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Newly discovered compound blocks signalling pathway of immune response

The substance opens up enormous potential for the treatment of systemic lupus.

Scientists at CeMM, the Medical University of Vienna and the University of Lausanne 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 signalling pathways in the body. In particular, patients with autoimmune diseases such as systemic lupus (SLE) could benefit from inhibiting the signalling pathway. The study has now been published in Nature Communications.

(Vienna, 24 October 2023) 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 previous 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 defence- to the pro-inflammatory transcription factor IRF5 (interferon-regulatory factor 5). (Heinz et al, Nature 2020). From these findings, the group hypothesized that regulation of SLC15A4 and TASL might be an important aspect of immune signalling 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 signalling mediated

by IRF5. The compound is named in honor of the Nobel Laureate Bruce Beutler's work on mutations in SLC15A4 signalling, 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 signalling 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.

To promote the therapeutic targeting of SLC15A4 towards benefiting patients, CeMM has licensed the exclusive rights to Solgate GmbH, an SLC drug discovery company co-founded by CeMM. Solgate is further advancing these discoveries as part of the SLC15A4-TASL therapeutic program.

Pictures attached: Leonhard Heinz, Giulio Superti-Furga and Manuele Rebsamen, © Bubu Dumjic, CeMM

The Study "A conformation-locking inhibitor of SLC15A4 with TASL proteostatic anti-inflammatory activity" was published in Nature Communications on 20 October 2023, DOI: 10.1038/s41467-023-42070-3

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Giulio Superti-Furga is Scientific Director of CeMM, and Professor of Medical Systems Biology at the Medical University of Vienna. He was trained as a molecular biologist at the University of Zurich, Genentech, IMP Vienna, and EMBL Heidelberg. He obtained four grants from the European Research Council, is a member of five scientific academies, and has published more than 250 papers. CeMM, which he has been directing since 2005, is located in the middle of the large general hospital campus in Vienna, where, together with some 300 scientists and medical doctors, he brings genomic and systems views close to the clinical world with a view to improving medical practice. For CeMM, he promoted a unique mode of super-cooperation, connecting biology with medicine, experiments with computation, discovery with translation, and science with society and the arts. Recent interests include ways to create functional precision medicine approaches and the role of the human transportome in pathophysiology and drug discovery. He is the scientific coordinator of the Innovative Medicine Initiative consortium “RESOLUTE”, dedicated to the deorphanization of SLC transporters.

The **CeMM Research Center for Molecular Medicine of the Austrian Academy of Sciences** is an international, independent and interdisciplinary research institution for molecular medicine under the scientific direction of Giulio Superti-Furga. CeMM is oriented towards medical needs and integrates basic research and clinical expertise to develop innovative diagnostic and therapeutic approaches for precision medicine. Research focuses on cancer, inflammation, metabolic and immune disorders, rare diseases and aging research. The Institute's research building is located on the campus of the Medical University and the Vienna General Hospital.
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