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Short Communication Open Access

Cytokines: Key Biomarkers in Elucidating the Pathogenesis of Inflammation

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Ocular surface diseases are defined as disorders that cause damage to the exposed surface of the eye and are associated with symptoms of ocular discomfort [1]. Dry eye disease (DED), a multifactorial ocular surface disease, is one of the most common conditions for which patients seek eye treatment. Though changes in the tear volume and/or tear evaporation rate are considered key to leading to OSD, the pathogenesis of DED is not entirely understood.

Current research suggests that inflammation of the ocular surface may be a core mechanism in the development and chronicity of DED [2,3]. Inflammation of the ocular surface is often associated with tear hyperosmolarity and tear film instability, however limited research has been conducted to evaluate the inflammatory mediators in tears associated with DED [4-6]. Tear cytokine analysis may provide a useful method in understanding and evaluating the inflammatory profile of DED. Variability in the methodology of tear collection and the inability to collect sufficient volume has been a limiting factor in maximizing the usefulness of tear cytokine analysis.

Recent literature has demonstrated that a change in tear cytokine expression in both humans and animals is inherent to the pathogenesis of dry eye [7,8]. It has been suggested that ubiquitous inflammatory cytokines, specifically those related to Th1 and Th17 cells, as well as chemokines and their receptors, play a vital role in the development of inflammation on the ocular surface in DED [9-11]. These inflammatory mediators are most cited in literature reports of dry eye animal models and in patients with DED.

Most of the evidence on inflammation and DED to date is from animal models, with limited data obtained from human subjects. In order to adequately quantify and analyze tear cytokine profiles, a standardized operating procedure (SOP) was established and validated for tear collection and analysis as part of multi-center clinical trials of DED and other ocular surface diseases [12]. Recent developments in laboratory assays have allowed for more sensitive detection of multiple inflammatory cytokines, as well as other biomarkers, in small volume samples, enabling us to better characterize the inflammatory profile behind DED [13]. It is vital to maximize the information from tears and have a standardized analysis methodology, since volumes are small and therefore it is not possible to do duplicate analysis form any one sample from one eye. Even with the small volume samples from DE patients the SOP allows for the simultaneous detection of multiple protein targets with a wealth of accurate, reproducible, and sensitive data.

Biomarkers, or quantifiable physiological variables, provide an impartial perspective into disease state and progression, and provide a benchmark by which the efficacy of potential treatments can be assessed [14,15]. Data regarding biomarkers is invaluable to clinical trials, which are normally plagued by observer-bias of signs and symptoms. Biomarkers, such as tear analysis, provide minimally invasive objective metrics by which disease progression and response to treatment can be characterized and evaluated. Inflammation is a complex process resulting from a concerted cascade of biological signaling at the molecular and cellular levels, and thus requires multidimensional analysis to best capture and elucidate mechanisms at play.

Biomarkers in other fields, such as oncology, allow for early detection of malignancy and are also useful in determining clinical response to treatment. For example, CA125 is an antigen present in 80% of ovarian carcinoma cases. CA125 is elevated in early stages of the cancer and follows the patient's clinical course, and is consequently lower after surgical intervention or chemotherapy [16,17]. This has provided a standardized criterion for clinicians to more accurately diagnose and oversee treatment. Much like dry eyes, inflammatory bowel disease (IBD) is an epithelial mucosal disease [18]. Both mouse and human models have suggested that IBD is driven by Th17 and T-reg dysregulation, and it has been shown that in the IB disease state, biomarkers normally attributed to the pro-inflammatory Th17 cells have been found on the traditionally anti-inflammatory T-reg cells [19-21]. These same biomarkers were then used to illustrate successful treatment of IBD with omega-3 supplementation [22]. Biomarkers have also played a role in other fields, such as neurology [23], rheumatology [15], and cardiology [24].

Development of minimally invasive objective metrics, such as tear analysis, will allow for better diagnosis, classification and analysis of response to treatment for patients with inflammatory ocular surface disease. Cytokine profiling and the evaluation of biomarkers associated with inflammation could be key to understanding the mechanisms leading to diseases such as DED and its persistence, providing new opportunities for treatment targets.

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