Do purines influence cancer development?

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Numerous disease development processes are linked to epigenetic modulation. One protein involved in the process of modulation and identified as an important cancer marker is BRD4. A recent study by the research group of Giulio Superti-Furga, Principal Investigator and Scientific Director at the CeMM Research Center for Molecular Medicine of the Austrian Academy of Sciences, now shows that the supply of purines as well as the purine synthesis of a cell can influence BRD4 activity and thus play a role in the carcinogenesis process. The findings were published in *Nature Metabolism*.

(Vienna, May 10, 2021) Chromatin is a central component of the cell nucleus. It refers to the complex of the approximately two-meter-long human DNA with proteins that organize it so that – depending on the cell type – certain genes are activated or deactivated. In order to be able to adapt to diverse situations and influences, cells read the information relevant to them from the DNA. If this process is disturbed, diseases such as cancer develop. Scientists have been researching for many years what influences this process. The protein BRD4, which makes a decisive contribution to the unpacking and packaging of DNA in chromatin, was identified as a marker for cancer. Since then, scientists have been investigating how BRD4 can be modulated. A recent study by scientist Kai-Chun Li and the research group of CeMM Scientific Director Giulio Superti-Furga makes an important contribution to answering this question. She investigated how certain externally supplied nutrients, so-called purines, influence BRD4 and thus the development process of various cancer diseases. Purines are basic building blocks of the cell. Disturbances of the purine metabolism in the cell have already been associated with some disease patterns in the past. The study showed, on the one hand, that inhibiting purine supply as well as disturbing purine synthesis can trigger a functional disturbance of BRD4 and thus impact chromatin accessibility. On the other hand, BRD4 functionality could be restored by adding adenine.

Analysis of the transport pathways

Giulio Superti-Furga's research group focuses particularly on those transport proteins in the genome that transport numerous important substances such as nutrients and metabolites into and out of the cell – so-called solute carriers (SLC). First author Kai-Chun Li explains: "Our aim was to investigate the involvement of SLC-mediated purine uptake and cellular metabolism in the modulation of cellular epigenetic states, because purine metabolism plays an essential role in cell

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metabolism." With the help of SLCs, the scientists were able to modulate the purine supply for their study and observe the direct effects. They used both a genetic screening based on a CRISPR/Cas9 library focused on transporters, and a drug screening using a compound library mainly consisting of cellular metabolites and drugs, both to track down the modulation of BRD4-dependent chromatin states in myeloid leukemia cells. The scientists compared "normal" cancer cells with those cancer cells in which the SLCs that transport purines were inhibited. In addition, purines were added to or omitted from the growth medium of the cells in various experiments, thus modulating purine biosynthesis in the cells.

Adenine brings BRD4 back into balance

The study shows that an imbalance of intracellular purine pools leads to a dysfunction of BRD4-dependent transcriptional modulation of chromatin, which means that the correct reading of DNA information is disturbed. "These results demonstrate a pharmacologically effective axis between purine metabolism and BRD4-dependent chromatin states," explains study leader Giulio Superti-Furga. Drugs that influence BRD4 have already been developed in the past. At the same time, some cancer types also became resistant to such BET inhibitors. "With our study, we show another way to modulate BRD4 – by influencing the purine metabolism." The scientists also found an answer to the question of how BRD4 functionality could be restored: they were able to show that adenine, a purine-derived compound, plays a strong role in BRD4 interaction. "Our results suggest that adenylates (adenine, ATP, etc.) are important for healthy cells. This could be a significant starting point for developing new therapies against BRD4-induced cancer types," says Superti-Furga.

Attached pictures: First author Kai-Chun Li and last author Giulio Superti-Furga, © Laura Alvarez, CeMM.

The study "Cell-surface SLC nucleoside transporters and purine levels modulate BRD4-dependent 2 chromatin states" was published in Nature Metabolism on May 10, 2021, DOI: 10.1038/s42255-021-00386-8.

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Giulio Superti-Furga is Scientific Director of CeMM, and Professor of Medical Systems Biology at the Medical University of Vienna. He was trained as a molecular biologist at the University of Zurich, Genentech, IMP Vienna and EMBL Heidelberg. He obtained four grants from the European Research Council, is a member of five scientific academies, and has published more than 200 papers. CeMM, which he has been directing since 2005, is located in the middle of the large general hospital campus in Vienna, where, together with some 180 scientists and medical doctors, he brings genomic and systems views close to the clinical world with a view to improving medical practice. For CeMM, he promoted a unique mode of super-cooperation, connecting biology with medicine, experiments with computation, discovery with translation, and science with society and the arts. Recent interests include ways to create functional precision medicine approaches and the role of the human transportome in pathophysiology and drug discovery. He is the scientific coordinator of the Innovative Medicine Initiative consortium "RESOLUTE", dedicated to the deorphanization of SLC transporters.

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