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The granulin linker region is necessary for proper folding, trafficking, and rescue of lysosome dysfunction

Paola Merino, Jessica Root, Ludmilla Troiano Araujo, Georgia Taylor, Thomas Kukar

Background: Haploinsufficiency of progranulin (PGRN) is a major cause of frontotemporal dementia (FTD). Deficiency of PGRN causes neuronal ceroid lipofuscinosis. PGRN is a glycoprotein composed of 7.5 tandem domains called granulins (paragranulin and granulins 1-7) that are joined together by intervening peptide linkers (L1-8). We, and others, find that PGRN is cleaved into granulins by cathepsins in the lysosome. However, the exact lysosomal function of granulins is unknown. Moreover, there are conflicting reports whether granulins are benign, beneficial, or detrimental to neuronal health and function. In this project, we dissected the contribution of the linkers between each granulin in human PGRN to help understand the trafficking and function of granulins in the lysosome.
Methodology: Granulins with, or without, linkers were expressed in mammalian cells and purified from media. Free thiol groups of granulins were measured using the Measure-IT thiol assay. Electrophoresis and total protein staining was used to measure folding and presence of higher-weight oligomers. Stable HeLa cell lines were generated expressing individual granulins to evaluate secretion, lysosomal trafficking, and granulin cleavage.
Results: We find that peptide linkers at the carboxy-terminus of granulins are necessary for proper protein folding, secretion, and lysosomal trafficking.
Conclusions: Our data provide additional evidence that granulins themselves are the bioactive component of PGRN. Taken together, we find that granulins are sufficient to maintain lysosome function, homeostasis, and are potential therapeutics to treat FTD caused by *GRN* mutations.

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Conflicts of interest

N/A