Novel Dual Inhibitors of PARP and HDAC Induce Intratumoral STING-Mediated Antitumor Immunity in Triple-Negative Breast Cancer

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Abstract

Background and Purpose: PARP and HDAC inhibitors are approved for the clinical treatment of malignancies, but acquired resistance or limited effects on solid tumors with single-agent present challenges. Therefore, there is an urgent need to design and synthesis of dual inhibitors involving a different mechanism of action can provide new treatments. Experimental Approach: We validate the correlation and synergy between PARP and HDAC by database analysis and colony formation assay. Novel dual PARP and HDAC inhibitors antitumor effects in vitro were validated by flow cytometry and cell biology analysis. Pharmacological characterization was characterized by enzymatic inhibition assays, cell viability assays, western blot, real-time PCR, immunofluorescence analyses. The antitumor effect in vivo was validated in MDA-MB-436 and 4T1 xenograft mouse models. Key Results: Bioinformatics analyses and a combination of experiments demonstrate the synergistic effects of PARP and HDAC inhibitors in triple-negative breast cancer. Novel dual PARP and HDAC inhibitors were rationally designed and synthesized, and exhibited high enzyme inhibition activity, showing excellent antitumor effects in vitro and in vivo. Mechanistically, dual PARP and HDAC inhibitors significantly induced BRCAness to restore synthetic lethality and the accumulation of cytosolic DNA to activate the cGAS–STING pathway and produce proinflammatory chemokines through type I IFN-mediated JAK–STAT signaling. Moreover, these inhibitors promoted neoantigen generation and upregulated antigen presentation genes and PD-L1. Conclusion and Implications: Novel dual PARP and HDAC inhibitors showing excellent antitumor effect via the activation of the tumoral IFN signaling and cytokine production to enhance the immune response for triple-negative breast cancer.

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