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Anti-Tumor Activity of HDAC Inhibitors Through Cell Cycle Arrest and Apoptosis In Vitro and In Vivo Breast Cancer Model

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In this study, we evaluated the anti-tumor activity of histone deacetylase inhibitors (HDACi) in the human breast cancer cell lines and MMTV/c-Neu transgenic mice model, erb-B2 over expressing mammary tumor model. We have found that HDACi decreased the proliferation of human breast cancer cells in a time- and dose-dependent manner. IC50 was ranging from 0.028 μM to 1.898 μM. ER positive breast cancer cell was more sensitive to HDACi than ER negative breast cancer call. However, the rank of potency for HDACi (LAQ, TSA, HC toxin >> IN2001 > SAHA) is comparable in both ER positive and ER negative breast cancer cell line. HDACi induced cell cycle arrest at G2/M phase through induction of Cdk inhibitor, p21WAF/Cip1 and down-regulation of cyclin D1. In addition, HDACi induced apoptosis, which is related with the activation of caspase cascade and increase of ratio between Bax/Bcl-2. Interestingly, HDAC inhibitors in ER negative breast cancer cell line, MDA-MB-231, resulted in significant increase of ER mRNA transcript. Furthermore, re-expression of an estrogen responsive gene, progesterone receptor (PR), indicated that induced ER is functional. In vivo experiment using MMTV/c-Neu mammary tumor model showed that HDAC inhibitors, IN2001 (15 mg/kg) or SAHA (120 mg/kg), exhibited apparent tumor regression with increase of apoptotic tumor cells. Furthermore, treatment of IN2001 (30 mg/kg) dose dependently induced re-expression of ERα and increase of p21WAF/Cip1 expression in mammary tumor and uterus tissue. Taken together, HDACi showed potent anti-tumor activity against breast cancer in vitro and in vivo, mediated by cell cycle arrest and apoptotic cell death, supporting HDAC inhibitors as novel breast cancer therapeutics

Keyword: HDAC inhibitor, human breast cancer, anti-tumor activity