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Drugs against class I histone deacetylases interfere with cancer-associated metastatic programs

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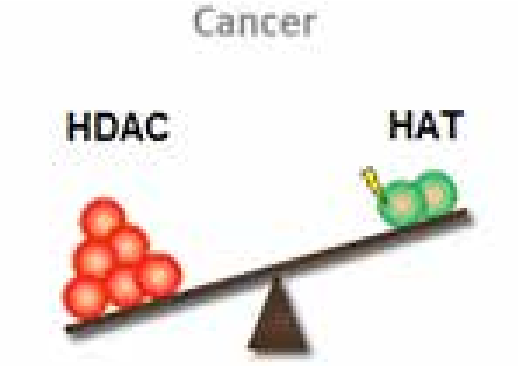
The spreading of metastases from primary cancers leads to poor prognosis and tumor-related deaths. Inhibitors of histone deacetylases (HDACi) are promising epigenetic drugs that are tested in clinical trials. There are conflicting data on the regulation of metastatic epithelial-mesenchymal and mesenchymal-epithelial transitions (EMT/MET) by histone deacetylases (HDACs) and their inhibitors. To address this issue, we chose a systems toxicology approach, in which we combined morphological, cellular, functional, and global proteomic analyses. We tested whether and how HDACi affect the growth and metastatic behavior of transformed kidney and breast cells *in vitro* and in a murine kidney-to-lung cancer dissemination model *in vivo*. In addition to this pharmacological approach, we investigated how the genetic elimination of HDACs affects cancer cell fate. HDACs fall into four classes (I-IV). Class I HDACs have cancer-relevant functions. We analyzed how the class I HDACi valproic acid (VPA) affects the growth and spreading of syngeneic kidney cancer cells into the lungs of BALB/c mice. We tested *in vitro* how VPA and another class I HDACi, Entinostat (MS-275), affect tumor cell growth, apoptosis, migration, and the expression of metastasis modulators. Methods include flow cytometry, immunoblot, immunofluorescence, qPCR, proteomics on a global scale, RNAi against the class I HDACs HDAC1/HDAC2, and tumor analysis *in vivo*. Inhibition of HDAC1/HDAC2 causes growth arrest, morphological alterations, and apoptosis of kidney cancer cells. HDACi block cancer cell migration, integrin-dependent cell adhesion, and EMT induced by the cytokine TGF-β. Global proteomics and qPCR analyses illustrate that HDACi abrogate EMT and MET programs that are necessary for metastatic spread. Moreover, we elucidate pro-apoptotic molecular mechanisms that trigger apoptosis in HDACi-treated cancer cells. Our data suggest class I HDACi as treatment options for cancer. Such drugs disturb the expression of proteins controlling the EMT/MET balance for metastasis formation.



HDACs are epigenetic modifiers that are often mutated or aberrantly regulated in cancer cells. Small molecule inhibitors can correct this disequilibrium and are therefore appreciated anti tumor agents.

Recent Publications

1. Schäfer C, Göder A, Beyer M, Kiweler N, Mahendrarajah N, Rauch A, Nikolova T, Stojanovic N, Wieczorek M, Reich TR, Tomicic MT, Linnebacher M, Sonnemann J, Dietrich S, Sellmer A, Mahboobi S, Heinzel T, Schneider G and Krämer OH (2017) Class I histone deacetylases regulate p53/NF-κB crosstalk in cancer cells. Cell Signal 29:218-225.
2. 2. Noack K, Mahendrarajah N, Hennig D, Schmidt L, Grebien F, Hildebrand D, Christmann M, Kaina B, Sellmer A, Mahboobi S, Kubatzky K, Heinzel T and Krämer OH (2017) Analysis of the interplay between all-trans retinoic acid and histone deacetylase inhibitors in leukemic cells. Arch Toxicol. 91(5):2191-2208.

3. Mahendrarajah N, Paulus R and Krämer OH (2016) Histone deacetylase inhibitors induce proteolysis of activated CDC42-associated kinase-1 in leukemic cells. J Cancer Res Clin Oncol. 142(11):2263-73.
4. Wagner T, Kiweler N, Wolff K, Knauer SK, Brandl A, Hemmerich P, Dannenberg JH, Heinzel T, Schneider G, Krämer OH (2015) Sumoylation of HDAC2 promotes NF-κB-dependent gene expression. Oncotarget. 6(9):7123-35.
5. Brandl A, Wagner T, Uhlig KM, Knauer SK, Stauber RH, Melchior F, Schneider G, Heinzel T, Krämer OH (2012) Dynamically regulated sumoylation of HDAC2 controls p53 deacetylation and restricts apoptosis following genotoxic stress. J Mol Cell Biol. 4(5):284-93.

Biography

Oliver H Krämer investigates HDACs, HDAC inhibitors, the crosstalk between post-translational modifications, and cancer-relevant transcription factors. He studied Biology and Pharmacology at the Ruprecht-Karls-University Heidelberg, Germany and Biochemistry and Molecular Biology from University of Adelaide, Australia. He investigated how valproic acid acts as HDAC inhibitor at the Georg-Speyer-Haus, Germany. For these works, he obtained his PhD in Biochemistry from the Johann-Wolfgang-Goethe University, Germany. He then joined Center for Molecular Biomedicine, Friedrich-Schiller-University Jena, Germany, where he worked as Post-doctoral fellow and later as group leader and Associate Professor. In 2013, he moved to the Department of Toxicology of the University Medical Center, Mainz, Germany, as a Full Professor.

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