

Research Progress on the SERPINE1 Protein and Chronic Inflammatory Diseases of the Upper Respiratory Tract: A Literature Review

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Keywords

SERPINE1 · Upper respiratory diseases · Airway remodelling · Chronic rhinosinusitis · Allergic rhinitis

Abstract

SERPINE1 protein is one important member of the serine proteinase inhibitor E superfamily that plays a crucial role in the fibrinolytic system. It has been identified which is related to chronic inflammatory lung diseases like allergic asthma and lung fibrosis. Recently, researchers have focused on the impact of SERPINE1 and its genetic polymorphisms on inflammatory diseases of the upper respiratory tract. In this review, we conclude that SERPINE1 is widely involved in the pathological process of chronic rhinosinusitis and allergic rhinitis (AR) and may play a pivotal role in tissue remodelling in chronic rhinosinusitis without nasal polyps. It is also found that the 4G allele of SERPINE1 gene is associated with the risk of upper respiratory diseases. More studies are needed to further clarify how SERPINE1 influences chronic rhinosinusitis and AR, which would be conducive to improving the therapeutic efficacy of treatments for upper respiratory diseases.

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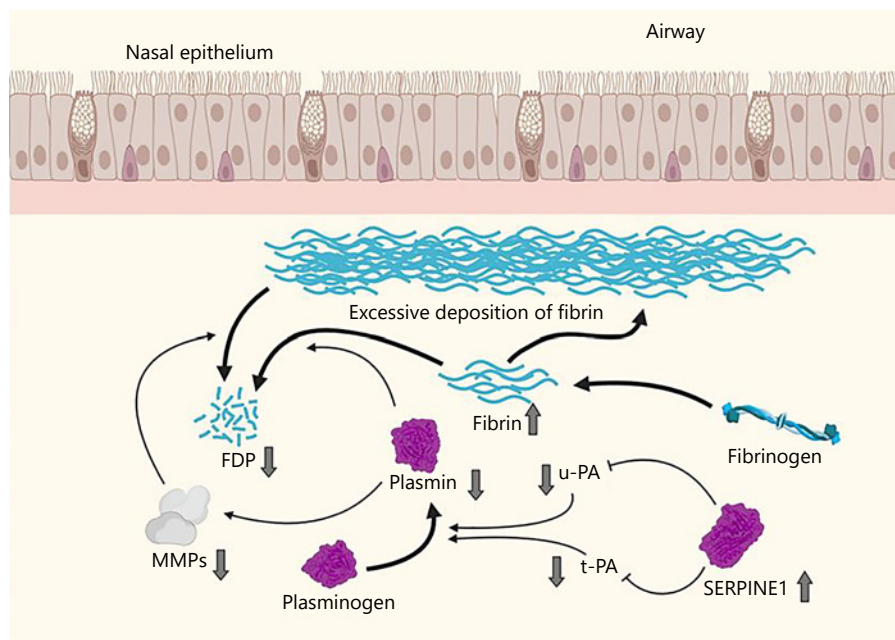
Introduction

The SERPINE1 protein is an important member of the E superfamily of serine proteinase inhibitors. The SERPINE1 protein can quickly inhibit the formation of plasmin [1]. Basing on its effects on fibrinolytic functions, SERPINE1 is involved in chronic inflammation [2, 3], tumour metastasis [3, 4], tissue fibrosis [5], and other pathological processes involving the heart [6, 7], lung [8], kidney [9], breast [10], and other organs and has a wide range of biological activities.

In recent years, research on the relationship between pulmonary interstitial fibrosis, bronchial asthma and certain important lower respiratory tract diseases and the SERPINE1 protein has been relatively systematic, and there have been some attempts to explore the application of SERPINE1 inhibitors to treat pulmonary fibrosis and asthma diseases [11, 12]. The role of SERPINE1 in chronic inflammatory diseases of the upper respiratory tract has also recently received further attention. Our previous study showed that the expression of SERPINE1 in chron-

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Fig. 1. The inhibitory effect of SERPINE1 on plasminogen activators under pathological conditions. Normally, the SERPINE1 protein binds t-PA or u-PA, mediating the conversion of plasminogen into active plasmin, which can hydrolyse fibrin into FDPs. Plasmin can also activate MMPs, and both proteins can degrade the extracellular matrix. While in pathological conditions, increasing SERPINE1 further inhibits u-PA and t-PA and indirectly inhibits the proteolytic action of plasmin and MMPs, leading to the deposition of the extracellular matrix, mainly formed as fibrins. SERPINE1, plasminogen activator inhibitor-1; u-PA, urokinase-type plasminogen activator; t-PA, tissue-type plasminogen activator; FDP, fibrin degradation products; MMPs, matrix metalloproteinases.



ic sinusitis (CRS) exosomes was higher than that in healthy sinus mucosal tissues [13]. To clearly illustrate the role of SERPINE1 in chronic inflammation in the upper respiratory tract, we will review the relationship between SERPINE1 and common chronic inflammatory diseases of the upper respiratory tract, such as CRS and allergic rhinitis (AR), in the present article.

Basic Features of SERPINE1

Molecular Structure and Biological Function of SERPINE1

The SERPINE1 protein is a single-chain glycoprotein composed of 379 amino acids that are mainly synthesized and secreted by platelets, megakaryocytes, hepatocytes, adipocytes, smooth muscle cells, and vascular endothelial cells. The active site of the protein is Arg346-Met347. The expression levels of SERPINE1 are associated with the circadian rhythm, with a peak in the morning and a significant decrease at night. Protein expression is positively correlated with age and insulin resistance [14, 15]. The SERPINE1 protein exists as an activated, lytic, or latent form. The plasma levels of free, activated SERPINE1 are low (approximately 6–80 ng/mL), and this form of the protein is very unstable. The half-life of activated SERPINE1 at 37°C is 1–2 h, transforming spontaneously into the latent form. Otherwise, after SERPINE1 binds to the target protease and is

cleaved, it irreversibly becomes the cleaved form or substrate form [1, 16, 17]. Due to the instability of the monomeric form, SERPINE1 mostly exists as a complex within the body. SERPINE1 binds to vitronectin, increasing its activity more than 10-fold and exerting inhibitor-independent effects, and this binding is reversible and does not affect the ability of SERPINE1 to inhibit plasminogen activators [18, 19].

Additionally, in the fibrinolytic system, SERPINE1 plays a physiological role as an inhibitor of fibrinogen activators. Urokinase-type plasminogen activator (u-PA) could bind reversibly to its specific receptor uPAR to form a u-PA-uPAR complex, and the active peptide bond on the surface of SERPINE1 could irreversibly form a 1:1 complex with the uPA-uPAR complex via a covalent bond. The SERPINE1 protein becomes deactivated after this binding [20]. Tissue-type plasminogen activator (t-PA) and u-PA, both of which are plasminogen activators, can mediate the conversion of plasminogen into active plasmin which hydrolyses fibrin into small peptides, such as fibrin degradation products [1]. Plasmin can also activate matrix metalloproteinases (MMPs), and both proteins can degrade the extracellular matrix, while under pathological conditions, abnormally elevated SERPINE1 exerts further inhibitory effects on u-PA and t-PA and indirectly inhibits the proteolytic action of plasmin and MMPs, resulting in the deposition of the extracellular matrix [21, 22], as shown in Figure 1.

SERPINE1 Gene Promoter Polymorphisms in Allergy and Asthma

The human SERPINE1 gene is located on the long arm of chromosome 7 (7q21.3-q22). 4G/5G polymorphism (rs1799762), allele in the SERPINE1 gene promoter region at -675 bp, is a common SERPINE1 gene single nucleotide polymorphism that manifests as a single guanine base deletion or insertion and affects the transcriptional activity of SERPINE1. Usually, there are 5 guanine base sequences around this single-nucleotide variation region, and so, it is often referred to as a 5G allele, while the 4G allele manifests a deletion of 1 nucleotide. The existence of the 5G site of SERPINE1 enables combination with a repressor factor, producing lower levels of SERPINE1 protein [23]. It has been reported that nearly a quarter of people with homozygous for 4G allele have approximately 30% higher levels of SERPINE1 proteins than those with homozygous for 5G [24]. According to this feature, the 4G/4G genotype, 4G/5G genotype, and 5G/5G genotype are 3 kinds of SERPINE1 genotypes [25]. Some previous studies have shown that SERPINE1 4G/5G polymorphisms are closely related to asthma airway remodeling. SERPINE1 polymorphisms and early lower respiratory tract infections in the Latino population may correlate with asthma severity and decreased lung function [26, 27]. A meta-analysis suggested that SERPINE1 gene polymorphisms are significantly related to an increased risk of allergic diseases, which is a risk factor for asthma and is closely related to asthma susceptibility [28, 29].

The Relationship between SERPINE1 and Chronic Inflammation of the Upper Respiratory Tract

The Relationship between SERPINE1 and CRS

Microscopic Distribution of Fibrinolytic and Inhibitory Components in the Mucosa in CRS

Yasuda et al. [30] analysed the fibrinolytic components of the inferior turbinate mucosal tissues and nasal secretions of patients with common nasal diseases during surgical resection or biopsy who had mainly been diagnosed with purulent sinusitis or AR. The immunohistochemical staining results showed that the SERPINE1 protein was mainly distributed in the serous cells of the lamina propria glands. There was no significant difference in the staining of the mucosal epithelium between the patient and normal groups. Moreover, the average level of SERPINE1 in the nasal secretions of patients with purulent sinusitis was higher than that of the normal group.

However, they collected samples from limited patients with different kinds of diseases in one group. Large individual differences might impact on credibility of the results [30]. Sejima et al. [31] further explored the differences in the expression of fibrinolytic components and SERPINE1 in the pathological process of CRS with nasal polyps (CRSwNP) and without nasal polyps (CRSsNP). The researchers collected ethmoid sinus mucosa in CRSsNP, nasal polyp tissue in CRSwNP, and inferior turbinate mucosa from volunteers without sinus disease as a control group. They found that SERPINE1 in the control and CRSwNP group was distributed in glands and fibroblasts, respectively, whereas SERPINE1 in the CRSsNP group was intensively present in glands, epithelium, endothelium, fibroblasts and infiltrated cells, especially infiltrated cells in the submucosal area. The concentration of SERPINE1 in the CRSsNP group was significantly higher than that in the other 2 groups, as determined by ELISA, whereas the ratio of SERPINE1/u-PAR in the CRSwNP group was significantly lower than that in the other groups [31]. This finding suggests that the expression of u-PA plays a dominant role in CRSwNP, while SERPINE1 plays a more important role in the pathological process of CRSsNP. In addition, the concentration of transforming growth factor- β 1 (TGF- β 1) in CRSsNP was positively correlated with SERPINE1 expression. TGF- β 1 can induce p53 to form a complex with the SERPINE1 gene promoter Smad2/3 and promote the transcriptional activity of SERPINE1, which was consistent with the results of this study [32]. A study conducted in mainland China showed that SERPINE1 was distributed in the cytoplasm of inflammatory cells in the epithelium, vascular endothelium, glands, and stroma in nasal polyp tissue, which was consistent with the results of the study by Sejima [31, 33].

Differences in Fibrinolytic Components and SERPINE1 Expression in the Various Phenotypes of the CRS Mucosa

Takabayashi et al. [34] further explored the pathological mechanism of fibrin deposition in CRSwNP patients and found that the t-PA level and activity in nasal polyp samples were significantly lower than those in mucosal tissues from the uncinate process in CRS patients and normal controls, which negatively correlated with level of eosinophilic cationic proteins, whereas level of SERPINE1 protein in polyp tissues did not increase. Therefore, the researchers hypothesized that the reason for the decrease or inactivation of t-PA in nasal polyps was not SERPINE1 but could be the immune response of Th2 cy-

tokines, such as IL-4 and IL-13, downregulating t-PA and reducing t-PA expression. In addition, the researchers also measured the fibrinolytic components in the uncinata mucosa and inferior turbinate mucosa of patients and normal volunteers and found that the expression levels of t-PA and u-PA in the uncinata mucosa of patients with both CRSwNP and CRSsNP were significantly lower than those in the inferior turbinate mucosal tissue, whereas there was no significant difference in the t-PA expression levels in the two types of mucosal tissues in the normal group. This finding suggests that studies on SERPINE1 and the two different CRS phenotypes may need to adopt different research strategies in the future [34].

Mueller et al. [35] compared the correlation between CRSwNP and different serine protease inhibitor subfamily members. The researchers selected 4 serpin proteins, SERPINB2, SERPINE1, SERPINF2, and SERPING1, as the research indicators. Western blot results showed that all serpin proteins, including SERPINE1, were overexpressed in the mucosal tissues of patients with CRSwNP. Excessive serpin protein expression caused an imbalance in the proteolytic cascade and downregulated fibrinolytic activity, which may lead to fibrin deposition in nasal mucosal tissue. However, the expression of SERPINE1 in this study was not as significant as that of other serine protease inhibitors. Therefore, the role of other types of serine protease inhibitors in CRSwNP may also warrant further study in the future [35].

SERPINE1 Gene Promoter Polymorphisms in CRS

As research on the polymorphisms of the SERPINE1 gene promoter have been carried out in multiple disciplines, the characteristics of SERPINE1 gene polymorphisms in upper respiratory diseases have gradually attracted attention. Research on SERPINE1 gene polymorphisms in CRS was subsequently conducted and showed that the frequency of 4G alleles in the mucosa or polyp tissue from CRS patients without eosinophil infiltration was higher than that of CRS patients with eosinophil infiltration and normal mucosa, but there was no statistically significant difference, suggesting that the 4G allele of SERPINE1 may correlate with non-eosinophil-infiltrating CRS, but more studies are still needed to verify this hypothesis [36].

The Relationship between SERPINE1 and AR SERPINE1 in Fibrinolytic System in AR

Sejima not only focused on the role of the SERPINE1 protein in CRS but also studied the characteristics of the fibrinolytic system in AR patients in the early stage and

found that the mRNA expression of u-PA and SERPINE1 in the nasal mucosa of AR patients was significantly higher than that in normal human nasal mucosa. SERPINE1 mRNA can be detected in serous cells and the epithelium. The immunohistochemical results showed that SERPINE1 was mainly distributed in the serous cells of AR submucosal glands, while the epithelium was hardly stained [37]. Another study showed that the mRNA expression levels of coagulation system components such as coagulation factor II and coagulation factor X were significantly increased in AR mice. Although the expression of SERPINE1 mRNA showed an increasing trend, there was no significant difference compared with that of control mice. u-PA mRNA expression was significantly downregulated in AR group mice, suggesting that the difference in the composition of the coagulation and fibrinolytic systems may be related to mucosal fibrin deposition in mice [38].

SERPINE1 and Immune Response in AR

To further clarify the relationship between SERPINE1 and the type of immune response in AR patients, Sejima et al. [39] carried out another animal experiment and found that the level of active SERPINE1 detected in the nasal lavage fluid of SERPINE1-knockout (SERPINE1^{-/-}) OVA-sensitized mice was lower than that of wild-type OVA-sensitized mice in the research. Interestingly, reduced IL-4 and IL-5 levels as well as increased IFN- γ levels were detected in SERPINE1^{-/-} mice. In addition, mucous cells such as goblet cells in the nasal septum and infiltrated eosinophils were significantly increased in wild-type mice, while only a few neutrophils could be detected in SERPINE1^{-/-} mice. IL-4 and IL-5 are important cytokines in Th2 immune response, while IFN- γ is one of the most crucial cytokines in Th1 immune response. The study suggested that SERPINE1 might be closely related to Th2 immune response and the lack of SERPINE1 appeared to impact on immunotype in AR. In another study, the t-PA gene was knocked out in AR model mice, and the expression of the u-PA and SERPINE1 genes increased significantly in both t-PA knockout mice and wild-type mice sensitized by OVA, while the expression of MMP-9 was reduced. The collagen deposition in AR model mice in the knockout group was significantly more severe than that in the wild-type group, suggesting that the t-PA-induced extracellular matrix deposition in the nasal mucosa may not be directly related to u-PA or SERPINE1 [40]. Moreover, some studies have preliminarily examined whether fibrinolytic components differ in intermittent and persistent AR and showed no significant

differences in serum u-PA, uPAR, and SERPINE1 levels between the two kinds of rhinitis, but some factors may have led to negative outcomes in this study, such as the limited sample size and low average age of the selected patients. In addition, the patients included in the study were limited to those who had a positive reaction to grass pollen or house dust mites, which may be one of the possible factors contributing to bias. More large-sample clinical trials are needed for further corroboration [41].

SERPINE1 Gene Promoter Polymorphisms in AR

SERPINE1 gene polymorphisms in AR patients have also been examined by some scholars. A Turkish study showed that SERPINE1 4G alleles were common in AR children and the lung function of children with the 5G/5G genotype was significantly better than those with the 4G/5G or 4G/4G genotype. There is little evidence that SERPINE1 gene polymorphisms are related to the total serum IgE level, total eosinophil count, or positive skin prick test outcomes in children with AR [42]. In addition, in people with asthma, patients with AR symptoms carry the SERPINE1 4G/4G genotype more frequently (28.1%), and asthma patients with at least one 4G allele have an increased risk of developing AR symptoms [43]. However, in recent years, few studies have focused on the 4G/5G SERPINE1 polymorphism in AR patients. Additional supporting studies are needed to further explore the relationship between different populations or subtypes of AR and gene polymorphisms.

Conclusion

According to current studies on chronic inflammation of the upper respiratory tract, SERPINE1 is mainly involved in the pathological processes of CRS and AR. SERPINE1 may play a more important role in the pathological process of CRSsNP than in CRSwNP, such as in tissue remodelling. The roles of the SERPINE1 protein and gene polymorphisms in CRS and AR have been preliminarily explored, and there is a certain correlation between 4G

alleles and the risks of diseases. Future research should focus on the SERPINE1 protein to explore its roles in the pathological processes of different CRS phenotypes and the way in which SERPINE1 participates in the immune response in upper respiratory tract inflammatory diseases. The relationship between SERPINE1 gene polymorphisms in AR and asthma, as well as their different characteristics, require further research. Whether the SERPINE1 protein is suitable for evaluating the severity of CRS, especially tissue fibrosis in CRSsNP, and whether it is suitable for the clinical evaluation of the efficacy and prognosis of CRS medications is also a research direction that deserves attention. In-depth research on the mechanism of chronic inflammatory diseases of the upper respiratory tract would be beneficial to understanding the common pathological mechanisms of upper and lower respiratory tract diseases and further enrich the treatment of the respiratory system diseases.

Conflict of Interest Statement

The authors have no relevant conflicts of interest to declare.

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Author Contributions

Teng-yu Chen and Min Zhou conceptualized the main idea of this review and drafted most of the sections of the manuscript. They contributed equally to this work and should be considered as co-first authors. Man-qing Lin and Shu-ting Liang mainly completed the writing of "SERPINE1 Gene Promoter Polymorphisms in CRS" and "SERPINE1 Gene Promoter Polymorphisms in AR." Yan Yan completed the writing of the conclusion. Si-min Wang, Cai-shan Fang, and Dan Li mainly retrieved the information from databases, collected relevant references, and supplemented the content of the article. Yan Ruan critically revised the whole draft of the manuscript and provided details of authorship and disclosures of relationships.

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