Valproic acid synergistically enhances the cytotoxicity of gossypol in DU145 prostate cancer cells: An iTRAQ-based quantitative proteomic analysis.

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Source

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Abstract

Gossypol (GOS), a BH3 mimic, has been investigated as a sensitizing co-therapy to radiation and chemotherapy in treatment of metastatic prostate cancer. In this study, we found that valproic acid (VPA), a histone deacetylase inhibitor (HDACI), counteracted the suppressive effect of GOS on histone H3 acetylation and enhanced the cytotoxicity of GOS to DU145 prostate cancer cells. Significant synergistic effects were observed in combined GOS and VPA treatment, culminating in more DNA damage and cell death. The iTRAQ-based quantitative proteomic analysis revealed differential proteomic profiles in cells treated with VPA, GOS or their combination. In GOS-treated cells, oxidative phosphorylation-related proteins were depressed and endoplasmic reticulum stress markers were upregulated. In the presence of VPA, the GOS-induced mitochondrial stress was further enhanced since glycolysis- and hypoxia-associated proteins were upregulated, suggesting a disruption of energy metabolism in these cells. Furthermore, the DNA damage repair ability of cells co-treated with GOS and VPA was also decreased, as evidenced by the downregulation of DNA damage repair proteins and the enhancement of DNA fragmentation and cell death. These findings suggest that GOS in combination with an HDACI has the potential to increase its clinical efficacy in the treatment of prostate cancer.