PRESS RELEASE
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Neuromuscular diseases
A pharmacological therapeutic approach for certain sarcoglycanopathies

A research team led by Dr Isabelle Richard (CNRS-FRE3087) from the Généthon laboratory financed by the AFM through Téléthon donations has just demonstrated the efficacy of a novel pharmacological strategy in the mouse for certain mutations of alpha-sarcoglycanopathy or LGMD2D, a recessive limb girdle dystrophy. This pharmacological strategy could be applied to other limb girdle muscular dystrophies characterised by the same type of genetic mutation. This work is published online in the review Human Molecular Genetics.

Limb girdle muscular dystrophies (LGMD) form a group of neuromuscular diseases characterised by progressive muscular weakness which affects mainly the limb girdle scapular and pelvic muscles. At present the different sub-types of LGMD are distinguished by protein and genetic analyses. Type 2D LGMD or alpha-sarcoglycanopathy is inherited autosomal recessively and is caused by mutations of the *Sgca* gene located on chromosome 17 and coding for alpha-sarcoglycan, a protein from the sarcoglycan complex. In normal conditions this complex – situated in the muscle cell membrane – ensures the stability and mechanical resistance of the cell membrane during muscle contractions. In case of mutation in one of the cells of this complex, as is the case in alpha-sarcoglycanopathy, the repetition of contractions create microlesions in the muscle fibre membrane which eventually finish by destroying the muscle tissues irreversibly and therefore lead to a loss of muscle strength. At the present time no treatment exists to cure this disease.

It is known that one third of all alpha-sarcoglycanopathy patients are carriers of the same mutation (R77C), which is the most frequent mutation in this disease. In partnership with the Luminy Immunology Centre at Marseille, Généthon researchers produced a mouse model that reproduces this mutation and noted that it presented no dystrophic signs. From these observations of cell and animal models, Généthon researchers were able to demonstrate that the consequence of the R77C mutation was the production of a malformed protein which cannot reach the membrane once it is synthesised, as it is eliminated by the “quality control” mechanism of proteins in the endoplasmic reticulum. Therefore, the disease is not caused by a loss of protein function but by its premature degradation which prevents it from reaching the cell membrane and integrating into the sarcoglycan complex.

Exploiting this discovery, the researchers used molecules capable of inhibiting *alpha-mannosidase*, one of the elements of the quality control system. They administered one of these inhibiting molecules by intramuscular injection to mice into which a gene coding for the mutated human protein (R77C) had already been injected and showed that, using the product, the mutated alpha-sarcoglycan could be redirected in the cell membrane, thus restoring functionality to the sarcoglycan complex. Also, the researchers noted a reduction of dystrophic damage in the muscle fibres treated.

This work opens up prospects for a novel pharmacological therapeutic approach for the LGMD2D caused by this type of mutation, but also for other sarcoglycanopathies due to the same type of mutation – that which disrupts the transport of a fully-functional protein to the membrane.

The “Limb girdle muscular dystrophies” team at Généthon, led by Dr Isabelle Richard since 1999 illustrates perfectly the amount of ground covered since the AFM set up the laboratory in 1991, financed by Téléthon donations. In fact, this team has identified many genes and mechanisms at the origin of limb girdle muscle dystrophies. At present it is working on the development of innovative therapies for these diseases and – in particular – preparing a gene therapy trial for calpainopathies.

Généthon in the age of treatments

Financed by the AFM since 1990, today Généthon represents 10 000 m² of laboratories and 200 researchers, technicians, engineers, pharmacists and physicians. After mapping the human genome and identifying the genes responsible for hereditary diseases, it tackled gene therapy techniques and later the development of gene and cell therapies. Thus Généthon is the first non-pharmaceutical laboratory to be authorised to produce batches of vectors for trials in humans. In 2006 it launched its first gene therapy trial on 9 gamma-sarcoglycanopathy patients in partnership with the Pitié-Salpêtrière Hospital and the Institute of Myology. Thus Généthon has moved on from fundamental research into the genome to the era of clinical trials – illustrating the ground covered by the AFM thanks to Téléthon donations.

For further information:

Mannosidase I inhibition rescues the human {alpha}-sarcoglycan R77C recurrent mutation -- Bartoli et al., 10.1093/hmg/ddn029 -- Human Molecular Genetics

Marc Bartoli[1], Evelyne Gicquel[1], Laetitia Barrault[1], Tayebeh Soheili[1], Marie Malissen[2], Bernard Malissen[2], Nathalie Vincent-lacaze[1], Norma Perez[1], Bjarne Udd[3], Olivier Danos[1] and Isabelle Richard[1,]

[1] Généthon, CNRS-FRE3018, Evry, 91000, France [2] Centre d'immunologie de Luminy, Université de la Méditerranée, Marseille, 13009, France [3] Neurological Department, Vaasa Central Hospital, Finland

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For more information about the disease :

Association Française contre les Myopathies
www.afm-france.org
Tél. : 0 810 811 088 (local call rate)

Press contact :

AFM – Estelle Assaf, Delphine Carvalho : 01 69 47 28 28, presse@afm.genethon.fr