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CT45 – A key to long-term survival in ovarian cancer

The diagnosis of ovarian cancer is still comparable to a death sentence. Only one in six patients survives more than 10 years after diagnosis. In a new study, an international research team from Germany, the USA, and Denmark, identified a molecular mechanism that is linked to patient long-term survival for those roughly 20% of the patients. By proteomic analysis, the protein CT45 was identified as a novel prognostic cancer cell marker. The authors further showed that the protein itself increases cancer cell death after platinum chemotherapy and activates the patient's immune system. This work will be published in the renowned scientific journal *Cell*.

Ovarian Cancer

Ovarian cancer is a very aggressive disease. Only every sixth patient survives more than 10 years after the first diagnosis. The majority of patients succumb to the disease within the first two years, which is mainly due to late detection of the disease when the tumor has already spread from the ovaries to the surrounding organs in the abdomen. Standard treatment involves surgical debulking followed by platinum-based chemotherapy. "Although, for the majority of patients, this typically leads to an immediate response to therapy and reduction of tumor mass, the therapeutic effects are rarely permanent", explains Prof. Dr. Ernst Lengyel from the University of Chicago, a world-leading gynecological oncologist. With over 42,000 deaths per year, ovarian cancer is the deadliest gynecologic malignancy in Europe.

Cause analysis

Scientists from the Max Planck Institute (MPI) of Biochemistry in Martinsried, Munich, have now in collaboration with researchers from Chicago and Copenhagen set out to elucidate the molecular basis for patient long-term survival. "Only if we understand the molecular causes and differences between patients who respond well or poorly to therapy, will we improve the treatment of ovarian cancer in the clinic, and also pave the way for more personalized treatment options in the future" explains Lengyel, who initiated the study together with Prof. Dr. Matthias Mann, a pioneer and leading scientist in the field of mass spectrometry based proteomics. Mann is director at the MPI of Biochemistry and head of the department "Proteomics and Signal Transduction". The DNA within our cells contains the instruction how to assemble proteins, the molecular machines that form the main players of most biological processes such as for metabolism or cellular signaling. In recent





years, Mann and his team has developed and refined the technology of mass spectrometry for protein analysis to be for clinical use. "Using mass spectrometry, we can identify for the first time almost all of the proteins, the proteome, in the tumor tissue of the patients," says Mann. "Our highly sensitive methods now enable profiling thousands of proteins simultaneously, allowing us to search for the proteins that are critical to the disease by comparing the tissue samples," Prof. Mann continues.

CT45 influences long-term survival

For their analysis, the researchers used archived biobank material from the University of Chicago collected over many years, most of which originated from the initial operation of the patients. "This way, we can look back to the past in a way because we know exactly how the patient reacted to chemotherapy," says Dr. Fabian Coscia, first-author of the study and a Ph.D. student with Dr. Mann and now a postdoctoral fellow in Copenhagen. With the help of mass spectrometry, the researchers discovered a protein called CT45, completely unknown till then, which was significantly increased in long-term survivors. Subsequent tests in the laboratory have confirmed the CT45 findings. When cancer cells produced the protein in cell culture, cells died much faster from standard chemotherapy.

CT45 a suicide gene?

But why does the cancer produce the protein CT45 if it promotes its own killing after chemotherapy? "The simple answer to this is that the cancer does not 'know' that it will be treated with platinum based chemotherapy" explains Coscia. "The samples we analyzed with proteomics were taken before chemotherapy. An adaptation of the tumor to the treatment has not yet taken place. We made similar observations in laboratory studies with isolated ovarian cancer cells."

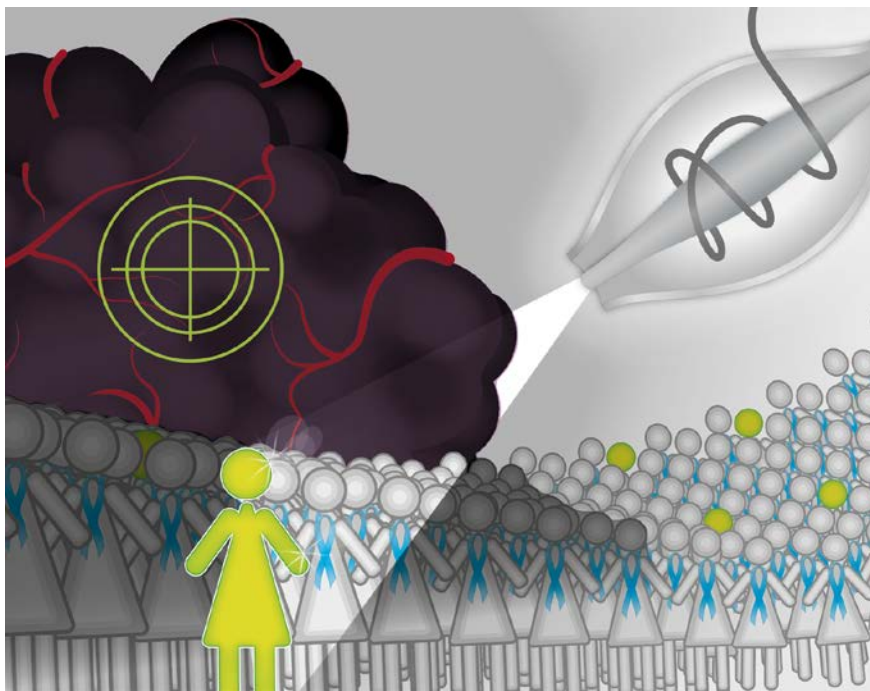
Healthy cells normally only produce proteins that are needed for their specific tasks, for example, tasks typical for ovarian function. Although the blueprint for proteins, DNA, is the same in all cells, most of the protein assembly instructions are biochemically sealed. This means that only the ovary-specific "program", i.e. DNA, can be accessed. However, once a cell transforms and becomes a cancerous cell, it can lose its seal, the so-called methylation, and often proteins such as CT45 are then produced. Currently there are the first drugs in clinical trials that have a de-methylating effect. Experiments in cell culture indicate that the effectiveness of chemotherapy can be improved by these so-called DNA-de-methylating drugs. "We suspect that CT45 plays a major role in this because it is one of the most abundant proteins in the tumor induced by the drug. This gives us hope that patients who do not have the protein in their tumor could still benefit from combination chemotherapy," says Dr. Marion Curtis, a postdoctoral fellow in the Lengyel laboratory and the last author of the study.





Blessing in disguise

The researchers have made great progress in understanding CT45's function. This gives hope for the development of new and more targeted therapeutic approaches. "We have evidence that tumor-specific expression of CT45 stimulates the patient's immune system to fight the cancer, as it would be the case with a virus or bacterial-infected cell. "Our long-term goal is to find new ways to improve patient outcomes based on these exciting new insights," summarizes Prof. Dr. Lengyel.



Caption:

The protein CT45 seems one key for patient long term survival in ovarian cancer. The protein was discovered by analyzing tissue samples of cancer patients using Mass Spectrometry.

Illustration: Monika Krause © MPI of Biochemistry

Original publication

F. Coscia, E. Lengyel, J. Duraiswamy, B. Ashcroft, M. Bassani-Sternberg, M. Wierer, A. Johnson, K. Wroblewski, A. Montag, S. D. Yamada, B. López-Méndez, J. Nilsson, A. Mund, M. Mann, and M. Curtis: Multi-level proteomics identifies CT45 as a chemosensitivity mediator and immunotherapy target in ovarian cancer, *Cell*, September 2018





About Matthias Mann

Matthias Mann studied physics at the Georg August University in Göttingen and obtained his PhD from Yale University, New Haven, USA. 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. With over 200,000 citations, Mann is the most highly cited researcher in Germany.

About Prof. Lengyel

Dr. Lengyel is a gynecologic oncologist who is board certified in general gynecology and gynecologic oncology. He attended medical school at the University of Munich (LMU) and went to the TU Munich, UCSF, and Stanford for postgraduate clinical training. In 2003, Dr. Lengyel joined the faculty of the University of Chicago. Since that time he has established a clinical practice specializing in radical debulking surgery for ovarian cancer and a translational research laboratory focused on understanding ovarian cancer biology. Recently, his group elucidated how stromal cell/cancer cell interactions promote ovarian cancer metastasis through the metabolic reprogramming of tumor cells. The laboratory uses high-throughput screening technology to find novel drugs for the treatment of ovarian cancer. Dr. Lengyel is the Arthur L. and Lee G. Herbst Professor of Obstetrics and Gynecology and the Chair of the Department of Obstetrics and Gynecology at the University of Chicago.

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).





About the University of Chicago Medicine

The University of Chicago Medicine and its Comer Children's Hospital rank among the best in the country, most notably for cancer treatment, according to U.S. News & World Report's survey of the nation's hospitals. The University of Chicago's Pritzker School of Medicine has been named one of the Top 20 medical schools in the nation, by U.S. News' "Best Graduate Schools" survey. University of Chicago physician-scientists performed the first organ transplant and the first bone marrow transplant in animal models, the first successful living-donor liver transplant, the first hormone therapy for cancer and the first successful application of cancer chemotherapy. Its researchers discovered REM sleep and were the first to describe several of the sleep stages. Twelve of the Nobel Prize winners have been affiliated with the University of Chicago Medicine.

About the Novo Nordisk Foundation Center for Protein Research

Novo Nordisk Foundation Center for Protein Research (CPR) was established in 2007 at the Faculty of Health and Medical Sciences, University of Copenhagen, to promote basic and applied discovery research on human proteins of medical relevance. The establishment of the centre was made possible by a generous donation of 600 million DKK (~113 MUSD) from the Novo Nordisk Foundation as well as through significant contributions from the University of Copenhagen for the renovation of the centre facilities. At the beginning of 2015, the Novo Nordisk Foundation donated additional 180 million DKK for the next funding period. The Center comprises a wide range of expertise and skills within its research programs spanning disease systems biology, proteomics, high throughput protein production and characterisation, chemical biology, disease biology, and protein therapeutics. The centre contributes to the progress of translational research within medicine and provides fundamental insights which can be used to promote drug discovery and development. More detailed descriptions of the research conducted at Novo Nordisk Foundation Center for Protein Research see the overview of all CPR Research groups.





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