Targeted manipulation of the sortilin-progranulin axis rescues progranulin haploinsufficiency


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Abstract

Progranulin (GRN) mutations causing hipoinsufficiency are a major cause of frontotemporal lobar degeneration (FTLD-TDP). Recent discoveries demonstrating sortilin (SORT1) is a neuronal receptor for PGRN endocytosis and that a determinant of plasma PGRN levels portends the development of enhancers targeting the SORT1/PGRN axis. We demonstrate the efficacy of several approaches through which impairing PGRN’s interaction with SORT1 restores extracellular PGRN levels. Our report is the first to demonstrate the efficacy of enhancing PGRN levels in iPSC-neurons derived from FTD patients with PGRN deficiency. We validate a small molecule preferentially increases extracellular PGRN by reducing SORT1 levels in various mammalian cell lines and patient-derived iPSC-neurons and lymphocytes. We further demonstrate that SORT1 antagonists and a small molecule binder of PGRN588-593, residues critical for PGRN-SORT1 binding, inhibit SORT1-mediated PGRN endocytosis. Collectively, our data demonstrate that the SORT1/PGRN axis is a viable target for PGRN-based therapy, particularly in FTD-GRN patients.

1. SORT1-mediated endocytosis in M17 neuroblastoma cells

2. MPEP decreases SORT1 expression and increases extracellular PGRN

3. MPEP decreases SORT1 expression and increases extracellular PGRN in cellular models of FTD-GRN

4. Elastase-mediated removal of C-terminal motif of PGRN blocks PGRN endocytosis by SORT1

5. SORT1 ligands competitively inhibit PGRN endocytosis.


Conclusions

1. We have identified a compound termed MPEP that can selectively increase extracellular PGRN through reducing intracellular SORT1 in various models including iPSC-neurons from FTD patient.

2. SORT1 ligands competitively inhibit PGRN endocytosis in a quantitative cell-based endocytosis assay.

3. We have identified a compound termed BVFP that binds PGRN588-593 through compound library screen. As demonstrated in a human ES-SORT1 knockout cell model, BVFP inhibits PGRN endocytosis in a SORT1-dependent manner.

4. Hence we have demonstrated multiple strategies applied to inhibit SORT1-mediated PGRN endocytosis which support SORT1/PGRN axis as a target to develop PGRN enhancers for FTD therapeutics.