Researchers identify malignant cells responsible for relapse in high-risk neuroblastoma

August 14 2024

A. IHC staining for CD44 and ATF3, two markers of NF-κB/Stemness persister cell subtype, from a MYCN non-amplified tumor at diagnosis (D), definitive surgery (DS) and relapse (R) obtained from a patient who suffered from relapse (CN18). Credit: Cancer Discovery (2024). DOI: 10.1158/2159-8290.CD-24-0046
Researchers at Children's Hospital of Philadelphia (CHOP) announced a significant breakthrough in understanding chemotherapy resistance in high-risk neuroblastoma, a common and potentially deadly childhood cancer arising within the peripheral nervous system.

The study marks the first time that researchers identified malignant cells responsible for relapse in neuroblastoma and offers insights into potential new therapeutic targets.

The findings were published recently in the journal *Cancer Discovery*.

In the United States, about 800 new cases of neuroblastoma are diagnosed each year, more often in boys. The average age of diagnosis is about 18 months but occasionally the disease is seen in teens and young adults. Neuroblastoma has a high mortality rate and despite extensive studies, the malignant cells responsible for relapse were not well understood until this research.

This study is part of research conducted by the Human Tumor Atlas Network (HTAN), a National Cancer Institute (NCI) Moonshot initiative led by Kai Tan, Ph.D., an investigator in the Center for Childhood Cancer Research at CHOP, and a multi-institutional NCI Program Project Grant (PPG) focused on neuroblastoma and led by John M. Maris, MD, a study co-author and pediatric oncologist at CHOP.

"This study is a major step forward in identifying why neuroblastoma is so difficult to cure," said Maris, who also holds the Giulio D'Angio Chair in Neuroblastoma Research. "Targeting specific cells and pathways responsible for relapse empowers us to chart a new path forward, allowing us to develop potentially safe and effective treatments for children and families battling this aggressive cancer."
The CHOP research team employed advanced single nucleus RNA sequencing (snRNA-seq) and bulk whole genome sequencing techniques to analyze the genetic and transcriptional profiles of tumor samples from 20 pediatric patients with high-risk neuroblastoma who were treated between 2007 and 2022. The samples included matched diagnostic biopsies and definitive surgery specimens obtained after several cycles of induction chemotherapy.

"HTAN played a crucial role in generating the powerful multi-omics dataset that led to the hypothesis we tested in this paper," said Tan, who is also a professor in the Department of Pediatrics at CHOP and spearheads CHOP's participation in the HTAN. "It supports the broader application of the identified therapeutic targets and resistance mechanisms in high-risk neuroblastoma."

The investigators discovered and validated the fact that neuroblastoma can evade chemotherapy by becoming dormant and not constantly multiplying—a major hallmark of cancer. Thus, these "non-cycling" cells are resistant to chemotherapy, which is designed to kill cells that are actively multiplying. These "persister cells" can hide in the body for months or even years and see a relapse when they later awaken.

To validate their findings and enhance the analysis, the researchers leveraged independent post-induction chemotherapy data generated by other groups in the HTAN. By assessing the primary study's findings within the context of other datasets, the researchers ensured consistency and reliability in the transcriptional subtypes they identified.

For example, researchers were able to study the expression level of the MYCN gene and its relationship to the transcriptional subtypes. This provided several insights into the biology of neuroblastoma and offered promising new therapies. As a result, Maris noted that the neuroblastoma PPG is actively pursuing research and that several immunotherapeutic
strategies to eliminate persister cells are already being tested.

"This research could have far-reaching implications beyond neuroblastoma, as it enhances our understanding of chemotherapy resistance mechanisms," said Liron Grossmann, the study's lead author, who managed the research during his Hematology-Oncology fellowship at CHOP, and is currently a Senior Attending Physician at Sheba Medical Center in Israel.

"We've gained invaluable insights that can inform new approaches for various cancers, potentially improving treatment outcomes and reducing relapse rates across a broad spectrum of malignancies."


Provided by Children's Hospital of Philadelphia

Citation: Researchers identify malignant cells responsible for relapse in high-risk neuroblastoma (2024, August 14) retrieved 17 August 2024 from https://medicalxpress.com/news/2024-08-malignant-cells-responsible-relapse-high.html

This document is subject to copyright. Apart from any fair dealing for the purpose of private study or research, no part may be reproduced without the written permission. The content is provided for information purposes only.