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Glial pathology in frontotemporal dementia: insights from Progranulin deficiency

Dominant mutations in the human Progranulin (GRN) gene are a leading cause of frontotemporal dementia (FTD). Patients with GRN mutations have much lower progranulin (PGRN) protein levels in the cerebrospinal fluid (CSF) and serum, suggesting that haploinsufficiency in PGRN could be a major cause of disease. To investigate the impacts of PGRN deficiency, we and others have generated mouse models and show that mice with a complete loss of PGRN (Grn-/-) and those that carry humanized GRNR493X mutation exhibit age-dependent microgliosis that preferentially affects the thalamocortical circuit, where it promotes excessive synaptic pruning, neuronal degeneration, and TDP-43 proteinopathy in the thalamocortical circuits. My presentation will focus on our ongoing work and the strategies to provide more mechanistic insights on how PGRN deficiency contribute to neurodegeneration. Specifically, we block both complement pathways and proinflammatory cytokines to mitigate neuroinflammation caused by PGRN deficiency. These results uncover the essential role of Progranulin in intracellular vesicle trafficking and how these defects impede lysosome-mediated lipid degradation and secretion. In addition, our results revealed lipid-mediated toxicity carried out by progranulin deficient microglia during the late phase of neurodegeneration in the Grn-/- mouse model. Finally, to determine the contributions of the glial pathology to human disease, we perform single cell transcriptomic analyses in the thalamocortical circuits in Grn-/- mice and in FTD patients with GRN mutations. This approach provides a comprehensive understanding of the impacts of glial pathology to neurodegeneration in mice and human.