Anti-inflammatory and Antioxidant Effects of SERPINA3K in the Retina

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PURPOSE. Previous studies by the authors have shown that retinal levels of SERPINA3K, a serine proteinase inhibitor, are decreased in an animal model with diabetic retinopathy (DR). The purpose of this study was to investigate the function of SERPINA3K and its role in DR.

METHODS. For the oxygen-induced retinopathy (OIR) model, newborn rats were exposed to 75% \( O_2 \) from postnatal day (P) 7 to P12. Cultured retinal cells were treated with \( CoCl_2 \) or 2% \( CONCLUSIONS.

Intravitreal injection of SERPINA3K significantly reduced retinal vascular leakage and leukostasis in the OIR model. SERPINA3K also prevented the hypoxia-induced decrease of occludin, a tight junction protein, in the OIR rat retina and in cultured retinal capillary endothelial cells and retinal pigment epithelial cells. Further, SERPINA3K blocked the upregulation of proinflammatory factors, such as VEGF, TNF-\( \alpha \), and ICAM-1, downregulated the expression of VEGF in the OIR model and in cultured retinal cells exposed to hypoxia. VEGF was downregulated by SERPINA3K at the transcriptional level. Knockdown of SERPINA3K by siRNA resulted in the overexpression of proinflammatory factors, such as VEGF, TNF-\( \alpha \), and ICAM-1, and downregulation of tight junction proteins, such as occludin, have been reported in the retina of diabetic models. These proinflammatory factors play important roles in leukostasis or leukocyte adherence to the retinal vasculature. Local hypoxia is responsible for the overexpression of VEGF and retinal NV, a characteristic change in proliferative diabetic retinopathy.

In DR, oxidative stress plays an important pathogenic role in retinal inflammation. Reactive oxygen species (ROS) such as superoxide, a highly reactive hydroxyl radical, and hydrogen peroxide are physiological mediators of cellular responses. The elevation of intracellular ROS generation in the retina is a characteristic of the oxidative stress found in DR.

In the present study, we identified a novel endogenous anti-inflammatory and antioxidant factor in the retina and investigated a new pathogenic mechanism of retinal inflammation in DR.

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**Materials and Methods**

**Experimental Animals**

Brown Norway (BN) rats were purchased from Charles River Laboratories (Wilmington, MA). Care, use, and treatment of all animals in this study were in strict agreement with the ARVO Statement for the Use of Animals in Ophthalmic and Vision Research and the guidelines in the Care and Use of Laboratory Animals set forth by the University of Oklahoma.

**Proteins and Chemicals**

SERPINA3K was cloned into the pET28 vector (Novagen, Madison, WI), and the construct was transformed into *Escherichia coli* strain BL-21/DE3 (Novagen). Expression and purification followed the protocol described previously. Endotoxin levels were measured with a limulus amebocyte kit (BioWhittaker, Walkersville, MD). Bovine serum albumin (BSA) and \( H_2O_2 \) were purchased from Sigma (St. Louis, MO), and the inhibitor of ROS (DPI) was purchased from EMD (San Diego, CA).
Oxygen-Induced Retinopathy (OIR) Model
OIR was induced as described previously. Briefly, newborn BN rats at postnatal day (P) 7 were exposed to hyperoxia (75% O2) for 5 days and then returned to room air at P12. SERPINA3K was injected into the vitreous of the right eye (10 μg/2 μl) through the pars plana at P14. The left eye received the same amount of BSA as the control. At P16, vascular permeability was quantified by measuring albumin leakage from blood vessels into the retina using the Evans blue-albumin leakage method as described previously. For retinal dissection, animals were anesthetized and perfused with prewarmed (37°C) PBS to remove the blood from the retina vasculature, and the retina was dissected and homogenized.

Cell Culture
rMC-1 cells, a cell line derived from rat retinal Müller cells, were a kind gift of Vijay Sarthy (Northwestern University, Chicago, IL) and were cultured in Dulbecco’s modified Eagle’s medium (DMEM) containing 10% fetal bovine serum (FBS; Invitrogen, Carlsbad, CA). R28, a cell line derived from rat retinal precursor cells and expressing photoreceptor and Müller cell markers, was a generous gift of Gail Seigel (State University of New York at Buffalo). ARPE19 cells, a cell line derived from human retinal pigment epithelial (RPE) cells, were purchased from American Type Culture Collection (Manassas, VA). R28 and RPE cells were cultured in DMEM containing 10% FBS. Primary human retinal capillary endothelial cells (RCECs) were purchased from Cell Systems (Kirkland, WA) and were cultured in DMEM containing 10% FBS and 1% insulin transferrin selenium. All the common cell culture materials were purchased from Cellgro (Manassas, VA). Cultured cells were starved in DMEM containing 1% FBS for 4 hours before addition of the proteins or compounds, and all experiments were performed in the same medium.

Fluorescent Detection of Intracellular ROS
A ROS-sensitive, probe-based method was used as described previously. To measure intracellular ROS generation, cells were preincubated with 10 μM 5(6)-chloromethyl-2′,7′-dichlorodihydrofluorescein diacetate acetyl ester (CM-H2DCFDA; Invitrogen) for 30 minutes in the dark. After the CM-H2DCFDA entered the cells, the diacette group was removed by intracellular esterases, trapping the probe inside the cells. Then the incubation buffer was replaced by DMEM containing 1% FBS for 3 hours in PBS. Generation of ROS was quantified by measuring the fluorescent oxidation product CM-DCF in the cytosol, at 570 nm. The viable cells were quantified by the MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-2H-tetrazolium bromide; Roche, Indianapolis, IN) cell viability assay. CoCl2-treated rMC-1 cells were simultaneously processed in the same sample as an internal control. Reaction cocktail (iQ SYBR Green Supermix; Bio-Rad, Hercules, CA) was used for real-time PCR reaction according to the manufacturer’s instruction. Normalization was performed using the housekeeping gene 18S rRNA.

ELISA for Soluble ICAM-1 and VEGF
Soluble ICAM-1 (sICAM-1) concentrations in the retina homogenates and VEGF concentrations in the cell culture medium were measured using an ELISA kit purchased from R&D Systems (Minneapolis, MN) according to the manufacturer’s instruction. Total protein concentration was measured by Bradford protein assay.

Western Blot Analysis
Cell lysates or retinal homogenates were resolved by SDS-PAGE and then blotted with specific antibodies. Antibodies for CD45, VEGF, and ICAM-1 were purchased from Santa Cruz Biotechnology, Inc. (Santa Cruz, CA) and were used at the 1:500 dilution. Western blot analysis of VEGF showed the most prominent band of VEGF164 in the rat samples and VEGF165 in human samples. Antibodies for occludin (catalog numbers 40–6100 and 71–1500; 1:1000) and β-actin (1:3000) were purchased from Invitrogen. Antibody for TNF-α was purchased from Abcam Inc. (Cambridge, MA) and was used at 1:1000 dilution. Antibody for HIF1-α was purchased from R&D Systems (Minneapolis, MN) and was used at 1:1000 dilution.

Immunohistochemistry and Immunostaining
Frozen sections of rat retinas were incubated with 1:100 dilution of an anti-CD45 antibody (BD Biosciences, San Jose, CA). After extensive washes, the sections were incubated with a biotin-labeled monoclonal anti-rabbit antibody and were then developed using the ABC method (Vector Laboratories, Burlingame, CA), with 3,3’-diaminobenzidine as a chromogen.

Cell Viability Assay
The viable cells were quantified by the MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-2H-tetrazolium bromide; Roche, Indianapolis, IN) cell viability assay, as described previously. Briefly, 10% culture volume of buffer 1 (MTT) was added to the cell culture after desired treatments and incubated for 4 hours. Then 100% culture volume of buffer 2 (10% SDS in 0.1 M HCl) was added and incubated with the cells for 16 hours. Optical absorbance at 570 nm was measured using an ELISA reader.

Real-Time PCR
Total RNA was isolated (RNeasy Mini Kit; Qiagen Sciences, Germantown, MD), and mRNA was reverse transcribed to cDNA (TaqMan kit; Roche). This cDNA was then used for specific real-time PCR. To amplify all the VEGF isoforms, primers complementary to exon 2 (5GAGCGGCAATCATCAGAGG-3) and exon 3 (5CATACAGGATGGCTTGAGATG-3) were used. Forward primer complementary to exon 4 (5AGATGAGCTTCCATACAGGAC-3) was used to specifically amplify VEGF165. A reverse primer complementary to exon 8 (5TACCCCGGCTTGGTGTGCACT-3) was used to detect VEGF165b but not VEGF165. Another reverse primer complementary to exon 9 and the terminal five nucleotides of exon 7 (exon9/7, 5CAGTCTTTTCCTGGTGAAGATGCA-3) was used to detect VEGF165b. The primers were synthesized from Sigma (St. Louis, MO). To normalize the variation of the amount of mRNA in each reaction, 18S rRNA (primers 5TTTGTGTTTCTTGGCAAATGTA-3 and 5GGTTATGCTGGAACAAGCTGCA-3) was simultaneously processed in the same sample as an internal control. Reaction cocktail (iQ SYBR Green Supermix; Bio-Rad, Hercules, CA) was used for real-time PCR reaction according to the manufacturer’s procedure.

Glutathione Assay and Superoxide Dismutase Activity Assay
The glutathione (GSH) assay kit (BioAssay Systems, Hayward, CA) and the superoxide dismutase (SOD) assay kit (Cayman Chemical Company, Ann Arbor, MI) were used to measure GSH levels and SOD activities in cultured cells and in the retina. CoCl2-treated rMC-1 cells...
and OIR rat retinas were lysed, and supernatants were used for the assays according to the protocols recommended by the manufacturer. For GSH and SOD activity assays, optical absorbance at 405 nm or 450 nm was measured using an ELISA reader.

Statistical Analysis

Student’s *t*-test was used in all statistical analyses, and statistical significance was accepted for *P* < 0.05.

RESULTS

Inhibitory Effect of SERPINA3K on Inflammation in the Retina with Ischemia-Induced Retinopathy

The anti-inflammatory effect of SERPINA3K was evaluated using retinal leukostasis and vascular leakage as parameters in the OIR model, an ischemia/hypoxia-induced retinopathy model. OIR rats at age P14, 2 days after they were returned to room air, received intravitreal injection of SERPINA3K (10 μg/eye) into the right eye and the same amount of BSA into the contralateral eye as a control. Retinas were dissected at P16 after a thorough perfusion to remove the blood in the retinal vasculature. As measured by Western blot analysis, retinal levels of CD45, a leukocyte common antigen, were significantly increased in the retinas of OIR rats (*P* < 0.05) compared with normal rats at P16 (Figs. 1A, B). The normal group was composed of rats raised in constant room air. (C) Retinal vascular leakage was measured at P16 using Evans blue-albumin as tracer and expressed as a percentage of that in normal control rats maintained in constant room air (mean ± SD; *n* = 6). Vascular leakage in the retina of OIR rats was significantly decreased by SERPINA3K. *P* < 0.05; **P** < 0.01. In the OIR retinas, the effect of SERPINA3K on leukocyte infiltration was also confirmed by immunohistochemistry with an anti–CD45 antibody (Supplementary Fig. S1; all Supplementary Figures are online at http://www.iovs.org/cgi/content/full/50/8/3943/DC1).

At the same time point, retinal vascular permeability assay demonstrated that the retinal vascular leakage in the OIR rats was significantly reduced by the intravitreal injection of SERPINA3K (*P* < 0.05; Fig. 1C), providing more evidence supporting the anti-inflammatory effect of SERPINA3K.

Prevention of the Hypoxia-Induced Decline of Tight Junction Protein Expression

Because the decline of tight junction proteins in retinal endothelial cells is known to contribute to vascular leakage and inflammatory cell infiltration,26,27 we measured the effect of SERPINA3K on expression levels of occludin, one of the tight junction proteins, in the retina and in cultured cells. Occludin levels were reduced in the retina of OIR rats at age of P16, to 40% of that in the age-matched normal rats maintained in the constant room air (Figs. 2A, B). In OIR rats, the effect of SERPINA3K on leukocyte infiltration was also confirmed by immunohistochemistry with an anti–CD45 antibody (Supplementary Fig. S1; all Supplementary Figures are online at http://www.iovs.org/cgi/content/full/50/8/3943/DC1).

Because the blood-retinal barrier is composed of the retinal vascular endothelium and the RPE,28 we measured the direct effects of SERPINA3K on the tight junction protein in cultured primary RCECs and RPE cells. As shown in Figure 2, exposure to 200 μM CoCl₂ for 24 hours downregu-
lated occludin levels in both cell types. SERPINA3K attenuated the decline of occludin in RCECs and RPE cells under hypoxia (Figs. 2C–F). The effects of CoCl2 in the absence and presence of 100 nM SERPINA3K on occludin were also confirmed using immunostaining in cultured RPE cells (Supplementary Fig. S2).

Reduction of Ischemia/Hypoxia-Induced Proinflammatory Factors Overexpression

The anti-inflammatory effect of SERPINA3K was also evaluated by measuring inflammatory markers such as VEGF, TNF-α, and ICAM-1. In the OIR rat retinas, VEGF and TNF-α levels were significantly elevated compared with those in the age-matched normal rats (Figs. 3A, B). A single injection of SERPINA3K mitigated the overexpression of VEGF and TNF-α in the OIR retina. Similarly, ELISA showed that sICAM-1 levels were elevated in OIR rat retinas, which was blocked by SERPINA3K (Fig. 3C). Because VEGF165/164 is the major VEGF isoform in pathologic conditions in the eye, Western blot analysis showed the most prominent band for VEGF164 in the rat samples.

To evaluate the anti-inflammatory effect of SERPINA3K in vitro, primary RCECs and RPE cells were exposed to 2% O2 because RCECs and RPE cells are important cell types in BRB and important sources of proinflammatory factors. VEGF, TNF-α, and ICAM-1 were induced by hypoxia, which was prevented by 100 nM SERPINA3K. Densitometry revealed the significant effects of CoCl2 and SERPINA3K on occludin in (E) RCECs and (F) RPE cells (mean ± SD; n = 3). *P < 0.05; **P < 0.01.
induced VEGF overexpression in a dose-dependent manner (Figs. 4C, F). At the same time, the secretion of VEGF was measured in the RCECs, RPE, and Müller cells exposed to 2% O₂, and CoCl₂-treated Müller cells. VEGF secretion was increased under hypoxia and decreased by SERPINA3K in a concentration-dependent manner (Supplementary Fig. S4). Together, these data indicate that SERPINA3K has anti-inflammatory activity.

**Endogenous Inflammatory Inhibitor**

To investigate whether SERPINA3K is an endogenous suppressor of inflammation, we downregulated the expression of endogenous SERPINA3K using siRNA in R28, a cell line derived from rat retinal precursor cells expressing endogenous SERPINA3K. Two specific siRNAs for SERPINA3K, RNAi-1 and RNAi-2, and the control siRNA were transfected into R28 cells, which were then cultured under 2% O₂ for 24 hours. SERPINA3K expression was knocked down by both of the specific siRNAs but not by the control siRNA (Fig. 5). In the same cells, VEGF and TNF-α levels were significantly increased by RNAi-1 and RNAi-2 compared with those in cells treated with the control siRNA, indicating that the downregulation of SERPINA3K results in inflammation.

**Amelioration of the Hypoxia-Induced Inflammation by SERPINA3K via Its Antioxidant Activity**

Given that oxidative stress is known to induce inflammation in some pathologic conditions such as diabetes, we investigated whether the anti-inflammatory effect of SERPINA3K occurs through mitigating oxidative stress. Cultured Müller cells were treated with 200 μM CoCl₂ to create a hypoxic condition. Intracellular ROS generation was increased, correlating with the CoCl₂ exposure time, to a peak 60% higher than the control at 24 hours of exposure time (Fig. 6A). In the cells exposed to CoCl₂ for 24 hours, SERPINA3K (100 nM) decreased ROS levels by 50% compared with the BSA
control (100 nM; Fig. 6B). The effect of SERPINA3K on intracellular ROS generation was confirmed with fluorescence microscopy (Supplementary Fig. S6).

To determine whether decreased ROS generation was responsible for the anti-inflammatory effect of SERPINA3K, a specific inhibitor of ROS generation, DPI, and a known oxidant, H$_2$O$_2$, were applied. Induction of oxidative stress by 20 μM H$_2$O$_2$ induced VEGF overexpression in cultured Müller cells (Fig. 6C). On the other hand, blocking ROS generation by 1 μM DPI prevented VEGF overexpression induced by CoCl$_2$ (Figs. 6C, D), suggesting that oxidative stress plays a causative role in hypoxia-induced inflammation in retinal Müller cells. HIF1-α stabilization in the Müller cells exposed to CoCl$_2$ was confirmed by Western blot analysis (Figs. 6C, E). As shown by
the cell viability assay using MTT, there was no increase of viable cells after CoCl₂ exposure, suggesting that overproduction of VEGF was not from the cell number change (Supplementary Fig. S7).

**Figure 5.** Knockdown of endogenous SERPINA3K induced overexpression of proinflammatory factors. (A) R28 cells were separately transfected with two siRNAs (RNAi-1 and RNAi-2) specific for SERPINA3K and control (Con) siRNA, followed by exposure to hypoxia (2% O₂) for 24 hours. Expression levels of SERPINA3K, VEGF, and TNF-α were measured by Western blot analysis and normalized by β-actin levels. (B) Densitometry revealed significant changes of SERPINA3K and cytokines induced by the siRNAs. *P < 0.05 compared with nontransfected (No-Tran) control cells.

**Figure 7.** Overexpression of SOD2 alone downregulated hypoxia-induced VEGF expression (Figs. 7E, F), suggesting that the upregulation of SOD2 by SERPINA3K contributes, at least partially, to the anti-inflammatory effect of SERPINA3K.

**DISCUSSION**

SERPINA3K is an extracellular serpin and has been found to function as an antiangiogenic factor. The present study revealed a novel function of this serpin, inhibition of the inflammation induced by ischemia/hypoxia in the retina. Further, our results demonstrate that the anti-inflammatory effect of SERPINA3K occurs through mitigation of intracellular oxidative stress.

SERPINA3K is known to specifically bind to tissue kallikrein, forming a covalent complex and inhibiting proteolytic activities of tissue kallikrein. Through interactions with the kallikrein-kinin system, SERPINA3K participates in the regulation of blood pressure and local blood flow. Later, SERPINA3K was found to have other functions such as antiangiogenic activity, independent of interactions with tissue kallikrein. SERPINA3K has been shown to inhibit ischemia-induced NV in different animal models and thus is considered an endogenous angiogenic inhibitor. The mechanism for its antiangiogenic activity remains elusive. The present study demonstrates that SERPINA3K has potent anti-inflammatory and antioxidant activities. Oxidative stress and inflammation can lead to NV, and the anti-oxidant and anti-inflammatory activities of SERPINA3K may contribute to its anti-angiogenic effect.

Previous studies have shown that SERPINA3K expression was downregulated during acute inflammation, suggesting that it is a negative acute-phase protein. However, the significance of the decreased SERPINA3K levels in inflammation responses has not been investigated. Our data showed that SERPINA3K decreases retinal levels of CD45, suggesting a reduced leukocyte adherence to the retinal vasculature or leukocyte infiltration into the retina induced by ischemia in the OIR model.

ICAM-1 is an adhesion molecule that plays a major role in leukocyte adherence and subsequent endothelium injury. Our results showed that SERPINA3K blocks ICAM-1 expression in the OIR retina, which may be responsible for its effects on leukostasis. Moreover, SERPINA3K inhibits the overexpression of inflammatory cytokines such as VEGF and TNF-α. Taken together, these results suggest that SERPINA3K has anti-inflammatory activities.

SERPINA3K levels are significantly decreased in the diabetic rat retina, as shown in our previous study. However, we did not find a significant reduction of SERPINA3K in the retina of the OIR model (data not shown). Several factors may be responsible for the disparity. First, OIR is an ischemia-induced retinopathy model that is not identical with the DR model; thus, the molecular responses may be different. Secondly, unlike streptozocin-induced diabetes, the OIR model develop a more severe but transient retinopathy. Our measurements might not have caught the proper time point for the SERPINA3K change. The last factor was that more severe vascular leakage and often hemorrhage develop in the OIR retina. Given that SERPINA3K levels in the serum are substantially higher than in the retina, retinal levels of SERPINA3K in the OIR model may be influenced by vascular leakage or hemorrhage. Therefore, it is not conclusive at this time whether SERPINA3K levels are decreased in the OIR retina.

Retinal vascular leakage or BRB breakdown is an important pathophysiological feature of retinal inflammation, as found in some ocular disorders such as DR. BRB resides on the tight junctions between RPE cells and between endothelial cells in the retinal vasculature.
data showed that ischemia and hypoxia downregulate the tight junction protein occludin-1. The downregulation of occludin induced by hypoxia was blocked by SERPINA3K in the retina of the OIR model and in cultured EC and RPE cells. Further, SERPINA3K also reduces retinal vascular leakage in the OIR model. These findings further support that SERPINA3K has an anti-inflammatory activity. However, there were no significant differences in phosphorylated occludin levels between the SERPINA3K- and BSA-treated groups (Supplementary Fig. S3).

Inflammation is regulated by the balance between endogenous proinflammatory factors and anti-inflammatory factors. To determine whether SERPINA3K is an endogenous anti-inflammatory factor, we knocked down the expression of SERPINA3K using siRNA. The knockdown of SERPINA3K is sufficient to induce the expression of inflammatory cytokines, including VEGF and TNF-α. This observation suggests that SERPINA3K is an endogenous inhibitor of inflammation and that it participates in the regulation of the inflammation response. Previously, we have shown that SERPINA3K expression in the retina is decreased in streptozocin-induced diabetic rats. Decreased SERPINA3K levels in the diabetic retina are likely to contribute to inflammatory responses. To further study the mechanism by which SERPINA3K regulates VEGF expression, real-time PCR was performed to measure mRNA levels of VEGF isoforms. mRNA levels of total VEGF and VEGF165a were increased by hypoxia and decreased by SERPINA3K (Supplementary Figs. S5A, B). VEGF165b showed a smaller change toward the opposite direction, compared with VEGF165a (Supplementary Fig. S5C). These results suggest that the major mechanism for the regulation of VEGF by SERPINA3K is to suppress VEGF165a transcription in the retinal cells.

Inflammation and vascular injury can be induced by multiple intracellular signaling processes. Among these, oxidative stress is believed to play a major pathogenic role in retinal inflammation in DR. Oxidation also plays an important role in angiogenesis. To investigate how SERPINA3K inhibits inflammation, we determined the effect of SERPINA3K on hypoxia-induced ROS generation. Our results showed that SERPINA3K blocks ROS generation induced by hypoxia in cultured Müller cells. This effect correlates with the downregulation of VEGF and TNF-α expression by SERPINA3K. To prove that the anti-inflammatory effect of SERPINA3K occurs through reducing ROS generation, we used H2O2, a commonly used oxidant in cultured cells, and DPI, a specific inhibitor of ROS generation. In cultured cells, our results showed that exposure to H2O2 likely to contribute to inflammatory responses. To further study the mechanism by which SERPINA3K regulates VEGF expression, real-time PCR was performed to measure mRNA levels of VEGF isoforms. mRNA levels of total VEGF and VEGF165a were increased by hypoxia and decreased by SERPINA3K (Supplementary Figs. S5A, B). VEGF165b showed a smaller change toward the opposite direction, compared with VEGF165a (Supplementary Fig. S5C). These results suggest that the major mechanism for the regulation of VEGF by SERPINA3K is to suppress VEGF165a transcription in the retinal cells.

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alone induced VEGF expression. On the other hand, DPI decreased the overexpression of VEGF under hypoxia (Fig. 6). These results suggest that ROS generation is a major inducer of inflammation and that the anti-inflammatory effect of SERPINA3K occurs at least partially through reducing ROS generation under hypoxia.

ROS generation is regulated by the intracellular redox systems. To elucidate the mechanism by which SERPINA3K inhibits ROS generation, we evaluated the effect of SERPINA3K on one of the antioxidant enzymes, SOD2. The result showed that SOD2 was upregulated by SERPINA3K under hypoxia. This result suggests that upregulation of endogenous antioxidant enzymes is responsible for the antioxidant activity of SERPINA3K. However, the mechanism by which SERPINA3K regulates SOD2 remains to be investigated. On the other hand, the concentration of GSH, which was shown to be correlated with SOD, was increased in the same trend as SOD activity by SERPINA3K (Supplementary Figs. S8C, D). However, expression of catalase, another potent antioxidant enzyme, was not regulated by SERPINA3K (Supplementary Fig. S9).

In summary, our results revealed novel antioxidant and anti-inflammatory activities of SERPINA3K. The decreased levels of SERPINA3K in the retina of the diabetic animal model may contribute to retinal inflammation and NV. Therefore, restoration of SERPINA3K levels in the retina has therapeutic potential for retinal oxidative and inflammatory disorders such as DR.

References


