10. A Tear Inflammatory Biomarker

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Submission date: 16-May-2023 02:19PM (UTC+0800)
Submission ID: 2094416912
File name: 10._A_Tear_Inflammatory_Biomarker.pdf (347.55K)
Word count: 2639
Character count: 15073

A Tear Inflammatory Biomarker in Dry Eye Disease

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Abstract

Background: Dry eye disease is a chronic ocular condition and significantly impacts visual function with multifactorial origin. It is characterized by tear instability and inflammation on the ocular surface. The inflammatory response initiates by synthesis and release of cytokines, Recently, there has been increasing scientific interest using tear film biomarkers that play a role in pathophysiology of dry eye disease. The objective of this study to explain relationship of tear film biomarker in dry eye.

Methods: The research design of this study used literature review. The data was collected from electronic database in PubMed, Google Scholar, and website of science and predominantly published in the last 10 years.

Result: The defect on the tear film component due to oxidative stress lead to ocular surface epithelial exposure, and intracellular signaling pathways are triggered, involving an inflammatory mediator which plays a role in the pathophysiology of dry eye. Using biomarker lead to better diagnosis, drug development, and effective management for dry eye disease.

Conclusion: In conclusion, TNF-a, IL-6, IL-8, IL-1 by number studies to consistently reflect disease severity and strong correlation with schirmer tear test and another test for the ocular surface in dry eye disease.

Keywords: *Dry eye disease, Tear Biomarker, Inflammation*

Introduction

In recent years, the epidemiology of DED is changing. The new paradigm impacting younger patients, mostly related to the rise of smartphone use. In America, an estimated 16 million had been diagnosed with DED and many countries worldwide with a range of 9.5-90 %. The prevalence is higher among women than man and increases with age[1]. In Indonesia, the majority of DED is 37,6 % by 40-49year age group and 1,4 times higher for men than women[2,6].

Defect on tear film components due to oxidative stress lead ocular surface epithelial exposed and triggered intracellular signaling pathways. The inflammatory response initiates the synthesis and release of cytokines, matrix metalloproteinases (MMPs), and chemokines. Pro-inflammatory cytokine

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could activate T-cell to raise inflammation, and MMPs promote extracellular degradation, causing exposure to epithelial barrier[3,6].

Recently, there has been increasing scientific interest in the use of tear biomarkers in DED. Biomarker or biological marker is an objective indicator medical sign or biological stated of normal and pathogenic processes[4]. Using biomarker will lead to better diagnosis, drug development, and effective management for dry eye disease. However, it is challenging to access ocular specimen—alternatively, many studies identifying protein biomarker in tear fluid. A biomarker originated anatomically close to the disease and noninvasive for dry eye disease is crucial to increase specificity. This article aims to describe an overview of the use of tear fluid biomarker in diagnosing and managing DED.

Pathophysiology Dry Eye Disease

Dry eye disease can divide into several significant subtypes, such as aqueous deficient and evaporative. The etiology of aqueous deficiency is disruption of the sensory drive to the lacrimal gland, decreased reflex tearing due to nerve damage (refractive surgery), and systemic drug (such as beta-blocker, diuretic, antihistamine), and aging. Aqueous deficiency most common is related to systemic inflammation, such as Sjogren syndrome. Sjogren syndrome is a chronic autoimmune disorder characterized by lymphocytic infiltration in the exocrine gland, resulting in dry mouth and dry eye[3,5].

Evaporative dry eye resulting in low covering of lipid to the surface of the eye. The most common cause by Meibomian gland dysfunction (MGD). The obstruction of the Meibomian gland leads to tear film instability, hyperosmolarity, and increased tear evaporation. Disruption Meibomian gland function impacts the quantity and quality of Meibomian secretion, affecting changes in tear film composition. The risk factor of MGD including hormonal aspect (imbalance androgen and estrogen), systemic medication (administration of 13-cis retinoid acid), and topical medication (e.g. beta-blocker, prostaglandin analogs, topical epinephrine) [4].

Diagnosis Dry Eye Disease

To assess DED required a combination of symptom and sign. Dryness symptom assessed on validated questionnaires such as ocular surface disease index (OSDI), MacMonnies dry eye questionnaire, and dry eye questionnaire (DEQ). Clinically, DED routinely assessed using a Schirmer tear test to evaluate production aqueous, tear break up time (TBUT) to measure tear film stability, defect on ocular surface-specific corneal and conjunctival staining. The tear film quality could be assessed using an osmometer that measures tear film osmolarity [5].

Tear Film Composition

The tear film is composed of three main layers. The outermost layer is formed predominantly of lipid, which function is to prevent water evaporation and reduce the tension of the ocular surface. The middle is an aqueous layer and plays a role in protecting against pathogens and particle and hydration ocular surface. Its contain insoluble and soluble component such as proteins, electrolytes, peptides, and small molecules. The innermost layer is a mucin layer that resides directly at the surface of the cornea. Mucin originated from the goblet cell. The primary function is to maintain the hydration of the ocular surface[7].

Dysfunction of the lacrimal functional unit cause tear film instability and change any component of the tear fluid. The lacrimal functional unit consists of the lacrimal gland, ocular surface, ocular nerves, goblet cell, and accessory gland (e.g. Meibomian). Hyperosmolarity would activate innate immune response by generating a pro-inflammatory microenvironment on the ocular surface[9]. Initially, natural immune response mediated by pattern recognition receptor such as a toll-like receptor. Receptor recognition and triggers activation of inflammasomes to secretion pro-inflammatory cytokines such as interleukin -1b[10,11]. The murine

model demonstrated that hyperosmolar condition activated protein kinase and stimulates cytokines (IL-8, IL-6, TNF-a), matrix metalloproteinases (MMP9, MMP1)[10,11]. Another study showed that hyperosmolarity induces apoptosis of corneal epithelial cell in vitro condition.

Hyperosmolar stress also activates adaptive immune response through activation antigen-presenting cells (APCs), mainly corneal dendritic cells, and recruitment of inflammatory mediators. Hyperosmolar state on the ocular surface also increased the level of chemokines such as CCL20 and CXCL9 in tear film[9,10]. Mature APCs migrate the regional lymph nodes and prime CD4+ T cell, including T helper 1 (Th1) and Th17. These inflammatory mediators interferon-gamma (IFN-g) through angiogenesis and lymphangiogenesis. IFN-g is secreted by T helper 1 and NK cell related loss of conjunctival goblet cell. Goblet cell produces mucins. In vitro study demonstrated goblet cell is susceptible to IFN-g with significantly reduced proliferation[12,13,14].

Tear Inflammatory Biomarkers

Interleukin-6

Interleukin-6 (IL-6) is an important pro-inflammatory cytokine that is produced by T-lymphocytes and activated macrophages. IL-6 promptly and transiently acute responses to infection, inflammation, immune response, and hematopoiesis. However, dysregulated continue synthesis of IL-6 play a significant effect on chronic inflammation. Interleukin 6 is a representative cytokine with increased expression in tear fluid and conjunctival epithelium and has been known as one of the key molecules in DED.

In many studies, the expression of IL-6 in tear fluid up-regulated in chronic condition[17]. Another study revealed that IL-6 was significantly related to the schirmer tear test. IL-6 levels can be used as indicators to determine the severity and efficacy of anti-inflammatory drugs for DED[18]. Using enzyme-linked immunosorbent assay in tear sample patients with DED that are reported IL-6 level is elevated[19,22]. Another study showed IL-6 level was significantly increased in evaporative DED and correlated with meibography and schirmer tear test[18].

Interleukin 1

The IL-1 family consist of three forms, namely IL-1a, IL-1b, and IL-1 receptor antagonist. The mechanism action of IL-1a and IL-1b activate an immune response that trigger activation to a cascade of inflammation by infiltration, the proliferation of lymphocyte and macrophage, and increasing chemokine production. In ocular surface, IL-1 has been related to corneal neovascularization, bullous keratopathy and reported increasing level in Sjogren Syndrome and ocular rosacea[19,20]. This study noted the pro-inflammatory cytokines IL-1 associated with the intensity of corneal defect epithelium and density of goblet cell [21]. IL-1 receptor antagonist is a form anti-inflammatory of interleukin-1, which has a role to be a natural homeostatic mechanism for preventing undesirable activation of IL-1 mediated inflammatory events on ocular surface[20,21] .

Interferon-gamma

Interferon-gamma (IFN-γ) is secreted mainly through lymphocyte T helper type 1, cells, cytotoxic T cells, and natural killer. IFN-γ have a role in the innate and adaptive immune response. In tear fluid, the increase IFN-γ level inducing conjunctival goblet cell loss and apoptosis of lacrimal gland cell. In the ocular surface, elevated IFN-γ in tear correlated with tear hyperosmolarity and corneal fluorescein. Another study revealed the IFN-γ level associated with TBUT[28]. In murine model, high IFN-γ expression correlates with severity of conjunctival pathology[23]

Interleukin 8

The chemokines IL-8 is a potent pro-inflammatory cytokine that are chemotactic for lymphocytes, neutrophils, and basophils. IL-8 significantly

increases in the tear of DED. The IL -8 contributes to the occurrence of dry eye disease through infiltration and activation of T lymphocytes, leading to damage lacrimal gland and ocular surface[18].

Tumor necrosis factor alfa

Tumor necrosis factor alfa (TNF-a) is a potent mediator inflammatory produced mainly through macrophages during the acute phase of inflammation. The primary role is responsible for the regulation immune system and selectively cytotoxic, leading to necrosis or apoptosis[24]. TNF-a significantly raised in DED and correlated with MMP activation and limit fibrosis. Multiple studies have concluded that TNF-a related to decreased tear production, disease severity, and correlation with OSDI score and schirmer tear test [8,24-26]. In the dry eye mouse model, TNF-a, IL-1, IL-6 level were detected in the tear fluid and conjunctival epithelial[27].

Conclusion

In summary, the identification of molecules in tear fluid as biomarker provide evidence that inflammation is a key feature of the pathophysiology of DED. For dry eye disease, IL-6, TNF-a, IL-8, IL-1 by number studies to consistently reflect disease severity and strong correlation with schirmer tear test and another test for the ocular surface.

Conflict of Interest: Nil

Ethical Clearance: Nil

Funding : The funding is supported by Dana Hibah Mandat Project, Universitas Airlangga Surabaya, Indonesia.

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