HG-23. BET INHIBITORS WORK SYNERGISTICALLY WITH PANOBINOSTAT IN TREATING DIFFUSE INTRINSIC PONTINE GLIOMA

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Diffuse intrinsic pontine glioma (DIPG) is a devastating childhood brain tumor with a median survival of ~9 months. Epigenetic dysregulation has been shown to play a critical role in DIPG pathogenesis since the identification of H3-K27M mutation. We have recently reported that the histone deacetylase inhibitor (HDACi) panobinostat is effective in treating DIPG in preclinical models, suggesting epigenetic therapy could be a promising strategy for DIPG treatment. Bromodomain and Extraterminal-motif inhibitors (BETi) are a novel class of epigenetic drugs that has been shown to effectively inhibit many treatment-refractory cancers through targeting epigenetic cis-element super-enhancers. To evaluate the therapeutic potential of BET inhibitors against DIPG, multiple patient-derived DIPG cell cultures were treated with BET inhibitors as single agents or in combination with panobinostat. Our results showed that BETi alone inhibited cell viability of DIPG in vitro. Therapeutic effects were exerted through inhibiting proliferation and inducing apoptosis. BETi treatment resulted in strongly enriched HDACi-related gene signatures. Moreover, BETi together with panobinostat synergistically reduced DIPG cell viability. Compared to single drug treatment, combination treatment resulted in much stronger inhibition of proliferation and induction of apoptosis. Our study suggests that BET inhibition could be a novel therapeutic strategy against DIPG either as a single agent or in combination with panobinostat. The synergistic therapeutic effects may result from their similar effects on gene expression. Since many BETi drugs are currently undergoing early-phase clinical trials, our study provides a rational for BETi or BETi + HDACi trials for DIPG as these agents become clinically available.