Göteborg, 2019

In vitro models of the blood-brain barrier using iPSC-derived cells

Akademisk avhandling

Som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin, Göteborgs universitet kommer att offentligen försvaras i Arvid Carlsson salen, Medicinaregatan 3, fredagen den 13 december, klockan 13.00

av Louise Delsing

Fakultetsopponent:

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Avhandlingen baseras på följande delarbeten

I. Delsing L, Dönnes P, Sánchez J, Clausen M, Voulgaris D, Falk A, Herland A, Brolén G, Zetterberg H, Hicks R, Synnergren J. Barrier Properties and Transcriptome Expression in Human iPSC-Derived Models of the Blood-Brain Barrier.
Stem Cells. 2018 Dec;36(12):1816-1827.

II. Lundin A, Delsing L, Clausen M, Ricchiuto P, Sanchez J, Sabirsh A, Ding M, Synnergren J, Zetterberg H, Brolén G, Hicks R, Herland A, Falk A. Human iPS-Derived Astroglia from a Stable Neural Precursor State Show Improved Functionality Compared with Conventional Astrocytic Models.
Stem Cell Reports. 2018 Mar;10(3):1030-1045.

III. Delsing L, Kallur T, Zetterberg H, Hicks R, Synnergren J. Enhanced Xeno-Free Differentiation of hiPSC-Derived Astroglia Applied in a Blood-Brain Barrier Model.
Fluids and Barriers of the CNS. 2019 Aug;16(1):27.

IV. Delsing L, Zetterberg H, Herland A, Hicks R, Synnergren J. An iPSC-Derived Microphysiological Blood-Brain Barrier Model for Permeability Screening.
Manuscript

SAHLGRENSKA AKADEMIN
INSTITUTIONEN FÖR NEUROVETENSKAP OCH FYSIOLOGI

GÖTEBORGS UNIVERSITET

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In vitro models of the blood-brain barrier using iPSC-derived cells

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Abstract

The blood-brain barrier (BBB) constitutes the interface between the blood and the brain tissue. Its primary function is to maintain the tightly controlled microenvironment of the brain. Models of the BBB are useful for studying the development and maintenance of the BBB as well as diseases affecting it. Furthermore, BBB models are important tools in drug development and support the evaluation of the brain-penetrating properties of novel drug molecules. Currently used in vitro models of the BBB include immortalized brain endothelial cell lines and primary brain endothelial cells of human and animal origin. Unfortunately, these cell lines and primary cells have failed to recreate physiologically relevant control of transport in vitro. Human-induced pluripotent stem cell (iPSC)-derived brain endothelial cells have proven a promising alternative source of brain endothelial-like cells that replicate tight cell layers with low paracellular permeability. Given the possibility to generate large amounts of iPSC-derived brain endothelial cells they are a feasible alternative when modelling the BBB in vitro.

This thesis aimed to develop iPSC-derived models of the BBB that display a barrier like phenotype and characterize these models in terms of specific properties. The BBB model development was based on investigations into mechanisms important for barrier formation in iPSC-derived endothelial cells and development of high-quality supporting cells. The possibilities to use the model in drug discovery, and in determination of brain penetrating capacity of drug substances were specifically considered. These studies have increased knowledge of molecular mechanisms behind the restricted permeability across iPSC-derived endothelial cells and identified transcriptional changes that occur in iPSC-derived endothelial cells upon coculture with relevant cell types of the neurovascular unit. Furthermore, high quality iPSC-derived astrocytic cells were developed, and the biological relevance and model diversity between astrocytic models were evaluated. Both astrocytes and brain endothelial cells have been adapted to xeno-free culture conditions and used in the BBB models, demonstrating a xeno-free BBB model. Finally, a more biologically relevant microphysiological dynamic BBB model was generated. This model demonstrated improved permeability modelling and compatibility with high-throughput substance permeability screening.

Taken together these results show that iPSC-derived BBB models are useful for studying BBB-specific properties in vitro and that both marker expression and functional evaluation of iPSC-derived cells are important in assessing cell identity and cell quality. In addition, these results show that iPSC derived BBB models are feasible for high-throughput permeability studies.

Keywords: Blood-brain barrier, iPSC, in vitro model, permeability

ISBN: 978-91-7833-634-0 (PRINT) http://hdl.handle.net/2077/61824
ISBN: 978-91-7833-635-7 (PDF)