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Commentary

Smart Polymeric Nanoparticles for siRNA Delivery in Cystic Fibrosis: Targeting Epithelial Sodium Channels

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DESCRIPTION

Cystic Fibrosis (CF) is characterized by dysregulated ion transport across airway epithelia, resulting in dehydrated mucus and impaired mucociliary clearance. While Cystic Fibrosis Transmembrane conductance Regulator (CFTR) modulators have transformed treatment for some patients, they are ineffective for certain mutations and fail to address complementary pathways that could ameliorate disease symptoms. We have developed smart polymeric nanoparticles for pulmonary delivery of small interfering RNA (siRNA) targeting Epithelial Sodium Channels (ENaC), which are hyper activated in CF airways and contribute significantly to mucus dehydration. These nanoparticles, approximately 120 nm in diameter, incorporate features specifically designed to overcome the unique barriers of the CF lung environment, enabling efficient transfection of airway epithelial cells while resisting inactivation by the tenacious mucus and inflammatory factors characteristic of CF.

The nanoparticles were synthesized using a block copolymer of poly (dimethylaminoethyl methacrylate) and poly (propylene sulfide), creating a pH-responsive core for endosomal escape and an oxidation-responsive segment that facilitates carrier disassembly in the oxidative environment of CF airways. Surface modification with N-acetylcysteine provides mucolytic properties that enhance particle penetration through the viscoelastic mucus barrier, while incorporating a cell-penetrating peptide derived from the Transactivator of Transcription (TAT) protein facilitates cellular uptake. This multifunctional design creates a delivery system specifically tailored to the pathophysiological features of CF airways, addressing multiple barriers to effective nucleic acid delivery.

In vitro characterization using air-liquid interface cultures of primary human bronchial epithelial cells derived from CF patients demonstrated efficient transcellular transport, with approximately 68% of nanoparticles reaching the basolateral compartment within 4 hours compared to less than 15% for conventional polyethylenimine complexes. Functional siRNA delivery was confirmed through quantitative PCR and Western blot analysis, revealing approximately 76% reduction in ENaC α-subunit expression following treatment. This molecular effect translated to functional improvements in epithelial ion transport, with using chamber studies demonstrating significant reduction in amiloride-sensitive sodium currents and corresponding increases in airway surface liquid height as measured by confocal microscopy.

In vivo evaluation utilized the βENaC-overexpressing mouse model, which recapitulates key features of CF lung disease including mucus hyperproduction and neutrophilic inflammation. Administration of siRNA-loaded nanoparticles via nebulization achieved widespread distribution throughout the conducting airways, with fluorescence microscopy confirming successful transfection of bronchial epithelial cells. Treatment twice weekly for 4 weeks resulted in significant reduction in ENaC activity, as evidenced by reduced nasal potential difference measurements. This molecular effect correlated with improved mucociliary clearance assessed through tracking of fluorescent microspheres, and reduced mucus obstruction as quantified by morphometric analysis of lung sections.

Inflammatory markers, including neutrophil counts and pro-inflammatory cytokine levels in bronchoalveolar lavage fluid, showed significant reduction following treatment, suggesting that addressing the underlying ion transport dysfunction produces downstream improvements in the inflammatory microenvironment. Bacterial burden, assessed through quantitative culture of lung homogenates, demonstrated approximately 1.5-log reduction in total bacterial load, likely reflecting improved clearance mechanisms rather than direct antimicrobial effects. Importantly, pulmonary function parameters, including resistance and compliance measurements, showed significant improvement compared to control groups, correlating with the observed reduction in mucus obstruction.

CONCLUSION

Safety evaluation revealed no evidence of pulmonary toxicity following repeated administration, with histopathological examination confirming normal airway architecture and absence

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of inflammatory infiltrates attributable to the treatment. Comprehensive blood chemistry and hematological analysis demonstrated all parameters within normal ranges throughout the treatment period. These smart polymeric nanoparticles represent a promising approach for addressing ion transport abnormalities in CF through targeted siRNA delivery, potentially complementing existing CFTR modulator therapies while offering benefit to patients with mutations not responsive to current treatments.