A Study to Reveal the Role of GRN in Pathogenic Pathways

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1. The GRN gene encodes Progranulin (PGRN), a 593-amino-acid protein composed of 7 repeating domains called granulins (GRNs 1-7) and a half-repeat (para-granulin) that are joined by linker regions. A signal peptide (SP) directs secretion of PGRN from neurons, microglia, and other cells.

2. Mutations in GRN are a common cause of Frontotemporal dementia (FTD), the most common dementia in people under 60 years of age.[2]

3. GRN mutations reduce the levels of PGRN & GRNs by ~50%, strongly supporting haploinsufficiency (loss of function) as the pathogenic mechanism.

4. We have recently found that PGRN is processed into ~6kDa GRNs within the lysosome.[1]

5. However, the molecular mechanisms caused by loss of lysosomal PGRN/GRNs that lead to neurodegeneration are still unknown.

RESULTS

1. Proteomic analysis of whole-brain tissue revealed 29 up and 26 down-regulated proteins in 3-month-old GRN+/- versus GRN+/- mice, while 119 proteins were up- and 20 proteins were down-regulated in 19-month-old GRN+/- mice.

2. According to WGCNA on the brain proteome of GRN+/- mouse brains, 3 of 29 modules were strongly correlated with PGRN deficiency and increased with age and were enriched with lysosomal and inflammatory proteins.

3. Proteomics data suggest PGRN plays a critical role in lysosomal homeostasis.

4. Galectin-3 robustly and significantly increases in aged GRN+/- mouse brain tissues, indicating neuroinflammation.

5. Lysosomal proteins (CTSZ, CTSK) are increased in old GRN+/- mouse brain.

6. High levels of GPNMB are found in GRN+/- mouse brain and human FTD-GRN samples.

REFERENCES


CONCLUSIONS

CONCLUSION: We have found that PGRN is processed into ~6kDa GRNs within the lysosome. However, the molecular mechanisms caused by loss of lysosomal PGRN/GRNs that lead to neurodegeneration are still unknown.