A group of researchers from around the world reverses the effect of a mutation in the COL6A1 gene that causes muscular dystrophy by means of gene therapy

Dr. Eduard Goñalons, Scientific Advisor, Fundación Noelia

In a recent article, Dr. Carsten Bönnemann from the NIND[1] (USA) shows how the effect of a pathological mutation of the collagen-6 alpha-1 chain (COL6A1) gene can be reversed in cells obtained from patients suffering from collagen VI-relatedmuscular dystrophy.

The work was conducted by numerous researchers from 20 centers around the world (from the US to Australia), including our collaborator, Dr. Cecilia Jiménez-Mallebrera, from the Sant Joan de Déu University Hospital in Barcelona.

As a framework of reference for the results presented, we need to remember that genes are encoded in the DNA. To produce the corresponding protein, the information contained in the DNA needs to be transcribed first to an RNA messenger (mRNA). This messenger, in turn, must go through a maturation process, in which the parts that do not contain informationare removed, before being read by the protein synthesis machinery of the cell. In this specific case, the mutation under study causes that, during the maturation process, a part of the sequence that should be eliminated remains in the messenger. This extra piece causes the resulting protein to contain an additional fragment that prevents it from carrying out its function adequately and, thus causing the disease.

By means of two different types of gene therapy, one with a temporary effect and another more permanent, researchers have managed to significantly reverse the effect of the mutation (which is quite frequent among COL6A1-deficient patients) in fibroblasts obtained from patient biopsies.

As a first approach, specific oligonucleotides (small DNA sequences) were used. When injected into the nucleus of the cells, these nucleotides are capable of producing an RNA that binds specifically to the messenger of the defective COL6A1 gene. This union interferes with the maturation process of the defective messenger and makes the cutting machinery ignore the additional fragment (the one that causes the COL6 protein to be dysfunctional) and produces, mostly, mature messengers with the correct sequence. The result is that the extracellular matrix of the treated cells shows a structure very similar to that of a healthy cell, with much thicker and longer collagen fibrils than cells expressing the mutation.

However, if we think about the clinical applicability of this therapy, since fibroblasts do not live forever, when they die, the therapeutic DNA fragment that we have injected disappears with them. It is, therefore, necessary to repeatedly administer the therapy to the patient in order to maintain the effect over time.

For this reason, the authors have also worked on another approach, which is more risky but at the same time provides a more permanent effect. Instead of preventing the faulty maturation process of the defective messenger, they reach out to the source and removed the mutation at the DNA level.

To achieve this, they designed a system based on the CRISPR/Cas9 technology that specificallycuts and extracts the part of the DNA that includes the mutation. Since, in this particular case, the mutation is located in a region of the DNA that does not contain information (and is removed during the process of maturation of the messenger) the authors expected that the extraction of this small part of the genome would not cause changes in the overall production of COL6. Indeed, once the fragment was eliminated, the levels of collagen production intreated cells were comparable to healthy cells, while the presence of the defective protein was significantly reduced.

Although these results have been achieved *in vitro*,rather than in patients, and the effect observed is not 100%, they do prove that it is possible to reverse the effects of a mutation through gene therapy in Col6 patients, which makes it an extraordinary achievement in the development of targeted gene therapiesfor these types of genetic conditions.

Original article:

V. Bolduc et al. A recurrent COL6A1 pseudoexon insertion causes muscular dystrophy and is effectively targeted by splice-correction therapies. JCI Insight. 2019;4(6):e124403. https://doi.org/10.1172/jci.insight.124403.

[1]Neuromuscular and Neurogenetic Disorders of Childhood Section, National Institute of Neurological Disorders and Stroke, NIH, Bethesda, Maryland, USA.