Effect of astrocytes on blood-brain barrier modeling

The blood-brain barrier has a strict control of what molecules that are allowed access to the brain, making it problematic for drug development. Usually tests of new drugs are carried out in animal models, but new types of models based on cell cultures are becoming more promising. However, there is a need for increased reliability of these models, something that this study aims to investigate.

Drug development is a long and costly process. Even though a lot of money is being invested in it, the amount of drugs reaching the market is decreasing. This is due to a high failure rate in late stages of research, partly caused by the absence of reliable models for testing. Today, most tests are carried out in animals before being introduced to humans. However, the differences between humans and animals can lead to different responses. The need for more reliable testing models is increasing, and a new type of model called organs-on-chips is trying to meet these needs.

One biological structure being modeled is the blood-brain barrier. The blood-brain barrier is a physical barrier where tightly connected endothelial cells create blood vessels in contact with the brain. The exchange between the blood and the brain is very limited, causing problems for drugs to access the brain. In blood-brain barrier-on-chips, the aim is to model the barrier created by the endothelial cells. However, the barrier is not only controlled by the endothelial cells and there are several different cell types inside the brain that will have an impact on the barrier. One of these cell types is called astrocytes. In the healthy brain these cells induce properties in the endothelial cells characteristic for the blood-brain barrier, while during damage to the brain they will become reactive and change their function.

To improve modeling of the blood-brain barrier, co-culture systems of endothelial cells and astrocytes are used. For this project, the influence of astrocytes and their culture environment inside a blood-brain barrier-chip was investigated (see figure 1). This was achieved by firstly evaluating the reactivity of astrocytes cultured in different hydrogels. Afterwards, endothelial cells and astrocytes were co-cultured in a blood-brain barrier-chip and the influence of astrocytes on the barrier was evaluated.

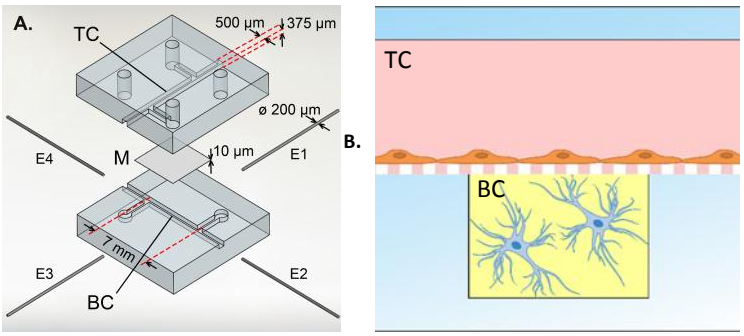

Figure 1. In **A** the chip design (developed within the BIOS Lab on a Chip group) is shown. The chip consists of two parts, with a microchannel in each (**TC** - top channel and **BC** – bottom channel). Separating the two channels is a porous membrane (**M**), and connected to the two channels are four electrodes (**E1**-**E4**) allowing for measurements inside the chip. In **B** a schematic of the aim of this project is seen, where an endothelial cell layer is grown in the top channel, and astrocytes inside a hydrogel in the bottom channel.

For astrocytes cultured in different hydrogels a lower reactivity was found for cells cultured in a lower total gel concentration, when compared to cells grown in higher gel concentrations or directly on a plastic dish. These results indicate a difference in reactivity of cells, dependent on their culture environment. Especially in co-culture systems where astrocytes are used it is important to be aware of the effect of their culture environment, as the state of the astrocytes may influence the barrier function. Unfortunately in this study no conclusions could be drawn about astrocytes influence on barrier function, however for future work it is important to be aware of the differences shown here and the effects it may have on the model.

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