

Novel Combination Strategies Targeting HDAC and IKK in Solid Cancer

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Histone deacetylase (HDAC) inhibitors (HDIs) were developed as anticancer agents based on their ability to induce apoptosis and cell cycle arrest in cancer cells. Unfortunately, while HDIs have been remarkably effective in the treatment of hematological malignancies, they have been far less effective, as single agents, in solid tumors, however, the responsible mechanisms are not fully understood. Interestingly, our recent studies have shown that, in addition to inducing apoptosis in cancer cells, HDIs induce expression of the pro-inflammatory and pro-angiogenic chemokine interleukin-8 (IL-8), which induces survival, proliferation and migration of solid tumor cells. In ovarian cancer (OC) cells, the IL-8 expression induced by HDAC inhibition is dependent on I κ B kinase (IKK) activity and associated with a gene-specific recruitment of p65 NF κ B to IL-8 promoter. In addition, HDAC inhibition induces acetylation of p65 and its occupancy at the IL-8 promoter in OC cells. Importantly, inhibition or neutralization of the HDI-induced IL-8 expression attenuates proliferation of OC cells *in vitro* and combining HDAC and IKK inhibitors significantly reduces ovarian tumor growth *in vivo*, when compared to either drug alone. Together, our results suggest that using IKK inhibitors may increase effectiveness of HDAC inhibitors in treating ovarian cancer and perhaps other solid tumors characterized by the increased IL-8 expression. Future studies and clinical trials should examine whether IKK inhibitors might potentiate the effectiveness of HDIs in OC and other solid cancers.

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Biography:

Ivana Vancurova, Ph.D, is a Professor of Biological Sciences at St. John's University in New York. Dr. Vancurova is the author of more than 75 peer-reviewed publications. Her research focuses on understanding the transcriptional mechanisms that regulate expression of immuno-regulatory genes, as they relate to cancer development and progression, as well as to numerous inflammatory disorders. Dr. Vancurova has trained many graduate and undergraduate students, who after graduating from her laboratory, assumed research positions at premier research institutions. Her research has been funded by the National Institutes of Health.