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Histone Deacetylases Inhibitor - Valproic Acid Sensitizes Human Melanoma Cells for alkylating agent and PARP inhibitor

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Abstract : The inhibition of histone deacetyles (HDACs) holds promise as a potential anti-cancer therapy because histone and non-histone protein acetylation is frequently disrupted in cancer, leading to cancer initiation and progression. Additionally, histone deacetylase inhibitors (HDACi) such as class I HDAC inhibitor - valproic acid (VPA) have been shown to enhance the effectiveness of DNA-damaging factors, such as cisplatin or radiation. In this study, we found that, using of VPA in combination with talazoparib (BMN-637 – PARP1 inhibitor – PARPi) and/or Dacarabazine (DTIC - alkylating agent) resulted in increased DNA double strand break (DSB) and reduced survival (while not affecting primary melanocytes)and proliferation of melanoma cells. Furthermore, pharmacologic inhibition of class I HDACs sensitizes melanoma cells to apoptosis following exposure to DTIC and BMN-637. In addition, inhibition of HDAC caused sensitization of melanoma cells to dacarbazine and BMN-637 in melanoma xenografts in vivo. At the mRNA and protein level histone deacetylase inhibitor downregulated RAD51 and FANCD2. This study provides that combining HDACi, alkylating agent and PARPi could potentially enhance the treatment of melanoma, which is known for being one of the most aggressive malignant tumors. The findings presented here point to a scenario in which HDAC via enhancing the HR-dependent repair of DSBs created during the processing of DNA lesions, are essential nodes in the resistance of malignant melanoma cells to methylating agent-based therapies.

Keywords : melanoma, hdac, parp inhibitor, valproic acid
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