New factor in the development of childhood lymphoma

The immune system is highly complex and a detailed understanding of many underlying mechanisms is still lacking. Only the precise interaction of a variety of factors guarantees a reliable and correct immune response in a healthy body. Dysregulated immune responses are a major cause of a variety of diseases, including cancer, autoimmunity, and immune deficiency.

A study recently published in the renowned journal Blood, led by Kaan Boztug, Scientific Director of the St. Anna Children’s Cancer Research Institute, the Ludwig Boltzmann Institute for Rare and Undiagnosed Diseases (LBI-RUD), Adjunct Principal Investigator at the CeMM Research Center for Molecular Medicine of the Austrian Academy of Sciences and Associate Professor at the Medical University of Vienna, together with scientists from Israel, Germany, Turkey, Colombia, Argentina and the USA, investigated four patients from independent families with malignancy, autoimmunity and immunodeficiency. All four patients had a germline mutation in the gene encoding CD137, which led to a dysfunction of the co-receptor protein CD137. This dysfunction impaired crucial factors for immune surveillance, in particular for the prevention of viral infections and the development of lymphoma associated with Epstein-Barr virus (EBV) infection. "Not only did we discover a new tumor predisposition syndrome particularly for childhood lymphomas in this study, we also learned more about the basic function of CD137 in the immune system," says Kaan Boztug, joint corresponding and last author, together with colleagues Raz Somech from the Chaim Sheba Medical Center in Tel Aviv and Christoph Klein from the Dr. von Hauner Children's Hospital of the LMU Munich.

The disease mechanism in detail:

Co-receptors play a fundamental role in regulating and fine-tuning the signal strength of so-called antigen receptors, which help immune cells to recognize foreign bodies. An impaired function of these immune receptors can lead to an increased susceptibility to infections, autoimmune disorders and cancer. CD137 or 4-1BB is a co-stimulatory molecule which is frequently expressed on activated T cells to ensure a proper T cell function. Recent studies have also investigated CD137 as an attractive target for cancer immunotherapy.

EBV is a herpes virus that infects more than 90% of all people and remains latent in the body for life. In individuals with impaired T-cell function, EBV infection can lead to lymphoproliferative disorders all the way to malignant lymphomas. Co-first author Marini Thian states: "For me as a biologist and PhD student in the lab, it's exciting to see how we bridge the gap from deep genetic analysis to understanding the disrupted immune response, in particular to EBV virus infection."

Diseases caused by a defect in a single gene, e.g. for CD137, provide unique opportunities to investigate the consequences of such errors for the whole organism. Thus, we can gain mechanistic insights into the signal pathways necessary for a robust immune surveillance of the host against EBV.

In summary, this study demonstrates the key role of CD137 in the control of EBV virus by the immune system. If the body fails to keep the virus under control, it can lead to the development of lymphomas. In the future, the scientists want to use their findings to develop and use targeted therapeutics that can stop this dangerous disease process.

Funding:
The study was funded by the European Research Council (ERC, Consolidator Grant 820074 “iDysChart” and ERC Advanced Grant), the Jeffrey Model Foundation (JMF), the Care for Rare Foundation, the German Research Foundation (DFG, Gottfried-Wilhelm-Leibniz Program, CRC1054) and the Else Kröner-Fresenius Foundation (Research College Rare Diseases of the Immune System). Marini Thian was further supported by a doctoral fellowship from the Austrian Science Fund (FWF CCHD) and a DOC fellowship (ÖAW 25225) from the Austrian Academy of Sciences.

About Kaan Boztug
Kaan Boztug studied human medicine in Düsseldorf, Freiburg and London, after which he graduated with Ian Campbell at the Scripps Research Institute (La Jolla, US). He completed his clinical training and postgraduate research with Christoph Klein at Hannover Medical School prior to his first appointment as an independent group leader in 2011 at the CeMM Research Center for Molecular Medicine of the Austrian Academy of Sciences. Since 2011, he holds a dual appointment as Associate Professor at the Department of Paediatrics and Adolescent Medicine at the Medical University of Vienna. Since 2016, Kaan Boztug is director of the Ludwig Boltzmann Institute for Rare and Undiagnosed Diseases. He is furthermore director of the CeRUD Vienna Center for Rare and Undiagnosed Diseases as well as the Jeffrey Modell Diagnostic and Research Center Vienna at the Medical University of Vienna and the St. Anna Childrens’ Hospital.

St. Anna Children’s Cancer Research Institute (CCRI)
The St. Anna Children’s Cancer Research Institute (CCRI), founded in 1988, develops and optimizes diagnostic, prognostic, and therapeutic strategies for the treatment of children and adolescents with cancer by combining basic research with translational and clinical research. The focus is on the specific characteristics of childhood tumour diseases in order to provide young patients with the best possible and most innovative therapies. Around 120 scientists and students are involved in ongoing research projects at CCRI. Dedicated research groups in
the fields of tumour genomics and epigenomics, immunology, molecular biology, cell biology, bioinformatics and clinical research are working together to harmonize scientific experimental findings with the clinical needs of physicians.

Every year, about 250 children and adolescents in Austria are diagnosed with cancer. Thanks to interdisciplinary research work on an international level, 70 to 80% of the children affected can already be cured.

https://science.ccri.at

The Ludwig Boltzmann Institute for Rare and Undiagnosed Diseases (LBI-RUD) under the leadership of Kaan Boztug was launched by the Ludwig Boltzmann Gesellschaft in April 2016 together with its partner institutions CeMM, the Research Center for Molecular Medicine of the Austrian Academy of Sciences, the Medical University of Vienna, and the Children’s Cancer Research Institute (CCRI) of the St. Anna Children's Hospital Vienna.

http://rud.lbg.ac.at/

The CeMM Research Center for Molecular Medicine of the Austrian Academy of Sciences seeks 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.

http://www.cemm.at

Medical University of Vienna

Medical University of 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 centre in the German-speaking countries. With 5,500 employees, 26 departments and three clinical institutes, 12 medical theory centres and numerous highly specialised laboratories, it is also one of Europe's leading research establishments in the biomedical sector.

https://www.meduniwien.ac.at/web/en
For further information please contact:

Lisa Huto
Head of PR & Marketing,
Science Communication and Donations

St. Anna Children’s Cancer Research Institute (CCRI)
Zimmermannplatz 10, 1090 Vienna, Austria
Tel.: +43 1 40470-4006
Cell: +43 664 8476687
E-Mail: lisa.huto@ccri.at