Post-transcriptional gene dysregulation as a novel mechanism in severe asthma.

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Background: 5-10% of asthma patients are severe asthmatics(SA), defined as poor responders to high-dose glucocorticoids(GC). SA present frequent exacerbations which cause lung function decline over time. The underlying mechanisms of GC non-responsiveness in SA are poorly understood. MicroRNAs and RNA binding proteins(RBPs) control post-transcriptional processes, often overlooked in asthma.

Method: We applied Frac-seq (subcellular fractionation and RNA-sequencing) in bronchial epithelial cells(BECs) from healthy controls and SA to investigate genome-wide mRNA expression, combined with small RNA-seq to determine miRNA expression. Frac-seq determines total (transcribed) and polyribosome-bound (translated) mRNA.

Results: A network of 6 miRNAs potentially regulates ~50% of differentially translated mRNAs in SA and render cells non-responsive to GCs following transfection into primary BECs. We found two RBPs, ZFP36L1(L1) and ZFP36L2(L2), down-regulated in SA. L1 and L2 expression correlate positively with FEV1 and inversely with airway reversibility. Data from U-BIOPRED confirmed lower levels of L1/L2 in SA patients on oral GCs compared to moderate asthmatics and SA on inhaled therapy. L1/L2 are potentially inhibited by miRNAs up-regulated in SA according to miRNA target predictions and preliminary results. Frac-seq on primary BECs depleted of L1/L2 and treated with GCs demonstrated a major level of genome-wide post-transcriptional regulation by GCs mediated by L1/L2.

Conclusion: Our results demonstrate that GCs act post-transcriptionally in an L1/L2-dependent manner. We propose a novel post-transcriptional mechanism that may underlie impaired GCs responses in SA, opening new avenues in the understanding and management of SA.