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Title: CFTR regulation by microRNA-145, -223 and -494 is altered in deltaF508 cystic fibrosis airway epithelium

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Body: Expression of CFTR is altered in individuals with the delF508CFTR mutation. Herein we investigated the role of miRNAs in CFTR regulation in vivo in bronchial brushings from individuals homo or heterozygous for delF508CFTR, validated our observations in vitro and assessed the impact of defective chloride ion conductance, genotype and Pseudomonas aeruginosa, Staphylococcus aureus or Aspergillus species colonization status on miRNA expression. miRNA target prediction was performed in silico, expression of miRNA and target genes was measured by qRT-PCR and western blotting. Overexpression and inhibition studies were performed with premiRs or antimiRs, respectively, and a reporter gene was used to elucidate miRNA/target interactions. CFTR function was quantified using a fluorescent membrane permeable chloride indicator. miR-145, -223 and -494 were upregulated in CF (n=14) versus non-CF (n=9) bronchial brushings and CFBE41o- versus 16HBE14o- cell lines; in delF508CFTR homozygotes vs. heterozygotes; in subjects positive for P. aeruginosa (n=9) and; in cells treated with a CFTR inhibitor or IL-1beta. Reciprocal down or upregulation of CFTR gene and/or protein expression and function was observed following miRNA manipulation and direct miRNA/target relationships demonstrated via a reporter system containing a wildtype or mutated CFTR 3’UTR. Increased expression of miR-145, -223 and -494 in vivo in bronchial epithelium of individuals carrying the delF508CFTR mutation correlates with decreased CFTR expression. Defective CFTR function, Pseudomonas colonization and inflammation may affect miRNA expression and contribute to the regulation of delF508CFTR.