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Dopamine Receptor D2 (DRD2): Potential therapeutic target for H3K27M-pediatric glioblastoma

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Glioblastoma (GBM) is a highly prevalent and aggressive brain tumor in adults and pediatrics. In high-grade pediatric glioma, the median survival ranges from 14 to 20 months, with a 5-year survival rate of <20%. Transcriptomic analyses of pediatric glioblastoma (pGBM) tissues have shown high histone mutation (H3K27M- aggressive glioma subtype) compared to adult GBM (aGBM) samples. H3K27M-glioma is highly correlated with a subtype of midline brain tumors known as diffuse midline gliomas. This mutation results in a global loss of trimethylated histone (H3K27me3), leading to epigenetic silencing and activation of various regions of the genome and tumorigenesis. Dopamine Receptor D2 (DRD2) expression increased in several cancers and its activation prompts transcriptomic and metabolic plasticity in GBM. Interestingly, DRD2 expression is higher in H3K27M mutant gliomas than in wild-type gliomas. DRD2 antagonists reportedly reduce the aGBM cell lines by inhibiting the Akt/phosphoinositide 3-kinase (PI3K) pathway and inducing apoptosis. Therapy for diffuse midline gliomas is not well defined, but the current standard of care includes maximal safe resection and conventional aGBM chemotherapy and radiation. Deep-seated and difficult to access, resection is often not safely possible which further necessitates the need for development of more effective adjuvant therapeutics. We hypothesize that DRD2 antagonists will preferentially suppress pediatric GBM, especially H3K27M cells, *in vitro*. We set out to repurpose prior FDA-approved DRD2 antagonists with blood-brain barrier permeability to identify novel therapeutic agent against H3K27M pGBM. The selected drugs were tested using *in-vitro* H3K27M pGBM cell lines. The viability and proliferation of the pGBM cells were evaluated with 3-(4,5-dimethylthiazol-2-yl)-2,5diphenyltetrazolium bromide (MTT) assay and colony formation assay. Apoptosis was measured by flow cytometry using the annexin V-propidium iodide. DRD2 antagonists (Aripiprazole, Paliperidone, and Risperidone) treatment resulted in a dose-dependent decrease of H3K27M (SF8628 and SF7761) cells proliferation. DRD2 antagonists effectively suppressed the pGBM cells proliferation and colony formation potential at lower concentrations (12-50 μM). The antiproliferation effect was evidenced by an increase apoptosis through caspase activation, cleaved PARP, and decreased ERK activation. Furthermore, immunoblot results showed that aripiprazole treatment decreased cMyc and preserved trimethylated histones (H3K27me3). Altogether, these results support the hypothesis that the tested DRD2 antagonists can suppress the proliferation of H3K27M-pGBM cells. DRD2 antagonists may represent an innovative strategy for treating H3K27M-pGBM, and further studies are warranted in glioma xenograft models.