Commentary

Ocular surface inflammation in dry eye disease: What we know and what we do not

Dry eye disease (DED) has been the subject of intense laboratory and clinical research, more so in the past couple of decades. Concurrently, our understanding of DED has evolved, with each incremental piece of evidence akin to a small part of a very large jigsaw puzzle. One such piece is the role of ocular surface inflammation in DED. Multiple *in vitro* and *in vivo* studies have established beyond reasonable doubt that ocular surface inflammation is a consistent component of DED. This is reflected in the incorporation of surface inflammation as an element in the definition of DED, arrived at by consensus and updated at regular intervals.[1]

This issue of the journal carries a study by Luo *et al.*, who have attempted to further unravel the intricately intertwined strands of surface inflammation and DED.[2] The study specifically focuses on interleukin-33 (IL-33) levels in tears and serum and attempts to correlate these with disease severity and T-helper-2 (Th2) cytokine levels. Unsurprisingly, the investigators have found higher symptom scores and corneal staining grades in the Sjogren syndrome dry eye (SSDE) group as compared to the non-SSDE and control groups. Levels of IL-33 in tear fluid were also found to be higher in the SSDE group compared to the other two groups. The finding that elevated IL-33 levels correlate with higher symptoms scores needs to be interpreted with caution, as a perusal of the baseline characteristics makes it evident that the disease severity in the SSDE group was greater compared to the other two groups. The study results also show a positive correlation between tear levels of IL-33 with tear levels of IL-4 and IL-5. The authors suggest this may indicate elevated IL-33 levels driving ocular surface inflammation through the Th2 pathway. However, readers need to carefully interpret the data, as the coefficients of determination (R-squared values) are modest. This leads us to believe that factors other than IL-33 may be responsible for influencing the cytokines of the Th2 pathway. It is also important to remember that this is a cross-sectional study and therefore cannot tell us about the temporal course of the levels of these inflammatory molecules and their correlation with disease progression. Overall, the study is a commendable attempt to better understand the role of IL-33 and the Th2 pathway in mediating ocular surface inflammation in DED. It demonstrates raised IL-33 levels in tear fluid of SSDE patients but fails to conclusively establish a link with disease severity or progression.

In a broader context, we are still some way away from elucidating the precise role that surface inflammation plays in DED and the consequent implications on management strategies. In general, tear film hyperosmolarity is believed to stimulate a cascade of events involving both soluble and cellular components that lead to ocular surface inflammation, with subsequent effects on glycocalyx mucin expression, epithelial cell apoptosis, and loss of goblet cells.[3]

While this mechanistic explanation is largely acceptable, one needs to remember that DED is not one homogeneous entity. Multiple separate pathophysiological mechanisms may separately culminate in the constellation of symptoms, tear film hyperosmolarity, loss of tear film homoeostasis and surface inflammation that clinicians recognize as DED. Intuitively, inflammation in the context of DED is not always secondary to tear film hyperosmolarity. For instance, in SSDE, autoimmunity is the starting point, and inflammatory damage to the lacrimal glands occurs upstream to the effects of aqueous deficiency on the surface and the subsequent ocular surface inflammation that further propagates DED.

Translating evidence into practice can be tricky and is fraught with the dangers of oversimplification of concepts and extrapolation beyond available data. We do know for certain that ocular surface inflammation consistently accompanies DED. We should also remember that, as yet, no single cytokine or panel of markers has been shown to be absolutely diagnostic of DED or to discriminate with confidence between the various forms of this disease. Breakthroughs that alter management paradigms take years, and often decades, to manifest. In the meantime, each new bit of information throws light on the path that researchers need to follow. Knowing what we do not know is as important as, and sometimes more important than, what we do know.

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