Medical Xpress

Newly discovered compound blocks signaling pathway of immune response

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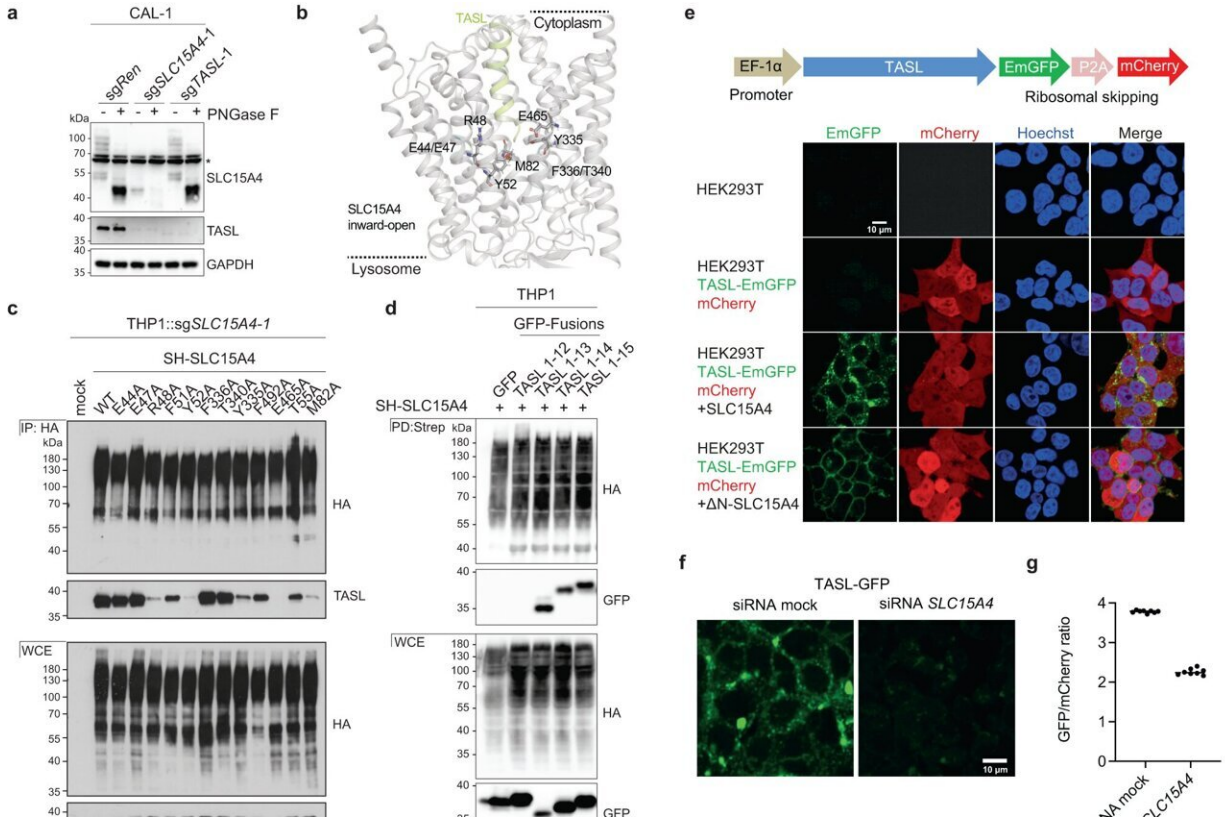

SLC15A4-TASL binding interface and drug screening for TASL stability. Credit: *Nature Communications* (2023). DOI: 10.1038/s41467-023-42070-3

Scientists at CeMM, the Medical University of Vienna, and the University of Lausanne have succeeded for the first time in identifying

and characterizing a new small molecule called "Feeblin," which can inhibit the interaction of the transporter protein SLC15A4 with the adapter protein TASL. Both proteins are part of proinflammatory signaling pathways in the body. In particular, patients with autoimmune diseases such as systemic lupus (SLE) could benefit from inhibiting the signaling pathway.

The study is published in the journal *Nature Communications*.

In autoimmune diseases, inflammation is chronic and leads to severe tissue damage. Several complex molecular pathways are involved in this process, but therapies and drugs targeting specific parts of these pathways remain scarce.

Giulio Superti-Furga, Principal Investigator and Scientific Director of the CeMM Research Center for Molecular Medicine of the Austrian Academy of Sciences, in a 2020 study published in *Nature*, identified that a new adapter protein called TASL plays an essential role in signal transduction from the endo-lysosomal membrane transporter SLC15A4 and Toll-like receptors 7 and 9 -central players in innate immune defense- to the pro-inflammatory transcription factor IRF5 (interferon-regulatory factor 5).

From these findings, the group hypothesized that regulation of SLC15A4 and TASL might be an important aspect of immune signaling that could be therapeutically targeted to improve SLE. Giulio Superti-Furga and his team have now taken an important step towards achieving this goal and embarked on a drug discovery initiative that builds upon the group's expertise in solute carriers and drug discovery.

Discovery of Feeblin

For their study, the scientists developed a new test method that can be

used to specifically monitor the presence of TASL. If TASL is not bound to SLC15A4, it is very unstable. Working with the CeMM Molecular Discovery Platform, Andras Boeszoermenyi, study author and postdoctoral fellow in Superti-Furga's laboratory, identified a small molecule that regulated the stability of TASL protein, and found that this was dependent on the presence of SLC15A4.

The newly discovered compound called Feeblin achieved exactly what the team hypothesized; the compound turned off pro-inflammatory signaling mediated by IRF5.

The compound is named in honor of the Nobel Laureate Bruce Beutler's work on mutations in SLC15A4 signaling; the resultant mutant mouse strains were named "feeble."

"The results confirm the knowledge we have gained since we discovered the SLC15A4-TASL complex and imagined how to target it. This supports our belief in using Feeblin to open up new treatment options for patients with autoimmune diseases," said Manuele Rebsamen, formerly a scientist in the Superti-Furga group at CeMM and now an assistant professor at the University of Lausanne. His team helped to elucidate the compound's action.

In a parallel study, the team of Maojun Yang at Tsinghua University elucidated the cryo-electron microscope structure of SLC15A4 and revealed that SLC15A4 undergoes major conformational changes when binding TASL. In collaboration with the team around Superti-Furga, the Yang laboratory confirmed the interaction of Feeblin with SLC15A4 and clarified its allosteric mechanism.

From drug candidate to new drug

Project leader Giulio Superti-Furga explains, "It's a wonderful story. We

identified this new adapter for innate immunity, TASL, which binds to SLC15A4 and is essential for the IRF5 signaling pathway, and in just three years we were able to identify a drug candidate with a previously completely unknown mechanism of action, an allosteric regulator of protein interactions."

Validation of the compound under physiological conditions was carried out by the team of Leonhard Heinz, group leader at the Department of Rheumatology at the Medical University of Vienna and also a former member of the Superti-Furga team.

"There is a significant unmet medical need in lupus, and it is very gratifying to see how a mechanism we helped CeMM discover is now showing promise in the form of a compound in cells from SLE patients. We hope that this will translate into new treatment options in the coming years," says Leonhard Heinz.

More information: Andras Boeszoermenyi et al, A conformation-locking inhibitor of SLC15A4 with TASL proteostatic anti-inflammatory activity, *Nature Communications* (2023). DOI: 10.1038/s41467-023-42070-3

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