HDAC2 attenuates TRAIL-induced apoptosis of pancreatic cancer cells.

Abstract:
Pancreatic ductal adenocarcinoma (PDAC) is one of the most malignant tumors with a dismal prognosis and no effective conservative therapeutic strategies. Although it is demonstrated that histone deacetylases (HDACs), especially the class I HDACs HDAC1, 2 and 3 are highly expressed in this disease, little is known about HDAC isoenzyme specific functions. Depletion of HDAC2, but not HDAC1, in the pancreatic cancer cell lines MiaPaCa2 and Panc1 resulted in a marked sensitization towards the tumor necrosis factor-related apoptosis-inducing ligand (TRAIL). Correspondingly, the more class I selective HDAC inhibitor (HDACI) valproic acid (VPA) synergized with TRAIL to induce apoptosis of MiaPaCa2 and Panc1 cells. At the molecular level, an increased expression of the TRAIL receptor 1 (DR5), accelerated processing of caspase 8, pronounced cleavage of the BH3-only protein Bid, and increased effector caspase activation was observed in HDAC2-depleted and TRAIL-treated MiaPaCa2 cells. Our data characterize a novel HDAC2 function in PDAC cells and point to a strategy to overcome TRAIL resistance of PDAC cells, a prerequisite to succeed with a TRAIL targeted therapy in clinical settings.