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Title: microRNA-mediated inhibition of IL-8 production from cystic fibrosis bronchial epithelial cells

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Body: The pulmonary manifestations of cystic fibrosis (CF) are characterized by abnormally high levels of infiltrating neutrophils largely due to aberrant expression of interleukin-8 (IL-8) by airway epithelial cells. Thus inhibiting IL-8 expression within the CF lung represents an anti-inflammatory strategy. MicroRNAs (miRs) are post-transcriptional negative regulators. Overexpression of miRs is possible by the use of premiR mimetics. Here we profiled miRNA expression in CF vs. non CF endobronchial brushings (n=5 each) and CFBE41o- vs. 16HBE14o- bronchial epithelial cells lines. We identified a selection of lead miRs that are predicted to regulate IL-8 in silico and are under expressed in CF bronchial epithelium in vitro and in vivo. Based on further bioinformatic analysis and validation studies using an IL-8 3'UTR luciferase reporter we focused on four specific miRs. Levels of these miRs were quantified in whole lung homogenates from wild type (WT) and betaENaC-overexpressing (betaENaC-Tg) mice. All miRs were marginally decreased in the betaENaC-Tg compared to WT mice at 2 and 6 weeks of age, with miR-200b significantly lower at 6 weeks (*$p<0.05$). The KI of each premiR was calculated and collectively, a premiR-mix containing K0.25 for each miR inhibited basal (*$p<0.05$) and LPS-induced (***$p<0.001$) IL-8 protein production from CFBE41o- cells grown in monolayers. There was no off target effect on Cyclin D1(CCND1) protein expression; CCND1 is predicted to be regulated by two of the four miRs. These results indicate that aberrant IL-8 production by CF bronchial epithelial cells may have the potential to be corrected using miR-based medicines.