Embargo: Wednesday, 13 May 2020, 17:00 CEST

Missing component of innate immune signaling identified

How cells recognize pathogens and alert the immune system swiftly is a fundamental process of high importance for the survival of any species, including humans. A key role is ascribed to so-called adapters, that equal little molecular platforms inside cells where signals from pathogen detectors are integrated for safety and accuracy and conveyed to lasting signals leading to the activation of the major "red alarm" genes, like interferons. Researchers from the lab of Giulio Superti-Furga at the CeMM Research Center for Molecular Medicine of the Austrian Academy of Sciences in collaboration with Boehringer Ingelheim have identified a new key element of the multi-component machinery that is responsible for sorting out the nature and severity of the pathogen challenge. The new protein, named TASL, is indispensable for the signaling of so-called Toll-like receptors (TLR) in the endosomes leading to activation of the gene-activator IRF5 in certain immune cells. Sensitive "tuning" of the machinery is highly important as too much output causes inflammation also in the absence of the pathogen, as in auto-immune diseases. This particular version of the machinery seems particularly associated with disorders such as systemic lupus erythematosus (SLE). This discovery highlights a potential new target for the development of drugs to treat certain autoimmune diseases and possibly also overreaction to viral and other infections, and has been published in the renowned scientific journal *Nature*.

(Vienna, 13 May 2020) The immune system is the body's natural defense system and is made up of a network of cells, molecules, tissues, and organs working together to protect the body against infectious agents, such as viruses, bacteria or pathogenic fungi. The immune system is equipped with a sophisticated repertoire of sensing mechanisms which detect these pathogens and orchestrate an appropriate immune response. Autoimmune diseases originate when the immune system loses the ability to differentiate between itself and other foreign bodies.

Previous studies revealed that SLC15A4, a member of the body's biggest family of transporter proteins, was known as an essential component required for the correct function of these TLRs. Based on their strong research interests in pathogen-sensing by the innate immune system and the characterization of solute carriers, researchers in the group of CeMM Scientific Director Giulio Superti-Furga set out to investigate how SLC15A4 influences the ability of TLRs to sense pathogens, and, consequently, gain a better understanding on its implication in autoimmune conditions, and in particular SLE.

In their study, first author Leonhard Heinz and the team, including Boehringer Ingelheim researchers in Ridgefield, undertook a precise investigative work, not taking for granted previous findings on SLC15A4 and the connection to this group of specially located TLRs. They painstakingly determined by biochemistry and mass spectrometry the molecular interactions that involved SLC15A4. This led to the identification of an uncharacterized protein CXorf21, belonging to the functionally orphan genes that are merely numbered and assigned to the chromosome of origin. The gene, like *SLC15A4*, had been previously loosely associated with SLE.

The team demonstrated that the interaction between TASL and SLC15A4 was crucial for the localization and function of the TASL protein and could pinpoint the precise involved portions of both proteins. A eureka moment for the understanding of the protein came with the observation that TASL harbors a specific motif essential for the recruitment and activation of IRF5. "*After STING, MAVS and TRIF, the new protein TASL is the fourth key innate immunity adaptor functioning as a platform for the encounter of a kinase and a gene activator of the IRF family*", says Manuele Rebsamen, CeMM senior postdoctoral fellow and project leader of the study.

These findings raise the possibility that interfering pharmacologically with the SLC15A4/TASL complex could allow the regulation of TLR responses and, consequently, modulate inflammatory responses in the body. "*It was clear to us that SLC15A4 plays a key role in endosomal TLR function and is involved in disease, but the underlying mechanism was not understood. These are exactly the exciting scientific questions that we love to address at our institute*", says Giulio Superti-Furga, CeMM Scientific Director and responsible for the study. He adds: "*We are happy that the vision we share with Boehringer Ingelheim regarding Solute Carriers being a group of disease-relevant proteins worthy of investigation was rewarded in this successful and exciting partnership.*"

This study is the result of a collaboration between CeMM and the Drug Concept Discovery Group led by Charles Whitehurst and JangEun Lee in the Immunology and Respiratory Diseases Department at Boehringer Ingelheim (Ridgefield, CT, USA). Researchers also benefited from the support of the Proteomics and Metabolomics (Pro-Met-) facility and the Biomedical Sequencing Facility (BSF) at CeMM.

Attached pictures:

1. Giulio Superti-Furga, Manuele Rebsamen and Leonhard Heinz (© Laura Alvarez / CeMM)
2. Illustration of the role of TASL (in gold and blue) and SLC15A4 (in green) in the initiation of the immune response. After the detection of pathogen-derived genetic material by TLRs (in blue and pink), SLC15A4 and TASL activates IRF5, which moves to the nucleus and activates immune and inflammatory genes (© Ella Maru Studio / CeMM)

The study "TASL is the SLC15A4-associated adaptor for IRF5 activation by TLR7–9" was published in *Nature* on 13 May 2020. DOI: 10.1038/s41586-020-2282-0.

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Funding:
The study was funded with support by the Austrian Academy of Sciences, the European Research Council (ERC) under the European Union's Horizon 2020 research and innovation program (Grant Agreement No. 695214, awarded to Giulio Superti-Furga), the Austrian Science Fund (FWF SFB F4711) and by Boehringer Ingelheim (Research Collaboration Agreement BI-CeMM 238114).

Giulio Superti-Furga is CEO and 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 200 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 180 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 mission of **CeMM Research Center for Molecular Medicine of the Austrian Academy of Sciences** is to achieve maximum scientific innovation in molecular medicine to improve healthcare. At CeMM, an international and creative team of scientists and medical doctors pursues free-minded basic life science research in a large and vibrant hospital environment of outstanding medical tradition and practice. CeMM's research is based on post-genomic technologies and focuses on societally important diseases, such as immune disorders and infections, cancer and metabolic disorders. CeMM operates in a unique mode of super-cooperation, connecting biology with medicine, experiments with computation, discovery with translation, and science with society and the arts. The goal of CeMM is to pioneer the science that nurtures the precise, personalized, predictive and preventive medicine of the future. CeMM trains a modern blend of biomedical scientists and is located at the campus of the General Hospital and the Medical University of Vienna. www.cemm.oeaw.ac.at

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