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CHILDREN'S CANCER RESEARCH INSTITUTE

LUDWIG BOLTZMANN INSTITUTE
Rare and Undiagnosed Diseases

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Research Center for Molecular Medicine of the Austrian Academy of Sciences

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Press Release

From the god of sun to immunodeficiency: international research team identifies new rare disease affecting hematopoiesis and immunity

A disturbed Helios-dependent epigenetic regulation mechanism causes T and B cell defects in an inborn immune disease.

Vienna, 26.11.2021**. Together with international collaborators, scientists at the St. Anna Children's Cancer Research Institute discover a new inborn error of hematopoiesis and immunity, caused by an inherited genetic defect of the transcription factor Helios. In their research project, the team was able to define previously unknown roles of Helios in immune activation and homeostasis. The study is now published in the high-ranked scientific journal *Science Immunology*.**

The immune system is one of the most complex and fascinating networks in the human body. Comprised of cellular and humoral components, it not only protects us against external intruders such as viruses or bacteria, but also plays a fundamental role in detecting aberrant cells developing into cancer cells. The development and function of immune cells is tightly regulated by the temporal and spatial control of gene expression. This is mainly achieved by so-called transcription factors – special proteins that bind to regulatory sequences of genes and turn their expression on or off. In addition, there is another level of control: so-termed epigenetic remodelers control whether certain regions of the DNA are active or inactive, and thereby determine if transcription factors can bind to their target sequences or not.

The Ikaros family of zinc finger transcription factors represents a group of proteins that have been shown to play a central role in hematopoiesis and immune cell development and function. It is comprised of five known members: Ikaros, Helios, Aiolos, Eos and Pegasus. The roles of some of these transcription factors, in particular Ikaros, have been studied in detail with their aberrant function more recently being linked to the development of leukemia. The precise function of Helios, however, was only partially known.

Helios – a key player in T cell development and function

In a joint effort, the team of Kaan Boztug at the St. Anna Children's Cancer Research Institute (CCRI) and the Ludwig Boltzmann Institute for Rare and Undiagnosed Diseases (LBI-RUD), in close partnership with the Medical University of Vienna and the CeMM Research Center for Molecular Medicine of the Austrian Academy of Sciences, investigated a patient with an unknown defect of immunity and hematopoiesis, who had been suffering from recurrent respiratory infections and hypogammaglobulinemia since birth. In their study, the scientists identified an inherited biallelic mutation – i.e., a mutation carried on both copies of the gene – in the gene encoding Helios, a transcription factor named after the Greek god of the sun.

Helios is predominantly expressed in developing thymocytes, activated T cells and regulatory T cells – a subset of T cells that play a role in controlling the immune activation response. In regulatory T cells, Helios is known to be important for regulating the transcription of several genes. Although Helios has already been studied in mice, its role in human immune homeostasis and T cell development remains unclear.

Biallelic mutation of Helios causes epigenetic defect and immunodeficiency

At a molecular level, the defect resulting from the biallelic mutation in *IKZF*2 did not affect DNA binding or dimerization of Helios but had other consequences. “We found that the mutation affecting Helios leads to disruptions in the interaction with other proteins, including epigenetic remodelers, thereby compromising the precise control of activation of genes”, explains Tala Shahin, first author of the study and PhD student in Kaan Boztug’s research group.

The scientists used single-cell transcriptomics and *in vitro* functional assays to further study the effects of the mutation at a cellular level. They were able to show that the defect in Helios had detrimental effects on immunity: While $CD8^+$ T cells carrying the mutation shifted towards a pro-inflammatory, effector-like status, patient $CD4^+$ cells showed impaired activation. Additionally, a B cell defect was detected: there was a B cell loss over time, and peripheral memory B cells and plasmablasts were reduced, while transitional B cells were increased.

Impact on future research and treatment

As the proper activation of conventional T cells and the presence of B cells is important for mounting an immune activation response against infections and (pre)cancerous cells, these findings are of great interest. The results do not only characterize a novel inborn error of immunity, but also further define and expand our understanding of the role of Helios in immune activation and homeostasis. The Helios-dependent epigenetic regulation defect represents a novel molecular mechanism leading up to the severe loss of balance (homeostasis) of immunity as seen in the disease.

“This study represents a significant advance in our understanding of the precise role Helios plays in hematopoiesis and immunity and it will help future efforts to potentially target these regulators in both immunodeficiency and malignancy,” summarizes Kaan Boztug, senior and corresponding author of the study and scientific director of CCRI.

Collaboration

This work was possible thanks to a scientific collaboration of St. Anna Children’s Cancer Research Institute (CCRI), with the Ludwig Boltzmann Institute for Rare and Undiagnosed Diseases (LBI-RUD), the CeMM Research Center for Molecular Medicine of the Austrian Academy of Sciences, and the Department of Pediatrics and Adolescent Medicine, Medical University of Vienna in Austria, together with international partners including the Immunology Service, Department of Laboratory Medicine, Clinical Center, National Institutes of Health, Maryland, USA, the Institute of Biotechnology, Helsinki Institute of Life Science, Proteomics Unit, University of Helsinki, Finland, the Research Center for Immunodeficiencies, Children's Medical Center and the Department of Immunology, School of Medicine, Tehran University of Medical Sciences, Iran, the Network of Immunity in Infection, Malignancy and Autoimmunity (NIIMA), Universal Scientific Education and Research Network (USERN), Iran.

Publication:

Germline biallelic mutation affecting the transcription factor Helios causes pleiotropic defects of immunity

Tala Shahin, Hye Sun Kuehn, Mohamed R. Shoeb, Lisa Gawriyski, Sarah Giuliani, Peter Repiscak, Birgit Hoeger, Özlem Yüce Petronczki, Sevgi Köstel Bal, Samaneh Zoghi, Jasmin Dmytrus, Davide Seruggia, Irinka Castanon, Nima Rezaei, Markku Varjosalo, Florian Halbritter, Sergio Rosenzweig, Kaan Boztug*

* Corresponding author: Kaan Boztug
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Photo:
Tala Shahin, PhD, Assoc.-Prof. Kaan Boztug, MD

About St. Anna Children's Cancer Research Institute, CCRI

CCRI is an internationally renowned multidisciplinary research institution with the aim to develop and optimize diagnostic, prognostic, and therapeutic strategies for the treatment of children and adolescents with cancer. To achieve this goal, it combines basic research with translational and clinical research and focus on the specific characteristics of childhood tumor diseases in order to provide young patients with the best possible and most innovative therapies. Dedicated research groups in the fields of tumor genomics and epigenomics, immunology, molecular biology, cell biology, bioinformatics and clinical research are working together to harmonize scientific findings with the clinical needs of physicians to ultimately improve the wellbeing of our patients. www.ccri.at

About Ludwig Boltzmann Institute for Rare and Undiagnosed Diseases (LBI-RUD)

LBI-RUD was founded in April 2016 in a joint effort of Ludwig Boltzmann Gesellschaft, CeMM Research Center for Molecular Medicine of the Austrian Academy of Sciences, Medical University of Vienna, and St. Anna Children's Cancer Research Institute. The three founding partner institutions, and CeRUD Vienna Center for Rare and Undiagnosed Diseases, constitute LBI-RUD's most important collaboration partners.

Research at LBI-RUD focuses on the deciphering of rare immunological, hematopoietic, nervous, dermal, gastro-intestinal, and hepatic diseases. Those studies provide unique insights into human biology and are the basis for the development of tailored therapeutic concepts in the sense of the personalized medicine of the future.

The mission of LBI-RUD is – together with its partner institutions – to sustainably develop and maintain research infrastructure integrating scientific, societal, ethical, and economical aspects of rare diseases. www.rare-diseases.at

About CeMM Research Center for Molecular Medicine of the Austrian Academy of Sciences

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, and rare diseases. The Institute's research building is located on the campus of the Medical University and the Vienna General Hospital. www.cemm.at

About Medical University of Vienna (MedUni Vienna)

MedUni Vienna is one of the most traditional medical education and research facilities in Europe. With almost 8,000 students, it is currently the largest medical training center in the German-speaking countries. With its 30 university hospitals and two clinical institutes, 12 medical theory centers and numerous highly specialized laboratories, it is also one of Europe's leading research institutions in the biomedical sector. www.meduniwien.ac.at

Editing:

Barbara Brunmair, Robina Kuntara
St. Anna Children's Cancer Research Institute

Further Information:

Lisa Huto
St. Anna Children's Cancer Research Institute
1090 Wien, Zimmermannplatz 10
P: +43 1 40470 - 4006
E: lisa.huto@ccri.at.at