Abstract

Exploring Novel Therapeutic Strategies in Pancreatic Cancer: Epigenetic Reprogramming Induced by Small Molecule Combinations.

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Pancreatic cancer management presents significant challenges due to late-stage diagnosis, aggressive tumor biology, and limited efficacy of existing treatment options. Our study explores a small molecule combination to induce epigenetic reprogramming as a potential therapeutic strategy. We demonstrate that treatment with a combination of romidepsin and a novel small molecule initiates modulation of the histone code, with unexpected persistent H3K9 and H3K27 acetylation. It induces global transcription and causes DNA damage, which results in a synergistic anti-proliferative response in pancreatic cancer cells. Additionally, treatment with the combination demonstrates efficacy in inhibiting tumor growth in a xenograft mouse model of pancreatic cancer. Our studies into the mechanism of this combination treatment show the increase in global transcription is associated with significant R-loop accumulation that may contribute to the observed DNA damage and genome instability. Further, the combination treatment causes a significant reduction in the cellular acetyl-CoA levels, as well as a decrease in levels of c-MYC protein and its targets, and impairment of both glycolysis and OXPHOS processes. Forced overexpression of MYC appears to increase the sensitivity of pancreatic cells to this treatment, potentially indicating a therapeutic advantage for MYC-overexpressing/MYC-addicted PDAC tumors. Overall, the enhanced toxicity in cancer cells post-treatment with the combination appears to be driven by a simultaneous increase in genomic instability and a decrease in ATP production.