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Innovations in Regenerative Medicine

Monday, 24.04.2023, 13:00 – 14:00

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iPSC- and CRISPR-based brain tissue models recapitulate key features of neurodegenerative and neurovascular diseases

Background: Brain research heavily depends on models recapitulating key aspects of human brain physiology and disease pathology. Human iPSCs have great potential to complement existing rodent disease models, as they allow directly studying affected human cell types. In addition, recent developments in CRISPR genome editing revolutionized how impacts of genetic alterations on disease formation can be investigated. Co-culture of disease-relevant iPSC-derived cells with disease-relevant mutations enables studying complex phenotypes involving cellular crosstalk.

Methods: By combining iPSC-, CRISPR- and tissue engineering technologies, we established new brain tissue models for AD and FTD using iPSC-derived cortical neurons, astrocytes, microglia, and oligodendrocytes, as well as a microfluidic model of the neurovascular unit (NVU) based on co-culture of endothelial cells, mural cells and astrocytes.

Results: Our technology provides highly controllable and reproducible 3-dimensional tissues with typical cell morphologies and functional features, including widespread synapse formation, spontaneous and induced electrical activity, network formation, microglial ramification, tiling and phagocytosis, as well as formation of barrier-containing vessels interacting with astrocytic end feet for the NVU model. Interaction between neurons, glia and vascular cells become evident on morphological and functional levels. The models can be long-term cultured in a postmitotic state without proliferation or cell death, thus providing a more controllable, reproducible, and long-lived alternative to cortical organoids currently used for 3D disease modelling. CRISPR-engineering of disease-causing mutations for AD, FTD, or a neurovascular disease induced characteristic late-stage phenotypes, including protein misfolding and aggregation for AD/FTD models, or barrier impairment for models of the NVU.

Conclusions: We expect that our models will enable studies elucidating novel, potentially human-specific pathomechanisms and provide a human framework for translation and screening.

Chair: PD Dr. Christian Tackenberg