GENE THERAPY AGAINST NEURODEGENERATIVE DISEASES: PARKINSON'S DISEASE

Verónica Pérez Madrigal - Microbiology's Bachelor

Neurodegenerative diseases (ND)

They produce a progressive deterioration of the neuron until producing cell death. They affect elderly mostly. The causes of degeneration are unknown so treatments are symptomatic or palliative [1].

Parkinson's Disease (PD)

It is the 2nd most common ND, produced by the death of dopamine neurons in the substantia nigra. Characterized by the presence of both motor (bradykinesia), and non-motor symptoms. There is no known cause or treatment to stop the disease [2].

PD Treatment

There are pharmacological treatment, surgery and support therapy. The first one includes drugs that delay the clinical evolution of the disease. It may be by neurorestoration as L-dopa that compensate the loss of dopamine. Another way is by neuroprotection, inhibiting neurodegeneration.

Adeno-associated virus (AAV)*

- Non- enveloped dsDNA virus
- "*Ex vivo*" or "*in vivo*"
- High tropism and distribution capacity
- Low immunogenicity
- 4.8 Kb
- Non-pathogenic

Lentiviral vector (LV)**

- Enveloped, ssRNA virus
- "*Ex vivo*"
- 8.5 Kb

Objetives

- The aim of this review is to describe the strategies followed in gene therapy against PD using viral vectors and their future perspectives.

Gene therapy

It is the set of methods used to transfer a genetic material or other elements that modifies it, to a patient. The goal is to restore the missing function and achieve a lifelong treatment through a single low dose. Viral vectors (AAV* and LV** vectors) are the most used to deliver genetic material. For PD, there are three main strategies that have reached clinical trials. The first one includes those studies that are focused on rescuing damaged neurons through the delivery of neurotrophic factors as NTN or GDNF. Other studies attempt to reconstruct the loss of dopamine by delivering key enzymes involved in the synthesis and metabolism of dopamine (AADC). Finally, we have those that try to synthesize GABA by inserting the GAD gene in the subthalamic nucleus [3].

Gene therapy approaches

Glutamic acid descarboxylase (GAD)

GAD may modulate neuronal phenotype This is the enzyme responsible for the synthesis of gamma-aminobutyric acid (GABA), an inhibitory neurotransmitter of the nervous system.
This therapy improve the function of the basal ganglia in PD.

Aromatic L-Amino acid descarboxylase (AADC)

AADC can increase dopamine levels. It is the enzyme that converts L-dopa to dopamine. Some scientists hypothesize that the loss of efficacy of L-dopa treatment over time is due to the fact that this enzyme decreases with neuronal loss. Currently it is the most effective therapy.

Clinical trials

Gene therapy	Identifier (id)	Status
AAV2-GAD	NCT00643890	Terminated (phase II)
AAV2-NTN	NCT00400634 NCT00985517	Completed (phase II) Active (phase I/II)
AAV2-AADC	NCT00229736 NCT02418598	Completed Active (phase I/II)
LV-TH, ADDC, CH1	NCT00627588 NCT01856439	Completed (phase II) Active (phase I/II)

Image 1: Clinical trials with viral vectors against PD and currently status. Own source.

Neurturin (NTN)

It's a neurotrophic factor derived from the glial cell line. It's able to protect brain cells after damage as well as to restore their function. So, its main aim is the neuroprotection.

Other strategies

- **α-synuclein (α-sin)**: Nuclear protein, main component of Lewy bodies.
- **GDNF**: Glial cell line-derived neurotrophic factor.
- **Immunology:** Interrupt some immune signals, a neuroprotector role appears.

The Unified Parkinson's Disease Rating Scale (UPDRS) is a clinical rating scale that assesses the symptomatic burden of PD [4]. It allows us to compare studies. The three strategies described above reduced several points according to UPDRS[5]. 6 months after the treatment , the results were:

- **GAD** expression reduced between 26% and 28% of the UPDRS scale.
- **AADC** had a 31%-32% of reduction.
- **NTN** got a 31,8% but only in the off-medication state.

The expression of the genes was maintained on time in all the studies at least 12 months after the treatment. There is no therapy that has passed from phase II.

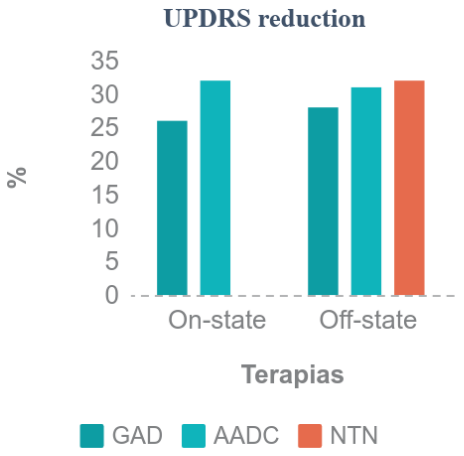

Image 2: It shows the maximum reduction of the UPDRS scale achieved in the different strategies of gene therapy against PD. Own source.

Conclusion

Despite the progress made to date, there is still a long way to find an effective treatment. The clinical results were unsatisfactory. The on-going approaches will probably end in combined and individualized therapies to be effective.

- **Personalized medicine**: There are genes whose mutations have been related to PD as LKKR2. Knowing the risk factors could give years and quality of life to patients.
- **Combined therapy**: Use more than one target in each trial. For example a therapy with AAV2-NTN combined with AAV2-hAADC and L-dopa will provide neuronal protection and survival while improving its function.

A problem that is currently being addressed with the aim of improving the PD gene therapy is the search of a non-invasive method of administration.

References:[1] Przedborski S, Vila M, Jackson-Lewis V. Series Introduction: Neurodegeneration: What is it and where are we? *J Clin Invest*. 2008;111(1):3-10., [2] Goetz CG. The History of Parkinson's Disease: Early Clinical Descriptions and Neurological Therapies. *Cold Spring Harb Perspect Med*. 2011;1., [3] Yu Gan, Zheng Jing, R. Anne Stetler and GC. Gene delivery with viral vectors for cerebrovascular diseases. *Front Biosci (Elite Ed)*. 2017;21(2):129-139, [4] Goetz CG. The Unified Parkinson's Disease Rating Scale (UPDRS): Status and recommendations. *Mov Disord*. 2003;18(7):738-750. [5] Christine CW, Starr PA, Larson PS, et al. Safety and tolerability of putaminal AADC gene therapy for Parkinson disease. *Neurology*. 2009;73(20):1662-1669. doi:10.1212/WNL.0b013e3181c29356. Keywords: Parkinson's disease, gene therapy, viral vectors.