RESCUE OF PROGRANULIN DEFICIENCY ASSOCIATED WITH FRONTOTEMPORAL LOBAR DEGENERATION BY ALKALIZING REAGENTS AND INHIBITION OF VACUOLAR ATPASE

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Introduction: Frontotemporal lobar degeneration (FTLD) is the second most abundant form of presenile dementia. 60% of FTLD patients are pathologically characterized by ubiquitin- and TAR-DNA binding protein 43- positive nuclear or cytoplasmic inclusions (FTLD-TDP). Genetic linkage studies and/or mutation screenings identified loss-of-function mutations in the progranulin gene (GRN) in patients with familial FTLD-TDP, which results in a severe reduction of GRN levels in tissues and biological fluids of patients. Additionally, missense mutations lead due to missorting, degradation and probably misfolding to reduced secretion of GRN. Since GRN is known to have neurotrophic properties these findings strongly indicate that GRN haploinsufficiency is causally linked to neurodegeneration.

Aims: We searched for compounds that are capable of stimulating GRN production.

Methods: We developed a sensitive ELISA for human and mouse GRN that enables us to detect endogenous GRN in body fluids and tissue culture supernatants.

Results: Using this ELISA we identified FDA-approved alkalizing reagents and vacuolar ATPase inhibitors that increase GRN production in neuronal and non-neuronal cells. These compounds were capable to compensate for GRN deficiency in organotypic cortical slice cultures of heterozygous GRN knockout mice and primary lymphoblasts from FTLD patients carrying a GRN mutation. In both model systems for GRN haploinsufficiency the identified candidate compounds increased GRN levels back to physiological amounts. The cellular mechanisms behind the GRN increase are currently further analyzed.

Conclusion: Alkalizing reagents, specifically those already used in humans for other applications, and vacuolar ATPase inhibitors may be therapeutically employed to prevent GRN dependent neurodegeneration.