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Title: Histone deacetylase inhibitor panobinostat reduces hypoxia-related cisplatin resistance in NSCLC cells by HDAC-mediated Hifα destabilization

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Body: Background: Lung cancer is one of the most frequent cancer types and a leading cause of cancer death worldwide. Cisplatin is an important chemotherapeutic for lung cancer; although, its positive effects are diminished under hypoxia. Aims and objectives: Hypoxia-based cisplatin resistance can be overcome by combining cisplatin with panobinostat, a potent histone deacetylase inhibitor. Methods: After co-treatment of NSCLC cells with cisplatin and low concentration panobinostat, cell viability and activation of apoptosis were analyzed. Results: Expression of most class 1 and 2 HDACs was increased in NSCLC cells and tumor samples. Cell proliferation was significantly inhibited by panobinostat in concentration- and time-dependent manner, both under normoxia and hypoxia. Compared to cisplatin treatment alone, co-treatment with 16 nM panobinostat markedly decreased cell viability. Those effects were more prominent in malignant NSCLC cells than in non-malignant bronchial epithelial cells. Co-treatment markedly induced apoptosis by causing chromatin fragmentation, activation of caspase 3 and 7 and activation of PARP. Apoptosis induction was of higher significance under hypoxic conditions, where cisplatin alone revealed only mild toxicity. In hypoxia co-treatment led to destabilization of Hif1α and Hif2α and to down-regulation of HDAC4, responsible for acetylation and thereby associated destabilization of Hifα. Conclusion: Co-treatment with panobinostat and cisplatin was able to reduce hypoxia-based cisplatin resistance in NSCLC cells, via HDAC4-mediated destabilization of Hifα. This may provide a new therapeutic strategy for NSCLC.