A MODEL FOR THE BLOOD-BRAIN BARRIER AND ITS APPLICATION IN MODELING METASTASIS TO THE BRAIN

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The blood-brain barrier (BBB) is known to be one of the least permeable portions of the vascular system, serving to protect the central nervous system from agents deleterious to the brain while also preventing or limiting the passage of drugs to treat neurological diseases. Despite this, the brain is recognized to be one of the primary sites of metastasis, especially for lung and breast cancers. While animal experiments have proven useful, realistic models of the BBB using human cells are limited and remain a subject of intense research. Work over the past several years has led to several promising systems, although it has proven difficult to achieve levels of permeability comparable to those observed in vivo.

We have recently sought to develop several systems, first with a mixture of primary rat and human cells (Adriani et al., 2017), and more recently, a model based entirely on human cells. This latter system relies on self-assembly of three critical cell types: human iPSC-derived endothelial cells, primary brain pericytes, and primary brain astrocytes. When suspended in a fibrinogen and thrombin gel solution and introduced to a microfluidic platform, the cells organize into a microvascular network in direct physical contact with pericytes and astrocyte end-feet. Over 7 days, the network forms and attains a relatively stable state that permits perfusion from the side channels of the device.

Once formed, the vascular network is characterized by immunofluorescent imaging, RT-PCR analysis, and functional measures such as permeability to fluorescent probes of various molecular weights. In comparing the networks as they increase in cellular complexity from endothelial cells alone, to ECs and pericytes, and finally, ECs, PCs and astrocytes, the expression of basement membrane and junctional proteins is seen to increase. Simultaneously, the network permeability is observed to progressively fall, indicating improved barrier function. Permeability values for a 10 kDa FITC-dextran are found to be comparable to those measured in the rat brain.

Preliminary experiments have been conducted to determine the rates of extravasation of circulating tumor cells past the model BBB. These experiments introduce breast cancer cells (MDA-MB-231) into the microvascular network with the flow of medium where they adhere to the endothelium or arrest due to physical trapping. Once immobilized, the cells are observed over time to quantify their tendency to undergo transendothelial migration. Results show that as the CTCs are increasingly invasive as the system complexity increases (mono-culture to tri-culture), opposite to what would be expected if tumor cells follow the trend of permeability. Studies are currently underway to understand the cell-cell interactions that give rise to this counterintuitive behavior.

Reference:
Adriani, G., Ma, D., Pavesi, A., Kamm, R. D., & Goh, E. L. K. (2017). A 3D neurovascular microfluidic model consisting of neurons, astrocytes and cerebral endothelial cells as a blood–brain barrier. *Lab on a Chip*, 17 (12), 2067-2075

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