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Metabolic changes of stromal cells promote ovarian cancer metastasis

Study focused on cancer-associated fibroblasts by researchers from Germany and USA exposes new tumor targets.

- **Ovarian cancer is a highly aggressive and frequently metastatic disease.**
- **Using highly innovative proteomic technology, researchers are looking for new therapeutic targets.**
- **The proteins of the tumor tissue were systematically investigated taking into account the surrounding 'normal' supporter cells.**
- **NNMT is a key protein of cancer-associated fibroblasts (supporter cells), whose metabolism is reprogrammed to promote tumor growth.**
- **The protein is a potential therapeutic target and highlights the importance of the tumor micro-environment for cancer metastasis.**

High-grade serous carcinomas (HGSC) make up the majority of ovarian cancer cases. Unfortunately, they have the lowest survival rates. HGSC is a tumor type that occurs primarily in the ovaries and spreads throughout the abdominal cavity. Most patients are diagnosed with late-stage disease that has already spread. Until recently, therapy has been limited to surgery and traditional chemotherapeutic agents. A systematic examination of the tumor and surrounding tissue — particularly normal cells called fibroblasts — has revealed a new treatment target that could potentially prevent the rapid dissemination and poor prognosis associated with high-grade serous carcinoma.

“Until quite recently, physicians have mainly focused on the tumor itself,” said the study’s senior author Ernst Lengyel, professor and chairman of Obstetrics and Gynecology at the University of Chicago Medicine. “Everyone does.” But, given the lack of progress with that approach and the fact the tumors are complex organs comprised of different tumor supporting cell types in their surrounding (often summarized as stroma), “we hypothesized it might be more promising to shed

light onto these supporter cells". In fact, "the stroma is often even bigger than the tumor fraction itself, which clearly shows how important it is to the disease and its progression," he added.

In close collaboration with Fabian Coscia, and Matthias Mann, from the Max Planck Institute of Biochemistry in Munich and University of Copenhagen, they profiled the expression of more than 5,000 proteins in both normal and cancerous tissues derived from minute amounts of patient biobank material. "For the first time, we were able to tell apart the molecular changes in the cancer cells from the ones happening in the adjacent stroma throughout disease progression", explained Matthias Mann, who is heading the Department "Proteomics and Signal Transduction" at the Max Planck Institute of Biochemistry. "When we then got our first data, we were fascinated to find that the metastatic stroma was characterized by a highly conserved protein signature, as opposed to the cancer cells", adds Fabian Coscia, postdoctoral researcher in Matthias Mann's group and one of the two first-authors of the study. As these metastatic changes were seen in all of their analyzed patients, the team then went on to understand its functional role during metastasis with the ultimate goal to find novel therapeutic targets.

Indeed, they discovered a metabolic enzyme, nicotinamide N-methyltransferase (NNMT), highly expressed in the stroma surrounding metastatic cancer cells. The researchers found that NNMT causes widespread gene expression changes in the tumor stroma, converting normal fibroblasts to cancer-associated fibroblasts that support and accelerate tumor growth. Stromal NNMT expression encouraged ovarian cancer migration, proliferation, growth and metastasis. It was associated with poor clinical outcomes in patients.

The researchers are now using high-throughput screening to find novel ways to inhibit this enzyme. "One method looked promising," said Mark Eckert, research assistant professor in Obstetrics and Gynecology at the University of Chicago and co-first author of the study. "We have sort of a backbone for the inhibitor. We know our target, we know the structure, we know how to apply this and we have a sense of the direction. We are starting to understand how a normal fibroblast is converted into a cancer-associated fibroblast by this metabolic enzyme."

They also found that inhibition of NNMT activity may be able to reduce or even reverse many of the tumor-promoting effects of cancer-associated fibroblasts. This suggests, they note, that the stroma should be explored as a new treatment target. Coscia, co-first author on the manuscript who led the proteomics analysis, added that "this method may be used to discover other proteins that are important for metastasis and to identify early changes during disease development."

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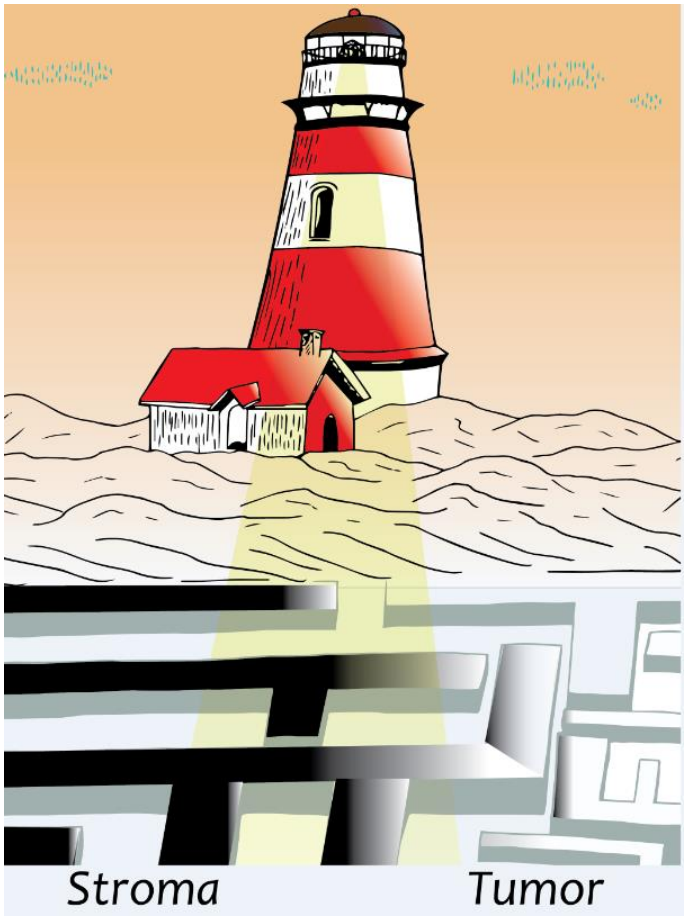
"When we put it all together," Lengyel added, "it gave us exciting results. We have linked high-end technology including proteomics and metabolomics to functional analysis to improve our understanding of the stroma."

Original Publication:

M.A. Eckert, F. Coscia, A. Chryplewicz, J.W. Chang, K.M. Hernandez, S. Pan, S.M. Tienda, D.A. Nahotko, G. Li, I. Blaženović, R.R. Lastra, M. Curtis, S.D. Yamada, R. Perets, S.M. McGregor, J. Andrade, O. Fiehn, R.E. Moellering, M. Mann & E. Lengyel: Proteomics reveals NNMT as a master metabolic regulator of cancer associated fibroblasts. *Nature*, May 2019
DOI: 10.1038/s41586-019-1173-8



Caption:

Innovative proteomic technology using laser-microdissected tumor material from patient samples sheds new light on the stroma (black) for ovarian cancer metastasis.
Illustration: Francesco Russo © Max Planck Institute of Biochemistry

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About Matthias Mann

Matthias Mann studied physics at the Georg August University in Göttingen and obtained his PhD from Yale University, New Haven, USA. He held group leader positions at the European Molecular Biology Laboratory (EMBL) and the University of Southern Denmark in Odense before becoming a director at the MPIB in 2005. His Department "Proteomics and Signal Transduction" uses mass spectrometry to study the proteome, the entirety of all proteins of an organism. Additionally, Mann was appointed director of the Department of Proteomics at the University of Copenhagen in 2007. Mann has received numerous awards for his research including the Louis-Jeantet Prize for Medicine, the Körber European Science Prize and the Gottfried Wilhelm Leibniz Prize.

- Press releases on research from the Mann Department can be found here.

About the Max Planck Institute of Biochemistry

The Max Planck Institute of Biochemistry (MPIB) belongs to the Max Planck Society, an independent, non-profit research organization dedicated to top-level basic research. As one of the largest Institutes of the Max Planck Society, about 800 employees from 45 nations work here in the field of life sciences. In currently about 35 departments and research groups, the scientists contribute to the newest findings in the areas of biochemistry, cell biology, structural biology, biophysics and molecular science. The MPIB in Munich-Martinsried is part of the local life-science-campus in close proximity to the Max Planck Institute of Neurobiology, a Helmholtz Center, the Gene-Center, several bio-medical faculties of the Ludwig-Maximilians-Universität München and the Innovation and Founding Center Biotechnology (IZB).
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