The Epigenetic Regulation of Immunotherapy Antigen Targets

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Abstract:

Ewing sarcoma is a bone and soft tissue tumor commonly seen in adolescents and young adults. One powerful strategy of immunotherapy, a non-chemotherapy approach for pediatric cancer treatment, utilizes chimeric antigen receptor CAR-T cells to target specific tumor cell surface antigens. Although CAR-T cells have demonstrated benefit in treating pediatric hematologic malignancies, they have had less success in the treatment of pediatric bone and soft tissue tumors such as Ewing sarcoma due in part to heterogenous expression of target antigens. One candidate antigen is the disialoganglioside GD2, which is the target of antibody therapy in relapsed/refractory and high-risk neuroblastoma. Given the paucity of mutations in pediatric tumors, we hypothesized that the expression of GD2 is epigenetically regulated and can be enhanced using small molecules targeting chromatin regulatory proteins. To address this question, we test changes in cell surface GD2 levels and the gene expression of the synthetic enzymes involved in the biosynthetic pathway of GD2 expression following treatment with small molecule inhibitors. Here, we identified a combination of two chromatin-directed small molecules (tazemetostat and pinometostat) that enhance GD2 expression in Ewing sarcoma, improving CAR-T cell killing efficacy. We also demonstrated that while constant exposure to tazemetostat is necessary for GD2 expression, only short-term co-exposure to pinometostat strongly increased GD2 levels compared to treatment with tazemetostat alone, correlating with increased levels of key enzymes within the GD2 biosynthetic pathway. The finding of shortened therapy time enhances clinical trial feasibility for CAR-T cell therapy and extends applicability to other cancer treatments and combination drug therapies.

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