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**Abstract**

**TITLE:** EPITHELIAL-SPECIFIC TRIGGERS OF NEUTROPHILIC INFLAMAMTION FOLLOWING HUMAN RHINOVIRUS (HRV) INFECTION IN CHILDREN WITH CYSTIC FIBROSIS (CF)

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**ABSTRACT BODY:** BACKGROUND: Neutrophilic airway inflammation is an early feature of CF lung disease. We have previously demonstrated that 1° CF airway epithelial cells (AEC), have damped IFNβ2 and apoptosis as well as increased viral replication and IL-8 release in response to HRV exposure,compared to controls1. These data suggest dysregulated innate immune responses to this viral pathogen could result in a cycle that promotes neutrophilic inflammation. The aim of this study was to characterise epithelial innate immune pathways linked to abnormal CFTR function that when stimulated by viral pathogens, result in pro-neutrophilic inflammatory signals. Specifically our hypothesis was that CFTR mutations cause dysregulation of innate immune pathways resulting in the stimulation of neutrophilic inflammation upon human rhinoviral (HRV) infection. METHODS: 1° AEC were obtained from 5 children with CF (2M, age 1.97-5.51 years (median 4.2 years)) and from 5 healthy children (2M; age 3.23-6.36 years (median 4.9 years)). Established AEC cultures were then infected with HRV1b (MOI 12) for 24 hours. Cells were collected, RNA extracted and quantified using RNA-seq and gene expression and analysed using a systems biology approach with Innate DB and MetaGEX. RESULTS: As a first step in understanding how genes with altered expression levels in response to viral infection interrelate functionally, gene ontology (GO) overexpression analysis was performed. This revealed that GO terms related to response to virus, immune response, inflammatory response, response to wounding and innate immune response were significantly overexpressed in CF AEC following HRV1b infection. More specifically, > 600 genes within these pathways were found to be differentially expressed. Network analysis was then used to understand how transcriptional changes induced by viral infection interrelated with CFTR and inflammation proteins in these pathways as network nodes interconnected by protein-protein interactions. CONCLUSION: We have identified epithelial specific pathways that can trigger neutrophilic inflammation within identified inflammatory networks with node and bottleneck genes that suggest

novel "druggable" targets.

REFERENCES:
1. Sutanto et al., 2011. Am J Respir Cell Mol Biol 44:761.

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