MINDFACE Abstract

Expansion of a (G4C2) repeat in C9orf72 is the most common autosomal dominant cause of frontotemporal dementia (FTD) and amyotrophic lateral sclerosis (ALS). Strong arguments indicate that immune-system related dysfunction may contribute as disease modifier to the large phenotypic variation in onset age, clinical presentation and disease progression in C9orf72ex. Novel tools now enable us to dissect the role of immune-related dysfunction in detail. Single-nucleus RNA sequencing (snRNAseq) of microglia in C9orf72exp brains from the Netherlands Brain Bank will allow us to reveal microglial-related biological pathways involved in the pathophysiology of C9orf72. Based on the high expression of C9orf72 protein, abundant RNA-foci and dipeptide repeats (DPR) in peripheral blood monocytic cells (PBMCs) from C9orf72exp patients, we will investigate the use of specific and sensitive assays as readouts for disease onset, severity and progression, and correlate these to other fluid neuroinflammation biomarkers. As changes on 7T MR imaging and MR spectroscopy can be sensitive to neuroinflammatory processes, we will investigate the dynamic process of neuroinflammation during the disease course in C9orf72 pre- and symptomatic carriers over time, and correlate MRI and MRS findings with fluid biomarkers and RNA foci in PBMCs. With mixed cultures derived from iPS cells and 3D multimodal co-culture models in human forebrain organoids (hFO) seeded with monocyte-derived microglia-like cells (MDMIs) directly derived from C9ORF72exp carriers, we aim to test the identified biological pathways from the snRNAseq data of C9orf72exp brains. Integrating generated data from snRNAseq of C9orf72exp brains, microglial activation on 7TMRI/MRS, neuroinflammatory proteins in human fluids, and neuron-microglial interactions in iPS cell and organoid models may provide immune-related biomarkers and targets to modify the disease activity in C9orf72exp.