Lysine deacetylase inhibitors enhance IRF1-Adenoviral gene therapy.

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Rationale. Immunotherapy treatments can enhance the ability of immune cells to target and eliminate tumors, leading to improved treatment outcomes and potentially long-lasting remissions. Different agents, ranging from therapeutic antibodies to live-attenuated bacteria, are employed for immune stimulation in cancer therapy. A current and critical challenge regards the prospect of concomitantly targeting tumor cells and the tumor microenvironment by combining immunotherapy agents with other forms of treatment, including epigenetic modifiers. Within the framework of this challenge, we aim to combine viral-mediated delivery of a transcription factor with tumor suppressor and immune stimulatory abilities with agents that open chromatin, thus allowing for its access to epigenetically silenced genes. We focus on Interferon regulatory factor 1 (IRF1), which is critically involved in immune regulation, anti-viral responses, apoptosis, and tumor suppression. We also focus on lysine deacetylase inhibitors (KDACIs), which are clinically employed against hematological malignancies but have yet to fulfill their potential against solid tumors.

Results. Our preliminary results, employing bladder cancer cells, revealed a substantial KDACi-mediated reduction in endogenous IRF1 expression, suggesting a potential incompatibility in the KDACi-IRF1 combination. Experiment aimed at unraveling the molecular basis of this phenomenon revealed that the KDACi-mediated reduction was not due to enhanced degradation and occurred even in conditions where IRF1 mRNA was increased. However, IRF1 expressed from transcripts devoid of endogenous untranslated regions (UTRs) was immune to KDACi-mediated repression. Currently, we are testing the hypothesis that KDACis regulate IRF1 at the translation level, with dependence on its message's UTRs. Importantly, the resistance of IRF1 devoid of its UTRs (IRFΔUTRs) to KDACi-mediated repression opened the possibility of combining them for cancer therapy. For this, I have developed an adenoviral vector delivering IRFΔUTRs, enabling efficient gene transfer and overcoming the translational blockade imposed by KDACIs. Combined treatment with KDACIs and IRF1ΔUTR increased adenovirus infection, enhanced IRF1 expression, and activated IRF1 target genes. Treated/infected bladder cancer cells also exhibited activation of innate immune signaling pathways and augmented cell death.

Significance. Our findings elucidate the role of acetylation in regulating IRF1 expression and demonstrate the potential of combining KDACIs with adenoviral delivery of IRF1ΔUTR as a novel therapeutic approach.