Researchers offer hope of cure for muscle wasting

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Foteini Mourkioti, Nadia Rosenthal

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Their work, which was partly funded by the EU's Sixth Framework Programme as part of the MYORES Network of Excellence, is published in the Journal of Clinical Investigation.

Muscles waste away when the processes which maintain the balance of protein production and breakdown are disrupted. This can happen as a result of genetic defects, heart failure, spinal injury, cancer, immobility or even old age.

Weakness resulting from a loss of muscle mass and strength has a severe impact on patients' quality of life, but developing effective treatments for it has proved extremely difficult.

In this latest piece of research, scientists looked at the role of the signalling molecule NF-kB in muscle wasting. It has been known for some time that NF-kB plays a key role in inflammation processes, and it was recently discovered to be involved in other degenerative conditions such as multiple sclerosis.

The scientists genetically removed the NF-kB molecule from the leg muscles of mice by blocking a protein called IKK2, which activates NF-kB. They then mimicked a

spinal injury in the mice by blocking communication between the spinal cord and the lower leg muscle, an intervention which normally leads to muscle wasting.

'What we observed was truly amazing,' said Professor Nadia Rosenthal, Head of the EMBL's Mouse Biology Unit. 'The mice showed hardly any muscle wasting after the injury; their muscle fibres maintained almost the same size, strength and distribution as in a healthy muscle. But that's not all; blocking IKK2 also helped muscle healing. Without the NF-kB signal the muscle regenerated much better and faster.'

According to the researchers, in response to injury or inflammation, NF-kB shuts down the production of proteins and stimulates their breakdown, leading to the loss of muscle mass. Blocking NF-kB in the mice's leg muscles therefore protected the muscles from wasting away and improved healing.

Another molecule of interest to the researchers is a growth factor called IGF-1. In previous studies, Professor Rosenthal and her group had found that IGF-1 is very good at promoting the repair of skeletal and cardiac muscles. The researchers added a gene coding for IGF-1 to the muscle tissue which was already lacking NF-kB, and found that this further enhanced protection against muscle wasting.

'The fact that NF-kB reduction helps maintain our muscle mass is a useful starting point to develop new therapies against muscle diseases,' explained Dr Foteini Mourkioti of the EMBL's Mouse Biology Unit. 'Adding IGF-1 has a similar effect as blocking NF-kB, but it must act, at least in parts, independently of NF-kB, because we observed a clear improvement when using the two treatments together.'

In an accompanying article, Michael Karin of the University of California highlights the implications of this new research, noting that until now muscular dystrophies and muscle wasting are generally not thought of as inflammatory diseases.

'These data ... strongly suggest that muscular dystrophies and atrophies should also be considered inflammatory diseases and raise the prospects of novel therapies that target IKK2 or other steps in the NF-kB activation pathway,' he writes.

A number of IKK2 inhibitors and other molecules which block NF-kB activation have recently become available, and Dr Karin calls for more research into the ability of NF-kB inhibition to prevent muscle degeneration, first in mice, then in humans.

'Given the prevalence of muscle degenerative diseases and their toll on life quality as well as their major economic impact, such trials are not only justified but also badly needed,' he concludes.

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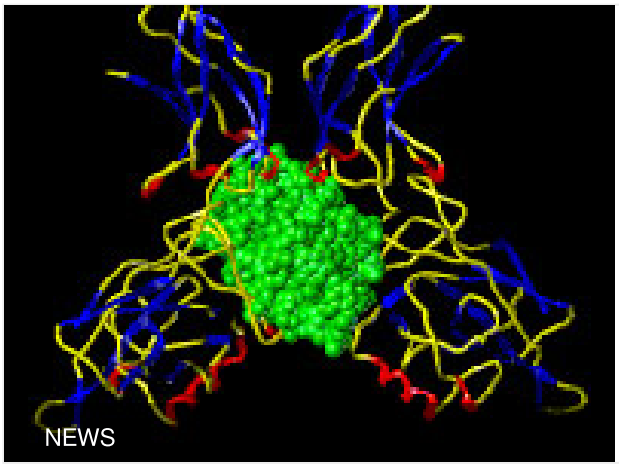

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