New clues about the basis of muscle wasting disease

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New findings that shed light on how genetic damage to muscle cell proteins can lead to the development of the rare muscle-wasting disease, nemaline myopathy, are reported today (15 March) in the *Biochemical Journal*.

Professor Laura Machesky and colleagues from the CRUK Beatson Institute for Cancer Research in Glasgow, tested cultures of muscle cells that displayed mutations of the ACTA1 gene to determine how the mutations affected the biochemical pathways leading to the muscle damage seen in nemaline myopathy.

The ACTA1 gene controls the production of actin, one of the main structural proteins in muscle; mutations in this gene cause 15-20% of cases of nemaline myopathy, an inherited muscle wasting disease similar to muscular dystrophy. Around 140 different mutations of the ACTA1 gene can occur; around a third of these have been biochemically characterized to determine how they affect actin. The mutations cause a wide variety of defects in the biochemical behaviour of actin, but all cause defects in the structure of muscle cells leading to cell and tissue damage and wasting. The researchers discovered that not only do disease-causing mutations in actin lead to weakening of the cell's internal support system, but they also cause changes in the genetic control of other biochemical pathways such as the serum-response factor pathway (SRF). When actin binds to a protein called MAL (originally named megakaryoblastic leukaemia-1) in the cell's nucleus, it switches on the SRF pathway. Actin damaged by mutations doesn't bind properly and the

SRF pathway isn't fully activated.

The SRF signalling pathway has a role in muscle development and maintenance. The presence of myopathy-causing mutant actin protein leads to alteration in the pathway that could promote muscle cell degeneration and death or interfere with normal growth and repair. The majority of ACTA1 mutants examined in this study altered the serum response factor signalling pathway, indicating that changes in this pathway may be a major factor in actin-based nemaline myopathy and that this area could be used to develop therapies for patients.

Nemaline myopathies are sometimes called rod body myopathies as the damaged proteins form abnormal thread-like rods, called nemaline bodies, in the muscle cells. There are a number of different types of rod myopathies and they affect both males and females. In the majority of cases (90%) the condition becomes apparent at birth or early childhood, although in very rare cases, it does not become apparent until adulthood. Rod myopathies are estimated to affect 1 in 50,000 individuals.

Commenting on the findings, Professor Machesky said, "More research now needs to be done to determine whether cells in patients have the same changes that we saw in cells in the laboratory. We used the drugs Jasplakinolide and Cytochalasin D, which target the actin-MAL complex, to reverse the effects of the mutant actin - but these drugs are toxic at high levels as they also disrupt the actin filaments and thus the cell's structure. If they could be modified or used at low concentrations they may prove useful leads to drug development."

Marita Pohlschmidt director of research at the Muscular Dystrophy Campaign said, "Nemaline myopathy is a very rare condition that can be difficult to diagnose, because it is caused by a defect in one of several genes. The research presented in this paper is an important contribution to understanding what causes the muscle wasting in about a fifth of all

people affected with this devastating condition. The results will be vital for the future development of treatments for those affected by nemaline myopathy."

More information: "Myopathy-causing actin mutations promote defects in serum response factor signalling" by Balazs Viegrady and Laura Machesky, will be published in the Biochemical Journal (2010) Vol 427, part 1, pp 41-48 at www.biochemj.org on 15 March 2010

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