ATS 2024 Highlights
Respiratory Structure and Function Early Career Professionals

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Is your research clinical, basic science or translational?
Basic and Translational

Tell us about your research? Our project delves into the molecular mechanisms underlying the phenotype of Ciliary Beat Frequency (CBF) delays in the airway epithelium and efforts to ameliorate this defect by using novel Adenylate cyclase 6 (AC6)-specific activators. Improving CBF delays and thus mucociliary clearance dysfunction remains a critical unmet need in patients with Cystic Fibrosis (CF) and Chronic Obstructive Pulmonary Disease (COPD). This study will improve our understanding of airway epithelial biology, focusing on the role of AC6 as the key CFTR-activating partner in the secretory cells to maintain airway hydration and support cilia function. (Mentors: Dr. AP Naren & Dr. Kavisha Arora)

Where do you see yourself in 5 years?
In the next five years, I plan to continue my research, focusing on the molecular pathways of respiratory physiology. I am committed to advancing our understanding of diseases such as CF, COPD, Primary Ciliary Dyskinesia (PCD), and Acute Respiratory Distress Syndrome (ARDS) and enable bench to bedside studies, with the aim of improving respiratory outcomes in patients.

What do you find is the major benefit of RSF Assembly Membership?
Belonging to the RSF Assembly provides a unique chance to connect with peers, mentors, and leading researchers in the field. This facilitates the development of a supportive and collaborative community, which is crucial for career advancement especially for early stage investigators, expanding scientific knowledge, and exploring prospective collaborations.

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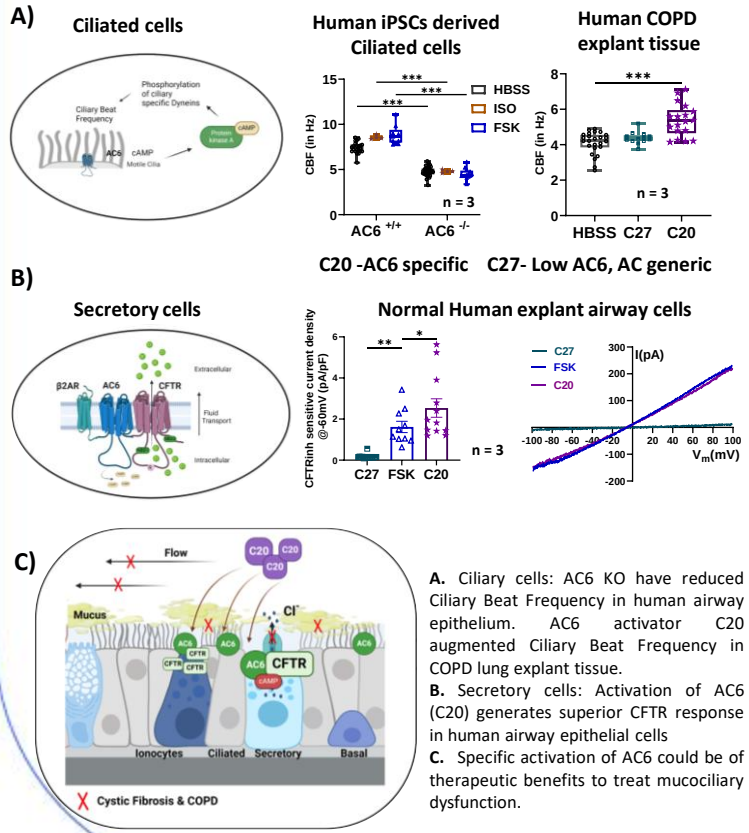
Loss of AC6 drives Mucociliary Clearance Defects

Rationale: Mucociliary Clearance (MCC) is a key airway defense process and is severely impaired in diseases such as CF & COPD. Identifying key molecular players that regulates MCC is a highly unmet need in the field. We discovered that cyclic AMP (cAMP) synthesizing enzyme Adenylate Cyclase 6 (AC6) is the predominant AC isoform that regulates ciliogenesis, cilia-generated flow, ciliary beat frequency (CBF) and cAMP-induced CFTR currents. Hence in this study we propose AC6 acts as a master regulator of the airway MCC process and that AC6 could be a key therapeutic target in treating MCC defects.

Methods: CBF was measured in epithelium-specific AC6 knockout (KO) mouse tracheal rings and Air-liquid interface (ALI) differentiated AC6 KO-iPSCs in response to cAMP agonists and compared to normal controls. Ciliary cAMP levels were determined by cAMP-PKA phosphorylation substrate specific immunostaining in mouse and human airway tissues. Single cell RNA sequencing (scRNAseq) was performed in AC6 KO and WT mouse tracheas to understand the mechanism of AC6 regulation in MCC. We developed the specific activators of AC6 (C20) and their effect on CBF in diseased (CF and COPD) lung explant tissues and ALI cultures was evaluated. We performed whole-cell patch clamping studies on freshly isolated epithelial cells from normal lung explant tissues followed by mRNA sequencing in the single collected cell to functionally profile CFTR specific to highly specialized secretory cells.

Results: Our findings reveal that AC6 regulates ciliary function as evidenced by reduced CBF in AC6 KO that is associated with the presence of a distinct cAMP-PKA signaling niche at the base of the cilia. Further, we observed that this cAMP-PKA phosphorylation signature was depleted in patients with respiratory diseases (CF and COPD). scRNA-seq studies demonstrated that the ciliated gene signature was altered in AC6 KO mice tracheas. Specific activators of AC6 were developed that augmented MCC in COPD explant tissues and CF airway ciliated cells. Additionally, direct activation of AC6 generated superior CFTR response in secretory cells using Patch sequencing studies.

Conclusion: This study will improve our understanding of epithelial biology uncovering a key pathway in the regulation of ciliary function. AC6-CFTR chloride channel activation and their effect on airway fluid properties is anticipated to further improve MCC. Our finding will advance the application of AC6-specific activators as potential therapeutic agents to treat MCC dysfunction associated with several respiratory diseases such as CF and COPD.



A. Ciliary cells: AC6 KO have reduced Ciliary Beat Frequency in human airway epithelium. AC6 activator C20 augmented Ciliary Beat Frequency in COPD lung explant tissue.
B. Secretory cells: Activation of AC6 (C20) generates superior CFTR response in human airway epithelial cells
C. Specific activation of AC6 could be of therapeutic benefits to treat mucociliary dysfunction.

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