HDAC2 mediates therapeutic resistance of pancreatic cancer cells via the BH3-only protein NOXA.

BACKGROUND: Although histone deacetylase inhibitors (HDACi) are promising cancer therapeutics regulating proliferation, differentiation and apoptosis, molecular pathways engaged by specific HDAC isoenzymes in cancer are ill defined.

RESULTS: In this study we demonstrate that HDAC2 is highly expressed in pancreatic ductal adenocarcinoma (PDAC), especially in undifferentiated tumours. We show that HDAC2, but not HDAC1, confers resistance towards the topoisomerase II inhibitor etoposide in PDAC cells. Correspondingly, the class I selective HDACi valproic acid (VPA) synergises with etoposide to induce apoptosis of PDAC cells. Transcriptome profiling of HDAC2-depleted PDAC cells revealed upregulation of the BH3-only protein NOXA. We show that the epigenetically silenced NOXA gene locus is opened after HDAC2 depletion and that NOXA upregulation is sufficient to sensitise PDAC cells towards etoposide-induced apoptosis.

CONCLUSIONS: In summary, our data characterise a novel molecular mechanism that links the epigenetic regulator HDAC2 to the regulation of the pro-apoptotic BH3-only protein NOXA in PDAC. Targeting HDAC2 will therefore be a promising strategy to overcome therapeutic resistance of PDAC against chemotherapeutics that induce DNA damage.