Medical & healthcare, Drug development

Development of blood brain barrier models with open networks

Division of Applied Chemistry, Graduate School of Engineering

Professor Michiya Matsusaki

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Abstract

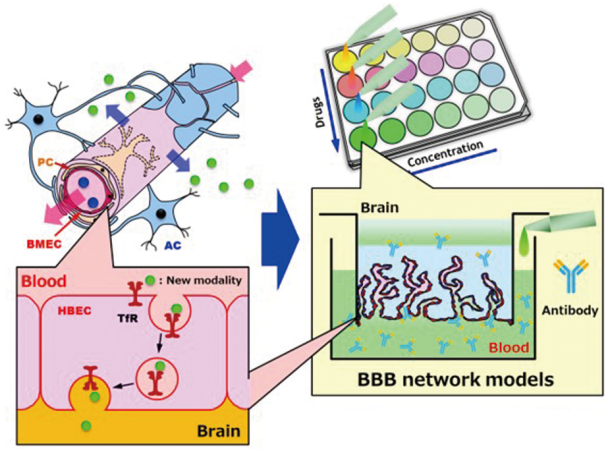
We developed in vitro human blood brain barrier (BBB) models with open network in microwell. This is expected as a new type of human BBB models which shows the molecular permeability depending on its molecular weight and can evaluate receptor-mediated transcytosis.

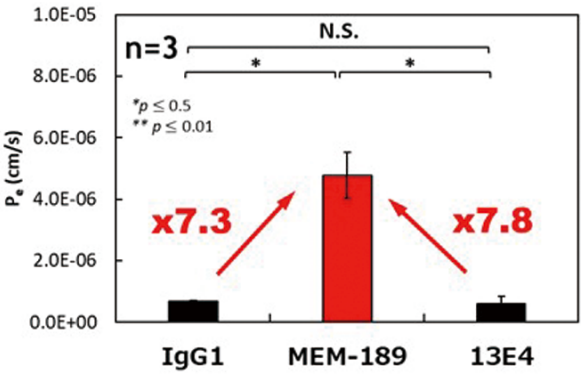
Background & Results

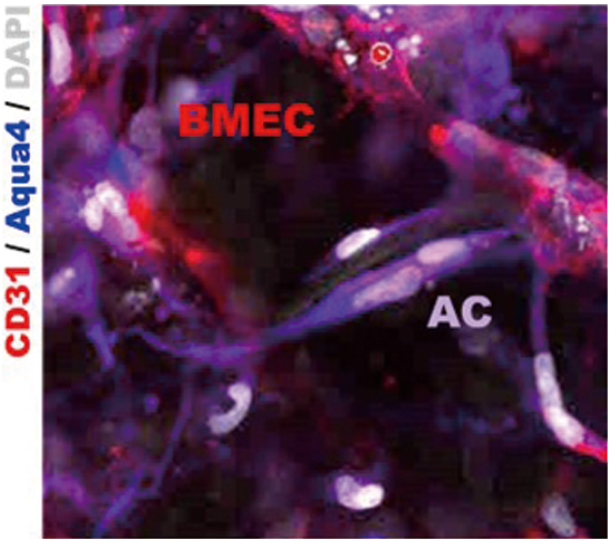
The blood-brain barrier (BBB) has a higher barrier than other organ vessels, basically allowing almost 100% of molecules above 500 Da and 98% of small molecules to pass through. This is due to a special three-dimensional network structure in which brain capillary endothelial cells (BMECs) are surrounded by pericytes (PCs) and the terminal feet of astrocytes (ACs) are attached to their outer surface. This cell-cell interaction leads to the development of tight junctions and efflux transporters in BMECs, a mechanism that suppresses the permeability of substances and actively expels foreign substances that have been taken in. Receptor-mediated transcytosis (RMT) transports specific proteins and peptides, making them a target for various pharmaceutical companies due to their potential to transport new modalities such as peptides, antibodies, and nucleic acid drugs. However, there is no in vitro human model that can evaluate RMT, and thus the development of in vitro human models that can evaluate RMT is an urgent issue.

Significance of the research and Future perspective

We reported that a tube network of BMECs could be fabricated inside 96 wells using BMECs, PCs, and ACs derived from human normal cell lines, fibrin gel as a scaffold, and collagen microfibers (CMF) for adhesion promotion and structure maintenance. From fluorescence immunostaining, tissue sample analysis, gene expression, and protein expression analysis, we found that the formed tube structures interacted with PCs and ACs like the actual BBB and were useful as BBB models for pharmacotoxicity studies. A bottom-opening BBB tube network was fabricated inside a 24-well insert by modifying our previously reported method of fabricating an opening capillary tube network. Permeability coefficient (Pe) value of transportable transferrin receptor (TfR) antibody indicated 7.8-fold higher than isotype antibody and lower transportable antibody, suggesting the highest transport function than the other previous reports. The BBB model with capillary openings could thus be a valuable tool for screening therapeutics that can be transported across the BBB, including those using TfR-mediated transport.







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Treatise Piantino, Marie; Kang, Dong-Hee; Furihata, Tomomi et al. Development of a three-dimensional blood-brain barrier network with opening capillary structures for drug transport assays, Mater. Today Bio 15, 100324 (2022). doi: 10.1016/j.mtbio.2022.100324

URL

Keyword BBB model, receptor-mediated transcytosis, tissue engineering, new modality