Gene therapy of Huntington disease using highly specific DNA endonucleases

Trinucleotide repeats are a class of microsatellites whose large expansions are involved in two dozen neurological or developmental disorders. Huntington disease, myotonic dystrophy type 1, fragile-X syndrome and Friedreich's ataxia are respectively triggered by the expansion of a CAG, CTG, CGG or GAA triplet repeat. No cure is available at the present time for any of these diseases. The pathology is always associated to an expansion of the microsatellite. Therefore, contracting the repeat to reduce its length was proposed to be a possible gene therapy approach for these dramatic disorders.

Huntington disease is a dominant neurodegenerative disorder, whose prevalence is 1/20,000 in the population. It is characterized by physical symptoms such as uncontrollable movements, lack of coordination, abnormal posturing and difficulties in chewing, swallowing and speaking, as well as decreased cognitive abilities and memory deficits appearing over time. Death occurs usually within 20 years following disorder onset but may occur faster with more severe forms of the disease. There is no cure for this neurodegenerative disorder. In order to contract the CAG repeat responsible for Huntington disease, four different nucleases will be assayed. First, a TALEN will be designed and built to be directed against the repeat tract. In addition, guide RNAs for the three Cas nucleases belonging to the three known families (Cas9, Cpf1 and CasX) will be designed. These four nucleases (TALEN and the three Cas) will be first expressed in yeast, in order to assess both their efficacy and specificity. Whole-genome sequencing of yeast cells in which each of these nucleases will be expressed will allow to determine whether unwanted mutations or chromosomal rearrangements are induced by their expression. The most efficient nuclease will be subsequently tested in a human cell model of Huntington disease and its efficacy will be assessed. Hopefully, these experiments should open the way to a therapeutic approach for Huntington disease.

Guy-Franck RICHARD

Natural & Synthetic Genome Instabilities
Department Genomes & Genetics
Institut Pasteur
25 rue du Dr Roux
75015 Paris, France
Tel: +33-1-45-68-84-36
guy-franck.richard@pasteur.fr