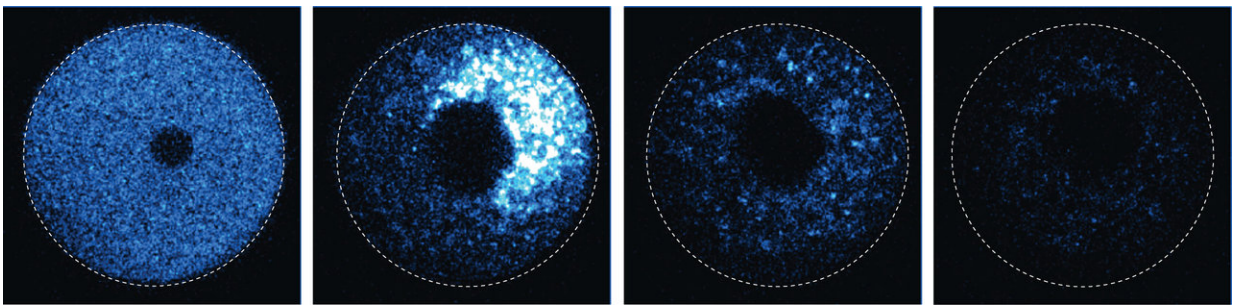


Scientists present a novel method to directly and rapidly destroy any protein in any kind of cell

November 16 2017



Trim-Away directly and rapidly destroys a fluorescent protein (blue) in an egg cell. The images show the cell before introduction of antibodies directed against the protein and 10, 30, and 60 minutes thereafter (from left). The protein amount is reduced by half within nine minutes. Credit: MRC Laboratory of Molecular Biology/ Dean Clift

In our bodies, proteins carry out almost all essential processes, and protein malfunction causes many diseases. To study the function of a protein, researchers remove it from the cell and subsequently analyze the consequences. The two methods they could typically use currently are genome editing by CRISPR/Cas, and RNA interference. They act on the level of DNA or RNA, respectively. However, their influence on protein amounts is indirect and takes time. Scientists from Germany and the UK now present a new method, called Trim-Away, which makes it possible

to directly and quickly deplete a protein from any cell type. As Trim-Away can distinguish between different variants of a protein, it also opens up new venues for the therapy of diseases.

In every living cell, many thousands of proteins are at work. Their repertoire comprises anything from catalyzing biochemical reactions to shaping a cell's surface or sending and receiving signals. Malfunctioning proteins cause various diseases, including cancer and neurodegeneration. Therefore, it is of major interest for molecular biologists to understand how proteins act in their natural environment - the cell.

To investigate a [protein](#)'s function, one of the most important strategies is to remove it from the cell and to study the effects on cellular processes. To deplete a protein, researchers have two main techniques at hand: [genome editing](#) by CRISPR/Cas, and RNA interference (RNAi). By targeting a cell's DNA or RNA, respectively, they efficiently shut down the production of a protein. However, these methods affect protein amounts only indirectly and are not applicable to every type of cell and protein. Until now, there was no universally applicable technique available that could overcome these limitations.

Scientists at the Max Planck Institute for Biophysical Chemistry in Göttingen (Germany) and the MRC Laboratory of Molecular Biology in Cambridge (UK) have now succeeded in developing a novel method, termed Trim-Away. "With Trim-Away, it is possible for the first time to directly target almost any protein in any type of cell," states Melina Schuh, Director at the MPI for Biophysical Chemistry. "It is very simple to use and removes proteins within minutes. This is much faster than anything you can achieve with genome editing or RNAi - with these techniques, it typically takes many hours or even days to deplete a protein. This gives the cell time to develop mechanisms to compensate for the loss, which sometimes masks the actual effects. Moreover, genome editing and RNAi are unsuitable for studying long-lived proteins

or proteins in primary [cells](#). With Trim-Away, we can now close this gap." "We can now take basically any cell from the body and rapidly destroy proteins inside this cell, allowing us to immediately study the effects on cellular processes," adds first author Dean Clift.

Exploiting the skills of a cellular protein

Central to the new technique is a protein that had been discovered in Leo James' lab at the MRC LMB: Trim21. Trim21 recognizes antibodies which enter the cell attached to viruses. It binds to these antibodies, tags the antibody-virus-complex as "garbage", and hands it over to the cell's "garbage chute", the proteasome. Schuh realized that this ability of Trim21 may help her to overcome a problem she had been facing in her research: It had proven exceptionally difficult to deplete specific proteins from egg cells by genome editing or RNAi, as many proteins in these cells are very long lived. Schuh now wanted to use Trim21 as a molecular tool: Together with Clift, she introduced antibodies into the egg cells which were directed against a specific [cellular protein](#), instead of being directed against viruses. Trim21 recognized the antibody and delivered the antibody-bound protein to the proteasome for destruction. Within minutes, the protein disappeared from the cell. This redirection of Trim21 to the protein of interest is the central principle of Trim-Away. "Basically, Nature's toolbox provided us with all the components we needed. The trick was to choose the right ones and to combine them into a system that works for our purpose," Schuh summarizes.

A difficulty was that many cell types do not have sufficient amounts of Trim21 to cope with the task of removing all of the antibody-bound protein. The researchers overcame this problem by delivering additional Trim21 protein into the cell together with the antibody. A small "electric shock" made the cell take up the proteins. "When we first identified Trim21 as an antibody receptor over ten years ago and subsequently showed how efficiently it destroys viral proteins we realized it could be a

powerful tool if retasked against cellular proteins. However, the results are even more remarkable than we could have imagined," James says. This also holds true for Trim-Away's applicability to long-lived proteins and primary cells, which are cells that are taken directly from a tissue.

Another application is in macrophages, a type of white blood cell: "Macrophages are completely inaccessible to genome editing or RNAi because they are particularly good at recognizing foreign DNA and RNA, which are central components of those techniques", James explains. "With Trim-Away it is now possible to deplete proteins from macrophages to study their function in this specific cell type."

Destroying disease-causing protein variants

A feature of Trim-Away is it can take advantage of the remarkable specificity of antibodies, which can not only distinguish between different proteins but also between two different variants of the same protein. Such variants play important roles in many diseases. A prominent example is Huntington's disease, an inheritable neurodegenerative disorder caused by a mutation in one of an individual's two copies of the gene coding for the protein huntingtin. The scientists showed that Trim-Away can be used to remove the disease-causing variant of huntingtin from tissue culture cells while leaving the "normal" variant unscathed. "Of course, getting this to work in cell culture is something completely different than curing the disease," Schuh emphasizes. "A therapeutic application is still far-off. But our work may open up new venues for treating diseases with antibodies in the future."

More information: A method for the acute and rapid degradation of endogenous proteins. *Cell*; 16 November, 2017, [DOI: 10.1016/j.cell.2017.10.033](https://doi.org/10.1016/j.cell.2017.10.033) , [www.cell.com/cell/fulltext/S0092-8674\(17\)31255-2](http://www.cell.com/cell/fulltext/S0092-8674(17)31255-2)

Provided by Max Planck Society

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