Glucocerebrosidase gene therapy for Parkinson's disease

Sucunza D, Rico AJ, Roda E, Marín-Ramos D, Lanciego JL
Center for Applied Medical Research (CIMA & CiberNed)
University of Navarra Medical School, Pamplona, Spain.

Abstract (300 word limit)

Mutations in the GBA1 gene coding for the lysosomal enzyme glucocerebrosidase (GCase) are related to increased incidence of synucleinopathies such as Parkinson's disease (PD) and dementia with Lewy bodies (DLB). Although the mechanisms through which GCase regulates the homeostasis of alpha-synuclein still are not fully understood, the identification of reduced GCase lysosomal activity as a common feature sustaining the neuropathological findings underlying PD and DLB -even when considering sporadic forms of these synucleinopathies- has recently attracted strong interest in the field. Accordingly, a number of novel strategies focused on increasing GCase activity to reduce alpha-synuclein burden and preventing dopaminergic neuronal death have been designed. Here we have performed bilateral injections of a recombinant adeno-associated viral vector serotype 9 coding for the mutated form of human alpha-synuclein (rAAV9-SynA53T) for disease modeling purposes, both in mice as well as in nonhuman primates (NHPs), further inducing a progressive neuronal death in the substantia nigra pars compacta (SNc). Next, another rAAV9 coding for the GBA1 gene (rAAV9-GBA1) was unilaterally delivered in the SNc of mice and NHPs one month after initial insult with rAAV9-SynA53T, together with the contralateral delivery of an empty rAAV9 (rAAV9-null) for control purposes. Obtained results showed that rAAV-mediated enhancement of GCase activity reduced alpha-synuclein burden, leading to improved survival of dopaminergic neurons together with a reduction in microglial-driven pro-inflammatory phenomena. Furthermore, the trans-synaptic "prion-like" spread of mutated alpha-synuclein was impeded upon treatment with rAAV9-GBA1. Data reported here support the use of glucocerebrosidase gene therapy as a disease-modifying treatment for PD and related synucleinopathies, also including sporadic forms of these disorders. *Supported by MINECO Ref: BFU2017-82407-R.*

Image

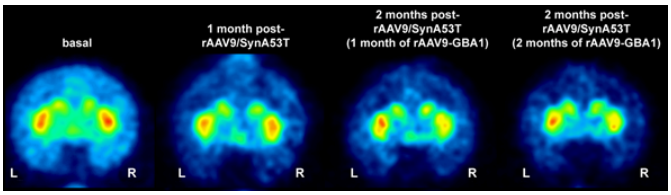


Figure 1: MicroPET scans with dihydrotetraenazine showing improved radiotracer uptake in the post-commissural putamen ipsilateral to the substantia nigra injected with rAAV9-GBA1. After a follow-up period of 3 months, obtained results showed a better preservation of the nigrostriatal system upon AAV-mediated enhancement of GCase.

Recent Publications (minimum 5)

1. Blandini F, et al. (2019) Glucocerebrosidase mutations and synucleinopathies: Toward a model of precision medicine. Movement Disorders 34:9-21.
2. Franco R, et al. (2018) Glucocerebrosidase mutations and synucleinopathies: Potential role of sterylglucosides and relevance of studying both GBA1 and GBA2 genes. Frontiers in Neuroanatomy 12:52.
3. Morabito G, et al. (2017) AAV-PHP.B-mediated global-scale expression in the mouse nervous system enables GBA1 gene thrapy for wide protection from synucleinopathy. Molecular Therapy 25:2727-2742.
4. Dopeso-Reyes IG, et al (2018) Glucocerebrosidase expression patterns in the non-human primate brain. Brain Structure and Function 223: 343-355.
5. Pignataro D, et al (2017) Adeno-associated viral vectors serotype 8 for cell-specific delivery of therapeutic genes in the central nervous system. Frontiers in Neuroanatomy 11:2.
6. Pignataro D, et al. (2018) Gene therapy approaches in the non-human primate model of Parkinson's disease. Journal of Neural Transmission 125:575-589

Photograph



Biography (150 word limit)

Dr Lanciego is currently ahead of the Functional Neuroanatomy of Basal Ganglia Lab at the Center for Applied Medical Research, University of Navarra. He has been working in the field of basal ganglia-related neurodegenerative disorders for more than 20 years. He has published more than 100 papers in indexed journals, with an *H* index of 35 (May, 2019). In December 2006, his group received the credentials of "group of excellence" in the field of neurodegenerative disorders, issued by the Spanish Ministry of Health. At present, his research group has a narrow focus on the implementation of a number of different gene therapy strategies targeting neurodegenerative disorders caused by the pathological aggregation of misfolded proteins.

Email: jlanciego@unav.es

Notes/Comments:

(Although this abstract has been submitted for oral presentation within Track 12, it can also be accommodated within Track 2)