St. Anna Kinderkrebsforschung
CHILDREN'S CANCER RESEARCH INSTITUTE

PARIS LODRON UNIVERSITÄT SALZBURG

Press Release

Childhood cancer: Vulnerability in the immune response against metastases discovered

(Vienna, 26.6.2023) **Scientists led by Sabine Taschner-Mandl, PhD, St. Anna Children's Cancer Research Institute, and Nikolaus Fortelny, PhD, Paris Lodron University of Salzburg, are the first to analyze bone marrow metastases from childhood tumors of the nervous system using modern single-cell sequencing analysis. It turns out that cancer cells prevent cells in their environment from fighting the tumor – a process that could be reversed with medication. The findings were published in the renowned journal *Nature Communications*.**

Neuroblastoma is the most common solid tumor in infants and young children. Despite constantly improving therapy options, more than half of the patients with a very aggressive form (high-risk neuroblastoma) still suffer from relapses. “We specifically studied bone marrow metastases because recurrences often originate there. The tumor cells seem to manipulate their environment so that it supports their growth instead of fighting them,” explains Sabine Taschner-Mandl, Head of the Tumor Biology Group at St. Anna Children's Cancer Research Institute (St. Anna CCRI).

How cancer cells manipulate their neighboring cells

The recently published study therefore examined the cell architecture and cell-cell communication of neuroblastoma metastases of two major genetic subtypes (*MYCN* amplification or *ATRX* mutations) and those without such changes using single-cell transcriptomics and epigenomics. “Until now, only primary tumors have been studied in such detail, but not neuroblastoma metastases,“ says Irfete Fetahu, PhD, co-first author as well as co-corresponding author of the study and postdoc in the Tumor Biology Group.

The team examined the interaction of metastatic tumor cells with healthy bone marrow cells in more detail. “We developed algorithms that enabled us to analyze different cells in the bone marrow as well as to model their interactions,” emphasizes Fortelny, head of the Computational Systems Biology Group, Paris Lodron University of Salzburg. "Our analysis has shown that certain cells, so-called monocytes, react to unwanted invaders. In the course of this, they foster growth processes and release cytokines that stimulate tumor growth,” explains Fetahu. Interestingly, investigations at the epigenetic level showed that although monocytes in the tumor microenvironment are activated to attack cancer cells, they are unable to respond appropriately to these signals. “These monocytes receive contradictory messages. As a result, they are no longer able to fight the tumor,“ Fetahu explains the dilemma.

Interfere with pathological immune cell states

The communication between neuroblastoma cells and bone marrow or monocytes is to a large extent regulated by the proteins MK (midkine), MIF (macrophage migration inhibitory factor) and associated molecules. Signaling pathways controlled by these proteins are upregulated in immune cells. “Drugs targeting MK and MIF disrupt this pathological interaction and are currently under investigation. Through selective inhibition, it could be possible to return these pathologically altered monocytes to their original state,“ says Taschner-Mandl.

Metastases act differently

The scientists also found that cellular plasticity, i.e. the ability of cells to change depending on environmental influences, is retained during metastasis. In addition, the gene expression of metastatic tumor cells depends on the neuroblastoma genetic subtype. For example, neuroblastoma cells that have a *MYCN* amplification only

slightly change when they metastasize from the primary tumor to the bone marrow, whereas tumor cells with *ATRX* mutation show pronounced differences upon metastasis. "The genetics of the tumor lead to characteristic signals and thus very specific changes in the microenvironment of the bone marrow, which is expressed in individual signatures," says Taschner-Mandl. "This could explain why neuroblastoma patients with *ATRX* mutations often respond poorly to therapy."

Photo
Dr. Sabine Taschner-Mandl, Dr. Irfete Fetahu
Credit: St. Anna Kinderkrebsforschung
Dr. Wolfgang Esser-Skala, Dr. Nikolaus Fortelny, Dr. Rohit Dnyansagar
Credit: Simon Haigermoser, Paris Lodron Universität Salzburg

Publication
Single-cell transcriptomics and epigenomics unravel the role of monocytes in neuroblastoma bone marrow metastasis
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About Sabine Taschner-Mandl, PhD
Sabine Taschner-Mandl, PhD has been head of the Tumor Biology group at St. Anna Children's Cancer Research since 2018, where she has been working as a scientist since 2008. In addition, she is a lecturer at the Medical University of Vienna and Vienna University of Technology. Dr. Taschner-Mandl completed her studies of biology at the University of Vienna with a diploma thesis in vaccine development at Intercell. This was followed by a PhD thesis and a post-doctoral position at the Institute of Immunology at the Medical University of Vienna. Besides her research work at St. Anna Children's Cancer Research Institute, Dr. Taschner-Mandl was a visiting scientist at Significo and the University of Helsinki as part of the EC-FP7 Marie Curie Program.
For her research, Dr. Taschner-Mandl has received numerous grants, among others from the Austrian Research Promotion Agency, the Vienna Science, Research and Technology Fund, and the European Commission's ERA-NET initiative.

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

About Dr. Nikolaus Fortelny (PhD)
Dr. Fortelny is assistant professor at the Department of Biosciences and Medical Biology at the Paris Lodron University of Salzburg. In his work, he is focused on the analysis and modeling of complex biological processes using methods from artificial intelligence and statistics. Dr. Fortelny studied molecular biology in Vienna and then bioinformatics in Geneva. He completed his dissertation in Vancouver, Canada. Dr. Fortelny then joined the Center for Molecular Medicine (CeMM) in Vienna, where he developed deep learning algorithms that simulate biological networks. His research group at the Paris Lodron University of Salzburg further develops models of biological processes, focusing on the robust and interpretable applications of complex algorithms.

About the Paris Lodron University of Salzburg
The Paris Lodron University Salzburg (PLUS, www.plus.ac.at) has six faculties with 34 departments and around 90 curricula in digital and analytical subjects, natural and life sciences, social sciences, cultural studies, theology, law and economics. Founded in 1622 and rebuilt in 1962, PLUS is now the largest educational and research institution in Salzburg. Research is driven by three focus research areas and interactions between scientists from all disciplines promote interdisciplinary cooperation. In biomedical research, research at the PLUS focuses on tumor biology, in particular in the interactions of the immune system with cancer.

Further Information:

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