Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

COVID-19 pathogenesis in a cellular model of CF lung disease in response to TGF-β1.

Methods: Human bronchial epithelial cell CFBE41o-, 16HBE-WT and 16HBE-F508del were used. For small RNA sequencing (RNA-seq), total RNA was used. Cluster generation and 75–base pair single-read, single-indexed sequencing was performed on Illumina NextSeq 500s. miRNA differential analysis was done by the edgeR package. Pathway analysis was done by Ingenuity Pathway Analysis (IPA) software. The significantly upregulated and downregulated miRNA from differential analysis were used as a query list for miRNA network analysis. IPA was used for analyzing COVID-19-associated pathways affected by differentially regulated miRNAs. miRNAs predicted to target the COVID-19-associated genes were collected from TargetScan Human release 7.2, miRmap, Diana-TarBase v.8, and miRBase bioinformatics tools. Anti-miRNA oligonucleotide miRCURY LNA Power Inhibitors or control (Exiqon) were used.

Results: Forty-eight miRNAs were dysregulated in TGF-β1-treated CFBE41o- cells, compared to control treated cells. We found 38 and 19 pathways uniquely affected by the upregulated and downregulated miRNAs, respectively. We found 43 miRNAs targeting 119 mRNAs of the proteins associated with the coronavirus pathogenesis pathway. Next, to examine how these miRNAs are affecting replication of coronavirus, we selected the coronavirus replication pathway and used the same strategy to build a network in IPA. We used the path designer feature and found 21 miRNAs targeting 21 mRNAs of the proteins associated with the coronavirus replication pathway. Next, we focused on miRNA upregulated by TGF-β1, miR-136-3p and miR-369-5p targeting ACE2. We confirmed by qRT-PCR that TGF-β1 increased miRNA expression and inhibited ACE2 mRNA and proteins levels, and the effects were prevented by specific anti-miRNA oligonucleotides. Studies in 16HBE cells demonstrated significantly elevated baseline ACE2 mRNA and protein levels in F508del-CFTR expressing cells, compared to WT-CFTR. TGF-β1 inhibited ACE2 levels in both cell lines. Elexacaftor/tezacaftor/ivacaftor (ELX/TEZ/IVA) had no effect on ACE2 mRNA or protein at baseline or after TGF-β1 stimulation in CFBE41o- and 16HBE cells.

Conclusions: miRNAs may be important effectors of TGF-β1 modulating SARS-CoV-2 invasion of the CF airway. ACE2 levels may be increased in bronchial epithelial cells by the F508del mutation.

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In vitro evaluation of TAVT-135, an artificial pan-genotypic chloride ion transporter

M. Gentzsch[1,2], D. Hill[2], J. Maleth[3,4], N. Quinney[2], K. Rouillard[2], S. Boyles[2], L. Molnar[6], E. Duus[6], A. Maetzel[6,7], I. Mandity[8,9]. [1]*Department of Cell Biology and Physiology, Marsico Lung Institute, University of North Carolina, Chapel Hill, NC;* [2]*Marsico Lung Institute, School of Medicine, University of North Carolina, Chapel Hill, NC;* [3]*ELKH-SZTE Momentum Epithelial Cell Signaling and Secretion Research Group, University of Szeged, Szeged, Hungary;* [4]*Epipharma, Szeged, Hungary;* [6]*TAVANTA Therapeutics, Radnor, PA;* [7]*Institute of Health Policy, Management and Evaluation, Dalla Lana School of Public Health, University of Toronto, Toronto, Ontario, Canada;* [8]*TAVANTA Therapeutics, Budapest, Hungary;* [9]*Lendület Artificial Transporter Research Group, Research Center for Natural Sciences, Budapest, Hungary*

Background: Cystic fibrosis (CF) transmembrane conductance regulator (CFTR) modulators have revolutionized the treatment of CF, but a significant unmet need remains for patients with ineligible genotypes, inadequate responses, or intolerance. Alternative agents, including those capable of mediating chloride (Cl^-) transport, are therefore being investigated. TAVT-135 is a novel cell-penetrating peptide derivative that facilitates passive ion transport of Cl^-, which could benefit all people with CF, independent of CFTR mutation. A series of in vitro and ex vivo studies were performed to characterize the electrophysiological and mucus-penetrating properties of TAVT-135.

Methods: Intracellular Cl^- levels were determined by measuring fluorescence after exposure of HEK293 cells to TAVT-135 (0, 1, 10, 100 μM). Ion transport in cultured primary airway cells with the W1282X/R1162X mutation was measured in a modified Ussing chamber system. TAVT-135 (0, 1, 10, 100 μM) was delivered to the apical side of the cultures, and the impact of acute or chronic (24-hour) exposure on short-circuit current (Isc) was measured with amiloride-induced suppression of sodium channels. Responses were studied in the presence of Cl^- transport agonists (forskolin, uridine triphosphate [UTP]) and an antagonist (CFTR inhibitor-172). Mucus-penetration times for diffusion of fluorescently labeled TAVT-135 through 100-μm mucus layers (harvested from human bronchial epithelial cell cultures) were calculated. Mucus was prepared to concentrations mimicking healthy airways and mild and severe CF airway disease, with 2%, 4%, and 8% solids (w/w), respectively. The impact of TAVT-135 on the viability of HEK293 cells was assessed using a commercially available apoptosis–necrosis detection kit.

Results: In HEK293 cells, TAVT-135 decreased intracellular Cl^- levels in a dose-dependent manner because of the transport of Cl^- from the cytosol to the extracellular space. In W1282X/R1162X CFTR primary airway cultures, acute exposure to TAVT-135 (10 and 100 μM) induced slightly, albeit significantly, greater Isc (10 μM: 0.16 ± 0.01 $\mu A/cm^2$; 100 μM: 2.20 ± 0.21 $\mu A/cm^2$) than in control (−0.012 ± 0.006 $\mu A/cm^2$) ($p < 0.001$). The effect on Isc was partially sustained over 10 minutes and was independent of CFTR. UTP-induced activity of Ca^{2+}-activated Cl^- channels was 1.7 and 2 times as great in the presence of TAVT-135 (10 and 100 μM, respectively). After chronic exposure to TAVT-135, mean potential difference of cultures exposed to TAVT-135 (100 μM) was significantly lower than in control, suggesting changes in the permeability of cultures by ion conductance. TAVT-135 readily penetrated mucus layers, with penetration times of 81.7, 146.7, and 120.5 seconds through 2%, 4%, and 8% solid-containing mucus, respectively. In cell-viability assays, no in vitro toxicity was observed after exposure to TAVT-135 (1, 10, or 100 μM).

Conclusions: Initial investigations show promising signs of a CFTR-independent effect of this candidate on Isc and Cl^- transport and evidence of it penetrating CF-like mucus. These data suggest that TAVT-135 could alleviate symptoms associated with highly viscous mucus by increasing electrolyte levels of the airway surface liquid layer and facilitating water transport out of epithelial cells. Additional studies of this novel artificial Cl^- transporter are ongoing.

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Wnt and transforming growth factor beta signaling imbalance in cystic fibrosis airway epithelium polarization

T. Idris[1], M. Badaoui[1], M. Bacchetta[1], M. Chanson[1]. [1]*Department of Cell Physiology and Metabolism, Faculty of Medicine, University of Geneva, Geneva, Switzerland*

Background: Cell proliferation and polarization are important processes in the maturation of epithelium during development and injury repair. These processes must be tightly regulated to ensure epithelium with good structural integrity. Cystic fibrosis (CF) is associated with lack of structural integrity of the airway epithelium, suggesting a defect in polarization, and ultimately results in infections and respiratory failure. We have recently shown that CF airway epithelia are associated with overexpression and apical localization of fibronectin, phenomena usually linked with defects in polarization, but the link between CF transmembrane conductance regulator (CFTR) and polarization defect is unclear.

Methods: We compared primary cultures of CF (F508del mutation) human airway epithelial cells (HAECs) and a HAEC line, Calu-3, knocked out for *CFTR* by CRISPR-Cas9 (*CFTR* KO) to control counterparts grown at an air-liquid interface (ALI) as a trigger for polarization through the inhibition of proliferation.

Results: Ribonucleic acid sequencing on HAECs and quantitative polymerase chain reaction revealed that the Wnt and transforming growth factor beta (TGFβ) signaling pathways were deregulated in CF airway epithelia, suggesting an imbalance between proliferation and polarization. Ki67 analysis revealed a significant decrease in cell proliferation after 3 days of ALI in the *CFTR* KO cells ($p < 0.001$). Furthermore, as shown by immunoblotting and immunofluorescence experiments, expression of the main signal transducer of the Wnt signaling pathway, β catenin, was significantly lower in *CFTR* KO cells at day 15 of ALI ($p < 0.05$). This decrease was caused by enhanced degradation of β catenin at D15 of ALI ($p < 0.05$), as demonstrated by a cycloheximide chase assay. This mechanism is known to be induced by Wnt pathway inhibition. Dickkopf1, an inhibitor of the Wnt