Press Release

New Discovery: Genetic Defect in Secondary Immune Organs Causes Life-Threatening Infections in Children

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(Vienna, November 22, 2024) **Secondary lymphoid organs are specialized regions in the body where immune cells multiply and develop to respond to new pathogens like viruses and bacteria. An international team led by Kaan Boztug, MD has identified a completely new form of a rare disease that affects these organs, shedding light on the significance of these structures for the human immune system. A genetic defect – discovered by the researchers – leads to either the absence or significant dysfunction of these organs in several children. As a result, affected children suffer from recurring, life-threatening infections. The findings, published in *Science Immunology*, could significantly improve treatment options for patients with similar diseases.**

Over the past years, the research group led by Univ.-Prof. Dr. Kaan Boztug has identified several rare genetic immune system disorders, characterizing the functions of key components of the immune system. Their work has also provided substantial new insights into the connection between immune deficiencies and the susceptibility to developing childhood tumors. Boztug, an expert in rare diseases, is the scientific director of the St. Anna Children's Cancer Research Institute (CCRI), and conducts research at the Medical University of Vienna (MedUni Vienna) and CeMM, the Research Center for Molecular Medicine of the Austrian Academy of Sciences.

A New Type of Disease

The current study, conducted in collaboration with leading centers in Istanbul and Ankara, describes a novel rare disease that is remarkable in multiple ways. "In the DNA of the affected individuals, we identified mutations in the LTβR gene, which encodes the lymphotoxin-beta receptor (LTβR)," explains Dr. Bernhard Ransmayr, the study's first author and a PhD student in Kaan Boztug's laboratory. The patients lack all lymph nodes, including tonsils, and have a non-functional spleen. However, these secondary lymphoid organs are essential for activating the immune system and facilitating the differentiation, proliferation, and maturation of specialized immune cells. Consequently, these patients are unable to produce a sufficient quantity of protective antibodies. Interestingly, the immune cells themselves are not directly affected by the genetic defect but are instead indirectly impaired due to the absence of the supportive environment provided by the secondary lymphoid organs. This was demonstrated by the team through laboratory experiments that mimicked the structure and function of lymph nodes. In this artificial environment, cells from the patients could develop normally into antibody-producing immune cells (B cells). This finding highlights the fundamental importance of interactions between surrounding cells (stromal cells) and immune cells for establishing an effective immune defense.

From Immune Genetics to Precision Medicine

Boztug emphasizes, "The discovery of the LTβR defect marks a significant advancement in our understanding of the architecture of immune organs and their role in human health. It illustrates how basic research can directly contribute to improving the lives of patients with rare diseases. Patients with LTβR mutations benefit from specialized care at immunodeficiency centers and corresponding medical support for their immune defense. A key insight from this research is that bone marrow transplantation—an established treatment for other immune deficiencies—would not succeed here, as the defect lies not within the immune cells themselves but in the

structural components of lymphoid organs." Future research aims to further decode the molecular mechanisms of LTβR within the human immune system and to develop potential therapeutic options.

Publication

LTβR deficiency causes lymph node aplasia and impaired B-cell differentiation

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About Kaan Boztug

Kaan Boztug, MD, is the Scientific Director of the St. Anna Children's Cancer Research Institute, Senior Physician in Pediatric Hematology and Oncology, Head of the Immunology Department at the St. Anna Children's Hospital, and Professor in the Department of Pediatrics and Adolescent Medicine at the Medical University of Vienna. He is an internationally recognized expert in rare diseases of blood formation and the immune system, and a two-time recipient of the ERC Grant (ERC Starting and Consolidator Grant). He has been honored with numerous awards for his scientific work. Under his leadership, scientific papers have been published in top journals such as the *New England Journal of Medicine*, *Blood*, *Nature Immunology*, and *Nature Genetics*. Kaan Boztug's research group focuses on inherited bone marrow failure syndromes, immune deficiencies, and inherited predisposition to childhood tumors. Their aim is to understand fundamental mechanisms of immune surveillance that are relevant to pediatric oncology and immunotherapy approaches.

After studying medicine in Düsseldorf, Freiburg, and London, and completing his doctoral studies at the Scripps Research Institute in La Jolla, USA, Kaan Boztug underwent clinical training and postdoctoral research at the Hannover Medical School. Since 2011, he has been working as a physician and researcher at the Medical University of Vienna in the Department of Pediatrics and Adolescent Medicine, as well as an Adjunct Principal Investigator at the CeMM Research Center for Molecular Medicine of the Austrian Academy of Sciences. In addition, Kaan Boztug is also the Director of the CeRUD Vienna Center for Rare and Undiagnosed Diseases at the Medical University of Vienna and has been the Director of the Ludwig Boltzmann Institute for Rare and Undiagnosed Diseases.

About the St. Anna Children's Cancer Research Institute

The St. Anna Children's Cancer Research Institute (CCRI) is an international and interdisciplinary research institution dedicated to advancing diagnostic, prognostic, and therapeutic strategies for the treatment of children and adolescents with cancer through innovative research. Incorporating the specific characteristics of childhood tumor diseases, dedicated research groups collaborate in the fields of tumor genomics and epigenomics, immunology, molecular biology, cell biology, bioinformatics, and clinical research. Their aim is to bridge the latest scientific and experimental knowledge with the clinical needs of physicians in order to significantly improve the well-being of young patients. For more information, visit www.ccri.at or www.kinderkrebsforschung.at.

About the Medical University of Vienna

The Medical University of Vienna (MedUni Vienna) is one of the most prestigious institutions for medical education and research in Europe. With approximately 8,000 students, it is the largest medical training institution

in the German-speaking region. With 6,000 employees, 30 university clinics, two clinical institutes, 13 medical-theoretical centers, and numerous highly specialized laboratories, it is considered one of the most significant biomedical research institutions in Europe. The MedUni Vienna also houses the Josephinum, a museum of medical history. For more information, visit www.meduniwien.ac.at.

About the CeMM Research Center for Molecular Medicine of the Austrian Academy of Sciences (ÖAW)
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 leadership of Dr. Giulio Superti-Furga. CeMM is guided by medical needs and integrates basic research with clinical expertise to develop innovative diagnostic and therapeutic approaches for precision medicine. The research focuses on cancer, inflammation, metabolic and immune disorders, rare diseases, and cellular aging processes. The research facility is located on the campus of the Medical University of Vienna and the General Hospital Vienna. For more information, visit www.cemm.at

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