“The use of integrative OMICs to decipher heterogeneous chronic complex disease mechanism: Severe Asthma as a model”

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Abstract:

In this work, we reanalyzed publicly available transcriptomic data to identify novel differentially expressed genes and pathways in asthma. We specifically took into account the confounding factors that might interfere with the analysis. Our bioinformatics, results showed that POSTN mRNA expression needs careful interpretation by recalling samples and patients’ clinical parameters and clinical details as it may affect the expression and mask its diagnostic meaning. Patients' gender, anatomical site of the sample taken, current steroid history, smoking, and presence of other respiratory diseases are significant confounding factors. Our analysis using the publicly available gene expression data and linking it to toxicological omics’ data was able to explain and predict the toxicity in terms of stimulating the differentially expressed genes between severe asthmatic and normal epithelium. Many of the identified chemicals using this approach have no special warning or precautions to avoid them by asthma patients. Our approach identified genes differentially expressed in asthmatic patients’ airway structural cells (bronchial epithelium and fibroblasts), circulating immune cells, and saliva. The genes identified are related to two interacting pathways (Wnt signaling and cell cycle/proliferation), which can mediate or counteract the effect of each other in healthy versus asthmatic tissue. Our analysis shows that Amphiregulin (AREG), a member of the EGFR family, is a putative biomarker for the detection and control of asthma. It is differentially expressed in structural cells, circulating immune cells, and saliva of asthmatic patients compared to healthy controls. Its protein levels in plasma and saliva show a promising diagnostic value for severe versus nonsevere asthma. Mechanistically, we predict that AREG participates in the response of structural cells to microbial stimuli through TLR4 mediated signaling pathway. Asthmatic fibroblasts respond differently to LPS due to different AREG-TLR4 interactions leading to different downstream response genes of the AP-1 system, and the noncanonical Wnt pathways. Our results propose that AREG can potentially protect against LPS-induced tissue damage by inhibiting the expression of some of the inflammasome regulated genes, such as IL1β, in lung and spleen immune cells and particularly natural killer cells. AREG can mediate cell survival and resistance to apoptosis, pyroptosis, autophagy, and senescence. Also, the results show that asthmatic fibroblasts respond differently to AREG compared to healthy fibroblasts. Adding AREG to TNFα or LPS augmented asthmatic fibroblasts apoptosis and inflammation opposite to its effect on healthy fibroblast. Furthermore, the results indicate that Wnt5B upregulation in asthmatic fibroblasts in response to LPS reverses the otherwise beneficial effects of AREG in healthy fibroblasts to become apoptotic in asthmatic cells. In summary, our re-analysis of publicly available transcriptomic data and experimental validation have uncovered novel pathways and key players in asthmatic tissue, which has translational relevance in the control of asthmatic fibrosis, which is the main culprit for tissue remodeling, severity, and resistance to steroids in asthma.

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  - Main Supervisor: Dr. Rifat Hamoudi
  - Co-Supervisor: Prof. Qutayba Hamid
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Publications from the PhD thesis:

1. Non-Provisional Patent Application as "Diagnostic And Prognostic Liquid Biopsy Biomarkers For Asthma" with registration number 16/562,861 on 06 September 2019.

2. Hachim, M.Y., et al., (2020) Blood and Salivary Amphiregulin Levels as Biomarkers for Asthma. Front. Med. 7:561866. doi: 10.3389/fmed.2020.561866

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