



The two faces of neutrophils in tumor biology

(Vienna, 26.3.2024) **Neutrophils are the most common white blood cells and an important component of the immune system. They help in the defense against pathogens and in the healing of injuries. They are also suspected to play a role in tumor development. A team from St. Anna Children's Cancer Research Institute (CCRI) has now compared the maturation process of neutrophils in several organisms to unravel developmental similarities. The findings help to better understand the role of neutrophil maturation in tumor development. The study was recently published in the renowned journal *Nature Communications*.**

Recently, the pro- and anti-tumor roles of neutrophils, cells of the innate immune system, have become a focus of cancer research. There appear to be subpopulations of these cells that interact with tumors in very different ways. Scientists suspect that the function in the tumor context is related to the degree of maturity of these immune cells. "We want to investigate this in the zebrafish model in the long term," says Martin Distel, PhD, head of the Zebrafish platform Austria for preclinical drug screening (ZANDR) at St. Anna Children's Cancer Research Institute (CCRI) and one of the last authors of the recently published study.

Stefanie Kirchberger, PhD, one of the first authors of the paper, investigated the maturation of neutrophil immune cells in zebrafish larvae. She used two different fluorescent markers for this purpose. While one marker lights up in all neutrophils, the second marker only shows mature neutrophils. The team was therefore able to draw conclusions about the degree of maturity of the observed cells, she explains. When these mature neutrophils encounter mutated cells, they enter into closer contact with them than immature neutrophils.

Comparison with human immune cells

By analyzing the genes expressed during neutrophil maturation in zebrafish and comparing them with data from other models from various previously published studies, the group of Principal Investigator Florian Halbritter, PhD, was able to summarize and compare gene activity patterns.

Mohamed Shoeb, PhD student in this group: "The activity patterns we identified represent groups of genes that are activated at certain stages of neutrophil development in our zebrafish model. To our surprise, we found that the same patterns are also common during neutrophil development in humans and mice." Halbritter adds: "This enabled us to assign the developmental stages of neutrophils in the three organisms and to better understand the biological process."

Bone marrow of neuroblastoma patients

In this phase, the researchers combined their data with analyses of the bone marrow of neuroblastoma patients. These data were contributed by the tumor biology group of Sabine Taschner-Mandl, PhD, at the St. Anna Children's Cancer Research Institute. The samples from bone marrow biopsies of neuroblastoma patients with infiltrating tumor cells were compared with samples without tumor cells. This made it possible to determine the degree of maturity of the neutrophils in the vicinity of the tumor cells by using the newly defined maturity signature. The effects of differently mature neutrophils on tumorigenesis can now be further investigated and results can be more easily transferred from model organisms to humans on the basis of the knowledge gained in this study.



Publication

Kirchberger S, Shoeb MR, Lazic D, Wenninger-Weinzierl A, Fischer K, Shaw LE, Nogueira F, Rifatbegovic F, Bozsaky E, Ladenstein R, Bodenmiller B, Lion T, Traver D, Farlik M, Schöfer C, Taschner-Mandl S, Halbritter F, Distel M. Comparative transcriptomics coupled to developmental grading via transgenic zebrafish reporter strains identifies conserved features in neutrophil maturation. *Nat Commun.* 2024 Feb 27;15(1):1792.
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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 Florian Halbritter

Florian Halbritter, PhD studied Cognitive Science at the University of Osnabrück and completed his PhD in Stem Cell Bioinformatics under the supervision of Simon Tomlinson and Ian Chambers at the MRC Centre for Regenerative Medicine at the University of Edinburgh. After graduating, he joined Christoph Bock's lab at the CeMM Research Center for Molecular Medicine. Since 2018, he has been a Principal Investigator at St. Anna Children's Cancer Research Institute. As a computational biologist, Florian Halbritter investigates the epigenome of stem cells, immune cells and cancer using functional genomics technologies. The aim of his research group is to better understand the earliest steps in the development of tumors and thus to pave the way for new diagnostic and therapeutic approaches.

About Martin Distel

Martin Distel, PhD, graduated in Molecular Biotechnology from the Technical University of Munich, Germany, and Lund University, Sweden. He did his PhD at Helmholtz Centre um Munich under the supervision of Reinhard Köster and developed genetic gene expression tools to study the development of the cerebellum in zebrafish. He also worked with Daniel Razansky at Helmholtz Centre Munich to develop opto-acoustic imaging for zebrafish. As a postdoctoral researcher, he worked in David Traver's lab at the University of California, San Diego, on zebrafish hematopoiesis. In 2014, Distel joined St. Anna's Children's Cancer Research Institute, where he established a zebrafish laboratory and facility. Since 2017, he has also been the head of the zebrafish platform Austria for preclinical drug screening at St. Anna Children's Cancer Research Institute.

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