).

Human TM Cell Culture
Human TM cells were isolated, characterized, and cultured as described previously.11,18 For comparison of SAA mRNA levels, seven non-glaucoma TM cell lines (NTM12B, NTM55C, NTM57C, NTM60B, NTM79B, NTM93, NTM94B) and seven glaucoma TM cells lines (GTM19A, GTM52C, GTM54A, GTM62E, GTM71B, GTM76D, GTM86B) were evaluated. To assess the effect of rhSAA on IL-8 expression, six non-glaucoma TM cell lines (NTM10A, NTM35D, NTM115-01, NTM153-00, NTM553-02, NTM625403-01) were studied. TM cells were grown to confluence in 24-well plates at 37°C and 5% CO2 in Dulbecco modified Eagle medium with supplement (Glutamax I; Gibco/BRL, Grand Island, NY) supplemented with 10% fetal bovine serum (Hyclone, Logan, UT) and 50 μg/ml gentamicin (Gibco/BRL).

For rhSAA treatment, cells were serum-deprived for 24 hours before incubation with rhSAA for 24 hours.

Human Ocular Perfusion Organ Culture
Human ocular perfusion organ culture was performed as previously described.19,20 Briefly, 16 to 20 hours after death, nonglaucomatous donor eyes were dissected at the equator, and the iris, lens, most of the ciliary body, and vitreous were removed. The anterior segment of the eye, including the cornea and the scleral ring containing the TM, was placed in a custom-made acrylic glass culture dish and sealed in place with an acrylic glass O-ring. Serum-free Dulbecco modified Eagle medium was perfused at a flow rate of 2.5 μL/min through a central cannula in the bottom of the dish. The IOP was monitored through a second cannula attached to a pressure transducer. The IOP was recorded every 5 minutes, and hourly averages were calculated. Anterior segments, cultured at 37°C and 5% CO2, were allowed to equilibrate for 2 to 4 days before SAA exposure. Tissues that did not reach a stable baseline IOP were discarded (approximately 50% of the eyes). Acceptable paired eye tissues were perfused with medium with or without rhSAA (1 μg/ml) for 24 hours.

At the end of each perfusion study, the ocular tissues were perfusion-fixed at 15 mm Hg constant pressure, processed, and assessed by light microscopy and transmission electron microscopy. The viability of the outflow pathway tissue was evaluated in a masked fashion.29
Studies were regarded as invalid and data discarded if more than one quadrant per eye had unacceptable morphologic findings, such as excessive TM cell loss, denudation of trabecular beams, excessive cellular debris in the TM region, loss of Schlemm canal endothelial cells, or breaks in the Schlemm canal inner wall lining. Based on these criteria, one pair of perfused tissues was rejected in this study.

**Statistical Analysis**

Data are presented as mean ± SEM. To compare between two groups, the unpaired Student’s t-test was used. However, the paired Student’s t-test was used to compare IOP and IL-8 data between the perfused human anterior segments, where paired tissues (left eye vs. right eye) from the same donors were studied. For data that did not pass the normality test (Fig. 1D), a nonparametric test, the Mann–Whitney rank sum test, was used. *P < 0.05 represented statistical significance.

**RESULTS**

In search of genes that are differentially expressed in the glaucomatous TM tissue, we pooled RNA samples from the TM of 9 donors with glaucoma and 13 donors without glaucoma and compared their gene expression profiles using Affymetrix gene chip microarrays. We found that the expression of 141 genes was increased by more than 2-fold and that 211 genes were downregulated in the glaucoma samples. Among them, the expression of SAA2 (accession numbers NM_030754 and M23699) was increased by 3.2-fold in the glaucoma TM tissue relative to control samples. This increased expression was confirmed by QPCR of SAA1/2 mRNA extracted from individual (nonpooled) TM tissues of donors with (n = 11) and without (n = 12) glaucoma. SAA mRNA content was significantly higher (*P < 0.05), by more than 5-fold, in glaucomatous TM tissues (Fig. 1A).

There are four SAA genes in humans. SAA1 and SAA2 are inducible acute-phase reactant genes that are dramatically upregulated by proinflammatory cytokines. They are 93.5% and 96.7% identical in their protein and mRNA sequences, respectively. In contrast, SAA3 is a pseudogene, and SAA4 is constitutively expressed in many tissues at low levels. In the QPCR experiments, the SAA primer/probe set was not specific for any of the SAA isoforms. To distinguish which of these genes are expressed in TM tissues, three TaqMan primers/probes specific for mRNA encoding SAA1, SAA2, and SAA4 were designed and used to examine their expression in glaucoma.

**Figure 1.** Upregulation of SAA expression in glaucomatous TM tissues and cells. (A) Increased SAA mRNA in TM tissues obtained from glaucoma patients (n = 11) compared with control donors (n = 12) as quantified by QPCR. *P < 0.05 versus control by Student’s t-test. Elevation in SAA1 (B) and SAA2 (C) mRNA in TM tissues from glaucoma (n = 11) compared with control donors (n = 10). *P < 0.05 versus respective control by Student’s t-test. (D) Increased SAA mRNA in cultured human TM cells derived from glaucoma patients (n = 7 cell strains) compared with control donors (n = 7 cell strains), as quantified by QPCR. **P < 0.01 versus control by Mann–Whitney rank sum test. (E) Elevation of SAA protein level in TM tissues from glaucoma patients (n = 6) compared with donors without glaucoma (n = 6), as assayed by ELISA. *P < 0.05 versus control by Student’s t-test.
tous and control TM tissues by QPCR. The level of SAA4 mRNA was very low and in most tissues below the sensitivity limit of the assay. In contrast, SAA1 and SAA2 mRNA were readily detectable, and, interestingly, the expression of both genes was elevated in glaucoma TM tissues. Mean levels of SAA1 and SAA2 mRNA were increased to 2.9- and 5.5-fold, respectively ($P < 0.05$; Figs. 1B, 1C).

The increased expression of SAA in glaucomatous TM tissues was confirmed in cultured human TM cells. As indicated in Figure 1D, the SAA mRNA level in TM cells derived from glaucoma patients was significantly ($P < 0.01$) higher by approximately 25-fold than the level in cells derived from donors without glaucoma.

In addition to mRNA levels, the SAA protein was significantly ($P < 0.05$) elevated in glaucomatous TM tissues compared with control TM tissues (Fig. 1E), as assayed by an ELISA that recognizes both SAA1 and SAA2. Normal human TM contained 3.8 ± 1.5 μg/mg protein of SAA (mean ± SEM; $n = 6$), whereas in the glaucoma tissues, the SAA contents increased to 2.9-fold: 11.2 ± 3.0 μg/mg protein ($n = 6$). The differential expression of SAA in glaucoma patients appeared to be specific to the eye. Serum SAA concentrations were not significantly different ($P = 0.41$) between glaucoma patients (15.4 ± 13.7 μg/mL; $n = 31$) and donors without glaucoma (18.6 ± 23.0 μg/mL; $n = 31$).

To determine the potential role of SAA in glaucoma pathogenesis, cultured TM cells were treated with or without rhSAA (40 μg/mL, a dose previously reported to produce maximum stimulation) for 24 hours, and mRNA expression was evaluated using Affymetrix gene chip arrays. The expression levels of 200 genes were significantly changed by more than 2-fold when compared with vehicle-treated cells: 169 genes were upregulated, and 31 genes were downregulated. An example of an upregulated gene is IL-8, whose signal from the rhSAA-treated cells increased more than 22-fold ($P < 0.001$; Fig. 2A).

Further quantification of IL-8 mRNA expression was corroborated when IL-8 protein levels were assayed by ELISA. Incubation of the TM cells with

![Figure 2](http://iovs.arvojournals.org/pdfaccess.ashx?url=/data/journals/iovs/932950/ on 06/24/2017)
various concentrations of rhSAA (0.5–40.0 μg/mL) increased IL-8 levels in the culture medium and the cell lysate in a concentration-dependent manner (Fig. 2C). This example shows that SAA can change cytokine expression and modify biochemical processes in the TM cells, which likely lead to altered TM functions.

One of the major functions of the TM is the regulation of aqueous humor outflow resistance and, consequently, IOP. To evaluate the potential effect of SAA on IOP, anterior segments from paired human donor eyes were cultured and perfused with culture medium at a constant flow rate of 2.5 μL/min. IOP was monitored continuously. After stabilization, which typically took 24 to 48 hours, one eye of each pair was continuously perfused with serum-free medium containing rhSAA (1 μg/mL), whereas the other eye was perfused with medium plus vehicle. IOP at the initiation of treatment (time 0) of the rhSAA-treated eyes was 9.9 ± 2.2 mm Hg (n = 5), which was not significantly different from that of their contralateral vehicle-treated eyes (7.8 ± 1.3 mm Hg). Within hours of perfusion, rhSAA increased IOP, which reached approximately 140% that of the vehicle-treated control eyes (P < 0.05) in approximately 24 hours (Fig. 3A). The elevation of IOP lasted throughout the 4-day study period. The rhSAA-induced change in IOP corresponded to a change of IL-8 in the perfusate. IL-8 levels were significantly (P < 0.05) increased in the perfusate collected from the rhSAA-treated eyes, also throughout the 4-day study period (Fig. 3B). These results demonstrate that anterior segments of the human eye responded to SAA, resulting in increased IOP. Interestingly, there was no observable morphologic difference in the outflow pathway between the rhSAA-treated and vehicle-perfused eyes. TM and Schlemm canal were apparently normal and healthy. There was no evidence of changes in trabecular beams or extracellular matrix deposits in these eyes (Figs. 4A, 4B).

### DISCUSSION

In this report, we demonstrated that TM tissues and cultured TM cells derived from donors with glaucoma had significantly elevated SAA mRNA levels, indicated by gene microarray studies and positively confirmed by QPCR. Moreover, the increased SAA protein levels in the TM tissue of POAG patients further corroborated the conclusion that the expression of SAA is elevated in glaucomatous eyes. We also showed that SAA can produce potentially important biological effects on the TM. Treatment of cultured human TM cells with rhSAA affected the expression of many genes, including a concentration-dependent upregulation of IL-8. Even though the consequences of these molecular changes are not yet totally clear, they are expected to cause phenotypical modifications and to alter the functions of the TM. Because TM is a critical component in the regulation of aqueous humor outflow, an excessive expression of SAA, as seen in the glaucomatous eyes, led us to speculate that these proteins may interfere with the control of aqueous humor outflow and, accordingly, IOP.

Indeed, when ex vivo-perfused human ocular anterior segments were treated with 1 μg/mL rhSAA, a significant and sustained increase in IOP was observed. This ocular hypertension is specific to rhSAA because other proteins, such as β-galactosidase, bovine serum albumin, or fetal bovine serum, in much higher concentrations (up to 25 mg/mL) did not raise the IOP of perfused human eyes (IHP, unpublished observations, 2007 and Ref. 22). In the rhSAA-perfused tissues, there were no apparent visible morphologic changes and no abnormal accumulation of extracellular material, suggesting that the induced IOP change was not simply a result of physical blockade of the outflow pathway by the protein. Taken together, these findings imply a likely involvement of SAA in the pathogenesis of glaucoma. Interestingly, dexamethasone, a glucocorticoid that is able to induce ocular hypertension, also induced SAA gene expression in cultured TM cells.25

The association of SAA in glaucoma is intriguing. SAA is an inducible acute-phase alipoprotein that regulates cytokine expression and causes amyloid deposition. The SAA family comprises a number of small, differentially expressed proteins encoded by genes localized on the short arm of chromosome 11. SAA plays important roles in infection, inflammation, and tissue repair. Under these conditions, the serum SAA concentration can increase by more than 1000-fold within 1 to 2 days. This acute-phase response is mediated primarily by a proinflammatory cytokine-induced upregulation of SAA biosynthesis in the liver. However, in addition to liver cells, macrophages, smooth muscle cells, and endothelial cells also produce SAA.24 Moreover, SAA has been located in atherosclerotic lesions and in the brains of Alzheimer patients.25

At present, the molecular mechanism (or mechanisms) involved in SAA-induced ocular hypertension and its association with glaucoma is not fully understood. Based on the identified biological actions of SAA, we propose two possible mechanisms: the amyloidosis mechanism and the cytokine mechanism. Overexpression of SAA1 or SAA2 in some tissues can lead to the development of linear fibrils in amyloid deposits, which hinder normal tissue functions.25,26 In its most severe manifestation, the formation of insoluble plaques in major organs because of chronically elevated SAA concentrations triggers secondary amyloidosis, a progressive and sometimes fatal disease. In a similar manner, the accumulation of excessive SAA deposits could theoretically generate physical resistance for the outflow of aqueous humor sufficient to produce IOP elevation (amyloidosis mechanism).

### Table 1. Effect of rhSAA on IL-8 Expression in Various Cultured Human TM Cell Strains

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<th>TM Cell Strains</th>
<th>IL-8 mRNA</th>
<th>Control (IL-8/18S)</th>
<th>rhSAA-Treated (IL-8/18S)</th>
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In addition to the amyloidosis-related abnormalities, SAA also has direct biological effects on many cells. It activates many cellular signal transduction pathways, such as the ERK1/2, P38MAPK, and NFκB-dependent pathways, increases the production of matrix metalloproteinases, cytokines, and cytokine receptors, and stimulates the release of tumor necrosis factor, IL-1β, and IL-8. These cytokine-like properties of SAA may induce functional changes in ocular tissues, such as the TM, which subsequently alters the outflow facility of aqueous humor and IOP.

Strong evidence supporting either hypothetical mechanism is lacking. Published reports suggest that amyloid deposits are associated with glaucoma. However, ocular amyloidosis occurs primarily in pseudoexfoliation glaucoma and certain secondary glaucomas but not in POAG. Moreover, we could not find any histologic or immunohistochemical indication of amyloid deposits in the TM of SAA-induced ocular hypertensive eyes or glaucomatous donor eyes (Fig. 4 and W-HW, unpublished observations, 2007). In contrast, the upregulation (such as IL-8) and downregulation of many genes by rhSAA in human TM cells suggest that the cytokine-like properties of SAA may be a significant contributing factor in the etiology of glaucoma. We assume that the biological actions of upregulated SAA in
glaucoma pathogenesis are more likely mediated through the cytokine mechanism rather than the amyloidosis mechanism.

In summary, we have demonstrated elevated SAA expression in glaucomatous TM tissues and cells and have shown that increased SAA causes the glaucoma phenotype of elevated IOP. Therefore, it appears that SAA is involved in the development or the pathogenesis of glaucoma. Future elucidation and consequent pharmacologic intervention of upstream inducers and downstream effectors of SAA in the eye may offer a revolutionary treatment for this prevalent and serious blinding disease.

Acknowledgments

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References


**FIGURE 4.** Lack of effect of rhSAA on morphology of tissues in the outflow pathway. (A) Transmission electron micrographs of the outflow pathway of vehicle-perfused eyes. (B) Transmission electron micrographs of the outflow pathway of rh-SAA-treated eyes. Scale bar, 50 μM.
Potential Involvement of Serum Amyloid A in Glaucoma


