Epigenetic analysis of aggressive brain tumors – a new perspective for precision medicine

Glioblastoma is a brain cancer with devastating prognosis. It is caused by numerous genetic defects, which make it difficult to treat. Yet there is an underappreciated aspect of glioblastoma biology – the role of epigenetic alterations that affect tumor progression independent of the genetic DNA sequence. A new study by scientists from CeMM, MedUni Vienna and the Austrian Brain Tumor Registry network demonstrates how epigenetic analysis of tumor samples collected in routine clinical practice could be used to better classify and treat the disease. The results were published in *Nature Medicine*.

(Vienna, August 27, 2018) Glioblastoma is a highly aggressive brain cancer that predominantly affects people in their 50s, 60s and 70s. Even under the best available care, half of the patients die within one year after diagnosis, and very few live on for more than three years. Many efforts to develop new, targeted treatments have failed over the last decade. The high degree of molecular heterogeneity among the cancer cells results in evolutionary selection for those cells that can withstand drug treatment.

In order to develop better therapies for glioblastoma, detailed knowledge about the molecular heterogeneity of the tumor cells will be crucial, given that this heterogeneity provides the substrate from which drug resistance evolves. Genetic factors such as the amplification of tumor-promoting genes and the deletion of tumor suppressor genes play an important role, but cancer is more than genetics. Recent research suggests a key role of epigenetics, which regulates gene expression and prevents the activation of harmful genes. Whether and how epigenetic regulation changes when a glioblastoma becomes therapy-resistant has been a largely unsolved question.

To investigate the role of epigenetics in glioblastoma disease progression, the research group of Christoph Bock, Principal Investigator at the CeMM Research Center for Molecular Medicine of the Austrian Academy of Sciences, analyzed DNA methylation (which is the classical epigenetic mark) in more than 200 glioblastoma patients, focusing on the epigenetic changes that occur during glioblastoma disease progression. In close collaboration with scientists at the Medical University of Vienna and clinicians at eight hospitals throughout Austria, a study published in *Nature Medicine* (DOI: 10.1038/s41591-018-0156-x) identified epigenetic changes that accompany glioblastoma progression and predict patient survival.

This research builds on the Austrian Brain Tumor Registry, spearheaded by Adelheid Woehrer from the Institute of Neurology at the Medical University of Vienna, who is a senior and corresponding author of the study. "A particular strength when working with a national patient registry is the integration across centers and creation of a cross-disciplinary team of disease experts. This approach enabled us to effectively address a relevant research question in the context of the Austrian population", Woehrer says.

Combining epigenetic data with brain imaging and digital pathology, the study established important links between glioblastoma at the level of molecules, cells and organs. These associations can be exploited for improving disease classification: "DNA methylation sequencing – as a single test – can be used to predict a wide variety of clinically relevant tumor properties", explains CeMM PhD student Johanna Klughammer who led the data analysis, "providing us with a powerful new approach for characterizing the heterogeneity of brain tumors".

This study thus establishes a rich resource for understanding the role of epigenetics in glioblastoma and a new toolset with broad relevance for personalized medicine. Moreover, it demonstrates the power of nationwide coordination and collaboration in medical research. Senior author Christoph Bock comments: "We have a high-quality healthcare system in Austria, which we need to make future-proof by incorporating rapid progress in precision medicine. Our study demonstrates what it will take to advance clinical care through biomedical research in Austria: interdisciplinary collaboration, access to the latest technologies, and the ambition and financial resources to successfully perform projects of this scale."

Attached pictures: 1. An aggressive brain tumor (glioblastoma), illustrated based on magnetic resonance data (© Karl-Heinz Nenning), 2. Microscopic image of a glioblastoma after surgical removal and staining for neuropathological diagnostics (© Adelheid Woehrer), 3. A methylated DNA molecule. Epigenetic changes play a role in the progression of glioblastoma (© Christoph Bock), 4. Microscopic image of a glioblastoma with individually stained immune cells (© Adelheid Woehrer), 5. Scientist at CeMM performing a DNA methylation analysis (© Wolfgang Däuble)

The study "The DNA methylation landscape of glioblastoma disease progression shows extensive heterogeneity in time and space" was published in *Nature Medicine* on August 27, 2018. DOI: 10.1038/s41591-018-0156-x

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Christoph Bock is a Principal Investigator at CeMM. Trained as a bioinformatician, he leads a team that integrates biology, medicine, and computer science – working on a vision of precision medicine that is driven by large datasets and a deep understanding of biological disease mechanisms. He is also a guest professor at the Medical University of Vienna, Department of Laboratory Medicine, group leader at the Ludwig Boltzmann Institute for Rare and Undiagnosed Diseases (LBI-RUD) and he coordinates the genome sequencing activities of CeMM and the Medical University of Vienna. Christoph Bock is a member of the Young Academy of the Austrian Academy of Sciences and recipient of major research awards, including the Max Planck Society's Otto Hahn Medal, an ERC Starting Grant and the Overton Prize of the International Society of Computational Biology.
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Adelheid Woehrer, MD, PhD, works as an expert neuropathologist at the Institute of Neurology of the Medical University of Vienna. Focusing on primary brain tumors, her research combines epidemiology and tissue-based analyses. During her residency, she graduated in clinical neurosciences (CLINS) as one of the first of this doctoral program. For her PhD thesis, she worked on the implementation of a national patient registry dedicated to brain tumors in Austria (Brain Tumor Epidemiology in Austria and the Austrian Brain Tumor Registry). In 2013, she was elected European President of the Brain Tumor Epidemiology Consortium (BTEC).
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