DEVELOPMENT OF A GENE THERAPY FOR THE TREATMENT OF SPINOCEREBELLAR ATAXIA TYPE 1

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The hereditary ataxic syndromes are a group of rare genetic diseases of the central nervous system whose main symptom is the progressive loss of motor coordination (ataxia). The pathology includes a progressive degeneration of the spinal cord, brain stem and cerebellum, which determines the onset of increasingly serious symptoms until inducing respiratory insufficiency, which is the main cause of death. The most common forms of spinocerebellar ataxia in our country are those of type I and type II, indicated respectively as SCA1 and SCA2. Spinocerebellar ataxia type 1 (SCA1) is an autosomal dominant genetic disease characterized by progressive neurodegeneration, and is caused by an excessive expansion of the CAG trinucleotide repeats, coding for the amino acid glutamine, which is why such repetitions take the PolyQ name, present in exon 8 of the ATXN1 gene, mainly expressed in the cells of the cerebellum. The aim of the project is to develop therapeutic strategies able to block or correct the ATXN1 gene directly in its gene locus, carrying out what is called "gene editing", ie direct modification of the genome. To directly modify the gene sequence, we are using the CRISPR / Cas system, composed of an endonuclease able to cut the DNA double helix in specific sites thanks to its interaction with small molecules of RNA (guide RNA or sgRNA).

GOALS

- Isolation of fibroblasts from SCA1 patients, starting from skin biopsies, their maintenance in culture and freezing.
- Genetic analysis of the haplotype of SCA1 patients, with the aim of identifying single nucleotide polymorphisms (SNPs) that provide a discrimination between mutated alleles and normal alleles, and which can be used to design custom CRISPR / Cas9 approaches able to silence the mutated allele.
- Development of the gene editing method based on the CRISPR / Cas9 system to develop therapeutic strategies aimed to correct the genetic defect and the optimization of customized approaches for the inactivation of the only mutant allele and their validation in SCA1 fibroblasts.

INSTRUMENTS AND METHODS

Virology, molecular and cell biology techniques. The instrumentation used is the standard for molecular biology, virology and cell cultures.

SUBJECTS

Molecular biology, microbiology, cellular biology, genetics.

WORKING GROUP

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COLLABORATIONS

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