# Press Release

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# Molecule linked to antagonistic mechanisms that keep muscle proteins in shape

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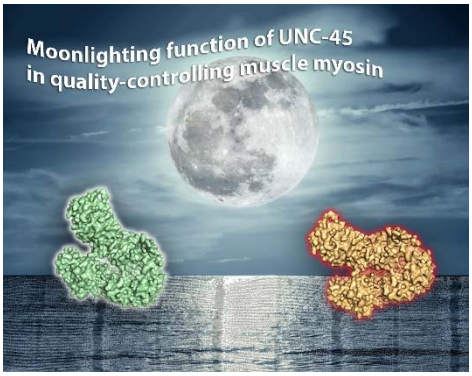
*Scientists in Vienna discover two distinct roles for the molecule UNC-45 in keeping muscle proteins in the right shape: on its own it steers the assembly of a muscle protein; in conjunction with a partner it triggers the degradation of severely damaged muscle proteins. The findings, reported in Nature Communications, may help to better understand muscular diseases.*




**UNC-45 is a "moonlighting" chaperone fulfilling distinct roles in quality-controlling muscle proteins. As a "good" chaperone (green), it promotes the maturation of myosin molecules, as a "bad" chaperone (orange) it supports the degradation of damaged molecules. (Credit: IMP/istockphoto)**

Quality control is important – not only in manufacturing, but also for cells that are constantly producing proteins. The cellular quality-control network assists proteins in maintaining their proper fold and full functionality, keeping the amounts of damaged, aggregation-prone molecules at a minimum. To this end, molecular chaperones help proteins reach their native state, while dedicated protease machines eliminate non-functional proteins that cannot be repaired.

In muscle cells, for example, the motor protein myosin needs to fold properly and assemble into filaments to eventually mediate muscle contraction. The UNC-45 protein plays a key role in this process. UNC-45 forms the core of a myosin assembly line allowing various cellular chaperones to work side-by-side when putting myosin filaments together. In a study published in *Nature Communications*, the groups of Tim Clausen (Research Institute of Molecular Pathology) and Alexander Dammermann (Max F. Perutz Laboratories, a joint venture of the University of Vienna and Medical University of Vienna) now show that the UNC-45 chaperone also participates in the degradation of myosin.

## "Moonlighting": two distinct roles for the same molecule

The scientists demonstrate a common wisdom known from daily life: it all depends on the partner in crime. Depending on its teammate, UNC-45 can fulfill dual roles when quality-controlling muscle proteins - an ambiguity that in the protein world is referred to as "moonlighting" function. Normally, UNC-45 collaborates with general chaperones to promote myosin maturation. The current study now shows that UNC-45 also has a "dark"



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side. The myosin chaperone can team up with the UFD-2 ubiquitin ligase, a component of the protein degradation system in the cell, marking client proteins for degradation by the proteasome.

Dammermann explains: “Using the nematode worm *C. elegans* as a model system, we show that UFD-2 is not required for the regulation of UNC-45 levels, as had previously been proposed. Instead, the UFD-2 ligase appears to target unfolded peptide stretches of damaged proteins, explaining its vital role in the protein-quality-control system”. Most strikingly, the authors show that the UNC-45 chaperone is not a substrate, but rather a co-factor of UFD-2.

“Without doubt”, Clausen points out, “the discovered death-tagging system, in which a degradation enzyme utilizes a specific molecular chaperone as *Substrate Positioning System*, has exciting implications for how to find and deal with problematic proteins in the cell.” Both UNC-45 and UFD-2 are known to be critical for muscle development and function in mammals. The scientists therefore believe that the described function in the quality-control of muscle proteins may help to understand protein misfolding defects connected with skeletal and cardiac muscle diseases.

**Original Publication**
"UFD-2 Is An Adaptor-Assisted E3 Ligase Targeting Unfolded Proteins."
Nature Communications, 2018.
Doris Hellerschmied, Max Roessler, Anita Lehner, Linn Gazda, Karel Stejskal, Richard Imre, Karl Mechtler, Alexander Dammermann and Tim Clausen.
doi: *not yet available*

**Image Caption**
UNC-45 is a "moonlighting" chaperone fulfilling distinct roles in quality-controlling muscle proteins. As a "good" chaperone (green), it promotes the maturation of myosin molecules, as a "bad" chaperone (orange) it supports the degradation of damaged molecules.

**Background Reading**
Press Release “A molecular assembly line brings muscles into shape”, January 2013.
https://www.imp.ac.at/news/detail/article/press-release-a-molecular-assembly-line-brings-muscles-into-shape/

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**About Vienna BioCenter**
Vienna BioCenter (VBC), home among others to the Max F. Perutz Laboratories (MFPL) and Research Institute of Molecular Pathology (IMP), is a leading life sciences hub in Europe. It offers an extraordinary combination of research, business and education in a single location. About 1,700 employees, 86 research groups, 17 biotech companies, 1,300 students and scientists from 70 nations create a highly dynamic and stimulating environment.
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**About the MFPL**
The Max F. Perutz Laboratories (MFPL) are a center established by the University of Vienna and the Medical University of Vienna to provide an environment for excellent, internationally recognized research and education in the field of Molecular Biology. The MFPL are located at the Vienna BioCenter, and host on average 60 independent research groups, involving more than 500 people from 40 nations. www.mfpl.ac.at

**About the IMP**
The Research Institute of Molecular Pathology (IMP) in Vienna pursues world-class research in basic molecular biology. It is located at the Vienna BioCenter and largely sponsored by Boehringer Ingelheim. With over 200 scientists from 40 countries, the IMP is committed to scientific discovery of fundamental molecular and cellular mechanisms underlying complex biological phenomena. www.imp.ac.at