Elucidating the Underlying Mechanisms of Unique TEAD Interactomes
Across Distinct Target-Gene Specificity in YAP Binary Classes

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Introduction: The corneal endothelium (CE) is composed of a monolayer of corneal endothelial cells (CECs) that rest on a specialized basement membrane called Descemet's membrane. Fuchs endothelial corneal dystrophy (FECD) is the leading cause of CE dysfunction and is characterized by the formation of guttae and progressive CEC loss. There is evidence that the CE is not a homogenous population of CECs, and that spatial differences exist with differential gene expression patterns. However, RNA-based transcriptomic analyses have not been extensively used to characterize cellular differences between central and peripheral spatial domains in healthy and FECD CE. We performed a transcriptomics study to characterize CEC populations isolated from the central and peripheral domains in healthy and FECD donors by bulk RNA sequencing (RNA-seq).

METHODS: The central 8 mm and peripheral rims from healthy human cadaveric donors (n=3) and FECD cadaveric donors (n=3) were dissected. RNA was isolated and sequenced at 40 million reads/sample. A list of differentially expressed genes (DEGs) was generated for 5 comparisons: normal central and peripheral CE; FECD central and peripheral CE; normal and FECD central CE; normal and FECD peripheral CE; and normal and FECD CE. DEGs were grouped in categories by molecular function and further analyzed by an over-representation test using a PANTHER Go-Slim molecular function annotation dataset. Additional pathway analysis was performed in Cytoscape where enrichment maps were generated for each gene list.Classification Random Convolutional Kernel Transform (ROCKET) [1] is applied to the collected full-field ERG data. The ROCKET transformer is a one-layer convolutional neural network, which computes 10,000 feature maps, which are then aggregated and passed to linear classifier. The novelty of the ROCKET algorithm is the number of descriptive features, generated foreach waveform.

RESULTS: A total of 369 DEGs (130 upregulated and 239 downregulated) were found between FECD compared to healthy controls. A total 167 DEGs (85 upregulated and 82 downregulated) were found between normal central and peripheral CE. Differential expression analysis of transcriptomic profiles and gene ontology analyses demonstrated an enrichment of genes involved in collagen degradation and integrin cell surface interactions between the central and peripheral CE, and collagen formation, crosslinking of collagen fibrils, and extracellular matrix (ECM) organization between healthy and FECD tissues. The dysregulation of ECM-associated pathways suggests a change in the ECM environment in the CE spatially and between healthy and FECD tissues.

Conclusion: There are spatial differences in gene expression, particularly in ECM proteins, between central and peripheral CECs, and between healthy and FECD CECs. This supports that the CE is composed of a heterogeneous population of CECs, which become altered in FECD. Future experiments using single cell RNA-seq will further characterize these cellular populations and will provide valuable insight into fundamental corneal biology and FECD pathogenesis.