p-276

Friday

The role of Progranulin in PINK1/Parkin mitophagy

J. Casey, D. Melandri, C. Arber, B. Costa, M. Soutar, B. O' Callaghan, C. Holler, T. Kukar, A. Isaacs, J. Rohrer, J. Pocock, H. Plun-Favreau, S. Wray

State of the art: We examined mitophagy, the selective clearance of damaged mitochondria, in frontotemporal dementia (FTD) caused by progranulin haploinsufficiency. A number of other genes involved in FTD have been found to play a role in mitophagy. Xenophagy, the clearance of pathogens, relies on some proteins involved in mitophagy (TBK1 and Parkin) and is impaired in GRN-/- mice.

Methodology: We induced mitophagy using antimycin A and oligomycin in neuroblastoma (PoE-SHSY5Y) and neuroglioma (H4) cell lines +/- *GRN* siRNA. We also investigated mitophagy in induced pluripotent stem cells (iPSCs) from 4 controls, 3 *GRN* FTD patients and an isogenic *GRN* mutation CRISPR series from the human iPSC Neurodegenerative Disease Initiative (iNDI). We used western blotting and immunofluorescence (ICC) to examine markers of PINK1/Parkin mitophagy (e.g. S65 phosphorylated ubiquitin (pUb)).

Results: Lower levels of mitophagy markers and pUb were detected in H4 cells and PoE-5Y, respectively, following *GRN* knockdown. There was a significant reduction in mitophagy in the homozygous R493X neurons. There was no significant difference in mitophagy between control and patient or heterozygous iNDI iPSC-derived neurons which may be due to upregulation of progranulin protein from the wild-type allele. CDC37, which traffics PINK1 to the mitochondria and effects its stability, was significantly reduced in homozygous R493X mutation neurons.

Conclusions: Loss of progranulin leads to impaired mitophagy in cell lines and iPSC-derived neurons. Current work aims to further understand the mechanisms of this process and to dissect cell-type specific contributions of progranulin to mitophagy.

Conflicts of interest

N/A