Mechanisms of Progranulin's Neurotrophic Effects

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Progranulin is a secreted pro-protein that maintains lysosomal function and exerts anti-inflammatory and neurotrophic effects. Loss-of-function progranulin (*GRN*) mutations cause frontotemporal dementia (FTD), and *GRN* polymorphisms increase risk for Alzheimer's disease and Parkinson's disease. Progranulin is constitutively secreted and can act as a signaling molecule before uptake and trafficking to lysosomes. It is not clear if progranulin's beneficial effects are mediated through extracellular signaling or through lysosomes. To address this question, we developed lentiviral vectors expressing progranulin (PGRN) or a non-secreted progranulin generated by fusing PGRN to the transmembrane/cytosolic domain of LAMP-1 (L-PGRN). L-PGRN was not secreted, but was delivered to lysosomes and normalized lysosomal enzyme activity in *Grn*$^{-/-}$ neurons. L-PGRN mimicked PGRN's neuroprotective effects against excitotoxicity in primary cortical cultures. L-PGRN exerted an even stronger neuroprotective effect when expressed with a neuron-specific vector, indicating that this effect was mediated in neuronal lysosomes. L-PGRN also mimicked PGRN's enhancement of dendritic outgrowth in primary hippocampal cultures. L-PGRN enhanced dendritic outgrowth when specifically expressed in astrocytes, but not neurons. L-PGRN–transduced astrocytes grown on transwell inserts increased dendritic growth of co-cultured neurons, suggesting changes to astrocyte secreted factors. Analysis of conditioned media indicated that L-PGRN suppressed secretion of proteins that inhibit dendritic growth. In support of this result, eliminating astrocytes from hippocampal cultures enhanced dendritic outgrowth and occluded the effects of L-PGRN. These data reveal distinct mechanisms underlying progranulin's neurotrophic effects in primary cultures, and provide insight into potential mechanisms of neurodegeneration and astrocyte dysfunction in FTD due to *GRN* mutations.

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