University of Rochester

BME PhD Defense Seminar

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Supervised by
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"An in vitro model to study the impact of systemic inflammation on the blood-brain barrier in neurodegenerative disease"

Seminar Abstract:

The blood-brain barrier (BBB) protects the brain from systemic inflammation in a healthy person. However, certain neurodegenerative diseases such as Alzheimer's disease (AD) can weaken the BBB, allowing systemic inflammatory factors to enter the brain more easily and cause neuroinflammation. This neuroinflammation can cause short-term delirium and worsen longer term cognitive decline. Animal models of neurological diseases such as Alzheimer's disease are limited and failed to recapitulate the full phenotype seen in humans. Therefore, it is important to develop human models of the BBB which can capture this vulnerability and use them to study response to inflammatory stimulation. Microphysiological systems (MPS) or tissue-chip models have emerged as a powerful technology which can create more complex in vitro models, enabling more accurate recapitulation of in vivo physiology. Induced pluripotent stem cells (iPSCs) are also an important technology which allow the generation of relevant cell types from donors who had the disease being studied.

In this thesis, I utilize an existing MPS model of the human BBB, called the μSiM-hBBB, which consists of iPSC-derived brain microvascular endothelial cells (BMECs) and iPSC-derived brain pericyte cells grown on either side of an ultrathin nanoporous membrane. Based on this model I created a BBB which recapitulates the vulnerability of the BBB in neurodegenerative diseases. First, I used a physical method, adding larger pores to the membrane to destabilize the BMECs alone such that they require the pericytes to form a strong barrier. The pores created defects in the basement membrane proteins created by the BMECs alone which were repaired by the addition of pericytes, suggesting that this stabilization is the result of basement membrane protein production by the pericytes. Next, I created a specific disease model, using iPSCs generated from a sporadic AD donor and age-matched healthy control to generate BMECs and brain pericytes and comparing their response in the model. The AD donor exhibited increased permeability in coculture with the pericytes, suggesting the pericytes contribute to barrier degeneration in AD. The AD BMECs were also more sensitive to proinflammatory stimulation. Together this work advances a human BBB MPS model to model neurodegenerative disease.

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