



Press Release

Tracing down linear ubiquitination

Group including Tübingen researchers devises a method which will help investigate the role of this protein modification in cancers, neurodegenerative diseases, and infections.

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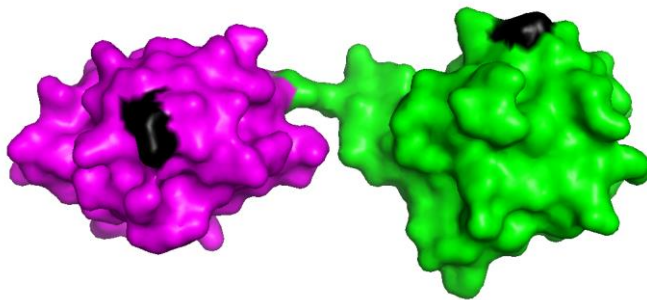
Ubiquitin is a small protein that can be linked to other cellular proteins, thereby controlling and modulating their functions. The attachment occurs in many different forms, either as single molecule or in the form of distinct ubiquitin chains, leading to diverse conformations and varying cellular outcomes. Errors in the ubiquitin system are linked with many diseases, such as cancer, neurodegenerative conditions such as Parkinson's, and also with infections and inflammations. In order to further decipher the role of ubiquitination, researchers at the Goethe University Frankfurt, together with partners from the University of Tübingen in Germany and Queen Mary University as well as Francis Crick Institute from London have now developed a novel technology.

A few years ago, scientists discovered that ubiquitin molecules are not only assembled in a non-linear manner, but also build linear chains, in which the head of one ubiquitin is linked to the tail of another ubiquitin molecule. So far, only two highly specific enzymes are known capable of synthesizing and degrading such linear ubiquitin chains, and both are being extensively studied at the Institute of Biochemistry II at the Goethe University Frankfurt. However, target proteins of linear ubiquitination, as well as their specific cellular functions, have largely remained elusive. The novel technology developed by the team headed by Dr. Koraljka Husnjak from the Goethe University Frankfurt now enables the systematic analysis of linear ubiquitination targets.

"The slow progress in this research area was mainly due to the lack of suitable methods for proteomic analysis of proteins modified with linear ubiquitin chains," explains Koraljka Husnjak. Her team solved the problem by internally modifying the ubiquitin molecule in such a way that it maintains its cellular functions whilst at the same time enabling the enrichment and further analysis of linear ubiquitin targets by mass spectrometry. It is now possible to identify target proteins modified by linear ubiquitin, and to

later detect the exact position within the protein where the linear chain is attached. This highly sensitive approach is an important breakthrough that will improve our understanding of the functions of linear ubiquitination and its role in diseases.

Working with the Proteome Center of the University of Tübingen, Dr. Husnjak has provided the proof of this concept and identified several novel proteins modified by linear ubiquitin chains. “Although a mass spectrometry analysis of enriched target proteins is well established, in this project we had to optimize our protocols and use the latest technology, since the modified proteins were only present in small amounts,” says Proteome Center director, Professor Boris Macek. The researchers discovered essential components of one of the major pro-inflammatory pathways within cells. “Linear ubiquitin chains relay signals that play an important role in the regulation of immune responses, in pathogen defence and immunological disorders. Until now we know very little about how small slips in this system contribute to severe diseases, and how we can manipulate it for therapeutic purposes” Husnjak says. The method has great potential to expand our knowledge of the hidden connections, she adds.



Schematic model of two linearly linked ubiquitin molecules.
The internal tagging site is marked in black. Graphic: Koraljka
Husnjak, generated by PyMOL Software

Publication:

Katarzyna Kliza, Christoph Taumer, Irene Pinzuti, Mirita Franz-Wachtel, Simone Kunzelmann, Benjamin Stieglitz, Boris Macek & Koraljka Husnjak. Internally tagged ubiquitin: a tool to identify linear polyubiquitin-modified proteins by mass spectrometry. *Nature Methods* 2017, doi:10.1038/nmeth.4228

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