Gene editing technique is capable of reverting effects of a rare disorder

Group researches new treatment to Mucopolysaccharidosis type I, a condition that causes the buildup of complex carbohydrates and affects 1 out of 100,000 people

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Researchers from the Pharmacy course at HCPA recommend procedure based on gene therapy - Image by Gustavo Diehl/UFRGS

A group of faculty members from the Pharmacy Program at UFRGS is researching a new alternative of therapy for Mucopolysaccharidosis type I in partnership with *Hospital de Clínicas de Porto Alegre* (HCPA), which holds a center specialized for diagnosing the disorder. After more than 20 years of study on the condition, the researchers recommend a procedure based on gene therapy, which consists in introducing DNA into the cell aiming to modify any defective function of the original cellular DNA. The results of the study were published on the *Journal of controlled release*, an international scientific publication.

The Mucopolysaccharidosis type I (MPS1) is a genetic disorder caused by the malfunctioning on the production of the alpha-L-iduronidase enzyme, which is responsible for the degeneration of complex carbohydrates that are present in our bones and joints, the glycosaminoglycans (GAGs). The condition is divided into three subtypes – attenuated, intermediate and severe –, and all of them result in enlargement of cells, tissues and, therefore, organs. Other symptoms can be bone joints stiffness, cognitive disability, blindness, limited language capabilities, movement and respiratory disorders, camptodactyly of the fingers (claw hands) and curved spine. People with the disorder may suffer from heart problems due to the enlargement of the aorta.

There are two available treatments for the condition today: enzyme replacement therapy and hematopoietic stem cell transplantation. In the former, the patient receives, once a week, an intravenous infusion of a solution containing the enzyme; however, studies show its incapability of reaching some tissues. In the latter treatment, a bone marrow is transplanted with the purpose of inducing the damaged cells to produce the enzyme. This treatment, however, is only effective in preserving neurological functions when received by patients no older than two years old.

In order to treat the Mucopolysaccharidosis type I, the professors indicate the use of a system called CRISPR-Cas9, which is a genome editing tool that works as a scissor, cutting a determined point of the gene. "Before that, we had to send the DNA without knowing for sure what to expect. Now there is a system called CRISPR-Cas9 that cuts the DNA exactly where I want, so I can deal with that specific issue," explained Roselena Schuh, a professor from the Faculty of Pharmaceutical Sciences at UFRGS and one of the members of the research group. This method of genome editing facilitates the dispatch of a correct sequence of gene information in order to restore the production of alpha-L-iduronidase. Even in case just a few cells begin to produce the enzyme, it would be capable of spreading throughout other cells, inducing the degeneration of the carbohydrates located there.

The development of liposomes was a critical point of the research. They are vesicles that ease the access of the new DNA into the cell due to the similarity between them. It is required that the liposomes go through the microfluidizer – a device that produces a pressure high enough to reduce the size of the vesicles to the nanometric scale, making them tens of thousands times smaller than a strand of hair. Mice with the disease and cells extracted at the time of biopsy from patients with MPS1 were used to analyze the potential and the effects of the therapy. The researcher pointed out that the experimental tests with animals indicated the reduction of the aorta size, the normalization of the systolic and diastolic heart movements, the decrease of the quantity of GAGs in the tissues, except for the brain, and also improvements in the respiratory functions, bones and even in the appearance of the mice.

It is expected that the new gene therapy will need to be administered fewer times than the enzyme replacement therapy. Also, as opposed to the bone marrow transplantation, it is aimed at patients of any age. The next step of the research group is the search for "new ways of reaching the brain, which is the most difficult organ to do so due to its natural barrier: just like it is shielded from toxins, it inhibits the access of the treatments," said Roselena. The professors also intend to look for other methods of administering the treatment, aiming at surpassing the natural barriers of other parts of the body, like the eyes and joints.

Preclinical tests with mice are yet to be conducted before starting clinical trials using human volunteers. Recently, however, the procedure was patented and bought by a NGO, which plans to develop the experiment to clinical trials in three years. Tests with patients will be conducted in order to analyze the therapy results, and only then it may be made available for use of health professionals.

Scientific Article

SCHUH, Roselena S. et al. *In vivo* genome editing of mucopolysaccharidosis I mice using the CRISPR/Cas9 system. *Journal of controlled release*, v. 288, p. 23-33, Oct. 2018.

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