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INSTITUTSKOLLOQUIUM

Gemeinsames Kolloquium der Physik und Chemie

Am Dienstag, dem 13. Oktober 2026, spricht um 17:15 Uhr im Faraday-Hörsaal,

Prof. Dr. Oliver H. Krämer und Dr. Al-Hassan M. Mustafa
Institut für Toxikologie, Johannes Gutenberg Universität Mainz

zum Thema:

"HDAC1 and HDAC2 Safeguard BCR-ABL-positive Cells from Replication Stress-Induced Apoptosis via the Nuclear to Mitochondrial p73-NOXA Axis"

Abstract:

Histone deacetylases (HDACs) are key epigenetic regulators that are frequently dysregulated in cancer cells. Context-specific dependencies of tumor cell survival on HDACs and the mechanisms through which HDACs determine cell stress responses by specific oncogenic pathways remain to be understood. Here we unravel how the class I deacetylases HDAC1 and HDAC2 control the fate of chronic myeloid leukemia (CML) cells undergoing DNA replication stress. Compared to normal myeloid cells (n=690), CML cells overexpress HDAC1 and HDAC2 (n=234-274). We reveal that HDAC1 and HDAC2 protect cultured and primary CML cells with the hyperactive BCR-ABL tyrosine kinase from programmed cell death through apoptosis upon DNA replication stress. Using transcriptomics and genetically defined knockdown and knockout model systems, we demonstrate that these effects depend on the transcription factor p73 and its pro-apoptotic target gene *NOXA*. Upon DNA replication stress, p73 binds to the *NOXA* promoter but only upon additional inactivation of HDAC1/HDAC2 the *NOXA* gene becomes transcribed. BCR-ABL translocate to the nucleus to catalyze p73 phosphorylation at tyrosine-99 for the induction of p73 and mitochondrial NOXA. Thus, the BCR-ABL oncogene creates a selective vulnerability to HDAC1/HDAC2 inhibitors, driving a cytotoxic shift in replication stress responses towards apoptosis. These data highlight HDAC1/HDAC2 as potential therapeutic targets in CML.

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Die Hochschullehrer der Institute für Physik und Chemie