Molecular pathways modifying progranulin deficiency phenotypes in mouse models

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Haploinsufficiency of the progranulin (PGRN) protein is a leading cause of frontotemporal lobar degeneration (FTLD). Mouse models have been developed to study PGRN functions. However, PGRN deficiency in the commonly used C56BL/6 mouse strain background leads to very mild phenotypes, and pathways regulating PGRN deficiency phenotypes remain to be elucidated. We generated PGRN-deficient mice in the FVB/N background and compared PGRN deficiency phenotypes between C56BL/6 and FVB/N backgrounds via immunostaining, western blot, RNA-seq, and proteomics approaches. We report that PGRN loss in the FVB/N mouse strain results in earlier onset and stronger FTLD-related and lysosome-related phenotypes. We found that PGRN interacts with sPLA2-IIA, a member of the secreted phospholipase A2 (sPLA2) family member and a key regulator of inflammation that is expressed in FVB/N but not C56BL/6 background. sPLA2-IIA inhibition rescues PGRN deficiency phenotypes, and sPLA2-IIA overexpression drives enhanced gliosis and lipofuscin accumulation in PGRN-deficient mice. Additionally, RNA-seq and proteomics analysis revealed that mitochondrial pathways are upregulated in the PGRN-deficient C57BL/6 mice but not in the FVB/N mice. In summary, our studies establish a better mouse model for FTLD-*GRN* and uncover novel pathways modifying PGRN deficiency phenotypes.

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