A new drug target for treating cancer and viral infections

An international team of researchers led by Konstanz biologists has identified a molecular mechanism that regulates the activity of N-myristoyltransferases. This enzyme plays a role in biological signalling pathways, where dysregulation can lead to serious illness.

Proteins are some of the most important molecular building blocks of life. Every second, a countless number of these macromolecules are produced in the body's cells. All the while, existing proteins interact with each other and are transported within the cell or are metabolized and broken down. If these vital processes fall out of balance, it can have catastrophic consequences for the entire organism and lead to serious illness. Knowing exactly how proteins are produced and regulated as well as how they interact can thus help prevent illnesses from developing or create suitable drugs for treating them.

In their latest study published in Molecular Cell, researchers from the University of Konstanz led by Elke Deuerling and Martin Gamerdinger collaborated with colleagues from ETH Zurich (Switzerland) and the California Institute of Technology (USA) to examine N-myristoyltransferases (NMTs). NMTs are enzymes that ensure the proteins' function by chemically modifying them during their production. The enzymes are also involved in biological signalling pathways, where dysregulation is tied to the development of cancer, for example. In their study, the research team was not only able to decode the details of the molecular mechanism that controls the activity of NMTs at the exit of the body's cellular "protein factories", but they also identified a potential new starting point for developing improved drugs targeting certain types of cancer and viral infections.

More than a direct translation of the gene

In order to understand the results better, we first need to go into a bit of (molecular biological) detail. The first step in protein production is translating the information from our genes into the corresponding sequences of amino acids that make up the proteins. But that is not all. Many of the newly forming proteins are being modified chemically even while they are still leaving their cellular production site – the ribosome – as a growing chain of amino acids. It is only in this modified form that the proteins can then fulfil their biological functions.

One of the most common modifications, which affects more than 40% of all proteins, is the excision of the amino acid methionine from a nascent protein. In a second, relatively rare modification, a saturated fatty acid called myristic acid can be added to the protein. This modification is facilitated by NMTs, the main focus of the recent study. More specifically, the researchers wanted to find out how these enzymes fulfil their function on the ribosome and how this activity is regulated when competing enzymes are present.

A signal motif controls the replacement

Using structural, quantitative and genetic analysis as well as biochemical experiments, the research team discovered that the nascent polypeptide-associated complex (NAC for short) plays a decisive role in the coordination of the activity of human NMTs on the ribosome. Using a kind of "grabbing arm", this protein complex positions both the enzyme that facilitates initiation of methionine excision as well as the NMTs at the ribosomal tunnel. This is the location where the forming proteins leave their production site as growing chains of amino acids.

"Since the docking sites of both enzymes partially overlap on the ribosome, they can't bind to it at the same time. This means, there must be a controlled exchange of the enzymes so that the methionine excision can take place before the NMTs can facilitate the addition of fatty amino acids", Elke Deuerling says. The results of the study show that this exchange always occurs when a nascent protein exhibits a certain signal motif. A binding pocket of the NMTs recognizes and responds to the protein's signal motif – like a lock only turning with the correct key. "However, this only works after methionine has been excised from the nascent protein, thus exposing the motif. When this is not the case, the methionine blocks access to the NMTs' binding pocket. This sequence of exchanging enzymes thus occurs naturally, on its own", Deuerling explains.

A small head start with a big impact

The research team knew from its previous studies that NAC also regulates the activity of other enzymes. This includes enzymes that facilitate the addition of an acetyl group on the remaining end of the nascent protein after methionine excision has taken place – a modification that takes place much more frequently than the addition of myristic acid. Yet why do NMTs not come into conflict with these other enzymes that also bind to the protein complex at the same time? The research team found a surprisingly simple answer to this question: "Our analyses show that the NMTs bind a bit closer to the ribosomal tunnel than the enzymes that catalyze acetylation. This means they have a head start of a few seconds to bind to the nascent proteins", Martin Gamerdinger says. This head start, along with the quick recognition of the target proteins' signal motifs, is enough so that the NMTs can reliably fulfil their function at the ribosomal tunnel even when other enzymes are present at the same time.

The fact that the researchers were able to decode the details of the molecular mechanism that controls the activity of NMTs on the ribosome could be a step towards better drugs to treat diseases where signalling pathways involving NMTs play a crucial role – including certain forms of cancer or various viral infections. "Current drugs that target NMTs, take aim at the enzymes' active centre and reduce their activity in the entire cell – sometimes with toxic effects. In our study, we identified the binding site between NMTs and the 'grabbing arm' of NAC as a possible new starting point for future drugs that could lead to a more selective inhibition of the NMTs with potentially fewer undesired side effects", Gamerdinger says.

Publication:
M. Gamerdinger, B. Echeverria, A. M. Lentzsch, N. Burg, Z. Fan, M. Jaskolowski, A. Scaiola, S. Piening, S. Shan, N. Ban und E. Deuerling (2025) Mechanism of cotranslational protein N-myristoylation in human cells. Molecular Cell; doi: 10.1016/j.molcel.2025.06.015

Key facts:

- An international team of researchers from the University of Konstanz, the California Institute of Technology and ETH Zurich has decoded a molecular mechanism of cotranslational protein modification by human N-myristoyltransferases.
- Participating researchers from the University of Konstanz include Professor Elke Deuerling, Dr Martin Gamerdinger, Nicolas Burg and Selina Piening from the Department of Biology.
- Funding sources: German Research Foundation (DFG), Swiss National Science Foundation (SNF), European Research Council (ERC) and National Institutes of Health (NIH).

Press release

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Further information

- University of Konstanz