MedicalXpress

Target gene identified for therapies to combat muscular dystrophy

November 12 2015

Researchers at the University of São Paulo's Bioscience Institute (IB-USP) in Brazil have shown that a gene called Jagged1, or JAG1 for short, could be a target for the development of new approaches to treat Duchenne muscular dystrophy (DMD), a genetic disorder characterized by progressive muscle degeneration.

The research was carried out at the Human Genome & Stem Cell Research Center (HUG-CELL), one of the Research, Innovation and Dissemination Centers (RIDCs) supported by São Paulo Research Foundation (FAPESP).

"All the genetic therapies tested so far, with little success, have targeted the gene that codes for the protein dystrophin. We're presenting a different approach, which opens up a range of new possibilities," said Mayana Zatz, Full Professor of Genetics at IB-USP and Head of HUG-CELL.

Duchenne muscular dystrophy, Zatz explained, primarily affects males and is the most common and most rapidly progressing type of muscular dystrophy. It is caused by a mutation, usually inherited, in the gene that encodes dystrophin, a protein that is essential for muscle health and is entirely absent in DMD patients.

"Dystrophin maintains the integrity of the membrane surrounding muscle cells," Zatz said. "When this protein is absent, the membrane becomes flaccid, so important proteins leak out of the muscle tissue and

enter the bloodstream. Conversely, substances that should remain outside, such as calcium, are able to get in."

The heart, diaphragm and skeletal muscles are affected. Difficulty with walking and running first appear in boys aged between 3 and 5. Patients are usually confined to a wheelchair by age 10-12.

"Without special care, patients don't reach the age of 20. Nowadays, with assisted breathing, they may survive until they're 40 or beyond," Zatz said.

Over the past 15 years, researchers at HUG-CELL have performed experiments to extend our knowledge of DMD. They have studied animals such as Golden Retrievers born with a dystrophin gene mutation, which develop a clinical condition similar to human DMD. Most dystrophic dogs live for only two years or less.

"Some time ago, we identified a dog that totally lacked dystrophin yet presented with a much milder form of the disease," Zatz said. "It survived for 11 years, considered normal for this breed, and left a descendant that inherited the mutation and is now nine years old."

Ringo and Suflair, as the dogs were called, became the center of attention for the research group, that compared gene expression in healthy dogs, dogs with severe muscular dystrophy, and the above two dogs with the milder form of the disease.

The researchers found some candidate genes, and in a partnership with Professor Louis Kunkel and his team at Harvard Medical School, and Professor Kerstin Lindblad-Toh at the Broad Institute of MIT and Harvard in the United States, it was possible to combine the results with genetic data. They identified a region of the genome that's associated with the benign clinical condition and found increased expression of

JAG1, a gene in this region, in Ringo and Suflair. This could explain why they have a more benign form of the disease

To confirm that alterations in JAG1 expression can indeed affect the severity of the disease, Vieira conducted experiments using a zebrafish model. The zebrafish (Danio rerio) shares approximately 70% of its genome with humans.

The experiments were performed in Prof. Kunkel's laboratory. Prof. Kunkel discovered the dystrophin gene and is currently a researcher at Harvard Medical School.

"The zebrafish model also has a dystrophin gene mutation," Zatz said. "As a result, its muscles are weak, and it can't move. When we increased JAG1 expression in zebrafish without dystrophin, we found that 75% failed to develop the dystrophic phenotype."Overexpression was induced in the model by injecting embryos with JAG1 messenger RNA.

Provided by Fundação de Amparo à Pesquisa do Estado de São Paulo