【P-38】

The Effect of Histone Deacetylase Inhibitors on the Cell Proliferation and Apoptosis in Human Breast Cancer Cell Lines

Kyung Nan Min, Dae Kee Kim and Yhun Yhong Sheen
College of Pharmacy, Ewha Womans University, Seoul

Although histone deacetylase inhibitors (HDACIs) are emerging as a promising new treatment strategy in malignancy, how they exert their effect on human breast cancer cells is as yet unclear. This study was undertaken to investigate the underlying mechanism of HDACIs-induced apoptosis in human breast cancer cell lines. Therefore, the ability of HDACIs, IN2001, trichostatin (TSA), suberoylanilide hydroxamic acid (SAHA), NVP-LAQ824 and HC-toxin to induce apoptosis and inhibit cell growth of ER-positive (MCF-7) and ER-negative (MDA-MB-468) human breast cancer cell lines was examined. We observed that HDACIs treatment inhibited breast cancer cell growth in a dose-dependent manner and induced accumulation of acetylated histones. FACS analysis revealed that MCF-7 cells cultured with 1 µM HDACIs for 24 h arrested in the G2/M phase of the cell cycle. MDA-MB-468 cells were arrested in the G0/G1 and G2/M phases when cells were cultured with 1 µM for 24h. Increasing exposure times of HDACIs led to an incremental accumulation of the sub-G1 fraction (apoptotic cells).HDACIs induced expression of p21CIP1/WAF1 mRNA and protein. HDACIs potently induced a increase in reactive oxygen species (ROS), which was detected by using DCF-DA, intracellular probe of oxidative stress. We measured caspase-3/7 activity using Z-DEVD-Rhodamine 110 as a substrate. HDACIs treatment of MDA-MB-468 cells showed an increase of caspase-3/7 activity. Also, western blot analysis revealed that HDACIs induce cleavage of caspase-3, suggesting that HDACIs-induced apoptosis may be mediated via caspase-dependent system. In summury, HDACIs exhibited growth arrest, up-regulation of p21CIP1/WAF1, a marked induction of ROS, caspase cascade activation and apoptosis. Taken together, these findings demonstrate that HDACIs might be a useful agent for the treatment of malignancy.

Keyword : histone deactylase inhibitor, human breast cancer cell