BREATHE
the lung association

Research Summary

Improved in vitro models for analyzing lung tissue contraction following asthma treatment

Lung function depends on complex interactions among multiple cell types, the extracellular matrix that the cells are in contact with and the environment. These interactions enable efficient gas exchange in the lung alveoli by way of progressively branching passages for air conduction, known as bronchioles, which regulate air flow by either constricting or dilating in response to stimuli [1]. Changes in bronchiole diameter are mediated by contraction of smooth muscle cells (SMCs) anchored within the elastic bronchiole wall, which receive biochemical signals from the airway epithelial cells (ECs) that line the luminal bronchiole surface. Disruption of this sensitive cellular communication system, which is yet to be fully elucidated in vivo and has been difficult to recreate in vitro, can result in excessive airway constriction that limits gas exchange in diseases such as asthma. In asthma, changes in airway SMC responsiveness, remodeling of the airway wall and chronic inflammation lead to excessive airway constriction in response to stimuli. These pathological changes manifest in acute difficulty breathing, i.e., an exacerbation, which can in some cases become life threatening if a medical intervention (usually inhalation of a nebulized bronchodilator) does not take place. Airway constriction has been linked to progressive alteration of the normal contractile function of airway smooth muscle. It has also long been accepted that allergenic responses and inflammation arising from the airway epithelium lead to airway SMC dysfunction in asthma [2,6]. Intrinsic changes in airway SMC function may also be associated with airway hyperresponsiveness in asthma. However, in spite of numerous in vivo and in vitro studies that have attempted to dissect the pathophysiology of asthma, the underlying cause of airway dysfunction that leads to hyper-responsiveness is still hotly debated, in part because it is inherently difficult to study lung cell interactions in intact bronchiole tissue, and because existing cell culture models for asthma are lacking in the complexity needed to recreate basic airway function in health and disease. As with many other complex diseases, this in vivo – in vitro gap has resulted in longer timelines for discovery of new therapeutics, with few examples of new and effective treatments for asthma emerging in the last 5-10 years. We will begin to close the in vivo – in vitro gap in asthma research by developing three-dimensional (3D) in vitro lung microtissues that better reflect the layered organization of the bronchial walls, provide more realistic cell-substrate and cell-cell interactions, and present more realistic exposure to asthma triggers and treatments compared to conventional two-dimensional (2D) culture systems. To accomplish this, we will draw upon some of the latest advances in engineering cell-rich microtissues and monitoring airway cell biochemical and mechanical signaling, using technologies pioneered by the Frampton and Maksym laboratories.