

How the cell keeps misdelivered proteins from causing damage in the cell nucleus

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In their research on protein quality control, Heidelberg scientists gained new insights into how the cell keeps proteins misdirected into the cell nucleus from causing damage. Their investigations focussed on a complex apparatus on the inner nuclear membrane that detects and marks the misdelivered proteins. In an international cooperation with researchers from France, Sweden and Canada, the team under the direction of Prof. Dr. Michael Knop at the Center for Molecular Biology of Heidelberg University (ZMBH) demonstrated how the cellular "waste disposal service" is triggered in this process. The results of their research were published in *Nature*.

Cells are quite small, but nevertheless very precisely organised in terms of structure – everything has its place. To find their proper place, proteins bear a type of signal built into their structure. These signals function like addresses, and the intracellular "postal service" delivers them to the correct destination. One of these destinations is the cell nucleus. It contains genomic information – the cell DNA. The DNA has to be read and decoded into new proteins in order for the cell to divide and respond to its environment. The nuclear proteins ensure this process runs correctly. But what happens when proteins accidentally find their way into the cell nucleus even though they do not belong there? "This endangers the reading of the [genomic information](#) and under certain conditions threatens the existence of the entire cell," explains Prof. Knop, who heads the yeast cell and systems biology research group at the ZMBH.

During the course of their investigations, Prof. Knop's research group developed a new method of detecting the misguided proteins and studying how the cell handles them. In collaboration with two research labs, from Rennes and Stockholm, the Heidelberg team at the ZMBH found that the cell contains a complex apparatus on the inner nuclear membrane, a ubiquitin ligase that participates in [protein](#) quality control. The ligase can detect and mark the incorrect proteins. Based on this so-called polyubiquitination, the cell "knows" that this particular protein does not belong in the nucleus and activates cellular waste disposal. A proteasome almost literally swallows and "digests" the marked proteins.

"Until now we assumed that the ubiquitin ligase we studied was linked to a special signal transmission process involved in supplying the cell with amino acids," says Prof. Knop. "We were all the more surprised when our research showed that they actually do not directly perform this function." Instead, the ligase triggers the removal of a protein that would disrupt the amino acid supply should it arrive in the nucleus at the wrong time. The Heidelberg scientist further explains that this "sophisticated control mechanism" also works with various other proteins. If they are not delivered correctly, the ubiquitin ligase sets off the process of removing the misdirected proteins from the [cell nucleus](#) and the [nuclear membrane](#). Prof. Knop: "But this question still remains: How can this [ubiquitin ligase](#) tell whether the proteins have landed in the right or the wrong place?"

More information: A. Khmelinskii, E. Blaszczyk, M. Pantazopoulou, B. Fischer, D.J. Omnus, G. Le Dez, A. Brossard, A. Gunnarsson, J.D. Barry, M. Meurer, D. Kirrmaier, C. Boone, W. Huber, G. Rabut, P.O. Ljungdahl, M. Knop: "Protein quality control at the inner nuclear membrane," *Nature* 516, 410-413 (18 December 2014), [DOI: 10.1038/nature14096](#)

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