

Abnormalities in glycosphingolipid degradation caused by progranulin deficiency

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State of the Art

Frontotemporal dementia (FTD) is a leading cause of early-onset dementia with no disease-modifying therapies, and heterozygous loss of function progranulin (*GRN*) mutations that cause haploinsufficiency of the progranulin protein are one genetic cause of FTD. Progranulin is a secreted and lysosome-resident protein with several identified functions, acting as a growth factor, an immunomodulator, and a regulator of lysosomal function. Complete loss of progranulin results in lipofuscinosis and aberrant activities of several lysosomal enzymes indicating a critical role of progranulin in lysosomal function. Recent reports by our lab and others have implicated abnormalities in glycosphingolipid degradation caused by progranulin deficiency, specifically a deficiency of the enzyme β -glucocerebrosidase (GCase).

Methodology

We measured the activities of several enzymes in the glycosphingolipid degradation pathway in progranulin knockout mice and performed co-immunoprecipitation assays and proximity ligation assays with progranulin to characterize the interactions.

Results

Enzymes upstream in the glycosphingolipid degradation pathway had elevated activities accompanied by transcriptional upregulation of the enzymes. GCase, downstream of these enzymes, appeared to be a unique case, as it had deficient activity with no transcriptional up- or downregulation, suggesting that the elevations upstream may reflect a compensatory mechanism due to overall lysosomal dysfunction. Other enzymes in this pathway also had impaired activity without transcriptional changes.

Conclusion

This discovery suggests that progranulin may play a broad role in regulating sphingolipid degradation, and that further investigation is needed to understand the effects of progranulin-regulated enzymes to determine the mechanism by which progranulin deficiency causes FTD.

Conflicts of interest

EDR has served as a consultant for AGTC and serves on the DSMB for Lilly.