New discovery reveals TRP14 is a crucial enzyme for cysteine metabolism, disease resistance

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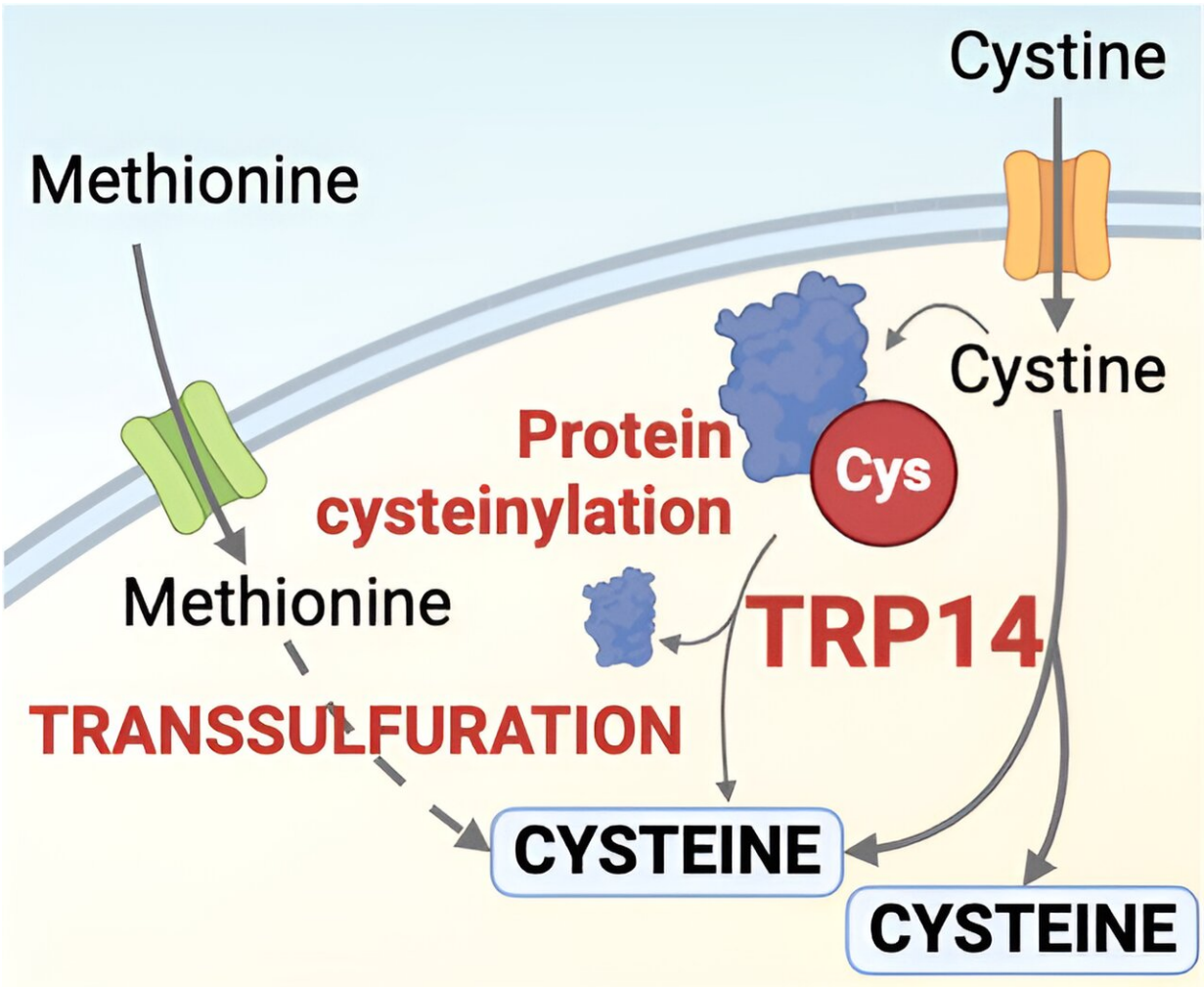

Credit: *The EMBO Journal* (2024). DOI: 10.1038/s44318-024-00117-1

A new study recently published in *The EMBO Journal* by researchers from the Department of Medical Biochemistry and Biophysics at Karolinska Institutet (Sweden) in collaboration with several other research groups has brought the enzyme TRP14 (also called TXNDC17) into the spotlight, discovering its fundamental role in reduction of cystine to form cysteine, which is an essential process for various life forms.

The research team discovered that TRP14 (thioredoxin related protein of 14 kDa, also named TXNDC17 for thioredoxin domain containing 17) is the rate-limiting enzyme for intracellular cystine reduction, a critical step in providing cells with cysteine.

This amino acid is not only essential for protein synthesis but also for production of glutathione, the thiol-containing low molecular weight molecule present at high concentrations in cells providing reducing equivalents, supporting defense against oxidative damage and conjugation of toxic metabolites.

A once-mysterious enzyme gains notoriety

"For a long time, TRP14 didn't have a clear function assigned to it," says Dr. Martí-Andrés, the lead author of the study. "Our study not only clarifies its role in cysteine metabolism but can also help to explain its evolutionary conservation across species.

"I believe that our findings open up new paths for understanding how cells maintain their viability and protect themselves against oxidative stress."

The study also found that cells switch to the transsulfuration pathway when TRP14 is deficient, synthesizing cysteine from methionine and highlighting an adaptive mechanism to ensure cysteine availability.

Linking cysteine metabolism to disease

The findings seem to have broad biomedical implications. Genetic deletion of txndc17 in mice showed protection from inflammation during acute pancreatitis, suggesting a direct link between cysteine metabolism and disease.

"This could provide a foundation for novel strategies to treat diseases related to cysteine metabolism," remarks Prof. Arnér, one of the corresponding authors. "The protective effects observed in mice lacking TRP14 during acute pancreatitis are especially promising, as they could hint at new treatment principles for diseases linked to inflammation."

A multispecies investigation

The team's approach was comprehensive, spanning from worms to humans. "We used both genetic, pathophysiological, and biochemical methods to dissect TRP14's functions," explains Prof. Arnér. "Collectively, our findings in cell cultures and whole organisms like worms and mice were quite revealing."

In C. elegans, the absence of TRP14 affected growth and the ability to handle cellular stress. In mice, the enzyme's role in acute pancreatitis and its regulation of the proteome in the pancreas were evaluated. In human cells, TRP14 was identified as the rate-limiting enzyme involved in cystine reduction. The findings in these three animal species supported each other and gave a more comprehensive view of the cellular functions of TRP14.

Moving into the future

The implications of this research are potentially far-reaching, with

TRP14 posed as a possible therapeutic target for pathophysiological conditions related to cysteine metabolism. The next steps may address a better understanding of TRP14's role in cell death pathways or drug responses, particularly in cancer therapy.

"The next step for us is to explore how we can apply our understanding of TRP14 to modulate the outcome of diverse cancer drug treatments," says Dr. Martí-Andrés. "Our goal is to bring this knowledge from the bench to the bedside, where it could potentially, in the end, make a real difference in patients' lives."

As the research continues, the collaboration between clinicians, computational chemists, and various experts should be crucial in potentially translating these findings into clinical applications.

"As we move forward, we're excited about the possibilities," Prof. Arnér reflects. "Could modulating TRP14 enhance the efficacy of different forms of chemotherapy or combat drug resistance? That's what we aim to find out."

More information: Pablo Martí-Andrés et al, TRP14 is the rate-limiting enzyme for intracellular cystine reduction and regulates proteome cysteinylation, *The EMBO Journal* (2024). DOI: 10.1038/s44318-024-00117-1

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