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| **Preclinical safety assessment of bacteriophage therapy using primary airway epithelial cells** |
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| **Introduction/Aim:** Bacteriophages (phage) are promising antimicrobial agents capable of treating bacterial infections in chronic lung disease patients. However, more evidence is needed to drive their translation into clinical practice. Here, we hypothesised that phages will neither elicit any detrimental effects on airway cell models in vitro nor stimulate inflammation.**Methods:** Primary airway epithelial cells (AECs) were collected from children (Age 3-7, 2 males) undergoing elective surgery via nasal brushings. Cells established on air-liquid interface (ALI) culture were exposed to 1 x 109 pfu/mL SYBR Gold-tagged phages (Kara-mokiny 3 (KM3), Boorn-mokiny 1 (BM1), Minga-mokiny 4 (MM4), and E79) over 24 hours. Barrier integrity was measured via transepithelial electrical resistance (TEER) and fluorescent permeability assays. Apical and basolateral collected supernatants were measured for cytotoxicity, inflammatory marker (IL-8) production and phage concentration using plaque assays. Cellular markers β-tubulin (cilia), Zona occludens-1 (ZO-1; tight junction), and Mucin 5A (MUC5AC; secretory mucus) were used to assess the localisation of tagged phages on ALI cultures via confocal microscopy. **Results:** ALI culture TEER post-exposure to various phage morphotypes did not differ from the control (p=0.65); however, cultures were less permeable after exposure to BM1 phage compared to untreated controls (5.7±1.9 x10−5 cm/sec vs 8.7±3.1 x10−5 cm/sec (SD), p<0.05). Additionally, no phages were recovered in the basolateral supernatant. Exposure of AECs with phages did not increase cellular cytotoxicity (p>0.05) both apically or basolaterally, nor did it induce IL-8 production (p>0.05). **Conclusion:** We demonstrated that no inflammatory or barrier-compromising effects were detected on the airway cells post-exposure to phages, providing preclinical safety evidence for phage therapy to be safe and reliable. In the primary airway model, no detrimental effects were observed, indicating the safety of applying and delivering treatments for pulmonary infections.**Grant Support:**Vertex Mentored Innovation AwardConquer Cystic Fibrosis Research Fellowship |