Valproic acid treatment response in vitro is determined by TP53 status in medulloblastoma.

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PURPOSE: Histone deacetylase inhibitors (HDACi), as valproic acid (VA), have been reported to enhance efficacy and to prevent drug resistance in some tumors, including medulloblastoma (MB). In the present study, we investigated VA role, combined to cisplatin (CDDP) in cell viability and gene expression of MB cell lines.

METHODS: Dose-response curve determined IC₅₀ values for each treatment: (1) VA single, (2) CDDP single, and (3) VA and CDDP combined. Cytotoxicity and flow cytometry evaluated cell viability after exposure to treatments. Quantitative PCR evaluated gene expression levels of AKT, CTNNB1, GLI1, KDM6A, KDM6B, NOTCH2, PTCH1, and TERT, before and after treatment. Besides, we performed next-generation sequencing (NGS) for PTCH1, TERT, and TP53 genes.

RESULTS: The most effective treatment to reduce viability was combined for D283MED and ONS-76; and CDDP single for DAOY cells (p < 0.0001). TERT, GLI1, and AKT genes were overexpressed after treatments with VA. D283MED and ONS-76 cells presented variants in TERT and PTCH1, respectively and DAOY cell line presented a TP53 mutation.

CONCLUSIONS: MB tumors belonging to SHH molecular subgroup, with TP53MT, would be the ones that present high risk in relation to VA use during the treatment, while TP53WT MBs can benefit from VA therapy, both SHH and groups 3 and 4. Our study shows a new perspective about VA action in medulloblastoma cells, raising the possibility that VA may act in different patterns. According to the genetic background of MB cell, VA can stimulate cell cycle...
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