p-277

Friday

Progranulin mutations in microglia and its impact in neurodegeneration

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Loss of function mutations in the progranulin gene (GRN), are the second most common genetic cause of frontotemporal lobar degeneration (FTLD), a disorder that accounts for 10-20% of all young-onset dementias. GRN, as other risk genes associated with dementia, is primarily expressed in microglia, the immune cells of the brain. However, the functional consequences of granulin deficiency on human microglia biology remain unknown. There are extensive differences in the transcriptomic profile of human and mouse microglia in their response to disease, hence it is essential to use human/humanized systems to understand the impact of disease-causing mutations on microglial homeostasis and their contribution to disease.
We have generated two homozygous and heterozygous *GRN*-/- induced pluripotent stem cell (iPSC) lines and differentiated them into microglia using our MIGRATE protocol (microglia in vitro generation refined for advanced transplantation experiments). We have performed a series of *in vitro* experiments exploring whether GRN deficiency leads to functional alterations. We found that GRN-deficient microglia show altered transcriptomic and functional features in their ability to phagocyte and react to inflammatory stimuli. To better understand the effect of microglial GRN deficiency *in vivo*, we xenotransplanted the iPSC-derived microglia progenitors into the mice brain and determined successful transplantation by flow cytometry and histological assessment of the mouse brain.
Overall, we present a novel model of iPSC-derived human microglia transplantation into the mouse brain that represents a unique opportunity to study human-specific aspects of microglia and neuroinflammation that can contribute to FTLD pathology.

Conflicts of interest

No conflicts of interests