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PRESS RELEASE

An effective gene therapy approach for dysferlin deficiencies: research scientists at Généthon find a solution to the problem of the dysferlin gene's size to transport it into muscle

A team of researchers led by Isabelle Richard (CNRS UMR8587 LAMBE) in the Généthon laboratory, created and funded by AFM through Téléthon, has just demonstrated the efficacy in animals of a gene therapy strategy for a group of muscle diseases: dysferlin deficiencies. The scientists managed to transfer the dysferlin gene using a newly developed technique for transporting a "large" gene into muscle. By splitting this gene into two and placing each part in two independent AAV vectors, they successfully obtained expression of a whole and functional protein in mice models for the first time. This research, published online in *Human Molecular Genetics,* paves the way for gene therapy for dysferlin deficiencies and provides new information for the transfer of other large genes.

Dysferlin deficiencies represent a heterogeneous group of recessive neuromuscular diseases in which the common characteristic is a dysferlin gene defect. Dysferlin is a protein that is notably involved in the repair of muscle fibre membrane. The commonest conditions resulting from its deficiency are limb-girdle muscular dystrophy type 2B (LGMD2B) and Miyoshi myopathy. The former affects the muscles of the shoulders (scapular girdle) and pelvis (pelvic girdle), whereas the latter mainly affects the extremities of the limbs (lower legs, feet, forearms, hands). The conditions are progressive and ultimately lead to loss of the ability to walk.

One of the key features of the dysferlin gene is its large size (7 Kb), preventing its incorporation in vectors such as AAV (*Adeno Associated Virus – 4.7 kb*), which is effective for gene transfer into muscle. Using the specific properties of AAVs, Isabelle Richard's team discovered a method for transporting all of this "large" gene to the damaged cells of mice used as dysferlin deficiency models. When AAVs penetrate cells, their genomes tend to combine with one another in a phenomenon known as "concatemerisation". Encouraged by this observation, scientists at Généthon split the dysferlin gene into two and placed each part of this gene in separate AAV vectors, some containing the start of the gene and others the end. After injection into mouse muscle, some of these viral genomes then joined together in pairs, forming a new genome, containing both the start and end of the dysferlin gene, in the right order. In addition, the introduction of specific sequences in this new genome at the junction of the two gene parts, known as splicing, enabled the cell machinery to retain only the encoding parts of the gene (the exons), leading to the production of a whole and functional dysferlin. The researchers noticed that the new dysferlin triggered muscle fibre membrane repair and an improvement in locomotor activity.

These results pave the way for the potential use of gene therapy for dysferlin deficiencies and provide new information that could be applied to the transfer of other "large" genes, such as

factor VIII, involved in haemophilia, as well as dystrophin, involved in Duchenne and Becker muscular dystrophy.

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