

Epigenetic study provides new approaches to combination therapies for aggressive cancers

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Epigenetic processes enable cells to respond to changes in their environment by regulating the activity of their genes. One of the proteins that plays a key role in gene activation is BRD4, a well-characterized "epigenetic reader" that binds to acetylated lysine residues on both histone and non-histone proteins. To measure cellular BRD4 activity, the laboratory of Stefan Kubicek at the CeMM Research Center for Molecular Medicine of the Austrian Academy of Sciences generated a cellular reporter system in 2016. Now, the researchers have applied this model to test whether loss of any of the approximately 23,000 human genes resembles BRD4 inhibition. Surprisingly, they discovered an interaction of folate metabolism with gene regulation. The results of the study, which included scientists from the Institute of Molecular Pathology (IMP) and the Medical University of Vienna, have now been published in the journal *Nature Genetics*.

Modern genome-wide screening techniques enable the generation of populations of mutagenized cells in which a single gene is disrupted in each cell. The BRD4 reporter cells enabled Stefan Kubicek's

laboratory at CeMM to precisely select from these cell populations those [cells](#) that behave as if BRD4 were inhibited. Next generation sequencing was then used to identify which [genes](#) were switched off. "We had expected to find one of the classic epigenetic factors," said Kubicek, "so we were all the more surprised that the best hit was MTHFD1." This enzyme is involved in folate metabolism, a process that had not previously been connected to BRD4. In addition, MTHFD1 is located predominantly in the cytoplasm, while BRD4 resides in the nucleus.

Coincidence and serendipity provided first author Sara Sdelci another piece of the puzzle, which confirmed the results. At a conference, she met Philipp Rathert from Johannes Zuber's laboratory at the IMP, who was also working on BRD4. Sara Sdelci: "Philipp Rathert had generated data showing that MTHFD1 also physically binds to BRD4." In subsequent experiments, she showed that the small portion of the MTHFD1 protein found in the nucleus interacts with BRD4. This interaction recruits MTHFD1 to the DNA, where the enzyme contributes to gene regulation.

The study by Sara Sdelci is of clinical relevance for BRD4-dependent tumors. This includes tumors that harbor genetic aberrations leading to BRD4 overexpression, but also many other cancers in which BRD4 contributes to cell growth by its gene regulatory function. Accordingly, [pharmaceutical companies](#) have developed highly active BRD4 inhibitors that are currently being tested in clinical trials.

In clinical oncology, monotherapy with a single chemical agent is rarely successful due to the development of drug resistance. The discovery of the interaction of BRD4 and the enzyme MTHFD1 from the folic acid metabolism promises new

approaches in cancer combination therapy, in the treatment of aggressive tumors. Antifolates, substances that inhibit the folate cycle, have been used for more than 70 years in cancer therapy and against diseases such as rheumatoid arthritis. The new study shows that antifolates can be combined with BRD4 inhibitors to more effectively combat tumors. The results may also help to stratify patients to ensure therapy success. "In the best case, based on our findings, patients can also be selected who, because of their folic acid level and their genetics, respond particularly well to BRD4 inhibitors," says Stefan Kubicek.

More information: Sara Sdelci et al, MTHFD1 interaction with BRD4 links folate metabolism to transcriptional regulation, *Nature Genetics* (2019).
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