Ivacaftor or Lumacaftor/Ivacaftor Treatment Does Not Alter the Core CF Airway Epithelial Gene Response to Rhinovirus

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RATIONALE: Respiratory viruses including rhinovirus can cause pulmonary exacerbations in cystic fibrosis (CF). Aberrant responses by the CF airway epithelium during rhinovirus infection, particularly reduced interferon production, may underly the clinical observations. Whether CFTR modulators affect antiviral responses by CF epithelia is presently unknown. We tested the hypothesis that treatment of CF epithelial cells with ivacaftor or ivacaftor/lumacaftor would improve control of rhinovirus infection. METHODS: Nineteen submerged CF epithelial cultures (CFTR Class 2: 10 homozygous for p.Phe508del, CFTR Class 3: 9 p.Phe508del/p.Gly551Asp) were infected with rhinovirus 1B at multiplicity of infection 12 for 24 hour. Culture RNA and supernatants were harvested to assess host gene and protein expression by RNAseq and ELISA respectively. For CFTR modulator treatment, cultures were treated with 3 µM lumacaftor and/or 100 nM ivacaftor from 24 hours prior to infection through to end of infection, which was validated as therapeutic by Usling chamber. Viral load was assessed by count of sequences aligned to rhinovirus 1B genome. RESULTS: RNA-seq analysis comparing rhinovirus infected CF cultures to uninfected CF control cultures identified 796 and 629 differentially expressed genes for Class 2 and Class 3, respectively. This gene response was highly conserved when cells were treated with CTR modulator; all infected cultures (+/- CFTR modulator treatment) were associated with the same top three over-represented biological pathways associated with interferon signalling, and were predicted to be driven by the same interferon-pathway transcriptional regulators (IFNA, IFNL1, IFNG, IRF7, STAT1). Direct comparisons between CFTR treatment and untreated infected cultures did not yield any differentially expressed genes for Class 3 and only 68 genes for Class 2. Changes in Class 2 response were predominantly related to regulators of lipid metabolism and inflammation, aspects of epithelial biology known to be dysregulated in CF and peroxisome proliferator-activated receptors were the most significant of the predicted upstream positive regulators. In addition, CFTR modulators did not affect viral copy number, nor levels of interferon or pro-inflammatory cytokines produced post-infection. CONCLUSIONS: Long-term clinical data is not yet available on viral exacerbations during CFTR therapy. These results suggest CFTR modulators do not interfere with core airway epithelial responses to rhinovirus infection, but in Class 2 CFTR mutations modulator therapy may ameliorate inherently defective biological pathways which contribute to worse viral infection outcomes in CF. Future work will assess these responses in differentiated CF epithelium and across fungal and bacterial
respiratory pathogens.

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