Neutrophilic asthma involves FPR1: evidence from transcriptomics and machine learning

Arpita Das[1], Tsong-Long Hwang[1]. Grad Inst Health Ind Tech, Ctr Drug Res Dev, Coll Human Ecol, Chang Gung Univ Sci & Tech[1], Taoyuan, Taiwan

Introduction. Neutrophilic asthma (NA), characterized by ≥65% airway neutrophils, is associated with steroid resistance, frequent exacerbations, and limited treatment options (Wan et al, 2020). Unlike type 2 asthma, NA lacks reliable biomarkers and effective targeted therapies.

Aims. To define molecular signatures and mechanistic pathways of neutrophilic asthma using transcriptomic analysis integrated with machine learning.

Methods. Sputum gene expression from GEO database was analyzed using GEO2R for normalization and differential expression. K-means clustering was performed, and its robustness was validated using machine learning algorithms, including random forest, naïve Bayes, decision trees, and k-nearest neighbors. Functional and pathway enrichment analyses were conducted using Gene Ontology, network analysis, transcriptomic data, and KEGG pathways. Immune infiltration was estimated with CIBERSORT, and the associations were validated using Spearman correlation ($P < 0.05$).

Results. Two NA-specific clusters were identified: Cluster 1, associated with immune effector functions, and Cluster 2, linked to granule exocytosis and degranulation. Cluster 2 showed the highest predictive performance (≥94% accuracy, F-measure ≥0.84). Hub gene analysis identified FPR1, FPR2, SYK, and CASP1 as central regulators across both clusters. Pathway enrichment highlighted PI3K–Akt as the common driver, with additional NOD-like receptor (Cluster 1) and MAPK (Cluster 2) contributions.

Discussion. Our findings extend ongoing debates in neutrophilic asthma by showing that FPR-driven pathways link neutrophil activation, NETosis, and immune dysregulation (Senthil et al, 2021; Yan et al, 2024). This systems perspective clarifies the mechanisms underlying steroid resistance and supports the inhibition of FPR as a rational therapeutic strategy.

Visaga SA et al (2021) J Clin Toxicol 12: 1-12.

Wan R et al (2020) Aging 12: 16820-16836.

Yan Q et al (2024) Commun Biol 7:181-199.