

Neuronal transduction of AAV-Progranulin rescues pro-inflammatory microglial morphology in a mouse model of progranulin deficiency

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State of the Art: Of the more than 70 *GRN* mutations associated with FTD, nearly all cause progranulin haploinsufficiency. Therefore, progranulin replacement is a straightforward therapeutic approach for the FTD-GRN patient population. There are two AAV-Progranulin gene therapeutics currently in clinical trials. PR006, manufactured by Prevail Therapeutics, is a human progranulin transgene product packaged in an AAV9 capsid which transduces both neurons and astroglia. PBFT02, manufactured by Passage Bio, is human progranulin packaged in an AAV1 capsid, which selectively transduces neurons. Our lab has demonstrated that mouse progranulin packaged in AAV1 rescues microglial lysosomal dysfunction in progranulin homozygous knockout (*Grn*^{-/-}) mice as measured by CD68 immunostaining, and reduces microglial soma size, as measured by IBA1-positive particle analysis of DAB micrographs. Here, we further characterized microglial morphological phenotypes of *Grn*^{-/-} mice and determined if neuronal restoration of progranulin influences microglial morphology.

Methodology: A blinded experimenter used 3D Slicer to manually segment and perform 3D reconstruction of microglia from 40X Z-stacks of IBA1-stained sections of *Grn*^{-/-} and *Grn*^{+/+} brains. We also used a MATLAB-based script which segments and skeletonizes microglia based on a threshold set by the user. We repeated these analyses with *Grn*^{-/-} mice that received AAV1m*Grn* or AAV1GFP.

Results: *Grn*^{-/-} mice had age-dependent increases in microglial cell volume, territorial volume, and average branch length and AAV1m*Grn* treatment rescued these morphologic phenotypes. Exogenous progranulin was detected only in neurons, not microglia.

Conclusions: Neuronal transduction of AAV-Progranulin rescues pro-inflammatory microglial morphology in *Grn*^{-/-} mice.

Conflicts of interest

Disclosures: EDR has served as consultant for AGTC and serves on the DSMB for Lilly.