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MECHANICAL MODELLING OF PULMONARY HYPERTENSION USING A PROTEIN-BASED CELL STRETCHING PLATFORM

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ABSTRACT

Organ on a chip (OOC) devices are microfluidic platforms that seek to mimic simplified aspects of human organs and tissues using cultured human cells and serve as a platform for conducting experiments that would otherwise be difficult. A subcategory of OOC devices modelling thin tissues that undergo mechanical strain are receiving increased attention as these tissues are common throughout the human body, with examples including the skin, gut, and blood vessel walls. The mechanical microenvironment of these tissues plays an important regulatory role in maintaining homeostasis, and abnormal mechanical conditions can lead to development or progression of disease. In vitro models capable of reproducing tissue mechanical microenvironments are therefore crucial for deepening our understanding of the role of mechanical stimulation in disease development and developing new treatments targeting these mechanisms. Here we present a mechanically active platform for modelling thin tissues based on our previously developed method for incorporating thin, protein-based cell culture membranes in OOC devices. We demonstrate the use of our platform by modelling the elevated hydrostatic pressure and mechanical strain experienced by the capillary endothelium in post-capillary pulmonary hypertension and examine the effects on junction integrity.

Our platform consists of a suspended protein-based membrane for culturing cells previously developed in our lab, integrated with a pneumatic system capable of pressurizing one side of the membrane to distend it and generate mechanical strain. Stress-strain curves for cross-linked membranes fabricated over a range of protein concentration, membrane thickness, and crosslinker concentration were obtained by applying cyclical ramping pressures to determine their elastic modulus and pressure-strain relationships. It was found that our membranes exhibit a J-shaped stress-strain curve typical of biological materials, and that the degree of viscoelasticity in the stress response as measured through creep-recovery and elastic hysteresis behavior can be varied with crosslinker concentration. This information was used to design a set of membrane fabrication parameters and applied pressures that were then used to evaluate the response of a model pulmonary capillary endothelium to pathological levels of pressure and strain. This work represents a significant extension of our previously developed protein-based membrane technology, enabling investigation of the effects of both pressure and strain on tissues cultured in a bioactive engineered microenvironment.