Gene expression and Pathway Analysis Reveal Distinctions between Eosinophilic Esophagitis pre and post treatment with Glucocorticoids

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Background

- Eosinophilic esophagitis (EoE) is a distinct entity causing significant morbidity and that which responded to anti-allergic treatment.[1]
- It is associated with atopy and an antigen-driven, TH2-type immune response.[2]
- Treatment involves dietary restriction of food allergens or systemic glucocorticoid therapy.
- The exact mechanism of glucocorticoid action in EoE needs to be elucidated. It allows to develop newer formulation strategies and improve drug efficacy.

Objectives

- To elucidate the genes that are upregulated and downregulated with glucocorticoid therapy and the gene enrichment network with glucocorticoid therapy in EoE.

Methods

- We performed a secondary analysis of gene expression microarray GSE36725 dataset published in the Gene Expression Omnibus (GEO) using samples of patients with EoE before and after successful treatment with glucocorticoids to understand the genes up/downregulated with glucocorticoid therapy.[3]
- Total RNA was extracted from the formalin fixed tissue and hybridized to Affymetrix Gene ST 1.0 Arrays and microarray data analyzed for 10 samples (5 pairs).
- The Affymetrix probe IDs of all the rows were converted to their respective gene IDs by DAVID (Database for Annotation, Visualization and Integrated Discovery) (https://david.ncifcrf.gov/) tool.[4,5]
- The converted dataset was analyzed using the Networkanalyst.ca software.[6,7,8,9,10]
- P < 0.05 was regarded as indicating statistical significance

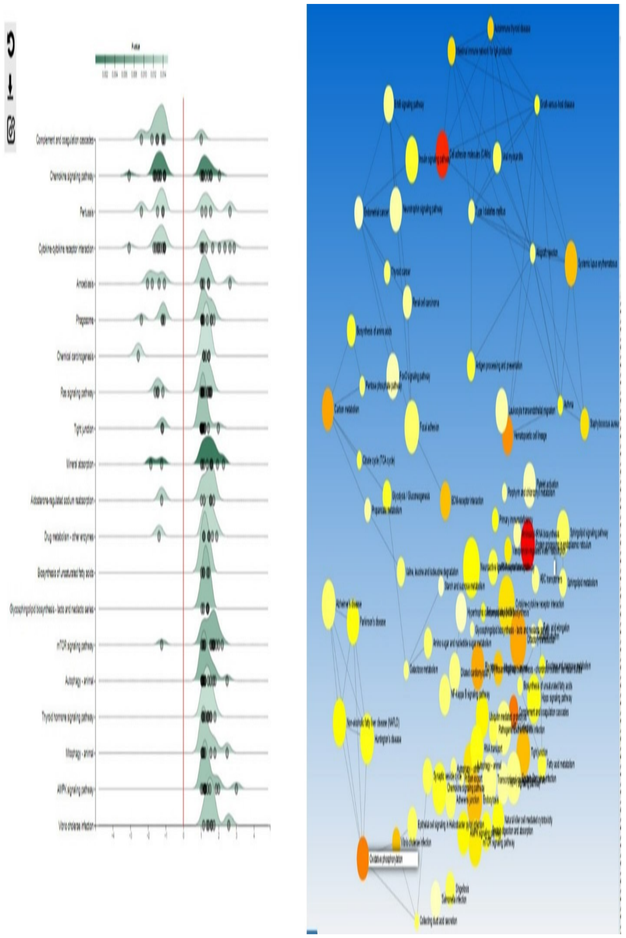
Results

- A total of 32 significant pathways were found after Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analysis by Welch's t test ranking.
- The top two enriched pathways were Mineral absorption (P=0.0067) and chemokine signaling (P=0.0084) and the top two enrichment categories were protein processing in endoplasmic reticulum (P< .05) and cell adhesion molecules (P< .05) (Figure1).
- The top genes upregulated with glucocorticoid treatment included CRISP3 (5.49-fold change), SPINK7 (5.49-fold change), TGM3 (5.49-fold change), EPGN (5.49-fold change) and UPK1A (5.49-fold change).
- Among genes downregulated with glucocorticoid treatment included TNFAIP6 (-5.29-fold change), POSTN (-4.57-fold change), JCHAIN (-4.55-fold change), ALOX15 (-3.36-fold change) and CCL26 (-3.07-fold change).
- Based on our results, CRISP3, SPINK7 and TGM3 genes seem to be upregulated with glucocorticoid treatment whereas, TNFAIP6, POSTN and JCHAIN are the top genes that are downregulated with glucocorticoid treatment that have the highest sensitivity and specificity as diagnostic markers for successful treatment of EoE.

Discussion

- CRISP3 (Cysteine-rich secretory protein 3) and SPINK7 (serine peptidase inhibitor, kazal type 7) are part of the differentiation program of human esophageal epithelium and that SPINK7 depletion occurs in a human allergic, esophageal condition termed eosinophilic esophagitis and are called as key barrier genes.
- TNFAIP6 (tumor necrosis factor alpha-induced factor 6) proinflammatory gene is downregulated by glucocorticoids as is periostin (POSTN) involved in osteoblast function and bone formation.
- JCHAIN gene that encodes J chain component of the antibodies, is downregulated. Arachidonate 15-lipoxygenase (ALOX15), positioned as a marker of eosinophilic inflammation, is downregulated after glucocorticoid treatment.

Figure 1. P-value of top enriched pathways and the Gene enrichment network.



Conclusion

- Glucocorticoid treatment improves the esophageal epithelial barrier integrity in cases of EoE and that eosinophilic inflammation reduces in severity with glucocorticoid treatment.

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