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ORAL ABSTRACTS

Role of retinoic acid-related orphan receptor gamma transcription factor (RORγ) in keratoconus pathology

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Introduction: Keratoconus (KC) is a complex, multifactorial, inflammatory disorder characterized by ectasia and steepening of the cornea, leading to visual impairment. The characteristic pathophysiological features of KC develop as a result of progressive dysregulation of the extracellular matrix proteins (collagens (COL) I and IV) and their regulators (lysyl oxidase (LOX) and matrix metalloprotease (MMP 9) as well as an aberrant inflammatory cytokine profile. The abundance of pro-inflammatory cytokines, including IL-17, in the tear fluid of KC patients could potentially trigger pathogenic signaling cascades culminating in aberrant ECM remodeling through yet to be explored mechanisms. Traditionally, IL-17 has been ascribed to regulate Th-17 cell maturation and development of autoimmunity. However, since KC is a stromal disease with epithelial contribution, we tested if the corneal epithelium has the capacity to produce IL-17. We investigate the potential regulation of increased IL-17 in tears of KC patients by evaluating the levels of its regulator, the transcription factor retinoic acid-related orphan receptor gamma (RORg).

Materials & Methods: Prior written informed consent was obtained from all enrolled subjects and the study was conducted with approval of the institutional ethics committee. Corneal epithelium was collected from non-KC control subjects undergoing refractive correction by PRK (n=12) and from KC patients undergoing collagen crosslinking (n=17). For 10 KC patients, epithelium was also collected from two different zones with the guidance of topography data: (1) cone-centered ectatic zone and (2) peripheral non-ectatic zone. The epithelial tissues were stored at -80°C until the time of processing. Appropriate medical standards of care were maintained during corneal epithelium collection. Gene expression analysis for RORg, RORgT, COLIVA1, COLIA1, LOX, and MMP9 were performed using quantitative PCR. Cytokine bead array was employed to measure levels of IL-17A, IL-17F and IL-21.

Observation: The corneal epithelium of KC patients demonstrated significantly higher expression of RORg ($P<0.01$) and RORgT ($P<0.01$) compared to healthy controls. We also found from the normalized gene expression ratio of RORgt/RORg that RORgT expression was elevated compared to RORg in the KC cohort. For the same KC subjects, in comparison to the peripheral non-ectatic epithelium, the cone ectatic epithelium demonstrated an increasing trend in RORg and RORgT expression. Our findings also indicate a positive correlation between RORgT and MMP9 ($r = 0.0669$; $P = 0.003$) in KC patients. Further, we observed a decrease in the expression of the ECM components COL IA1, COL IVA1, as well as in LOX in KC patient epithelium compared to controls. Results from the tear fluid from KC patients reveal upregulated levels of IL-17A, IL-17F and IL-21 compared to controls.

Conclusion: Elevated IL17 family cytokines in KC was associated with a concomitant elevation in RORg and its isoform RORgT. Further, the correlation of RORgT with MMP9 in KC patients strongly suggests its potential role as a driver in disease. These findings indicate that RORg or RORgT could be potential therapeutic targets in regulating KC progression.

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