Progeria: Promising results from new gene therapy on animals

October 27 2011

Researchers are continuing their efforts in an attempt to counter the consequences of the genetic defect that causes Progeria. Until now, no model had been able to accurately imitate the effects of the disease in humans. For several years, research has been conducted in close collaboration from teams led by Nicolas Lévy and Annachiara De Sandre-Giovannoli at Inserm/Université de la Méditerranée and from a team led by Carlos López-Otín (University of Oviedo) and has succeeded in making such a model possible. The lifespan of mice treated through gene therapy is significantly extended and several other parameters related to them are improved.

The research, published on 26 October 2011 in *Science Translational Medicine*, received backing from the AFM thanks to donations from a Telethon.

Progeria is a rare genetic disease. Children suffering from it seem to experience accelerated aging (chronic hair loss, joint pains, thin and hairless skin, cardiovascular problems). In 2003, Nicolas Lévy and his team identified the cause of the disease when they discovered the involvement of the LMNA (nuclear protein-coding) gene, lamin A/C. The mutation causes the production of a truncated protein, progerin, which accumulates in the nuclei of cells and its toxic effects cause their deformation and various other malfunctions. It has since been proven that progerin progressively accumulates in normal cells, thus establishing a link between the disease and physiological aging.

In 2008, European clinical trials began on twelve children suffering from Progeria. The treatment is based on a combination of two existing molecules: statins (prescribed in the treatment and prevention of atherosclerosis and cardiovascular risks) and aminobisphosphonates (prescribed in to treat osteoporosis and to prevent complications in some forms of cancer). The use of both these molecules aims to chemically alter progerin to reduce its toxicity. However, although this treatment aimed to slow down the development of the disease, it did not reduce the quantities of progerin. To study this aspect, researchers needed to obtain a relevant animal model.

An "authentic" Progeria model…

To generate a model of this kind, Spanish and French researchers decided to introduce a gene mutation (G609G), equivalent to that identified in humans (G608G), in mice to reproduce the exact pathological mechanism found in the children, with a view to then blocking it. The mice models were created under the supervision of Bernard Malissen using the IBISA platform located at the Marseille-Luminy Centre of Immunology . This approach made it possible to obtain young mice that produced progerin, characteristic of the disease in humans. After three weeks alive, the mutated mice displayed growth defects, weight loss caused by bone deformation and cardiovascular and metabolic anomalies mirroring the human phenotype and considerably reducing their lifespan (an average of 103 days compared with two years for wild mice). The progerin thus produced accumulates in mouse cells via genetic mechanisms (abnormal splicing) identical to those observed in humans, i.e. the source of anomalies characteristic of the disease.

… for a targeted gene therapy

Using this unique Progeria animal model, the researchers focussed their

efforts on implementing a mutation-targeted treatment, with a view to reducing, and, if possible, preventing the production of progerin. To this end, they used "vivo-morpholino" antisense oligonucleotide technology. "This technology, explains Nicolas Lévy, is based on introducing a synthetic antisense aglionecleotide into mice. As is the case with progeria, this sequence is applied to block (or facilitate) the production of a functional protein using a gene. In this case, the production of progerin, as well as lamin A from the gene, were reduced."

There was a highly significant increase in life expectancy of mice treated using this new technology, from an average of 155 days to a maximum of 190 days.

Nicolas Levy's team, with continued collaboration with Carlos López-Otín, now intend to translate this preclinical research into a new therapeutic trial for children, possibly combined with other pharmacological molecules. Other research is being conducted in parallel to find alternative administration channels for antisense oligonucleotides.

More information: Splicing-Directed Therapy in a New Mouse Model of Human Accelerated Aging, *Science Translational Medicine*, October 2011

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