HDAC inhibitor treatment of hepatoma cells induces both TRAIL-independent apoptosis and restoration of sensitivity to TRAIL.

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Abstract

Hepatocellular carcinoma (HCC) displays a striking resistance to chemotherapeutic drugs or innovative tumor cell apoptosis-inducing agents such as tumor necrosis factor-related apoptosis-inducing ligand (TRAIL). Recently, we found 2 histone deacetylase inhibitors (HDAC-I), valproic acid and ITF2357, exhibiting inherent therapeutic activity against HCC. In TRAIL-sensitive cancer cells, the mechanism of HDAC-I-induced cell death has been identified to be TRAIL-dependent by inducing apoptosis in an autocrine fashion. In contrast, in HCC-derived cells, a prototype of TRAIL-resistant tumor cells, we found a HDAC-I-mediated apoptosis that works independently of TRAIL and upregulation of death receptors or their cognate ligands. Interestingly, TRAIL resistance could be overcome by a combinatorial application of HDAC-I and TRAIL, increasing the fraction of apoptotic cells two- to threefold compared with HDAC-I treatment alone, whereas any premature HDAC-I withdrawal rapidly restored TRAIL resistance. Furthermore, a tumor cell-specific downregulation of the FLICE inhibitory protein (FLIP) was observed, constituting a new mechanism of TRAIL sensitivity restoration by HDAC-I. In contrast, FLIP levels in primary human hepatocytes (PHH) from different donors were upregulated by HDAC-I. Importantly, combination HDAC-I/TRAIL treatment did not induce any cytotoxicity in nonmalignant PHH. In conclusion, HDAC-I compounds, exhibiting a favorable in vivo profile and inherent activity against HCC cells, are able to selectively overcome the resistance of HCC cells toward TRAIL. Specific upregulation of intracellular FLIP protein levels in nonmalignant hepatocytes could enhance the therapeutic window for clinical applications of TRAIL, opening up a highly specific new treatment option for advanced HCC.

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Histone deacetylase inhibition by valproic acid down-regulates c-FLIP/CASH and sensitizes hepatoma cells towards CD95- and TRAIL receptor-mediated apoptosis and chemotherapy.

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Abstract

Hepatocellular carcinoma (HCC) is highly resistant to chemotherapy, leading to a poor prognosis of advanced disease. Inhibitors of histone deacetylation (HDAC) induce re-differentiation in tumor cells and thereby re-establish sensitivity towards apoptotic stimuli. HDACi are entering the clinical stage of tumor treatment, and several substances are currently being tested in clinical trials to prove their efficacy in the treatment of leukemias and solid tumors. In this study, we investigated the impact of the HDACi valproic acid (VA) on TRAIL- and CD95-mediated apoptosis in hepatoma cells, as well as its sensitizing effect on a chemotherapeutic agent. Treatment of HepG2 cells with VA increased sensitivity to CD95-mediated apoptosis (4% apoptosis vs. 42%), and treatment with epirubicin (74% vs. 90% viability). Caspase-3 activity was significantly enhanced in cells treated with VA plus anti-CD95 antibodies compared to cells treated with antibodies alone. In parallel, VA strongly augmented the effect of TNF-related apoptosis-inducing ligand (TRAIL or Apo2 ligand) on HepG2 cells (10% vs. 58% apoptosis). VA induced down-regulation of cellular FLICE-inhibitory protein (c-FLIP/CASH, also known as Casper/FLICE/FLAME-1/CLARP/MRIT/usurpin), providing a possible molecular mechanism underlying the increased sensitivity towards cell death-mediated apoptosis. HDAC inhibitors are a promising class for the treatment of leukemias. In addition, among other class members, VA deserves further evaluation as a treatment option for patients with advanced HCC.

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