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Reduced Levels of Resolvin D1 and Thrombospondin-1 in Vernal Keratoconjunctivitis

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ABSTRACT

Objective: To compare serum levels of resolvin D1 (RvD1) and thrombospondin-1 (TSP-1) between patients with vernal keratoconjunctivitis (VKC) and healthy controls and to investigate their potential relevance to disease pathogenesis.

Materials and Methods: A total of 72 individuals were enrolled in this case-control study, including 36 subjects diagnosed with VKC and 36 healthy counterparts matched for age and gender. Serum RvD1 and TSP-1 levels were measured using ELISA. Age and gender distributions were analyzed to ensure group comparability.

Results: No significant differences were observed between the groups in age (VKC: 10.31±4.43 years; controls: 10.66±3.90 years; p=0.724) or gender (15 females and 21 males in each group; p=1.00). Serum TSP-1 levels were significantly lower in the VKC group [60.68 (50.60–78.01) ng/mL] compared with controls [73.49 (64.40–90.67) ng/mL; p=0.011]. Similarly, RvD1 levels were significantly decreased in patients with VKC [67.80 (63.79–68.63) ng/mL] compared with controls [69.85 (65.38–85.60) ng/mL; p=0.009]. ROC curve analysis showed an AUC of 0.681 for RvD1 (sensitivity: 94.4%, specificity: 51.4%) and 0.677 for TSP-1 (sensitivity: 63.9%, specificity: 77.1%).

Conclusion: Reduced serum levels of RvD1 and TSP-1 in patients with VKC suggest disruption of inflammatory resolution and immune regulation. These biomarkers may play a role in VKC pathogenesis and offer potential diagnostic or therapeutic value.

Keywords: Biomarkers, inflammation, resolvin D1, thrombospondin-1, vernal keratoconjunctivitis.

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INTRODUCTION

Vernal keratoconjunctivitis (VKC) is a persistent and recurrent inflammatory disease of the ocular surface that primarily affects the corneal and conjunctival tissues and may cause significant visual impairment in advanced forms. It is most commonly observed in children and adolescents and presents with recurrent episodes of severe allergic inflammation. The clinical presentation is heterogeneous and varies according to the ocular tissues involved and the complex interaction between local and systemic immune responses.[1] In allergic conjunctival disease, histamine is

released early after mast cell activation and degranulation. Activation of histamine receptors on the conjunctival epithelium and surrounding vascular, neural, and immune compartments promotes vasodilation and edema, clinically presenting as conjunctival redness, chemosis, eyelid swelling, and severe itching.[2] Several clinical features are considered particularly suggestive of VKC, including oversized papillae on the tarsal conjunctiva (>1 mm) and limbal nodules resulting from lymphoid cell clustering. Another typical sign is the presence of Horner–Trantas dots, which are observed as whitish deposits composed mainly of degenerating eosinophils, with accompanying neutrophils and mast cells.[3,4]

High histamine exposure can weaken the conjunctival epithelial barrier, leading to increased permeability and promoting the upregulation of chemokines, adhesion molecules, and pro-inflammatory cytokines. Antigen-presenting dendritic cells are subsequently recruited and activated, driving CD4+ T-helper type 2 (Th2) responses. Both Th2 and Th1 CD4+ T cells, together with mast cells, are key mediators of the immunopathology underlying acute and chronic allergic inflammation of the ocular surface.[5] Allergen-specific T-cell responses further enhance IgE synthesis and perpetuate the inflammatory cascade, primarily through eosinophil activation, which is pivotal in late-phase and chronic allergic reactions.[5]

Thrombospondin-1 (TSP-1) is a multifunctional matricellular glycoprotein in the thrombospondin family with calcium-binding properties and was initially identified in platelet releasates after activation. Through interactions with a broad spectrum of binding partners, including extracellular matrix constituents, proteases, and diverse growth factors, TSP-1 orchestrates several essential cellular processes. These include intracellular signaling, regulation of cell proliferation and motility, tissue remodeling and repair, modulation of angiogenesis, and fine-tuning of inflammatory responses.[6] Experimental data indicate that TSP-1 can attenuate immune activation and inflammation primarily by engaging and activating transforming growth factor beta (TGF-β) signaling pathways.[7] Furthermore, TSP-1 has been implicated in the induction and expansion of regulatory T cells, thereby promoting immune tolerance and highlighting its potential relevance as a therapeutic target in allergic conditions.[8]

Resolvin D1 (RvD1) is an omega-3-derived specialized pro-resolving mediator formed from docosahexaenoic acid (DHA) through enzymatic steps involving 15- and 5-lipoxygenases. Functionally, RvD1 supports the active termination of inflammation by limiting polymorphonuclear leukocyte transendothelial migration and facilitating the clearance of pro-inflammatory cytokines and chemokines at sites of tissue damage.[9]

KEY MESSAGES

- Serum levels of thrombospondin-1 (TSP-1), an anti-inflammatory and wound-healing mediator, are significantly altered in patients with vernal keratoconjunctivitis (VKC).
- Resolvin D1 (RvD1), a pro-resolving lipid mediator, is decreased in patients with VKC, suggesting impaired resolution of ocular inflammation.
- These biomarkers demonstrate moderate diagnostic potential for VKC and may represent candidate targets for therapeutic modulation in chronic allergic ocular disease.

Building on these molecular properties, we investigated whether serum levels of the immunoregulatory glycoprotein TSP-1 and the pro-resolving lipid mediator RvD1 could serve as systemic biomarkers and potential therapeutic targets in children with vernal keratoconjunctivitis.

MATERIALS AND METHODS

This prospective case-control study was conducted in the Department of Ophthalmology at Tokat Gaziosmanpaşa University and adhered to the ethical standards outlined in the Declaration of Helsinki. The study protocol was formally approved by the Tokat Gaziosmanpaşa University Ethics Committee (Approval Number: 24-KAEK-029, Date: 06.06.24). Before enrollment, written informed consent was obtained from each participant or their legal representative.

The VKC group consisted of 36 patients younger than 18 years with a clinical diagnosis of VKC. The control group included 35 age- and sex-matched healthy children recruited from the ophthalmology outpatient clinic during routine vision screening. All controls were screened for a history of atopy, allergic conjunctivitis, or systemic inflammatory disease and underwent slit-lamp examination to confirm a healthy ocular surface. Both groups were from the same geographical region, ensuring similar environmental and allergen exposure.

All participants underwent a complete ophthalmologic examination, including visual acuity assessment using a Snellen chart, slit-lamp biomicroscopy, intraocular pressure measurement using a Goldmann applanation tonometer, and dilated fundus examination. The VKC group was diagnosed based on clinical symptoms, such as ocular itching, mucus discharge, and burning sensation, and biomicroscopic findings, including conjunctival hyperemia, chemosis, eyelid edema, papillary reaction, and the presence of Horner–Trantas dots.

Table 1. Comparison of demographic and biochemical parameters between the groups

Variable	VKC group (n=36)	Control group (n=36)	p
Age (years)	10.31±4.43	10.66±3.90	0.724
Sex (male/female)	15/21	15/21	1.000
TSP-1 (ng/mL)	60.68 (50.60–78.01)	74.93 (64.40–90.67)	**0.011**
Resolvin D1 (ng/mL)	67.80 (63.79–68.63)	69.85 (65.38–85.60)	**0.009**

VKC: Vernal keratoconjunctivitis; TSP-1: Thrombospondin-1; SD: Standard deviation; Q1: First quartile; Q3: Third quartile. Age is presented as mean±SD. TSP-1 and resolvin D1 are presented as median (Q1–Q3). Bold p-values indicate statistical significance (p<0.05).

Patients were excluded if they had received any systemic or topical medication within the previous 3 months or had a history of allergen-specific immunotherapy, any additional ocular disease, systemic infection, malignancy, or any acute inflammatory condition. The same exclusion criteria were applied to both the VKC and control groups.

Peripheral venous blood was collected from all participants and processed immediately. After centrifugation at 3000 g for 10 minutes (Nüve NF-800, Türkiye), sera were separated, aliquoted, and stored at −80°C until testing. For analysis, stored samples were thawed at room temperature on the day of the assay.

Serum TSP-1 concentrations were determined using a commercially available human ELISA kit (Bioassay Technology Laboratory, Cat. No. E1110Hu) and an automated microplate photometer. Concentrations were calculated from a standard curve. The assay sensitivity was 2.39 ng/mL, with a linear detection range of 5–700 ng/mL and an interassay coefficient of variation of 10%. Samples with values above the upper limit of detection were appropriately diluted and remeasured in duplicate.

Serum RvD1 levels were measured using a human ELISA kit from the same manufacturer (Bioassay Technology Laboratory, Cat. No. E7450Hu). The assay sensitivity was 19.01 ng/mL, with a linear range of 37.5–2400 ng/mL and an interassay coefficient of variation of 10%. As with TSP-1, concentrations were derived from a standard curve, and high-concentration samples were diluted and assayed in duplicate.

Statistical Analysis

To ensure the statistical robustness of the study, G*Power (version 3.1.9.7) was used for sample size estimation. Based on existing literature and pilot data on ocular surface biomarkers, we calculated that a minimum of 32 subjects per group would provide 80% power (1-β) at a 5% alpha level (α=0.05), assuming a medium-to-large effect size (d=0.65). To account for potential data exclusion or attrition, we ultimately enrolled 72 participants in total, including 36 with VKC and 36 healthy controls. Based on existing literature and pilot data on ocular surface biomarkers, we calculated that a minimum of 36 subjects per group would provide 80% power (1-β) at a 5% alpha level (α=0.05), assuming a medium-to-large effect size (d=0.67). Consequently, to meet this requirement and ensure a fully powered analysis, we enrolled 72 participants in total, including 36 with VKC and 36 healthy controls.

Data management and all comparative analyses were performed using IBM SPSS Statistics (version 22.0, IBM Corp., Armonk, New York, USA). The normality of continuous data distribution was assessed using the Kolmogorov–Smirnov test. For descriptive statistics, age, which was normally distributed, is reported as mean±SD, whereas nonparametric variables, including TSP-1 and resolvin D1, are presented as median with interquartile range (IQR; 25–75th percentiles). Categorical data are presented as frequencies and percentages.

Continuous data with a normal distribution were analyzed using Student's t-test, whereas the Mann–Whitney U test was used for variables with nonnormal distributions. Differences in categorical parameters were assessed using chi-square analysis. To determine how effectively serum RvD1 and TSP-1 levels differentiated between the VKC and control groups, receiver operating characteristic (ROC) curves were constructed. The area under the curve (AUC) is presented with its 95% confidence interval (CI). Finally, optimal diagnostic thresholds, or cutoff values, were identified using Youden's index, along with the corresponding sensitivity and specificity. All tests were two-tailed, and p<0.05 was considered statistically significant.

RESULTS

Seventy-two participants were analyzed, including 36 children with clinically diagnosed vernal keratoconjunctivitis (VKC) and 36 age- and sex-matched healthy controls. Sex distribution was identical in both groups, with 15 females (41.7%) and 21 males (58.3%) in each group. The mean age did not differ between the groups (VKC: 10.3±2.1 years vs. controls: 10.7±1.9 years; p=0.63).

Table 2. ROC curve analysis results for predicting VKC

Biomarker	AUC (95% CI)	p	Cut-off	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
TSP-1	0.677 (0.54–0.80)	**0.011**	63.25	63.9	77.1	74.2	67.5
RvD1	0.681 (0.55–0.81)	**0.009**	69.83	94.4	51.4	66.7	90.0

ROC: Receiver operating characteristic; VKC: Vernal keratoconjunctivitis; AUC: Area under the curve; CI: Confidence interval; TSP-1: Thrombospondin-1; RvD1: Resolvin D1; PPV: Positive predictive value; NPV: Negative predictive value.

Compared with controls, the VKC group showed significantly reduced serum TSP-1 concentrations [60.68 (50.60–78.01) ng/mL vs. 74.93 (64.40–90.67) ng/mL, respectively; p=0.011]. Serum RvD1 levels were also lower in patients with VKC [67.80 (63.79–68.63) ng/mL] than in controls [69.85 (65.38–85.60) ng/mL], and this difference was statistically significant (p=0.009) (Table 1).

ROC curve analysis was performed to assess the diagnostic potential of serum RvD1 and TSP-1. The AUC for RvD1 was 0.681, with an optimal cutoff value of 69.83 ng/mL (sensitivity: 94.4%, specificity: 51.4%). For TSP-1, the AUC was 0.677, and the cutoff value was determined to be 63.25 ng/mL (sensitivity: 63.9%, specificity: 77.1%) (Table 2, Fig. 1). These results indicate moderate discriminative performance for both biomarkers, with notably high sensitivity for RvD1 at the calculated cutoff value.

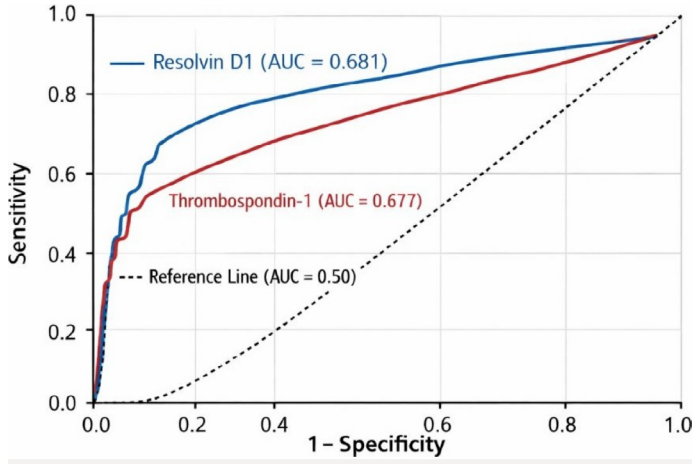

Figure 1. Receiver operating characteristic (ROC) curves of serum Resolvin D1 (RvD1) and Thrombospondin-1 (TSP-1) in patients with vernal keratoconjunctivitis (VKC). RvD1 (AUC=0.681) and TSP-1 (AUC=0.677) show moderate discriminative performance. The dashed line represents the reference (AUC=0.50).

DISCUSSION

Our analysis revealed significantly reduced circulating levels of both RvD1 and TSP-1 in children diagnosed with VKC compared with their healthy age-matched peers.

VKC is an immune-mediated inflammatory condition of the ocular surface characterized by periodic flare-ups. Its pathogenesis involves a complex interplay between type I (IgE-dependent) and type IV (IgE-independent) hypersensitivity reactions, primarily localized within the limbal and tarsal conjunctival tissues.[10] The hypersensitivity reaction that occurs within the conjunctival tissue is central to VKC pathogenesis. Compared with healthy controls, patients show elevated levels of histamine and tryptase, as well as upregulated expression of histamine receptors.[11] Various inflammatory mediators, including prostaglandins, leukotrienes, and cytokines such as TNF-α and IFN, are released by conjunctival mast cells. These mediators play a critical role in the systemic recruitment and local expansion of both basophils and eosinophils within the ocular surface.[12,13] Research has shown that the conjunctiva of individuals with VKC contains a high density of CD4+ Th2 lymphocytes. The subsequent upregulation of cytokines such as IFN-γ, IL-13, IL-5, and IL-4 enhances B-cell-mediated IgE synthesis, representing a key immunopathological feature of the disease.[14,15] This Th2-skewed microenvironment facilitates eosinophil activation and intensifies their interactions with mast cells, thereby sustaining inflammation and contributing to the chronic course of VKC.[15–17]

In ocular physiology, TSP-1 serves as a critical mediator of inflammation control and wound healing. It is strategically located within the trabecular meshwork, cornea, and conjunctiva, as well as in the aqueous and vitreous humors. The interaction of TSP-1 with extracellular matrix proteins, such as integrins and fibronectin, is essential for its diverse roles in maintaining ocular homeostasis.[6,18–20] TSP-1 can facilitate the conversion of latent TGF-β into its bioactive form.[21] Through TGF-β1-dependent signaling, pro-inflammatory immune activity may be attenuated by limiting effector Th1/Th2 responses and modulating B-lymphocyte and natural killer cell functions.[22,23] In addition to VKC, TSP-1 has also been implicated in other ocular inflammatory conditions, including dry eye disease and corneal graft rejection. Taken together, these findings suggest that TSP-1 may help support molecular and cellular pathways associated with ocular immune privilege and the maintenance of immune homeostasis in the eye.[24]

Experimental studies in animal models have shown that the absence of TSP-1 is associated with decreased lacrimal gland function, increased inflammatory cell infiltration in the conjunctiva and cornea, and disruption of corneal epithelial integrity, resulting in autoimmune responses similar to Sjögren's syndrome.[25] These models demonstrated a significant increase in pro-inflammatory cytokines, such as IFN-γ, IL-6, TNF-α, and IL-17A, particularly IL-17 from CD4+ T cells, suggesting that these cytokines play a critical role in disease pathogenesis.[25,26] The loss of the inhibitory effect of TSP-1 on dendritic cell (DC) maturation plays an important role in the development of these autoimmune responses.[27] When this inhibitory effect is removed, the accumulation and activity of corneal DCs increase, which is thought to enhance autoimmune susceptibility. Moreover, TSP-1 promotes the interaction of antigen-presenting cells, including macrophages, DCs, and B lymphocytes, with TGF-β, thereby supporting peripheral tolerance, which is impaired in the absence of TSP-1. Additionally, TSP-1 has been reported to inhibit the activation and maturation of Th1 cells, thereby limiting inflammatory responses.[28] Th1 cells, which also play a role in the pathogenesis of chronic allergic eye diseases, are known to exacerbate inflammation through DC activation. TSP-1 modulates allergic immune responses by suppressing DC maturation and reducing T-cell stimulation. In allergen-sensitized individuals, secondary T-cell responses can sustain IgE production and amplify pro-inflammatory cytokine release, thereby promoting eosinophil-driven late-phase reactions and the maintenance of chronic inflammation.[29]

Our finding of significantly reduced TSP-1 levels in VKC strengthens the evidence that TSP-1 is a key immunoregulatory checkpoint in allergic ocular inflammation. In a mouse model of TSP-1 deficiency, Smith et al.[23] showed that, after topical ovalbumin (OVA) challenge, OVA-sensitized animals exhibited significantly more intense allergic reactions than wild-type controls. Importantly, their data support a mechanism by which TSP-1 expression in dendritic cells constrains secondary allergen-specific T-cell responses, positioning TSP-1 as a central modulator in the pathophysiology of allergic eye disease.[23] Complementing these observations, topical administration of 4N1K, a TSP-1-derived peptide, effectively suppressed T-cell-driven responses and significantly limited disease progression in the same experimental context.[23] Together with our results, these findings underscore that TSP-1 exerts not only systemic immunoregulatory effects but also a decisive local role in shaping the conjunctival inflammatory milieu underlying allergic conjunctival disorders.

In this study, we also evaluated endogenous RvD1 levels in individuals diagnosed with VKC. Our findings suggest that RvD1 may play an important role in the pathophysiology of allergic conjunctivitis. RvD1 is a member of the specialized pro-resolving mediator (SPM) family, which plays a critical role in resolving inflammatory processes. RvD1 helps suppress inflammation by reducing the production of pro-inflammatory molecules, such as prostaglandins and leukotrienes, while promoting the biosynthesis of resolution mediators such as lipoxins, resolvins, and protectins.[30,31] Owing to these properties, RvD1 is thought to have protective and reparative effects not only in allergic disease but also in many other inflammatory diseases.

Animal studies of RvD1 have reported that, in chronic allergic eye diseases, RvD1 inhibits mucus secretion induced by mediators such as LTD4, LTE4, and histamine via ALX/FPR2 and GPR32 receptors in conjunctival goblet cells.[32,33] The study emphasized the importance of reducing mucosal hypersecretion in VKC to improve the disease course and reduce symptoms.

In another study, topical application of RvD1 was shown to reduce cytokine expression in conjunctival tissues, inhibit inflammatory cell infiltration, and provide local anti-inflammatory effects without altering systemic immune responses.[34]

In addition, RvD1 has been shown to inhibit dendritic cell maturation and reduce alloimmune responses in corneal transplant patients. This supports the contribution of RvD1 in conditions characterized by immune overactivity, such as allergic diseases.[35] In this context, it may help explain the RvD1 levels observed in patients with VKC. Accordingly, our findings suggest that RvD1 may play a role not only in terminating inflammation but also in alleviating mucosal symptoms and preserving tissue integrity in VKC. Our results also indicate that RvD1 could serve as a potential biomarker and therapeutic target.

The ROC curve analysis in our study provides further insight into the diagnostic potential of these biomarkers. In our revised analysis, RvD1 demonstrated more balanced discriminative power, with an AUC of 0.681 (95% CI: 0.556–0.806; p=0.009). At the optimal cutoff value of 69.83 ng/mL, it achieved high sensitivity of 94.4%, indicating its potential as a sensitive marker for identifying patients with VKC. Similarly, TSP-1 showed moderate diagnostic utility, with an AUC of 0.677 (95% CI: 0.548–0.805; p=0.011) and a cutoff value of 63.25 ng/mL, yielding sensitivity of 63.9% and specificity of 77.1%. Although these AUC values represent moderate rather than high discriminative performance, they underscore the clinical relevance of systemic inflammatory resolution pathways. These findings suggest that although these biomarkers may not serve as standalone diagnostic tools, they provide significant supportive data in the multifaceted diagnostic context of allergic ocular diseases.

Although evaluating serum resolvin D1 and thrombospondin-1 provides valuable pathophysiological insight into VKC in research settings, their routine clinical use is currently limited by the lack of standardized and cost-effective assays. However, with advances in analytical techniques, these biomarkers may have significant future potential in daily practice for monitoring disease severity, predicting seasonal flares, and guiding pro-resolving targeted therapies.

This study has several limitations. A primary limitation is the small sample size, which may restrict generalizability and limit statistical power. Furthermore, the cross-sectional design of the study does not allow monitoring of dynamic changes in TSP-1 and RvD1 levels throughout the course of VKC. A significant limitation is that only systemic serum levels were evaluated; investigating local ocular surface parameters, such as tear fluid concentrations or conjunctival expression of receptors such as ALX/FPR2 and CD47, would provide stronger pathophysiological insight. Another limitation of our study is that blood samples were collected at various times throughout the year. Additionally, dietary omega-3 fatty acid intake, which is a precursor of and can directly influence circulating resolvin D1 levels, was not assessed. Moreover, clinical severity scores were not recorded, which precluded correlation of biomarker levels with disease activity.

CONCLUSION

Overall, our findings show that children with VKC have reduced circulating levels of TSP-1 and RvD1, supporting the involvement of impaired immunoregulatory and pro-resolving pathways in VKC-associated inflammation. These biomarkers, which demonstrated moderate discriminative performance in ROC analysis, may have clinical utility for disease characterization and risk stratification. They also highlight candidate pathways that could be explored for therapeutic modulation in allergic ocular disorders. Although confirmation in larger independent cohorts is required, the present results suggest a potential role for TSP-1 and RvD1 in ocular inflammatory responses and the maintenance of allergic disease activity.

Ethics Committee Approval: Ethics committee approval was obtained from Tokat Gaziosmanpaşa University Ethics Committee (Approval Number: 24-KAEK-029, Date: 06.06.24).

Informed Consent: Written informed consent was obtained from each participant or their legal representative.

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REFERENCES

1. Bruschi G, Ghiglioni DG, Cozzi L, Osnaghi S, Viola F, Marchisio P. Vernal Keratoconjunctivitis: A Systematic Review. Clin Rev Allergy Immunol 2023;65(2):277-329. [CrossRef]
2. Bielory L, Delgado L, Katelaris CH, Leonardi A, Rosario N, Vichyanoud P. ICON: Diagnosis and management of allergic conjunctivitis. Ann Allergy Asthma Immunol 2020;124(2):118-34. [CrossRef]
3. Singhal D, Sahay P, Maharana PK, Raj N, Sharma N, Titiyal JS. Vernal Keratoconjunctivitis. Surv Ophthalmol 2019;64(3):289-311. [CrossRef]
4. Doan S, Papadopoulos NG, Lee JK, Leonardi S, Manti S, Lau S, et al. Vernal keratoconjunctivitis: Current immunological and clinical evidence and the potential role of omalizumab. World Allergy Organ J 2023;16(6):100788. [CrossRef]
5. Penagos M, Eifan AO, Durham SR, Scadding GW. Duration of Allergen Immunotherapy for Long-Term Efficacy in Allergic Rhinoconjunctivitis. Curr Treat Options Allergy 2018;5(3):275-90. [CrossRef]
6. Kaur S, Roberts DD. Emerging functions of thrombospondin-1 in immunity. Semin Cell Dev Biol 2024;155(Pt B):22-31. [CrossRef]
7. Murphy-Ullrich JE, Suto MJ. Thrombospondin-1 regulation of latent TGF-β activation: A therapeutic target for fibrotic disease. Matrix Biol 2018;68-69:28-43. [CrossRef]
8. Zhang HP, Wu Y, Liu J, Jiang J, Geng XR, Yang G, et al. TSP1-producing B cells show immune regulatory property and suppress allergy-related mucosal inflammation. Sci Rep 2013;3:3345. [CrossRef]
9. Ji RR. Specialized Pro-Resolving Mediators as Resolution Pharmacology for the Control of Pain and Itch. Annu Rev Pharmacol Toxicol 2023;63:273-93. [CrossRef]
10. Esposito S, Fior G, Mori A, Niesters HG, Principi N. An update on the therapeutic approach to vernal keratoconjunctivitis. Pediatr Drugs 2016;18(5):347-55. [CrossRef]
11. Leonardi A, Di Stefano A, Vicari C, Motterle L, Brun P. Histamine H4 receptors in normal conjunctiva and in vernal keratoconjunctivitis. Allergy 2011;66(10):1360-6. [CrossRef]

12. Tabbara KF. Tear tryptase in vernal keratoconjunctivitis. Arch Ophthalmol 2001;119(3):338-42. [CrossRef]
13. Bonini S, Bonini S, Schiavone M, Centofanti M, Allansmith MR, Bucci MG. Conjunctival hyperresponsiveness to ocular histamine challenge in patients with vernal conjunctivitis. J Allergy Clin Immunol 1992;89(1 Pt 1):103-7. [CrossRef]
14. Sacchetti M, Plateroti R, Bruscolini A, Giustolisi R, Marenco M. Understanding Vernal Keratoconjunctivitis: Beyond Allergic Mechanisms. Life (Basel) 2021;11(10):1012. [CrossRef]
15. Leonardi A, Daull P, Garrigue JS, Cavarzeran F, Docquier M, Di Stefano A, et al. Conjunctival transcriptome analysis reveals the overexpression of multiple pattern recognition receptors in vernal keratoconjunctivitis. Ocul Surf 2021;19:241-8. [CrossRef]
16. Chigbu DI, Karbach NJ, Abu SL, Hehar NK. Cytokines in Allergic Conjunctivitis: Unraveling Their Pathophysiological Roles. Life (Basel) 2024;14(3):350. [CrossRef]
17. Hehar NK, Chigbu DI. Vernal Keratoconjunctivitis: Immunopathological Insights and Therapeutic Applications of Immunomodulators. Life (Basel) 2024;14(3):361. [CrossRef]
18. Flugel-Koch C, Ohlmann A, Fuchshofer R, Welge-Lussen U, Tamm ER. Thrombospondin-1 in the trabecular meshwork: localization in normal and glaucomatous eyes, and induction by TGF-beta1 and dexamethasone in vitro. Exp Eye Res 2004;79(5):649-63. [CrossRef]
19. Sekiyama E, Nakamura T, Cooper LJ, Kawasaki S, Hamuro J, Fullwood NJ, et al. Unique distribution of thrombospondin-1 in human ocular surface epithelium. Invest Ophthalmol Vis Sci2006;47(4):1352-8. [CrossRef]
20. Sheibani N, Sorenson CM, Cornelius LA, Frazier WA. Thrombospondin-1, a natural inhibitor of angiogenesis, is present in vitreous and aqueous humor and is modulated by hyperglycemia. Biochem Biophys Res Commun 2000;267(1):257-61. [CrossRef]
21. Crawford SE, Stellmach V, Murphy-Ullrich JE, Ribeiro SM, Lawler J, Hynes RO, et al. Thrombospondin-1 is a major activator of TGF-beta1 in vivo. Cell 1998;93(7):1159-70. [CrossRef]
22. Reyes NJ, Saban DR. T helper subsets in allergic eye disease. Curr Opin Allergy Clin Immunol 2014;14(5):477-84. [CrossRef]
23. Smith RE, Reyes NJ, Khandelwal P, Schlereth SL, Lee HS, Masli S, et al. Secondary allergic T cell responses are regulated by dendritic cell-derived thrombospondin-1 in the setting of allergic eye disease. J Leukoc Biol 2016;100(2):371-80. [CrossRef]
24. Schöllhorn L, Bock F, Cursiefen C. Thrombospondin-1 as a Regulator of Corneal Inflammation and Lymphangiogenesis: Effects on Dry Eye Disease and Corneal Graft Immunology. J Ocul Pharmacol Ther 2015;31(7):376-85. [CrossRef]
25. Turpie B, Yoshimura T, Gulati A, Rios JD, Dartt DA, Masli S. Sjögren's syndrome-like ocular surface disease in thrombospondin-1 deficient mice. Am J Pathol 2009;175(3):1136-47. [CrossRef]
26. Contreras-Ruiz L, Regenfuss B, Mir FA, Kearns J, Masli S. Conjunctival inflammation in thrombospondin-1 deficient mouse model of Sjögren's syndrome. PLoS One 2013;8(9):e75937. [CrossRef]
27. Doyen V, Rubio M, Braun D, Nakajima T, Abe J, Saito H, et al. Thrombospondin 1 is an autocrine negative regulator of human dendritic cell activation. J Exp Med 2003;198(8):1277-83. [CrossRef]
28. Avice MN, Rubio M, Sergerie M, Delespesse G, Sarfati M. CD47 ligation selectively inhibits the development of human naive T cells into Th1 effectors. J Immunol 2000;165(8):4624-31. [CrossRef]
29. Vallejo AN, Mügge LO, Klimiuk PA, Weyand CM, Goronzy JJ. Central role of thrombospondin-1 in the activation and clonal expansion of inflammatory T cells. J Immunol 2000;164(6):2947-54. [CrossRef]
30. Serhan CN. Discovery of specialized pro-resolving mediators marks the dawn of resolution physiology and pharmacology. Mol Aspects Med 2017;58:1-11. [CrossRef]
31. Serhan CN. Treating inflammation and infection in the 21st century: new hints from decoding resolution mediators and mechanisms. FASEB J 2017;31(4):1273-88. [CrossRef]
32. Li D, Hodges RR, Jiao J, Carozza RB, Shatos MA, Chiang N, et al. Resolvin D1 and aspirin-triggered resolvin D1 regulate histamine-stimulated conjunctival goblet cell secretion. Mucosal Immunol 2013;6(6):1119-30. [CrossRef]
33. Dartt DA, Hodges RR, Li D, Shatos MA, Lashkari K, Serhan CN. Conjunctival goblet cell secretion stimulated by leukotrienes is reduced by resolvins D1 and E1 to promote resolution of inflammation. J Immunol 2011;186(7):4455-66. [CrossRef]
34. Saban DR, Hodges RR, Mathew R, Reyes NJ, Yu C, Kaye R, et al. Resolvin D1 treatment on goblet cell mucin and immune responses in the chronic allergic eye disease (AED) model. Mucosal Immunol 2019;12(1):145-53. [CrossRef]
35. Hua J, Jin Y, Chen Y, Inomata T, Lee H, Chauhan SK, et al. The resolvin D1 analogue controls maturation of dendritic cells and suppresses alloimmunity in corneal transplantation. Invest Ophthalmol Vis Sci 2014;55(9):5944-51. [CrossRef]