P1:106

Histone deacetylase inhibitors as potential therapeutic targets for chordomas: an immunohistochemical and functional analysis

Susanne Scheipl[1], Birgit Lohberger[1], Elke Verena Froehlich[1], Beate Rinner[1], Johannes Haybaeck[1], Andreas Leithner[1], Peter Pal Varga[1], Franz Quehenberger[1], Bernadette Liegl[1]

[1)] Medical University Graz, Austria

Introduction: Chordomas are rare malignancies of the axial skeleton. Therapeutic modalities are mainly restricted to surgery and irradiation. HDAC inhibitors are tested in many clinical trials as promising new treatment options for various types of cancer.
Objectives: We intended to study whether HDAC inhibitors could be regarded as therapeutic targets for chordomas.
Materials and Methods: Fifty chordomas (34 primary tumors, 16 recurrences) from 44 patients (27 male, 17 females) were evaluated immunohistochemically for the expression of HDACs1-6. HDAC inhibitors Vorinostad (SAHA), Panobinostad (LBH-589), and Belinostad (PXD101) were tested in the chordoma cell line MUG_Chor1 for dose-dependent apoptotic effects. Apoptosis induction was investigated by caspase 3/7 activity, caspase-3 cleavage and PARP cleavage. P-values > 0.05 were considered significant.
Results: IHC: HDAC1 expressed a slight nuclear positivity (n = 5; 10%). Expression of HDAC2 was positive in the majority of cases (n = 36; 72%). HDACs 3 to 6 stained positive in all specimens available (n = 43; 86%). The strongest expression was observed for HDAC6.
Cell line: Caspase 3/7 activity was measured by the Caspase-Glo® 3/7 Assay in MUG-Chor1 cells after 3, 6, 24, 48, and 72 h treatment with the IC50 of SAHA, LBH-589, and PXD101. It peaked after 48 and 72 h in SAHA and LBH-589 treated cells. PXD101 treatment did not lead to caspase 3/7 activity. Cleaved caspase-3 was detected in 54.5±7.4% of SAHA treated, and in 63.1±13.2% of LBH-589 treated cells. In contrast, the control and PXD101 treated cells showed almost no cleaved caspase-3 (2.7±1.5% and 8.2±3.4% of gated cells, respectively). The percentage of cleaved caspase-3 positive cells increased significantly over time (p=0.0003 for SAHA, and p=0.0014 for LBH-589 after 72h).
Discussion: HDACs were detectable by IHC in our series, with HDAC1 showing the weakest, and HDAC6 showing the strongest staining. SAHA and LBH-589 significantly increased apoptosis of chordoma cells. Although sufficient data from chordomas is still lacking, the efficacy of various HDAC inhibitors has been shown in several types of sarcomas, particularly in combination with other anticancer therapeutics. Our results provide evidence to support further research on HDACs as potential therapeutic targets for chordoma therapy.

E-mail (main author): susanne.scheipl@gmx.at