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Investigating a role for progranulin in PINK1/Parkin mitophagy using induced pluripotent stem cells

Mutations in GRN resulting in progranulin haploinsufficiency cause frontotemporal dementia (FTD). Mitophagy, the selective autophagy of damaged mitochondria, is impaired in several neurodegenerative diseases. The most well characterised pathway is PINK1/Parkin mitophagy, which is implicated in Parkinson's disease. However, a number of genes linked to FTD (e.g. OPTN, SQSTM, VCP and TBK1) are also known to play a role in mitophagy. Xenophagy, the selective autophagy of non-host pathogens, relies on some of the same proteins as mitophagy (Parkin and TBK1) and is reduced in GRN knockout mice. We therefore hypothesised that loss of progranulin could lead to defective mitophagy in neurons, astrocytes and microglia.

To investigate whether loss of progranulin results in cell type specific impairments in mitophagy, we used induced pluripotent stem cells derived from patients with GRN mutations (R493X, C31fs), together with an isogenic series from the human iPSC Neurodegenerative Disease Initiative (iNDI) with control, heterozygous and homozygous R493X gentoypes. IPSC were differentiated into cortical neurons, astrocytes and microglia. Mitophagy was induced using antimycin/oligomycin and monitored by immunofluorescence and western blot. We saw reduced mitophagy in the absence of progranulin and to different extents in neurons, astrocytes and microglia, suggesting cell type specific impact of progranulin loss.

Our results suggest that loss of progranulin results in altered PINK1/Parkin mitophagy, highlighting important mechanistic overlap between PD and FTD. Current work aims to identify the mechanisms linking GRN to mitophagy.

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