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EPIGENETIC REGULATION OF F508DEL-*CFTR* CYSTIC FIBROSIS LUNG DISEASE

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Cystic fibrosis (CF) is the most common life limiting recessive disease in the US and is due to mutations in the *CFTR* gene. CF mutations, of which the most common is F508del-*CFTR*, cause a massive pro-inflammatory phenotype in the lung arising from dysregulated expression of inflammatory genes. Recently, endogenous non-coding RNA (ncRNA) molecules, including long non-coding RNAs (LncRNAs) have emerged as important targets in the frontier of biomedical research. These ncRNAs coordinate with epigenetic factors to play a crucial role in the regulation of biological processes as well as in diseases. Long noncoding RNAs (LncRNAs) have emerged as novel regulators of gene expression, including inflammatory genes. Various diseases have been associated with the aberrant expression of LncRNAs. Here we report the role of LncRNA and associated epigenetic factors in the pathogenesis of CF lung disease. LncRNA nuclear enriched abundant transcript 1 (*NEAT1*) is aberrantly upregulated in CF cells including, IB3-1, CFPAC-1 and CFBE CF cells as well as in lung tissues of CF patients compared to the respective control cells. *NEAT1* has been shown to regulate the expression of pro-inflammatory cytokine IL-8 in other diseases. Consistently, we find that suppression of *NEAT1* in CF lung epithelial cells leads to reduced expression of IL-8. Additionally, *NEAT1* is induced by p38-MAPK signaling pathway, which is activated in CF, and our results indicate that inhibition of this pathway suppresses both *NEAT1* as well as IL-8. Our data indicate that SFPQ, a *NEAT1* interacting protein, is down-regulated in F508del-*CFTR* CF lung epithelial cells compared to WT-*CFTR* control cells and perhaps also contributing to increased expression of IL-8. Consistently, we find that increased exogenous expression of SFPQ not only attenuates expression of the pro-inflammatory IL-8 gene, suppresses pro-fibrotic CTGF protein, but also rescues F508del- *CFTR* expression in CF lung epithelial cells. Understanding these mechanisms will lead to novel therapeutic targets for CF and related pulmonary diseases.

Chronic diseases and even aging itself are known to damage the body by dys-regulated inflammatory processes. Dysregulated expression of the pro-inflammatory cytokine and chemokine genes are known to contribute to chronic inflammatory diseases. Recently, endogenous non-coding RNA (ncRNA) molecules, including long non-coding RNAs (LncRNAs) and microRNAs (miRNAs, miRs) have emerged as important targets in the frontier of biomedical research. These non-coding RNAs have been proven to be key regulators of gene expression. The ability to detect non-coding RNAs in biofluids has highlighted their usefulness as non-invasive markers of diseases, including lung diseases. The expression of specific non-coding RNAs is altered in many lung diseases and their levels in the circulation often reflect the changes in expression of their lung-specific counterparts. Therefore, exploiting these biomolecules as diagnostic tools seems an obvious goal. Our goal is to investigate the role of non-coding RNAs in Cystic Fibrosis lung disease and develop novel anti-inflammatory therapeutics for pulmonary disorders.

BIOGRAPHY

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