Development of microfluidic cell culture devices towards an in vitro human intestinal barrier model - DTU Orbit (09/11/2017)

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Existing in vitro models of the human intestine such as the established epithelial cell line, Caco-2, cultured on porous membranes have been extensively used for assessing and predicting permeability and absorption of oral drugs in the pharmaceutical industries. However, such in vitro human intestinal models fail to support any form of luminal flow conditions on the cells in order to more closely mimic in vivo conditions. Although these existing systems are easy to use, they require a large amount of cells, culture media, samples and reagents. Microfluidics is a technology that has the potential to revolutionise the way of in vitro cell culture. In particular, microfluidics provides avenues for researchers to tailor the cellular microenvironment to better mimic the cellcell and cell-extracellular matrix interactions, while at the same time reducing the scale of the experimental studies. Moreover, microfluidics also offers the possibility of dynamic cell culture in microperfusion systems to deliver continuous nutrient supplies for long term cell culture. When combined with electronic or optical components such as sensors, actuators, and control logic, microfluidics has the potential to enable real-time detection of cell responses, adjustment of cellular stimulation etc. leading to establishment of conditional experiments. In this project, microfluidic systems engineering was leveraged to develop an eight chamber multi-layer microchip for intestinal barrier studies. Sandwiched between the layers was a modified Teflon porous membrane for cell culture. The novelty lies in modifying the surface of the porous Teflon support membrane using thiol-ene ‘click’ chemistry, thus allowing the modified Teflon membrane to be bonded between the chip layers to form an enclosed microchip. Successful application of the multi-layer microchip was demonstrated by integrating the microchip to an existing cell culture fluidic system to culture the human intestinal epithelial cells, Caco-2, for long term studies. Under the continuous low flow conditions, the cells differentiated into columnar cells displaying folds that closely resembled the intestinal villi and formation of a tight barrier. Furthermore, the microelectrodes embedded in the microchip also allow real-time monitoring of the barrier integrity by means of measuring the trans-epithelial electrical resistance. Demonstrations of transport studies using different compounds on the in vitro human intestinal model in the microfluidic device showed comparable results with static cultures. In addition, a normal commensal intestinal bacteria, Escherichia coli (E. coli) was successfully co-cultured on the luminal surface of the cultured epithelium without compromising the epithelial cell viability and barrier function. Such a platform paves the way towards an alternative in vitro intestinal model for high throughput screening of drugs, chemicals, pathogens, intestinal diseases as well as toxicological studies.

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