

HDAC INHIBITORS RESTORE THE p53 PATHWAY IN NEUROBLASTOMA CELLS

Ilaria Gnemmi, Fabrizio Condorelli, Armando A. Genazzani and Pier Luigi Canonico

DiSCAFF&DFB Center, Università del Piemonte Orientale, Novara, Italy

HDAC inhibitors are emerging as a new and promising class of compounds useful in the treatment of cancer by modulating histone acetylation and gene transcription. A generic induction of transcription would hardly explain how HDACi specifically affect the viability of transformed cells vs. normal one. Given that, in this study we evaluated more in deep the molecular mechanisms by which HDACi, butyric (Bu) and valproic (VPA) acid, affect neuroblastoma viability.

1.HDACi-induced cell death relied on the mitochondrial pathway of apoptosis with the recruitment of BCL-2 family members. In accord with this, a cell line over-expressing BCL-2 became resistant to HDACi treatment.

2.Furthermore, HDACi (0.3 mM) caused a G1 cell-cycle arrest, as demonstrated by FACS analysis. Accordingly, we detected a marked increase in the protein levels of p21/Waf1/Cip1 and p27/Kip1 following HDACi treatment.

3.As described in literature NOXA, PUMA and p21/Cip/Waf1 are induced by p53 activation, an event usually impaired in neuroblastoma cells. Surprisingly, HDACi restored p53 re-localization and activity via an increase of its hyper-acetylated form without affecting its protein expression.

All these data together demonstrate that, in neuroblastoma, HDACi may overcome the resistance to classical chemotherapeutic drugs by enabling the p53 pathway via its hyper-acetylation.