



Cytotoxic potential of Mithramycin against DIPG cell lines

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Research Background

Diffuse Intrinsic Pontine Glioma (DIPG) is a glial tumor occurring primarily in children with extremely poor prognosis. Occurring outside of the pons, surgery following diagnosis is not viable for DIPG patients as the location of the tumor is vital for motor functions. There has yet to be a significant improvement in the survival median rate upon diagnosis outside of the effects of radiation therapy. Though radiation therapy has proven to improve neurological symptoms of DIPG patients, the results of this treatment have proven to be transitory at best. Currently, there is an interest in looking at specific oncogenic targets to find the most efficacious biological agent(s) to decrease tumor cell growth. Mithramycin is a relatively new anticancer drug reported to be effective against variety of cancers. It blocks Specificity protein-1 (Sp1) from binding to DNA through its guanine-cytosine (G-C)-specific DNA-binding ability and selectively downregulates an X-linked inhibitor of apoptosis protein (XIAP) levels, therefore increasing levels of apoptosis in cancer cells. SET Domain Bifurcated Histone Lysine Methyltransferase 1 (coded by SETDB1 gene) is an enzyme that reversibly catalyzes methylation in Histone 3 K9 (H3K9). SETDB1 is heavily involved in the downregulation of vital tumor-suppressive genes, adding to its pro-oncogenic nature and is recently found to be overexpressed in DIPGs by our lab. Mithramycin was reported to be a SETDB1 inhibitor by blocking the interaction between SP-1 and SETDB1 regulatory sites.

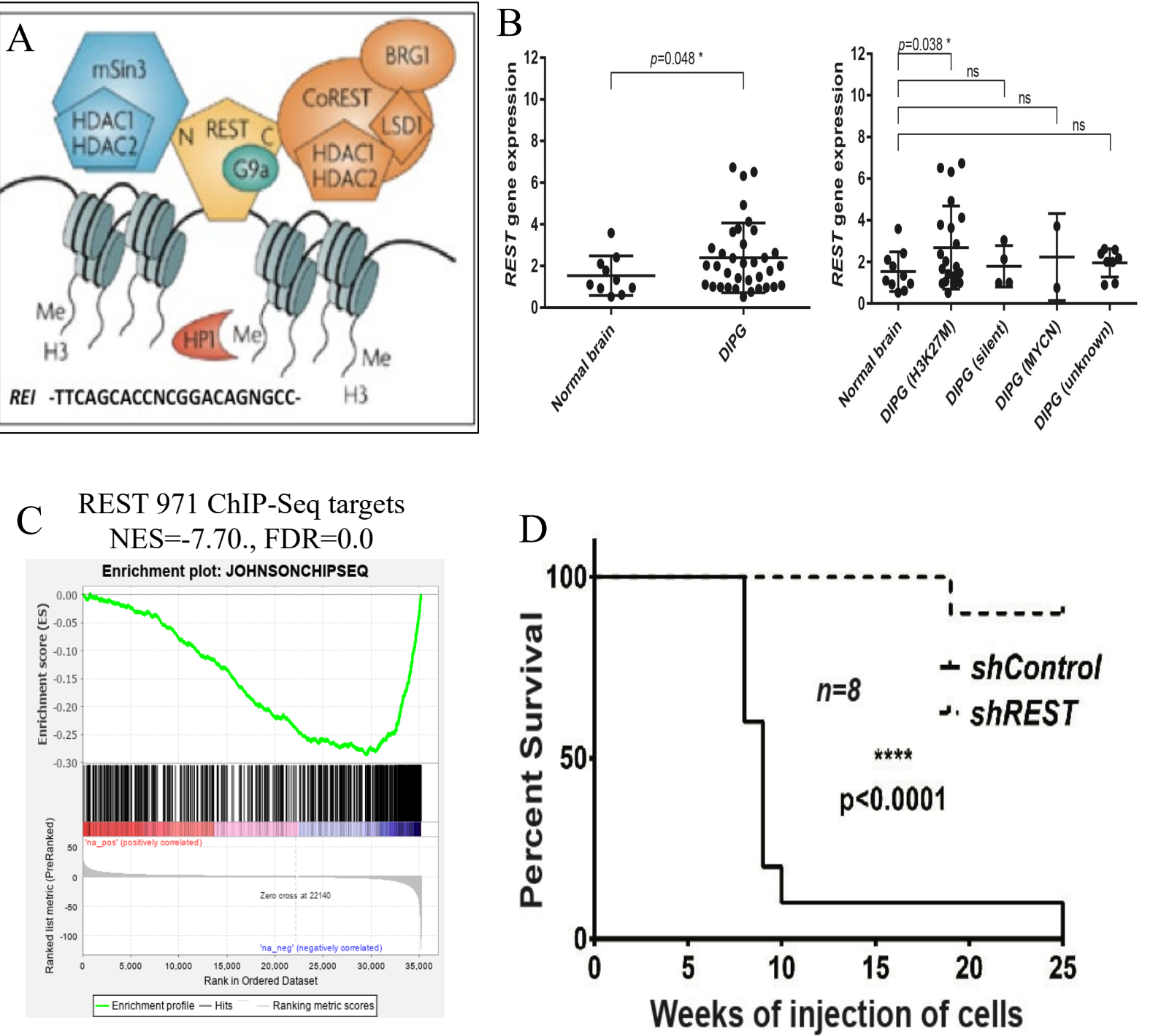


Figure 1: (A) REST complex & its binding to RE1 sites. (B) REST expression in DIPGs. (C) ChIPseq shows decreased expression of genes where promoters are bound by REST in DIPGs. (D) ATACseq and RNAseq combined analysis revealed REST and SETDB1 are hyperactive TFs in DIPGs. (E) REST knockdown block DIPG tumors and increase survival in mice models.

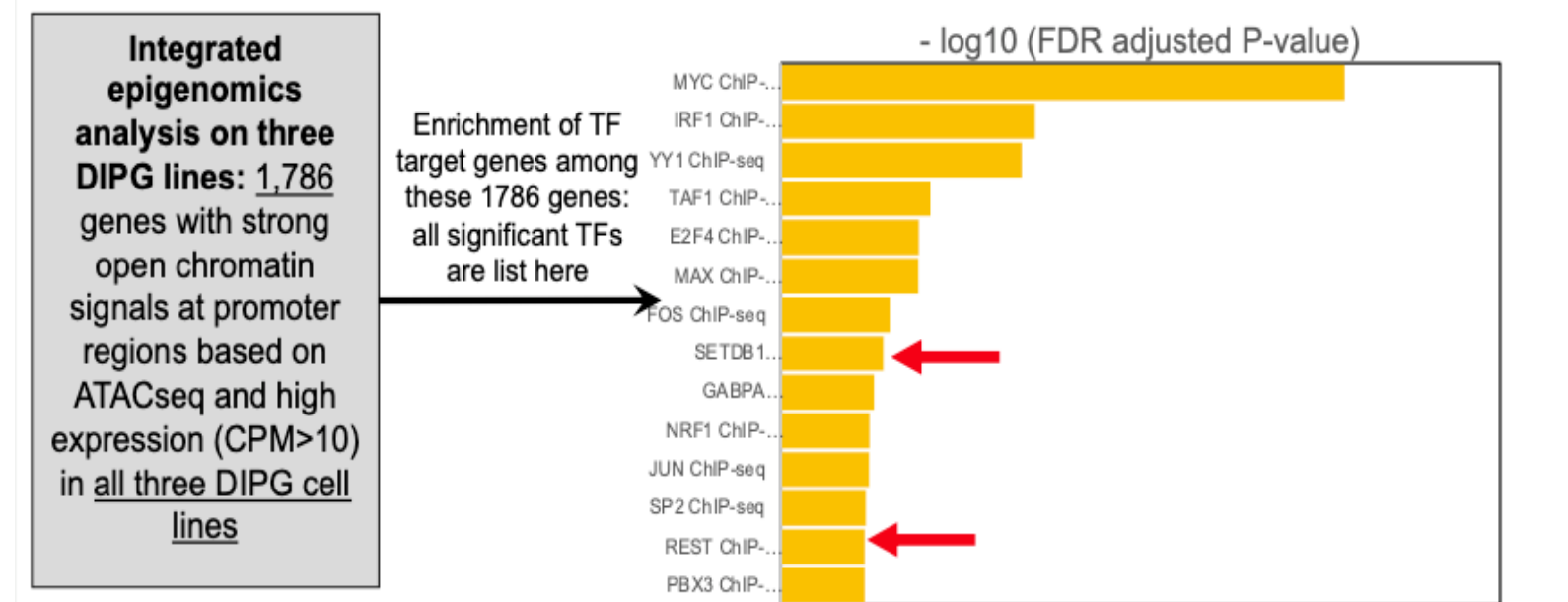


Figure 2: (A) DIPG 7 cells. (B) DIPG 4 cells. (C) DIPG 13 cells. (D) DIPG 7REST cells. (E) DIPG 4REST cells. (F) DIPG 13REST cells. (G) DIPG 7REST cells. (H) DIPG 4REST cells. (I) DIPG 13REST cells. (J) DIPG 7REST cells. (K) DIPG 4REST cells. (L) DIPG 13REST cells. (M) DIPG 7REST cells. (N) DIPG 4REST cells. (O) DIPG 13REST cells. (P) DIPG 7REST cells. (Q) DIPG 4REST cells. (R) DIPG 13REST cells. (S) DIPG 7REST cells. (T) DIPG 4REST cells. (U) DIPG 13REST cells. (V) DIPG 7REST cells. (W) DIPG 4REST cells. (X) DIPG 13REST cells. (Y) DIPG 7REST cells. (Z) DIPG 4REST cells. (AA) DIPG 13REST cells. (AB) DIPG 7REST cells. (AC) DIPG 4REST cells. (AD) DIPG 13REST cells. (AE) DIPG 7REST cells. (AF) DIPG 4REST cells. (AG) DIPG 13REST cells. (AH) DIPG 7REST cells. (AI) DIPG 4REST cells. (AJ) DIPG 13REST cells. (AK) DIPG 7REST cells. (AL) DIPG 4REST cells. (AM) DIPG 13REST cells. (AN) DIPG 7REST cells. (AO) DIPG 4REST cells. (AP) DIPG 13REST cells. (AQ) DIPG 7REST cells. (AR) DIPG 4REST cells. 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