Review

Role of Serine Protease Inhibitors A1 and A3 in Ocular Pathologies

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Serine protease inhibitors A1 (SerpinA1) and A3 (SerpinA3) are important members of the serpin family, playing crucial roles in the regulation of serine proteases and influencing various physiological processes. SerpinA1, also known as α-1-antitrypsin, is a versatile glycoprotein predominantly synthesized in the liver, with additional production in inflammatory and epithelial cell types. It exhibits multifaceted functions, including immune modulation, complement activation regulation, and inhibition of endothelial cell apoptosis. SerpinA3, also known as α-1-antichymotrypsin, is expressed both extracellularly and intracellularly in various tissues, particularly in the retina, kidney, liver, and pancreas. It exerts anti-inflammatory, anti-angiogenic, antioxidant, and antifibrotic activities. Both SerpinA1 and SerpinA3 have been implicated in conditions such as keratitis, diabetic retinopathy, age-related macular degeneration, glaucoma, cataracts, dry eye disease, keratoconus, uveitis, and pterygium. Their role in influencing metalloproteinases and cytokines, as well as endothelial permeability, and their protective effects on Müller cells against oxidative stress further highlight their diverse and critical roles in ocular pathologies. This review provides a comprehensive overview of the etiology and functions of SerpinA1 and SerpinA3 in ocular diseases, emphasizing their multifaceted roles and the complexity of their interactions within the ocular microenvironment.

Keywords: SerpinA1 (AAT), SerpinA3 (AACT, ACT), ocular diseases

Serine protease inhibitors (serpins) constitute a family of 36 proteins in humans that regulate the activity of a group of proteolytic enzymes known as serine proteases[1] and play pleiotropic roles in host–pathogen interactions.[2,3] The inhibition of serine proteases is a salient activity necessary for various biological processes, including inflammation, coagulation, angiogenesis, and tissue homeostasis.[4]

SerpinA1 and SerpinA3 are the two most abundant plasma serpins that have been shown to play an important role in ocular pathologies.[5–7] SerpinA1, also known as α-1-antitrypsin (AAT), is a secreted glycoprotein found in high levels in the serum.[8–10] It is primarily produced in the liver but also by a few inflammatory and epithelial cell types.[6,11] SerpinA1 has been found to regulate the secretion of several cytokines and chemokines, neutrophil activity, and expression of cathepsin G and proteinase 3 by cells of the immune system, in addition to reducing complement activation and immune cell infiltration.[12] Interestingly, it has been reported that SerpinA1 can be transported through vascular endothelial cells, and internalization by these cells has been observed to exert a protective role by preventing apoptosis through the inhibition of caspase-3 activity.[13,14]

SerpinA3, also known as α-1-antichymotrypsin (AACT or ACT), is a key serpin that has several biological functions and can be found both extracellularly and intracellularly. SerpinA3 has been shown to promote anti-inflammatory, anti-angiogenic, antioxidant, and antifibrotic activities,[5,7] and it is highly expressed in the retina, kidney, liver, pancreas, and plasma.[15] The targets of the inhibitory activity of SerpinA3 include cathepsin G and mast cell chymase,[16] both of which can convert angiotensin-1 to the active angiotensin-2.

Both SerpinA1 and SerpinA3 have been found to be independently produced in corneal epithelial cells.[16,17] An autosomal inheritable disorder that impairs SerpinA1, α-1-antitrypsin deficiency (AATD) has been associated with ocular allergy and uveitis.[6] SerpinA3 has been found to play a role as an antioxidant in retinal neuronal and Müller cells.[16,17] In patients with acute anterior uveitis, SerpinA3 has also been identified as a potential biomarker due to its increased levels in tear samples.[18] This review attempts to summarize the biological role of SerpinA1 and SerpinA3 in different ocular pathologies.

Role of SerpinA1 and SerpinA3 in Various Ocular Diseases

Ocular Infections

Ocular infections, particularly in conditions such as vernal keratoconjunctivitis (VKC) and phacoallergic endophthalmitis, have been associated with alterations in serum levels of SerpinA1. Notably, untreated patients with VKC exhib-

ited a significant elevation in serum SerpinA1 levels as compared to healthy subjects.[19] Moreover, following a 3-week topical steroid treatment for the disease, serum SerpinA1 levels returned to normal. In the context of phacoallergic endophthalmitis, a study identified a substantial increase in serum SerpinA1 levels in affected individuals compared to healthy subjects.[20] Corneal inflammation, whether induced by physical stress or foreign body infection, can contribute to the development of keratitis. Studies have indicated the involvement of SerpinA1 in both infectious and non-infectious keratitis. A phenome-wide association study (PheWAS) based on UK Biobank data revealed an association between AATD and keratitis.[21] Chidambaram et al.[22] compared transcriptomes from patients with bacterial and fungal keratitis, identifying increased SerpinA1 levels in both conditions compared to healthy controls. Another study analyzing tear samples at different stages of fungal keratitis reported an elevation in SerpinA1 levels throughout all stages.[23] SerpinA1 has also been implicated in blepharitis, where a study screening for prognostic or diagnostic tear protein markers reported a roughly 50% decrease in SerpinA1 levels in patients compared to controls.[24]

Diabetic Retinopathy

Diabetic retinopathy (DR) is characterized by damage to retinal blood vessels, neurodegeneration, and vision loss.[25] In our previously published study, we found elevated levels of SerpinA1 and SerpinA3 in the vitreous fluid of diabetic mice. Administering sgp130Fc, a selective IL-6 trans-signaling inhibitor, restored the SerpinA1 and SerpinA3 to baseline levels.[26] Interestingly, a recent study involving 240 subjects reported significantly lower levels of serum SerpinA1 in patients with DR compared to controls.[27] Some studies have shown that mice treated with SerpinA1 exhibit a deceleration of neurodegeneration in the early stages of DR, resulting in a delayed loss of ganglion cells and thinning of the retina,[9,28] as well as decreased apoptosis, extracellular matrix remodeling, and vascular damage.[10] Additionally, during inflammation, SerpinA1 has been shown to regulate the activity of protease-activated receptors (PARs) present on the cell membranes of innate immune system cells, such as macrophages and neutrophils.[29]

Age-Related Macular Degeneration

In vitro and in vivo studies investigating the immunomodulatory roles of SerpinA1 have shown its ability to shift microglia phenotype from pro-inflammatory M1 to anti-inflammatory M2, indicating its beneficial effects.[30] SerpinA1 has been found to reduce p38 mitogen-activated protein kinase (MAPK) activity and increase superoxide dismutase activity, thereby reducing oxidative stress.[31] Furthermore, SerpinA1 has been found to interact with complement C3 in vitro and in vivo, thus mediating both innate and adaptive immune responses.[32] Proteomic analysis of vitreous samples from 73 treatment-naïve patients with age-related macular degeneration (AMD) and 15 control subjects indicated that the expression of SerpinA1, along with 18 other proteins, was significantly upregulated in patients with AMD.[33] Cathepsin G, which is a target of SerpinA3, is associated with the degradation of proteoglycan, leading to increased choroidal destruction and thinning in AMD.[34] SerpinA3 was found to be present in lower levels in thinner choroids and higher levels in thicker choroids.[35] However, a study by Liang et al.[36] found that SerpinA3 expression is upregulated in the retinas of individuals with AMD.

Retinopathy of Prematurity

Babies born preterm are at a high risk of developing retinopathy of prematurity (ROP). Due to underdeveloped retinal vasculature, these infants are more likely to develop other vision-related diseases in the future. In a study conducted by Sugioka et al.,[37] a two-dimensional polyacrylamide gel electrophoresis comparative analysis of vitreous fluid from ROP subjects and cataract controls detected a total of 13 proteins, out of which nine were exclusively found in patients with ROP. SerpinA1 was one of the prominently identified proteins and was suggested to be a potential marker for disease progression.

Glaucoma

The trabecular meshwork plays a crucial role in draining the aqueous humor (AH), and its dysfunction leads to elevated intraocular pressure. Also, prolonged use of topical steroid medications, such as dexamethasone, is associated with the development of steroid-induced glaucoma.[38,39] A study using human trabecular meshwork cells exposed to dexamethasone found significant changes in several genes, including a more than 100-fold increase in SerpinA3.[40] In a chronic ocular hypertension mouse model, SerpinA1 inhibited microglial activation and promoted the survival of retinal ganglion cells.[41] Higher levels of SerpinA1 have been reported in patients with glaucoma.[42–44] Moreover, we found sex- and race-specific alterations in levels of both these serpins in the AH collected from patients with glaucoma.[45]

Cataracts

Mass spectrometry analysis of 24 AH samples identified 44 cataract-associated proteins, including SerpinA1 and SerpinA3, which were significantly upregulated in the AH of patients with simple nuclear cataract (SNC) and SNC complicated with high myopia as compared to controls.[46] Another study examined the sex-specific differences in AH proteome of those undergoing cataract surgery and found significantly higher expression of SerpinA3 in the female patients compared to the male patients.[47] Additionally, a study of AH from 29 patients with cataract and glaucoma with or without pseudoexfoliation syndrome identified higher expression of SerpinA1 than SerpinA3 in the human AH proteome.[48] RNA sequencing analysis of lens epithelial cells from cataract patients has shown that SerpinA3 levels decrease in patients with age-related cataracts.[49]

Dry Eye Disease

Decreased tear production or excessive tear evaporation leads to dry eye disease (DED). Both SerpinA1 and SerpinA3 have been identified in tear fluid and changes in their levels have been reported in DED.[50,51] Boehm et al.[52] conducted a study involving 38 healthy subjects and 105 patients with DED to assess the inflammatory cytokine profile in tear fluids. The expression levels of SerpinA1 were significantly higher in individuals with DED compared to several other cytokines measured in the tear fluids. In another study, SerpinA1 was found to be significantly decreased in evaporative DED but increased in aqueous-deficient DED.[53]

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Both tear and lacrimal fluids from DED patients showed decreased levels of SerpinA1 and SerpinA3 compared to controls.[51,54] Several studies using animal models have highlighted the role of SerpinA3 in DED. In one study, SerpinA3 inhibited the formation of benzalkonium chloride–induced dry eye, as evidenced by prolonged tear break-up time, reduced corneal fluorescein staining scores, and a lower inflammatory index.[55] Recently, a drug (UAMC-00050) has been developed that specifically targets and inhibits the functionality of serpins. In an in vivo study, it was observed that ocular surface damage was significantly reduced in mice undergoing the UAMC-00050 drug treatment.[56]

Keratoconus

Keratoconus is characterized by corneal thinning and irregular cone shape, resulting in vision impairment. SerpinA1 is produced and released by human corneal epithelial cells, indicating that the cornea has the ability to regulate the synthesis of this inhibitor, without relying solely on the vascular system for its supply.[57] This suggests that SerpinA1 may play a role in the regulation of the corneal extracellular matrix, which is crucial for maintaining the shape and structure of the cornea. Immunoperoxidase and dot blot assay analysis of corneas from individuals with keratoconus showed that the SerpinA1 levels in the corneal epithelium and stromal extracts were, respectively, 1/4 and 1/6 of healthy human control levels.[58]

Uveitis

Uveitis, characterized by increased inflammation in the uvea of the eye, can arise due to factors such as infection or autoimmune processes. Distinct subtypes of uveitis may impact different ocular components. Past reports suggest a potential involvement of SerpinA1 in the etiology and progression of uveitis. In a comprehensive investigation, one study reported increased prevalence of the carrier state of AATD, denoted by the PiMZ phenotype, among individuals afflicted with acute anterior uveitis, thereby suggesting the potential significance of SerpinA1 in the immunogenetics of uveitis.[59] Moreover, significantly reduced levels of SerpinA1 in the serum have been observed in individuals affected by uveitis when compared to those without this ocular condition.[20] Mass spectrometry analysis of tear fluid from unilateral acute anterior uveitis (AAU), bacterial keratitis, and healthy controls identified elevated SerpinA3 levels in the eyes of patients with AAU in comparison to healthy controls, suggesting a potential role of serpins in the local milieu of uveitic eyes.[18]

Pterygium

Pterygium is a degenerative ocular disorder marked by the proliferation of fibrovascular tissue originating from the bulbar conjunctiva and extending onto the cornea. Significant reduction in SerpinA1 and SerpinA3 levels in the tear samples from patients with pterygium compared to healthy controls was reported.[60] Furthermore, another study found increased concentrations of SerpinA3 in conjunctival tissues obtained from 18 patients with both pterygium and ocular trauma.[61]

A complete summary of the tissue specificity and roles of SerpinA1 and SerpinA3 in various ocular pathologies is shown in the Table.

Role of SerpinA1 and SerpinA3 in Different Cell Types

Vascular Endothelial Cells

SerpinA1 is an integral component of the innate immune system and is known to indirectly modulate PARs, particularly PAR-2, in processes associated with inflammation.[62,63] SerpinA1 has been suggested to regulate the serine proteases that activate PAR-2 in vascular endothelial cells, thereby resulting in decreased pro-angiogenic and pro-inflammatory effects.[29,63] On the other hand, SerpinA3 exerts a specific inhibitory effect on the proliferation of vascular endothelial cells. Studies have demonstrated that SerpinA3 elicits the upregulation of pigment epithelium-derived factor (PEDF) while concurrently suppressing the expression of vascular endothelial growth factor (VEGF), tumor necrosis factor-alpha (TNF-α), and other pro-inflammatory factors.[5,7] Furthermore, studies using rodent models indicated that SerpinA3 may play a significant role in the development of DR by affecting the transendothelial permeability of retinal microvascular endothelial cells.[64,65]

Müller Cells

Müller cells are the predominant glial cells in the retina, and their dysfunction is associated with various retinal diseases.[17] SerpinA3 provides protection to Müller cells against oxidative stress–induced cell death by blocking calcium overload through the phospholipase C (PLC) pathway.[17] In situ findings have demonstrated that the expression of SerpinA3 is increased in Müller cells from damaged or injured retinas.[66] Furthermore, upregulation of the endothelin-2 gene, which occurs due to photoreceptor degeneration, as well as stimulation of gliotic changes by ciliary neurotrophic factor, were found to induce higher levels of SerpinA3.[67]

Microglia

Microglia, which are specialized macrophages, play a crucial role as immune cells and contribute to proper development and protective neuro-inflammation in the retina. In a study conducted on rd1 mice retina, a reduction in SerpinA1 levels was reported in these mice compared to the C57 control at postnatal day 14, with a notable emphasis on the inner nuclear layer. As the pathological condition progressed, a further decline in SerpinA1 expression was evident in the rd1 mice retina, contrasting with the sustained stability of SerpinA1 levels in the control group.[30]

T Cells

T cells play a pivotal role in the adaptive immune system, orchestrating the elimination of infected host cells, cytokine production, and activation of other immune cells. SerpinA1 exerts indirect effects on T cells, culminating in the overproduction of IL-10 and influencing the activities of neutrophils, dendritic cells, and macrophages.[68,69] Additionally, SerpinA1 modulates the expression of specific chemokine receptors, notably CCR7, thereby fostering regulatory T-cell activity and differentiation.[70] Beyond these functions, SerpinA1 has been shown to modulate IL-1, caspase-1, caspase-3, and cell death in T cells.[13,71,72] In a study investigating the influence of betaine (trimethyl-

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Table. Role of SerpinA1 and SerpinA3 in Various Ocular Diseases

Eye Disease	Serpins	Tissue Expression	Roles	Models	References
Diabetic retinopathy	A1 ↓	Decreased in retinal endothelial cells	Inhibits pro-inflammatory molecules, regulates activity of protease-activated receptors	C57BL6J mice	Ortiz et al.,[9] Potilinski et al.[28]
	A3 ↑	Increased in retinal microvascular cells	Increases transendothelial permeability, inflammation, neovascularization, etc.	KK-A^{y} knockout mouse model of type 2 diabetes mellitus with obesity	Zhang et al.,[5] Liu et al.[7]
Age-related macular degeneration	A1 ↓	Decreased in retinal microglia	Mediates immunomodulatory functions	rd1 (FVB/N) mice, rat retinal microglia	Zhou et al.,[30] Potilinski et al.[75]
	A3 ↓	Decreased in thin choroids	Allows for increased proteolysis catalyzed by enzymes such as cathepsin G	Human donor eyes	Sohn et al.[35]
Retinopathy of prematurity	A1 ↑	Increased in vitreous fluid	Acute-phase response	Human vitreous fluid	Sugioka et al.[37]
Glaucoma	A1 ↑	Increased in human retina	Inhibits leukocyte migration, mediates anti-apoptotic and anti-inflammatory roles	Human retina, C57BL/6J mice	Yang et al.,[41] Liu et al.,[42] Auler et al.,[43] Rolle et al.,[76] Funke et al.[77]
	A3 ↑	Increased in trabecular mesh cells	Causes decreases in extracellular proteolytic activity	Human trabecular meshwork cells	Rozsa et al.[40]
Cataract	A1 ↑	Increased in aqueous humor	Inflammation and humoral immunity, association with compliment and coagulation complexes	Human aqueous humor	Wen et al.,[46] Kliuchnikova et al.[48]
	A3 ↓↑	Decreased in anterior capsule, increased in aqueous humor	Extracellular matrix regulation	Human aqueous humor, cataract lens, lens epithelial cells	Kliuchnikova et al.,[48] Wang et al.[49]
Dry eye disease	A1 ↑	Increased in lacrimal fluid	Mediates innate immune defense, particularly via the complement pathway	Human lacrimal and tear fluid	Jung et al.[51]
	A3 ↓↑	Decreased in corneal epithelium and endothelium, increased in lacrimal fluid	Ameliorates disease severity by inhibiting pro-inflammatory cytokine TNF-α	BALB/c mice, induction of dry eye in female Wistar rats, human lacrimal and tear fluid	Jung et al.,[51] Lin et al.,[55] Joossen et al.,[56] Hu et al.[78]
Keratoconus	A1 ↓	Decreased in corneal epithelium and stromal extracts	Regulates local control of corneal extracellular matrix	Human corneas, human tear fluid	Sawaguchi et al.[58]
	A3	No change in tear fluid	Involved in immunomodulatory roles	Human tear fluid	de Almeida Borges et al.[60]
Uveitis	A1 ↓	Decreased in human serum	Regulation of inflammation in eye	Human serum	Fearnley et al.,[59] Gupta and Sarin[20]
	A3 ↑	Increased in ciliary body and tear fluid	Mediates immunomodulation, acute phase response	Human tear fluid	Eidet et al.[18]
Pterygium	A1 ↓	Decreased in tear fluid	Mediates inflammatory responses	Human tear fluid	de Almeida Borges et al.,[60] Hou et al.[79]
	A3 ↓↑	Decreased in tear fluid, increased in conjunctival tissues	Role in extracellular matrix remodeling	Human conjunctival sample	de Almeida Borges et al.[60]

glycine) on the progression of experimental autoimmune uveitis (EAU) in Lewis rat models, betaine treatment led to decreased mRNA levels of SerpinA3 in T cells. Conversely, rats with EAU and notable inflammation, lacking betaine treatment, exhibited elevated levels of SerpinA3 in their T cells.[73]

Corneal Epithelial Cells

SerpinA1 is present in all layers of the cornea, including the epithelium, stroma, and endothelium.[6,57] Disruptions in SerpinA1 production can lead to the development of corneal diseases, such as ulcerations.[6] In rat corneal epithelium and cultured human corneal epithelial cells, SerpinA3 has been found to play a role in reducing reactive oxygen species (ROS) production by suppressing NOX4 and enhancing the activity of catalase and superoxide dismutase.[74]

Glycosylation of SerpinA1 and SerpinA3

SerpinA1 and SerpinA3 undergo significant posttranslational modifications, particularly glycosylation, which is crucial for their stability, secretion, and function. SerpinA1 possesses three *N*-linked glycosylation sites at positions 46, 83, and 247 in the mature protein.[80–82] A reported mutation disrupting the *N*-glycosylation site at position 83 leads to a defective allele contributing to α1-antitrypsin deficiency.[80] *N*-glycan on Asn271 modulates SERPINA1/A3-protease interactions, and the position of the fucose residue and *N*-glycan branching determines their regulatory function.[83] Studies have demonstrated that the degree of glycosylation in SerpinA1 can influence cytokine levels of TNF-α and transforming growth factor-beta (TGF-β).[82,84] On the other hand, SerpinA3 undergoes both *N*- and *O*-glycosylation,[85] and these variations have been observed in various inflammatory implications.[86,87]

Signaling Pathways Implicated by SerpinA1 and SerpinA3

ROS Signaling

The antioxidant properties of SerpinA3 show its potential in mitigating cellular damage induced by oxidative stress. SerpinA3 has the ability to prevent phosphorylation of PLC gamma1 and Ca^{2+} overload, leading to decreased ROS production. Additionally, it acts to inhibit the ROS-generating enzyme NOX4 while concurrently enhancing the expression of ROS-related antioxidant factors such as NAD(P)H quinone oxidoreductase 1 (NQO1), nuclear factor erythroid 2-related factor 2 (NRF2), and superoxide dismutase-2.[74,88] Additionally, SerpinA3 has been shown to modulate the Kelch-like ECH-associated protein 1 (KEAP1)/NRF2 pathway, providing protection against ROS generation and oxidative stress.[74]

Wnt Signaling

The involvement of Wnt signaling in DR, AMD, and ROP has been well documented, particularly in its modulation of neovascularization, rendering this pathway a potential target for therapeutic intervention.[89] SerpinA3 has been shown to impact tissue remodeling in diabetic patients and mitigate connective tissue growth factor–induced tissue fibrosis. Increased SerpinA3 blocked Wnt pathway activation in diabetic retinas and in cells treated with high glucose.[90] Likewise, elevated levels of SerpinA1 have been shown to indirectly influence Wnt signaling through the regulation of Akt pathway. This occurs by enhancing the expression levels of glycogen synthase kinase-3 beta (GSK3β), thereby leading to a reduction in β-catenin levels.[10] In summary, both SerpinA1 and SerpinA3 exhibit the capacity to directly or indirectly modulate Wnt signaling by affecting its mediators.

Nuclear Factor Kappa B Signaling

SerpinA1, by reducing transglutaminase 2 protein levels (TG2), indirectly elevates the levels of phosphatase and tensin homolog (PTEN), consequently leading to the attenuation of nuclear factor kappa B (NF-κB) signaling. Additionally, SerpinA1 has been demonstrated to modulate the activity of crucial pro-inflammatory cytokines, such as TNF-α and inducible nitric oxide synthase (iNOS), within the NF-κB signaling pathway.[9,91] Similarly, the impact of SerpinA3 on ocular inflammatory processes is characterized by its suppression of TNF-α, which influences the NF-κB

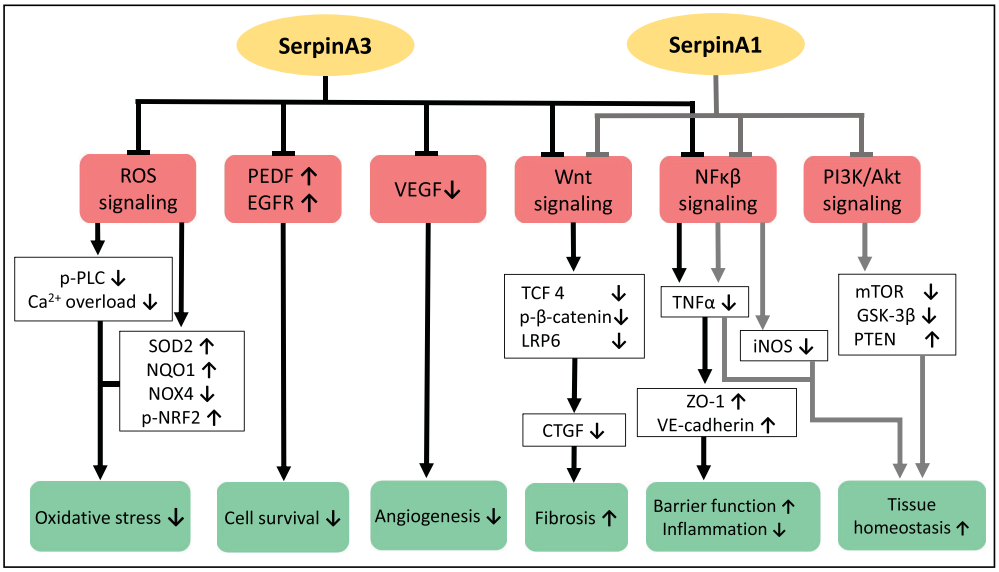

Figure. Signaling pathways and potential therapeutic targets of SerpinA1 and SerpinA3.

signaling pathway and contributes to the enhancement of cellular barrier and adhesion function.[55,78] Furthermore, SerpinA3 has been reported to upregulate the expression levels of PEDF, a crucial anti-angiogenic factor.[7] Collectively, the interactions of SerpinA1 and SerpinA3 with TNF-α and iNOS play pivotal roles in influencing inflammatory pathways and fostering immune tolerance within the ocular microenvironment.[9,10]

PI3K/Akt Signaling

Phosphoinositide 3-kinase (PI3K)/Akt signaling regulates a wide range of cellular processes that are often implicated in disease states.[92] SerpinA1 possesses a unique ability to decrease protein levels of Akt and its phosphorylation, thereby influencing downstream signaling events. The impact of SerpinA1 on this pathway (specifically, its regulation of Akt) mediates GSK3β protein expression—a key regulator of β-catenin—potentially contributing to the reduction of oxidative damage and influencing outcomes in ocular diseases.[10]

Furthermore, SerpinA1 has been demonstrated to reduce mammalian target of rapamycin (mTOR) expression, another downstream mediator in the Akt signaling pathway. Through the regulation of PI3K/Akt/mTOR, SerpinA1 was shown to decrease levels of hypoxia-inducible factor 1 alpha (HIF-1α) and E-cadherin proteins in a hyperglycemic environment.[10] This finding highlights the critical role of SerpinA1 in preserving tissue integrity and promoting cell survival. The Figure provides an overview of the SerpinA1- and SerpinA3-mediated signaling pathways.

Conclusions

This review discusses the roles of SerpinA1 and SerpinA3 in ocular diseases and the signaling pathways they modulate, highlighting their significance in contributing to the homeostasis of the ocular milieu. These serpins emerge as promising targets for potential therapeutic interventions in ocular disorders; however, advancing the field requires a fundamental shift from merely identifying correlations to conducting comprehensive mechanistic investigations. Thus, utilizing transgenic mouse models such as the SerpinA1 PiZ model and the transgenic SerpinA3n model will be helpful in unraveling their significance and offer insights into the functions of SerpinA1 and SerpinA3 in ocular pathologies.[93,94]

Interpreting the precise role of SerpinA1 and SerpinA3 in ocular diseases poses a challenge due to conflicting findings and varying interpretations. The literature reveals a dichotomy of observations, with some studies suggesting a decrease in serpin levels and others indicating an increase in the context of ocular diseases. The specific context of each disease, the stage of progression, and the cellular microenvironment may contribute to the observed discrepancies. Moreover, the varied outcomes across studies could be attributed to the heterogeneity of ocular diseases, each characterized by distinct etiologies, molecular pathways, and manifestations. The multifunctional nature of serpins, acting as regulators of protease activity and inflammation, adds an additional layer of intricacy. Thus, there is a critical need for more comprehensive investigations delving deeper into their localization within ocular tissues and their dynamic interactions with other molecules in the ocular microenvironment. Resolving the uncertainties surrounding the role of SerpinA1 and SerpinA3 in ocular health is essential for developing targeted interventions and improving our understanding of their biological effects.

There are some current roadblocks hindering the widescale implementation of serpins into clinical settings. Although a majority of serpin research has focused on biomarker discovery, limited progress has been achieved in therapeutic intervention primarily due to substantial developmental costs.[95,96] The inherent complexity of these proteins with varying half-lives and stability in circulation presents challenges in devising cost-effective alternatives.[97–99] Moreover, these proteins rely on transitioning from a metastable to a hyperstable conformation for proper function.[100] This transition becomes problematic if it occurs spontaneously or prematurely, leading to intracellular serpin accumulation and tissue damage.[101,102] Consequently, ongoing efforts are directed at developing a uniform serpin "backbone" structure with high stability and modality.[100] Despite these challenges in serpin therapeutic development, continuous research efforts and technological advancements offer promising avenues for innovative solutions and translation into clinical settings.

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