Acinus-on-a-chip microfluidic device with 3d spherical air-liquid interfaces

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Regulatory hazard assessment for airborne substances is still based on forced inhalation tests on animals. Therefore, there is a need for *in vitro* systems capable of producing human-relevant results. However, current lung-on-a-chip systems still have limitations, such as the use of 2D membranes. In this work, a microfluidic platform able to reproduce the dynamic air-liquid interface by incorporating an array of 3D transparent spherical micromembranes is presented. The membranes were fabricated by casting a 10mg/mL agarose-50 mg/mL gelatin solution in stereolithography-fabricated custom molds (Formlab, Somerville, USA). After agarose crosslinking, the array was treated overnight at 37°C with 100 U/g microbial transglutaminase, allowing gelatin crosslinking. The array was dried at 40°C for 24 hours before being UV-sterilised and then rehydrated in deionized water. Tensile tests were performed to calculate the apparent elastic modulus of the membranes (1.07±0.35 MPa). Finally, the membranes were integrated into an Acinus-on-a-chip platform fabricated by the stereolithography process and Biomed Clear resin. Preliminary cell tests were performed using A549 cells seeded on the membranes (100.000 cell/cm^2) and in PET Transwells as a control. Transepithelial electric resistance measurements (EVOM - WPI) and confocal (Nikon A1; Nikon, Minato, Japan) images were acquired to determine the presence of an integral cell monolayer. Transcellular (Pg-p activity) and paracellular transport were investigated using FITC-labelled dextran (0.5 mg/mL) and rhodamine 128 (10 μM).

The membranes outperformed the controls in terms of barrier tightness and transport properties, presenting lower FITC passage and increased Pg-p activity, which indicates cell polarisation. The 3D micro-membrane array integrated in the Acinus-on-a-chip paves the door for more reliable and human-relevant inhalation studies. Further research is on-going to evaluate the device performance, investigating novel approaches for reproducing breathing dynamics.

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