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Association of class I histone deacetylase expression with patients' prognosis in astrocytic tumors

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Malignant brain tumors, especially high-grade glioblastomas, are among the most lethal of all cancers. Epigenetic modifications of chromatin plays a critical role in carcinogenesis by causing transcriptional silencing of specific control regions related to cell differentiation. Histone deacetylases (HDACs) are responsible for chromatin packaging, which influences the transcription process. Thus far, there are no systematic data available on comparison between the expression of HDAC1 to HDAC11 family members in BTSC, GBM cell line cells and astrocytic tumor tissues. Our data showed for the first time that HDAC1, HDAC2, and HDAC3 were highly expressed in both cells and tumor tissues. In this study we also showed for the first time HDAC1, HDAC2, HDAC3 and NCoR1 expression in human astrocytic tumors by using a TMA consisting of a large patient cohort. 59.6% of the tumors showed nuclear expression of HDAC1, and about 19.1% of them showed more than 50% nuclear expression. 85.6% of the tumors showed nuclear expression of HDAC2, and about 33.5% of them showed more than 75% nuclear expression. Contrary to them, nuclear expression of HDAC3 and NCoR1 could only be found in small part of these tumors. Celluar expression of HDAC3 and NCoR1 could be found in half of these tumors. Kaplan-Meyer survival analyses and log rank tests confirmed that none of these protein markers could reach significant relevancy for overall survival in the WHO grade subgroup. Except that, HDAC2 showed a borderline significant correlation with shortened overall survival (p=0.0875). Further there was a significant correlation between HDAC2 and Ki-67 expression both in the whole cohort and in the WHO grade subgroup. Correlation analysis also showed a significant association between nuclear HDAC3 expression and nuclear NCoR1 expression. But interestingly, there was a discrepancy between cellular HDAC3 and NCoR1 expression. Celluar expression of HDAC3 showed a significant inverse correlation with nestin expression in the whole cohort. On the contrary, celluar expression of NCoR1 showed a significant positive correlation with nestin expression. This may suggest that in nuclei, NCoR1 and HDAC3 work synergistically. After their translocation into cytoplasm, they may act independently. In conclusion, our results emphasized the important role of class I HDACs, especially HDAC2, in astrocytic tumor biology. HDAC2 analysis may be useful for estimating aggressiveness of astrocytic tumors and for assessment of

patients' prognosis, thereby facilitating a better risk-adapted treatment. Further HDAC3 may act with other potential partners except NCoR1 in the cytoplasm. Clarifying the mechanism of HDAC3 and NCoR1 nuclear/cytoplasmic distribution may help to improve survival of patients with astrocytic tumors. Therefore, a more detailed analysis of HDAC protein function, interactions between HDAC and NCoR1, is required to establish HDAC inhibitors as drugs in the treatment of astrocytic tumors, and to establish a synergistic combination of therapeutic strategy which directly targets the undifferentiated compartment.