

Microfluidic Device for Modelling Lung injury

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Respiratory disease is one of the most common causes of death worldwide. The increase in the prevalence of respiratory diseases is mainly due to cigarette smoking, air pollution as well as bacterial/viral (COVID-19) infections. Despite this increasing frequency, the only option for treatment during end-stage disease is lung transplantation. Thus, development of reliable in-vitro models is necessary for lung disease modelling, regeneration and testing potential therapies.

In respiratory diseases like acute respiratory distress syndrome (ARDS), chronic obstructive pulmonary disease or COVID-19, breathing ability is impaired that essentially leads patient death. When patients are not able to breathe by themselves, they are connected to the mechanical ventilator. Mechanical ventilator provides enough oxygen to organs. Although it is lifesaving, it can also damage the patient's lung. Normally, the cells inside the lung are stretched 4-12%. However mechanical ventilation can cause ventilator induced lung injury (VILI) a condition where too much air or too high pressures can cause the alveolar cells to overstretch and eventually die. Patients with ARDS, COPD or COVID-19 for example are especially vulnerable to injury during mechanical ventilation due to their alveoli being exposed to larger levels of stretch.

To model VILI, animal studies have previously been conducted with debatable ethics. With the help of a lung-on-a-chip device VILI can be modeled and reproduced many times and different conditions or drugs can be tested. In this project a lung-on-a-chip device was developed and fabricated using 3D-printing of the molds used for casting the device. This makes the device considerably easier to manufacture compared to many other chips that use advanced microfabrication techniques that are typically used when fabricating modern electronics. In between of the channels of the chip, the fibrous membrane was made of synthetic polymer of polycaprolactone (PCL) membrane were placed. Mouse lung epithelial cells were grown on PCL membrane in the chip. 25 % of cyclic stretch, which resemble the applied stretch during mechanical treatment at a normal breathing rhythm (12 breaths per min) was applied. After the applied stretch, the cell we were shown to die or detach from the membrane to a larger extent than cells that were not stretched. These cells also responded to the stretch on a molecular level. YAP/TAZ a protein inside of the cell translocate to the nuclei when the cell is exposed to stretching and then regulates proliferation, differentiation and much more. This translocation was seen in cells exposed to the stretch but not in the cells that were not stretched, further validating the model.

To make our device as close as possible to the real conditions, we aimed to prepare new hybrid membranes. PCL is a synthetic polymer and it is foreign to lung cells. It doesn't have any biological cues that the cells like. To overcome this limitation, a hybrid membrane prepared using electrospinning (a technique that forms micro/nanofibers and produces a net-like structure) of the biodegradable polymer PCL and natural lung extracellular matrix (ECM) was characterized to confirm the presence of ECM proteins and fibrous structure of the membranes. Our initial data showed that the lung cells like these membranes and they grew more on this membranes compared to PCL ones.