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Recent Advances in Tear Fluid Analysis for Allergic Conjunctivitis Research

Xinhua Chen[1], Jinhua Wang[1*], Jing Chen[1], Guigang Li[2]

[1]Department of Ophthalmology, Jingzhou Hospital Affiliated to Yangtze University, Jingzhou, China
[2]Department of Ophthalmology, Tongji Medical College of Huazhong University of Science & Technology, Wuhan, China
Email: *395300060@qq.com

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Abstract

Allergic conjunctivitis (AC) is a common ocular surface allergic disease with a rising global incidence, significantly impacting patients' quality of life. Traditional diagnosis primarily relies on clinical presentation and medical history, which are highly subjective and present challenges for early detection. As a non-invasive and repeatable method, tear fluid analysis can directly reflect the inflammatory status of the ocular surface and has demonstrated significant value in the diagnosis, classification, severity assessment, and therapeutic monitoring of allergic conjunctivitis. In recent years, advances in biomarker research and detection technologies have led to notable progress in the application of tear fluid analysis in the diagnosis and treatment of AC. This paper provides a comprehensive review of recent developments in the study of biomarkers in tear fluid, including inflammatory cytokines, chemokines, immunoglobulins, enzymatic markers, and neurotransmitters. It introduces innovative detection techniques, ranging from traditional ELISA to proteomics and point-of-care testing (POCT), and analyzes the current status of clinical application. The paper also discusses existing challenges such as standardization, cost control, and clinical translation, and outlines future directions. Continuous advancements in tear fluid analysis technology will provide strong support for the precise diagnosis and personalized treatment of allergic conjunctivitis.

Keywords

Conjunctivitis, Vernal Keratoconjunctivitis, VKC, Allergic, Tear Fluid, IgE, Ocular Surface Lavage Fluid, Assay

1. Introduction

Allergic conjunctivitis is an abnormal immune response of the ocular surface tissue to allergens and is one of the most common diseases encountered in ophthal-

mology clinics. Based on pathogenesis and clinical manifestations, allergic conjunctivitis can be classified into subtypes such as seasonal allergic conjunctivitis (SAC), perennial allergic conjunctivitis (PAC), vernal keratoconjunctivitis (VKC), atopic keratoconjunctivitis (AKC), and giant papillary conjunctivitis (GPC) [1]. Globally, the prevalence of allergic conjunctivitis is approximately 15% - 20% and is increasing annually, significantly affecting patients' visual function and quality of life [2].

Traditionally, the diagnosis of allergic conjunctivitis has primarily relied on characteristic clinical manifestations (such as ocular itching, conjunctival hyperemia, edema, etc.) and detailed inquiry into the patient's allergy history. However, this diagnostic approach has significant limitations: first, some patients present with atypical clinical features, particularly in the early or chronic stages of the disease, making diagnosis challenging; second, assessment of subjective symptoms varies among individuals and is especially problematic for young children who cannot articulate their symptoms, resulting in a lack of objective and quantitative indicators; third, it is difficult to distinguish between different subtypes of allergic conjunctivitis, which affects the selection of appropriate treatment strategies [3]. Therefore, the search for objective, accurate, and noninvasive diagnostic methods has become an important research focus in this field [4].

Tear fluid is an essential component of the ocular surface microenvironment, providing not only lubrication, nutrition, and protection, but also carrying a wealth of biological information. It contains a variety of biomolecules such as proteins, cytokines, chemokines, and immunoglobulins, whose alterations can directly reflect the pathophysiological state of the ocular surface [5]. As a non-invasive, repeatable, and real-time detection method, tear fluid analysis offers distinct advantages in the diagnosis and monitoring of ophthalmic diseases. In recent years, with advances in molecular biology techniques, research on the application of tear fluid analysis in the diagnosis and treatment of allergic conjunctivitis has made significant progress, providing new tools for early diagnosis, differential classification, severity assessment, and therapeutic monitoring of the disease [6].

The reliability and reproducibility of tear biomarker research highly depend on standardized, non-invasive sample collection methods. The most commonly used methods in current clinical studies include: the capillary collection method, the microsponge/filter paper strip collection method, and the tear strip method [5]. After collection, tear samples should be immediately stored at low temperatures (typically −80˚C) to prevent protein degradation. Currently, no unified gold standard for tear collection has been established worldwide, which represents a major prerequisite challenge in improving the comparability of tear biomarker research results and facilitating their translation into clinical applications.

2. Advances in Research on Tear Fluid Biomarkers

2.1. Inflammatory Cytokines

Inflammatory cytokines play a critical role in the pathogenesis of allergic conjunc-

tivitis and represent important targets for tear-based diagnostics. Th2-type cytokines, particularly interleukin-4 (IL-4), interleukin-5 (IL-5), and interleukin-13 (IL-13), are central mediators in allergic inflammatory responses. Specifically, studies have shown that Th2 pathway-associated cytokines are important in the pathogenesis of Behçet's disease. Literature indicates that IL-4 levels are elevated in the tears of patients with VKC, AKC, and SAC [7]. IL-5 levels are increased in ocular allergy patients with proliferative lesions ($P < 0.05$), mainly promoting the activation, proliferation, and differentiation of eosinophils [8]. IL-13 is elevated in the tears of AKC patients (median: 197.1 pg/mL), significantly higher than healthy controls (median: 90.4 pg/mL, $P < 0.001$), VKC patients (median: 60.0 pg/mL, $P < 0.05$), and SAC patients (median: 80.9 pg/mL, $P < 0.001$), but its level is not associated with severe complications in AKC [9]. Among all allergic conjunctivitis patients and controls, tear IL-13 and periostin levels are weakly but significantly positively correlated ($r = 0.3329$, $P < 0.05$) [9]. However, tear periostin is elevated in AKC patients (median: 444.0 ng/mL), and its level is significantly associated with severe complications. In the large papillae group, periostin is markedly higher (median: 678.8 ng/mL) than in the no/mild papillae group (median: 23.6 ng/mL, $P < 0.001$), and is also significantly higher in the corneal damage-positive group (median: 543.7 ng/mL) compared to the negative group (median: 77.0 ng/mL, $P < 0.01$) [9]. Therefore, tear periostin is an effective biomarker for assessing AKC disease severity [9]. In addition to Th2-type cytokines, other inflammatory cytokines also play important roles in the pathogenesis of allergic conjunctivitis. Tumor necrosis factor-α (TNF-α) is significantly elevated in the tears of VKC patients [10]. Studies indicate that interleukin-6 (IL-6) and its soluble receptor (sIL-6R) are key in allergic conjunctivitis. In VKC and giant papillary conjunctivitis (GPC) patients, tear sIL-6R levels are significantly increased, with net optical density values over eight times higher than healthy controls, and this elevation is statistically significant (VKC group $P < 0.01$; GPC group $P < 0.01$) [11]-[14]. In chronic inflammatory conditions such as dry eye, sIL-6R is also characteristically upregulated, as seen in the tears of patients with Sjögren's syndrome (2.38 ± 0.98 ng/mL), which is significantly higher than normal controls (0.16 ± 0.34 ng/mL, $P < 0.01$) [11]. These findings suggest that sIL-6R is a potential quantitative indicator of ocular surface inflammatory activity. Interleukin-1β (IL-1β) is elevated in all types of allergic conjunctivitis and is involved in the initiation and amplification of the inflammatory cascade [12].

2.2. Chemokines

Chemokines play a central role in the recruitment and activation of inflammatory cells in allergic conjunctivitis. CCL17/thymus and activation-regulated chemokine (TARC) and CCL24/eotaxin-2 have recently attracted significant research attention. Simultaneous detection of CCL17/TARC, CCL24/eotaxin-2, and IL-16 levels in tear fluid helps differentiate between acute and chronic allergic inflammation [13]. Studies have demonstrated that the levels of CCL17/TARC, CCL24/eo-

taxin-2, and IL-16 in the tears of patients with AKC and VKC are significantly higher than those in patients with AC. Notably, CCL24/eotaxin-2 shows a distinct and significant increase in VKC patients' tears, with its net optical density intensity more than eight times higher than that of healthy controls, a difference that is statistically significant ($P < 0.05$) [14]. Antibody array analysis further confirmed that both eotaxin-1 (CCL11) and eotaxin-2 (CCL24) are markedly upregulated in the tears of VKC and GPC patients [14]. Monocyte chemoattractant protein-1 (MCP-1/CCL2) is elevated across all types of allergic conjunctivitis and is involved in the recruitment of monocytes/macrophages [15]. Additionally, research from other mucosal tissues also provides supporting evidence for the ocular surface chemokine network. Research indicates that in an HTLV-I-infected salivary gland epithelial cell (SGECs) model, the expression of RANTES/CCL5 is significantly upregulated in a time-dependent manner. Compared with the baseline at 0 hours without co-culture, the concentration of RANTES/CCL5 in the supernatant after 96 hours of co-culture is significantly increased ($P < 0.05$) [16]. Since mucosal epithelial cells (including those of the ocular surface, respiratory tract, and salivary glands) often share similar pattern recognition receptors and inflammatory signaling pathways (such as NF-κB) when responding to pathogens or inflammatory stimuli, this finding suggests that in the inflammatory environment of allergic conjunctivitis, activated ocular surface epithelial cells may also serve as an important source of RANTES/CCL5.

2.3. Immunoglobulins

In patients with seasonal allergic conjunctivitis (SAC), total tear IgE levels are significantly higher than those in healthy controls ($p < 0.01$) and show a significant positive correlation with total serum IgE levels ($r = 0.44$, $p < 0.01$) [17]. More importantly, tear IgE levels can more directly reflect the allergic status of the ocular surface. Improvement in symptoms and therapeutic response in SAC patients are significantly associated with decreased tear IgE concentrations (correlation coefficient $r = -0.71$, $P < 0.001$); the tear IgE level in patients with recurrence (278.5 ± 40.2 IU/mL) is significantly higher than in those without recurrence (125.3 ± 22.7 IU/mL), independent samples t-test $t(56) = 9.34$, $P < 0.001$ [18]. Recent studies have found that point-of-care testing (POCT) for tear IgE can effectively distinguish between type I and type IV allergic conjunctivitis, thereby providing guidance for personalized treatment [19]. Secretory immunoglobulin A (sIgA) plays an important role in maintaining ocular surface immune homeostasis. Studies have shown that the total sIgA level in tears of VKC patients (28.7 ± 6.8 μg/mL) is significantly lower than that of healthy controls (45.2 ± 5.1 μg/mL), with an independent samples t-test result of $t(38) = 8.45$, $P < 0.001$ [20]. The role of specific IgA antibodies in allergic conjunctivitis requires further investigation [21].

2.4. Enzyme Biomarkers

Matrix metalloproteinase-9 (MMP-9) plays a crucial role in corneal wound heal-

ing and inflammatory responses. Elevated levels of MMP-9 are observed in the tear fluid of patients with allergic conjunctivitis. Secretory phospholipase A2 Group IIa (sPLA2-IIa) is also upregulated in the tears of allergic conjunctivitis patients, potentially contributing to tear film instability by degrading the lipid layer and thereby exacerbating ocular surface inflammation [22]. Eosinophil cationic protein (ECP) is a specific marker for eosinophil activation. ECP levels are elevated in the tears of all types of allergic conjunctivitis patients, with the highest concentrations found in those with AKC and VKC [23]. ECP levels are significantly correlated with clinical severity; the mean ECP concentration in the severe group (38.74 ± 5.51 ng/mL) is significantly higher than in the moderate (35.42 ± 6.39 ng/mL) and mild groups (31.13 ± 8.74 ng/mL). One-way ANOVA indicates that the differences between groups are statistically significant ($F = 9.413$, $P < 0.001$), and post hoc pairwise comparisons (LSD-t test) show significant differences between the severe and moderate groups as well as between the severe and mild groups ($P < 0.05$), making ECP an important indicator of disease activity [24].

2.5. Neuromediators and Epithelial-Derived Factors

Neurotransmitters play a crucial role in both the itching symptoms and the maintenance of chronic inflammation in allergic conjunctivitis. Substance P levels are elevated in the tears of patients with SAC and VKC, contributing to neurogenic inflammatory responses [25]. Nerve growth factor (NGF) is increased in the tears of patients with AKC and VKC and may be involved in sustaining chronic neuropathic pain [26]. Vasoactive intestinal peptide (VIP) levels rise significantly in tears following allergen challenge, which may be associated with the exacerbation of allergic symptoms [27]. Additionally, thymic stromal lymphopoietin (TSLP) derived from epithelial cells plays a key role in initiating and amplifying Th2-type immune responses. Studies show that TSLP levels in the tears of VKC patients are significantly elevated and correlate with disease severity [28]. IL-13, which acts in synergy with TSLP, is not only a core cytokine in the Th2 pathway but also plays an important role in the dialogue between epithelial and immune cells, serving as a potential biomarker for disease subtyping and treatment response evaluation [9] [28].

3. Innovation in Detection Technology

3.1. Traditional Detection Methods

Enzyme-linked immunosorbent assay (ELISA) is a classical method for detecting tear fluid biomarkers, distinguished by its high specificity and good reproducibility. However, ELISA suffers from drawbacks such as low throughput, large sample requirements, and lengthy detection times, limiting its widespread adoption in routine clinical practice [29]. Although radioimmunoassay (RIA) offers high sensitivity, it poses risks of radioactive contamination and is now used less frequently.

3.2. Multiple Detection Techniques

The development of multiplex bead assay technology has greatly enhanced the efficiency and throughput of tear fluid analysis. This technique enables the simultaneous detection of dozens of biomarkers within a single sample, significantly reducing the required sample volume. Studies utilizing multiplex bead assays have measured cytokines such as IFN-γ, TNF-α, IL-2, IL-4, IL-5, and IL-10, and found that IL-10 levels are decreased in the tears of allergic patients, while the ratios of TNF-α/IFN-γ, IL-5/IFN-γ, and IL-5/IL-10 are significantly increased [12]. Membrane-based antibody array technology represents another multiplex detection approach. Using this method to assess 16 inflammatory mediators, researchers observed enhanced signals for IL-2, IL-4, IL-5, and IFN-γ in open-eye samples from allergic patients, and elevated levels of IL-1α and TNF-α in closed-eye samples [30]. Liquid-phase chip technology has also demonstrated advantages in the detection of tear cytokines [31].

3.3. Proteomics Techniques

The development of proteomics technologies has provided powerful tools for the discovery of tear fluid biomarkers. iTRAQ quantitative proteomics analysis revealed that levels of hemoglobin, transferrin, heme-binding protein, mammaglobin B, and secretoglobin 1D1 were significantly elevated in the tears of VKC patients compared to normal controls [32]. Liquid chromatography-mass spectrometry (LC-MS) offers higher precision and accuracy, enabling the identification of 890 proteins in tear samples as small as 4 - 10 μL, with high reproducibility [7]. Data-independent acquisition (DIA) mass spectrometry represents a significant advancement in recent years. This technique allows for the detection of all detectable proteins in a sample within a single analysis, providing more comprehensive data for biomarker discovery. Studies have demonstrated that DIA mass spectrometry has great potential in tear proteomics, with the promise of identifying additional disease-specific biomarkers [33]. Preliminary results from DIA-MS-based tear proteomics have already been achieved in AC research [34].

3.4. Rapid Diagnostic Techniques

The development of point-of-care testing (POCT) technologies has provided significant support for the clinical translation of tear fluid diagnostics. The i-ImmunDx™ tear IgE detection platform can complete testing within 15 minutes using only a minimal tear sample, greatly enhancing clinical convenience [18]. This platform demonstrated strong diagnostic performance in distinguishing between type I and type IV allergic conjunctivitis, with an area under the ROC curve of 0.896 [19]. This rapid and user-friendly testing method assists clinicians in promptly assessing the ocular surface inflammatory status of patients and guiding treatment decisions [35] [36].

4. Current Status of Clinical Applications

4.1. Disease Subtyping Diagnosis

Tear fluid analysis demonstrates significant value in the differential diagnosis of allergic conjunctivitis subtypes. Distinct types of allergic conjunctivitis are associated with unique profiles of tear fluid biomarkers. In patients with VKC, levels of IL-5, RANTES, and eotaxin-1 are significantly higher than those observed in SAC patients, facilitating differential diagnosis [16]. Tear fluid in AKC patients is characterized by elevated IL-4, whereas GPC is primarily associated with increased IL-8 [37]. The combined detection of multiple biomarkers enables more accurate disease classification and provides a basis for personalized treatment [38].

4.2. Severity Assessment

The levels of tear fluid biomarkers are closely associated with the severity of allergic conjunctivitis. Previous studies have confirmed that MMP-9 levels are elevated in the tears of contact lens wearers and are significantly correlated with corneal involvement and the formation of giant papillae, reflecting the extent of structural damage to ocular tissues [21] [39]. One key study demonstrated that during contact lens wear, the concentration of tear MMP-9 (median: 4.6 ng/mL; range: 0.0 - 41.7 ng/mL) was significantly higher than the baseline level prior to lens wear (median: 0.0 ng/mL; range: 0.0 - 0.0 ng/mL), $P < 0.001$ [21] [39]. Changes in the levels of HA, TSLP, ECP, and other markers in the tears of pediatric AC patients can also reflect disease severity [40].

4.3. Efficacy Monitoring

Tear fluid analysis provides objective indicators for monitoring the therapeutic efficacy of allergic conjunctivitis. Studies have shown that levels of multiple biomarkers in patient tears decrease significantly following effective treatment. In AKC patients treated with tacrolimus eye drops, tear ECP levels decreased markedly from 2680.22 ± 2342.7 ng/ml before treatment to 195.71 ± 164.46 ng/ml [41] ($P < 0.05$). In AC patients treated with emedastine eye drops for seven days, tear IL-16 levels significantly decreased ($P < 0.05$), corresponding with improvements in clinical symptoms [13]. Dynamic changes in tear cytokines may serve as sensitive indicators of therapeutic response [42].

4.4. Personalized Treatment Guidance

Tear fluid analysis can assist in guiding personalized treatment for allergic conjunctivitis. By measuring tear IgE levels, it is possible to differentiate between IgE-mediated type I hypersensitivity reactions and non-IgE-mediated type IV hypersensitivity reactions, thus providing a basis for selecting appropriate anti-allergic medications [19]. For patients exhibiting elevated levels of specific cytokines in tear fluid, targeted therapies may be considered. For instance, patients with increased IL-4 and IL-13 levels may benefit from anti-IL-4/IL-13 receptor antibody

therapy [43]. In pediatric AC patients, the expression of non-coding RNAs such as miR-19b and miR-146a in tears may also serve as potential therapeutic targets [44].

5. Challenges and Prospects

5.1. Current Challenges

Although tear fluid analysis demonstrates significant potential in the diagnosis and treatment of allergic conjunctivitis, several challenges remain. The first is the issue of standardization, as there is a lack of unified protocols for sample collection methods, storage conditions, and detection procedures, which affects the comparability and reproducibility of results [45]. The second challenge is cost control; high-throughput detection techniques such as proteomics analysis are expensive, limiting their adoption in routine clinical practice. Additionally, barriers to clinical translation exist, as the transition from research findings to clinical application requires rigorous validation, including large-scale clinical studies and assessment of diagnostic efficacy [46].

5.2. Future Directions

The future development of tear fluid detection technologies will primarily focus on the following aspects: First, establishing standardized testing procedures and quality control systems to enhance the comparability and reproducibility of results [38]. Second, developing more convenient, rapid, and cost-effective detection technologies to promote the widespread clinical application of POCT technologies [47]. Third, integrating multi-omics approaches, including proteomics, metabolomics, and transcriptomics, to construct a more comprehensive biomarker network [48]. For example, metabolomics can systematically analyze changes in small molecule metabolites in tears (such as lipids, amino acids, and energy metabolism products), revealing real-time metabolic reprogramming and oxidative stress states in ocular surface cells under allergic inflammatory conditions, and identifying more dynamic functional biomarkers distinct from proteins. Transcriptomics, on the other hand, can reveal molecular subtyping of the disease, activation of key signaling pathways, and potential new therapeutic targets at the gene regulation level by analyzing the expression profiles of extracellular RNA in conjunctival epithelial cells or tears. Finally, employing artificial intelligence and machine learning techniques to develop diagnostic models based on multiple biomarkers, thereby improving diagnostic accuracy and efficiency [49].

6. Conclusion

As a noninvasive, repeatable, and real-time method, tear fluid analysis has demonstrated significant value in the diagnosis and treatment of allergic conjunctivitis. In recent years, with advances in biomarker research and innovations in detection technology, tear testing has made notable progress in disease classification, severity assessment, therapeutic monitoring, and personalized treatment guidance

[50]. Although challenges remain in standardization, cost control, and clinical translation, ongoing technological advancements and in-depth clinical studies are expected to make tear fluid analysis increasingly important in the precise diagnosis and personalized treatment of allergic conjunctivitis, thereby offering patients improved therapeutic outcomes and quality of life [50].

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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