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Human airway tissue models to study respiratory infections

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Aim: The aim of the present study was to establish a complex tissue model of the human airway mucosa (hAM) that consists of differentiated primary epithelial cells and a fibroblast-loaded extracellular matrix. This model should be used to investigate the interaction with Bordetella pertussis, its virulence factor adenylate cyclase toxin (CyaA), and its enzymatically inactive but fully pore-forming toxoid (CyaA-AC-). Besides this approach, this study aimed to compare the response of tissue models generated from two different anatomical sites (upper and lower respiratory tract).

Patients and Methods: We isolated epithelial cells and fibroblasts from human nasal and tracheo-bronchial mucosa specimens and built 3D tissue models based on a small intestinal scaffold. We performed single-cell RNA sequencing for tissue model characterization, histology, analyses of intracellular cyclic adenosine _ production (cAMP), interleukin (IL)-6, IL-8, human beta defensin-2 (HBD-2) secretion on CyaA treatment. Moreover, we assessed adherence and invasion of B. pertussis in hAM.

Results: This is the first study that shows a differential susceptibility of primary nasal and tracheo-bronchial hAM to CyaA. We observed a cell type-specific response of intracellular cAMP production, IL-6, IL-8, human beta defensin-2 secretion when treated on the apical side with CyaA. Additionally, the CyaA treatment did not affect epithelial membrane barrier integrity, which differed from previous studies. Subsequently, we investigated the interaction of B. pertussis with both differentiated primary nasal and tracheo-bronchial tissue models and demonstrated bacterial adherence and invasion without observing host cell type-specific significant differences.

Conclusion: Our finding that the nasal tissue models showed an increased innate immune response towards the B. pertussis virulence factor CyaA compared to tracheo-bronchial tissue models may reflect the key role of the nasal airway mucosa as the first line of defence against airborne pathogens. Hence, in all experimental conditions, nasal epithelial cells could not substitute for bronchial epithelial cells. The data from primary cell-based tissue models suggest that B. Pertussis can adhere to and invade both differentiated primary nasal and tracheo-bronchial epithelial cells. The present study reveals novel insights into host-pathogen interaction of B. pertussis and its virulence factor CyaA with primary cell-based human airway mucosa tissue models.