Impaired protein degradation causes muscle diseases

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New insights into certain muscle diseases, the filaminopathies, are reported by an international research team led by Dr. Rudolf Andre Kley of the RUB's University Hospital Bergmannsheil in the journal *Brain*. The scientists from the Neuromuscular Centre Ruhrgebiet (headed by Prof. Matthias Vorgerd) at the Neurological University Clinic (Director: Prof. Martin Tegenthoff) cooperated with colleagues from eleven institutes in seven countries. Among other things they found that protection mechanisms to combat abnormal protein deposits do not work properly in filaminopathy patients. This opens up new starting points for therapies that the team aims to test on cell cultures.

How filaminopathies develop

Mutations in the filamin C gene (FLNC) cause filaminopathies, which are manifested through progressive muscle weakness to the point of loss of the ability to walk. Muscle fibres are composed of myofibrils, for the development and maintenance of which the protein filamin C is crucial. The mutations examined in the study bring about a so-called myofibrillar myopathy: the myofibrils disintegrate in certain places and mutant filamin C and other proteins aggregate massively in the muscle fibres.

Support of protein degradation does not start on time

The researchers showed that the diseased protein deposits interfere with the protein degradation usually occurring in cells. Normally, cells

produce what are known as heat shock proteins, which promote the degradation of protein deposits and make sure that other proteins assume their correct three-dimensional structure. "However, these protection mechanisms only seem to be increasingly activated when the critical point is exceeded. It looks as if the 'fire brigade' was called too late", says Dr. Kley. "We hope to positively influence the course of the disease by means of early treatment with substances that stimulate the production of heat shock proteins or affect the protein degradation in other ways. To study this, we have developed a cell culture model that allows us to carry out the first therapy studies in the laboratory."

Clinical picture more precisely characterised

The study of filaminopathy patients also enables the researchers to describe the disease more accurately now. The heart is more affected by the disease than previously thought, which may cause sudden cardiac death. It was also confirmed that pathological remodelling processes in the leg muscles conform to a specific pattern, which is visible on magnetic resonance imaging pictures. "This enables us to distinguish filaminopathies from other muscle diseases within the group of myofibrillar myopathies", explains Dr. Kley.

More information: R.A. Kley et al. (2012): Pathophysiology of protein aggregation and extended phenotyping in filaminopathy, *Brain*, doi: 10.1093/brain/aws200

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