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Review

Epigenetic pathways and plasticity in brain tumors

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ABSTRACT

Clinical studies have shown that treating many primary brain tumors is challenging due in part to the lack of safe and effective compounds that cross the blood brain barrier (BBB) (Tan et al., 2018). However, if we were to imagine that we have ideal BBB penetrant compounds that target brain tumor cells selectively, recent studies suggest that those compounds may still not be effective due to the heterogenous nature of the tumors. In other words, there are many subsets of cells within a brain tumor, and compounds that target all those different populations are needed. This is a considerable challenge. Targeting of the cell-of-origin of these brain tumors is equally important. And yet another impediment we face is that brain tumor cells-of-origin may be protean and are able to differentiate into other cell types to drive recurrence. Therefore, an ideal BBB-penetrant compound targeting a cell-of-origin in a brain tumor may be ineffective due to the cell's ability to differentiate into another resistant cell type. One possible means of combating the plastic nature of these cells is targeting epigenetic pathways used by the cells to differentiate into other cell types along with standard treatment regimens. We summarize here some of the epigenetic pathways that have been shown to be active in three different primary brain tumors, glioblastoma (GBM), medulloblastoma (MB), and diffuse intrinsic pontine glioma (DIPG). We also compare recent single-cell RNA sequencing analyses of these tumors in order to identify common epigenetic pathways to treat the respective cells-of-origin for these tumors. Lastly, we discuss possible combination therapies that may be generalizable for treating these and other brain tumors using multi-omics approaches. While our focus on these three tumor types is not exhaustive and certainly other brain tumors can have similar mechanisms, there has been significant recent evidence linking epigenetics, plasticity, and intratumor heterogeneity in these tumors.

Abbreviations: (EZH2), ENHANCER OF ZESTE HOMOLOG 2; (KDM4A), LYSINE-SPECIFIC DEMETHYLASE 4A; (RBBP5), RETINOBLASTOMA-BINDING PROTEIN 5; (SUZ12), SUZ12 POLYCOMB REPRESSIVE COMPLEX 2 SUBUNIT; (OCT4), POU DOMAIN CLASS 5 HOMEOBOX 2; (NANOG), HOMEOBOX PROTEIN NANOG; (SOX2), SRY-BOX TRANSCRIPTION FACTOR 2; (PDGFRA), PLATELET DERIVED GROWTH FACTOR ALPHA; (CDK4), CYCLIN DEPENDENT KINASE 4; (EGFR), EPIDERMAL GROWTH FACTOR RECEPTOR; (NF1), NEUROFIBROMATOSIS 1; (NF-Kb), NUCLEAR FACTOR KAPPA-LIGHT-CHAIN-ENHANCER OF ACTIVATED B CELLS; (CD24), CLUSTER OF DIFFERENTIATION 24; (PRC2), POLYCOMB REPRESSIVE COMPLEX 2; (BRD4), BROMODOMAIN-CONTAINING PROTEIN 4; (P-TEFB), POSITIVE TRANSRIPTION ELONGATION FACTOR B; (MYC), MYC PROTO-ONCOGENE; (MELK), MATERNAL EMBRYONIC LEUCINE ZIPPER KINASE; (MGMT), O-6-METHYLGUANINE-DNA METHYLTRANSFERASE; (HDAC1), HISTONE DEACETYLASE 1; (HDAC2), HISTONE DEACETYLASE 2; (PTCH1), PATCHED HOMOLOG 1; (SMO), SMOOTHENED HOMOLOG; (SUFU), SUPPRESSOR OF FUSED HOMOLOG; (GLI2), ZINC FINGER PROTEIN GLI2; (MYCN), N-MYC PROTO-ONCOGENE; (KMT2D), HISTONE-LYSINE N-METHYLTRANSFERASE 2D; (KMT2C), HISTONE-LYSINE N-METHYLTRANSFERASE 2C; (SMARCA4), SWI/SNF RELATED, MATRIX ASSOCIATED, ACTIN DEPENDENT REGULATOR OF CHROMATIN SUBFAMILY A, MEMBER 4; (ARID1A), AT-RICH INTERACTIVE DOMAIN-CONTAINING PROTEIN 1A; (CHD7), CHROMODOMAIN-HELICASE-DNA-BINDING PROTEIN 7; (ZMYM3), ZINC FINGER MYM-TYPE CONTAINING 3; (TRRAP), TRANSFORMATION/TRANSCRIPTION DOMAIN ASSOCIATED PROTEIN; (MED13), MEDIATOR COMPLEX SUBUNIT 13; (CREBBP), CREB-BINDING PROTEIN; (TP53), TUMOR PROTEIN 53; (BAI1), BRAIN-SPECIFIC ANGIOGENESIS INHIBITOR-1; Mdm2, E3 UBIQUITIN-PROTEIN LIGASE MDM2; (*BRPF1*), PEREGRIN; (GFI1), GROWTH FACTOR INDEPENDENT 1 TRANSCRIPTION REPRESSOR; (GFI1B), GROWTH FACTOR INDEPENDENT 1B TRANSCRIPTIONAL REPRESSOR; (OLIG2), OLIGODENDROCYTE TRANSCRIPTION FACTOR 2; (PI3K), PHOSPHATIDYLINOSITOL 3-KINASE; (APOE), APOLIPOPROTEIN E; (GFAP), GLIAL FIBRILLARY ACIDIC PROTEIN; (MBP), MYELIN BASIC PROTEIN

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1. Glioblastoma

Despite intensive efforts in basic, translational, and clinical research, GBM remains the most aggressive primary adult brain tumor, with a 5-year survival rate below 6% (Delgado-López and Corrales-García, 2016). The current standard of care for GBM includes maximal surgical resection of the tumor, radiotherapy, and treatment with the alkylating agent temozolomide (TMZ). Following current treatments, tumor recurrence is all but inevitable, reinforcing the need for new, more effective treatments. Interestingly, recent large genomic longitudinal studies published by the Glioma Longitudinal AnalySiS (GLASS) consortium indicate that any selection induced by current treatments appeared to be largely random, and did not lead to the expansion of any specific mutations (Barthel et al., 2019). If mutational evolution is not driving therapeutic resistance in GBM, epigenetic pathways may be major contributors. Consistent with this notion, resistance to TMZ treatment has been observed in patients with hypomethylation of the O^6-methylguanine-DNA methyl-transferase (MGMT) promoter. Most patients with an unmethylated MGMT promoter show longer progression free survival, implicating epigenetic factors as potential therapeutic targets. Other DNA modifications have recently been identified in GBM progression and survival as well, such as N^6-methyladenine (N^6-ma) epigenetic marks (Xie et al., 2018). N^6-ma levels are regulated by the DNA demethylase ALKBH1, and targeting ALKBH1 can attenuate tumor growth and extend survival in GBM models *via* the transcriptional silencing of oncogenes caused by N^6-ma accumulation (Xie et al., 2018). These critical studies suggest that epigenetic pathways controlling DNA modifications may be important therapeutic targets in newly diagnosed and recurrent GBM.

2. Epigenetics and heterogeneity in GBM

2.1. GBM epigenetic landscape

The targeting of epigenetic pathways is complicated by the heterogeneity of the GBM epigenetic landscape. For example, DNA methylation patterns within single GBM tumors are extremely heterogeneous when compared to other brain tumors such as meningiomas (Wenger et al., 2019). Further, looking at different regions within a single GBM tumor, intratumor methylation patterns vary more so than the typical observed variation among patients (Wenger et al., 2019). These methylation patterns also shift through time, wherein a recurrent tumor may show a separate methylation landscape relative to the newly diagnosed tumor from which it arose (Klughammer et al., 2018). To better define the heterogeneity of methylation in newly diagnosed and recurrent GBM, Klughammer et al. performed an integrative study of genome-wide methylation, clinical outcomes, MRI, and histopathology of longitudinally collected patient GBM tumors. They found that by utilizing a machine learning model, the transcriptional subtype of a tumor (classical, mesenchymal, and proneural subtypes) (Phillips et al., 2006; Verhaak et al., 2010) can be inferred from reduced representation bisulfite sequencing (RRBS) data. Interrogating the prediction probabilities output from their model as a measure of relative transcriptional subtype composition of their 112 patient cohort, they found that single tumors were representative of multiple transcriptional subtypes. Interestingly, the relative representation of a tumor's transcriptional subtype shifted longitudinally from primary occurrence to recurrence in about half of the cohort (Klughammer et al., 2018). Patients whose predicted subtype shifted to a more mesenchymal signature showed significant decreases in both progression-free and overall survival. (Fig. 1) Interrogating the methylome within these mesenchymal tumors, they found that hypomethylated loci were enriched for binding sites of the epigenetic regulators EZH2, KDM4A, RBBP5 and SUZ12, while the number of binding sites for pluripotency markers such as OCT4, NANOG, and SOX2 were decreased, suggesting that epigenetic factors prevailing over pluripotency factors may be a defining feature of recurrence in GBM. This theme of heterogeneity is conserved across multiple aspects of the epigenetic landscape of GBM. Mack et al. (2019), through an integrative multi-omics approach, reveal that another additional defining factor of GBM, independent of the mutational landscape, is the branching expression of at least two distinct super-enhancer (SE) related expression signatures among patient tumors and glioma stem cells. These SE signatures appear to be driven by distinct histone H3K27 acetylation (H3K27ac) profiles, and stratify patient tumors on a spectrum of proneural to mesenchymal or classical expression programs, reinforcing the notion of epigenetically driven plasticity (Mack et al., 2019).

2.2. GBM at single-cell resolution

Although targeting epigenetic pathways may be critical for treating GBM in the future, a better understanding of GBM intratumor heterogeneity is essential for achieving this goal. Single-cell resolution analysis of the transcriptional heterogeneity of GBM has revealed that GBM tumor cells exist on a spectrum of transcriptional states reminiscent of canonical neurodevelopmental cell types, namely, astrocyte (AC)-like, oligodendrocyte progenitor cell (OPC)-like, neural progenitor cell (NPC)-like, and mesenchymal (MES)-like states (Neftel et al., 2019). Deconvolution of The Cancer Genome Atlas (TCGA) GBM cohort (Cameron et al., 2013) reveals that relative proportions of cells within these transcriptional states is predictive of the transcriptional subtype determined from bulk data (classical, proneural, mesenchymal), and thus could also be correlated to the varying GBM methylome (Klughammer et al., 2018). The role of super-enhancer expression and histone acetylation patterns could be implicated as well (Mack et al., 2019). Thus, understanding the epigenetic mechanisms and how they modulate GBM intratumor heterogeneity will be essential. Single-cell ChIP-seq could be leveraged to provide an interesting perspective on the intratumor heterogeneity of chromatin states in GBM as it has for other cancers (Grosselin et al., 2019). Furthermore, copy-number inference analysis and further cross-analysis with TCGA GBM cohorts indicate that the NPC-like, OPC-like, and AC-like transcriptional-states are correlated with copy number aberrations in specific loci; *PDGFRA*, *CDK4* and *EGFR* respectively (Neftel et al., 2019). The mesenchymal cell transcriptional state, associated with *NF1* point-mutations, was also found to be correlated with loss of a chromosomal region encoding for different cytokines and chemokines associated with communication to different immune cells. Interestingly, through their methylation-based inference of transcriptional state, Klughammer et al. found that tumors associated with mesenchymal subtypes showed the most immune cell infiltration compared to other transcriptional subtypes, potentially due to the inverse relationship of NF1 and NF-κB activity. As tumor associated macrophage infiltration is inversely correlated with survival in GBM (Sørensen et al., 2018), these studies highlight the significance of single-cell analysis of GBM tumors to predict overall survival as well as to identify potential therapeutic interventions.

2.3. GBM single-cell plasticity

Critical preclinical studies of GBM tumors in animal models suggest that single GBM cells may have the intrinsic capacity to shift their expression to any of these transcriptional states. Using membrane associated markers such as CD24 to identify NPC-like cells, a homogenous sorted population comprised of a single transcriptional state implanted into a mouse is capable of recapitulating the original composition of states present before sorting (Neftel et al., 2019). Molecular barcoding experiments in patient-derived xenograft (PDX) and murine models of GBM indicate that a single clone of GBM cells can fit within multiple transcriptional states (Neftel et al., 2019). A similar phenomenon is observed of phenotypic states and canonical GBM cancer stem cell (CSC) markers. GBM CSCs have been described to exist across a spectrum of membrane expression phenotypes, exhibiting plasticity in the

canonical CSC membrane markers expressed at any given time, with no single membrane-associated antigen capable of identifying the entire stem-like population of GBM cells (Dirkse et al., 2019; Chen et al., 2010). As cellular phenotype is controlled *via* epigenetic gene regulation, tumor heterogeneity must be examined in an integrative context to begin to understand the epigenome, transcriptome, or proteome of GBM individually (Braun, 2015; Stern et al., 2007). Interestingly, these transcriptional and proteomic state transitions are starting to be deciphered using mathematical modeling, suggesting that the mechanism of state-transition may not be entirely stochastic, but regulated by cues of the tumor microenvironment, the spatial location of cells, and epigenetics (Dirkse et al., 2019; Celiku et al., 2019).

These findings are thought-provoking in the context of other heterogeneity-based studies such as those resulting from the Ivy Glioblastoma Atlas Project (Ivy GAP) (Puchalski et al., 2018; Celiku et al., 2019). Puchalski et al.'s anatomical transcriptional atlas connects anatomical location and histology with transcriptional heterogeneity, wherein the anatomical niches, namely the cellular tumor (CT), leading edge (LE), infiltrating tumor (IT), pseudopalisading region around necrosis (CTpan), and microvascular proliferation (CTmvp), all have unique representative transcriptional signatures (Puchalski et al., 2018). Celiku et al. leveraged this high-dimensional dataset with computational modeling to identify likely trajectories between transcriptional states within GBM (Celiku et al., 2019). Their findings support a hypothesis that GBM cells' exploratory shifting of expression allows for phenotypic shifts and thus their persistence through a diverse tumor microenvironment. It is becoming increasingly clear that understanding the dynamics and epigenetic regulation of GBM cell plasticity will be essential in identifying effective therapies for this disease.

2.4. Epigenetic dysregulation in GBM

GBM is a cancer characterized by chromosomal instability, with copy number aberrations (CNAs) playing a role in the transcriptional and phenotypic landscape of GBM tumors. Epigenetic regulation appears responsible for the exacerbation of the effect of these CNAs. Tumors predominately composed of GBM cells bearing an astrocyte (AC)-like transcriptional state appear to be driven by amplifications of the *EGFR* locus. In GBM, these *EGFR* amplifications are most commonly observed on circular, extrachromosomal DNA. Interestingly, these circular pieces of DNA also tend to harbor epigenetic enhancer regions that topologically interact with the *EGFR* locus to increase transcription factor binding and thus expression (Morton et al., 2019). Differences in the interaction capabilities of these extrachromosomal structures, when compared to genomic DNA, increase the overall effect these enhancers have on target transcription. Potentially, topological interactions such as these could drive other transcriptional states through increased enhancer function at extrachromosomal amplifications of the *CDK4* or *PDGFRA* loci.

2.5. Epigenetic targets in GBM

Targeting of epigenetic players has emerged as a possible means of combating the plasticity of GBM tumor cells (Dirkse et al., 2019). While the following is not exhaustive, some of these potential epigenetic targets include bromodomain & extra-terminal domain (BET) containing proteins, the PRC2/EZH2 complex, or histone deacetylases (HDACs), each playing critical roles in the persistence of these tumors. (Fig. 1)

2.6. BRD4 in GBM

The BET protein BRD4 is an epigenetic reader protein. Binding acetylated histones, BRD4 recruits P-TEFb to promoter regions facilitating the phosphorylation and activation of RNA polymerase II for transcription of target genes such as *MYC* (Donati et al., 2018). Similar to EZH2's role in development, BRD4 is essential for various developmental processes (Fernandez-Alonso et al., 2017; Hsieh et al., 2017; Korb et al., 2015; Korb et al., 2017; Li et al., 2018; Murray et al., 2008; Rudman et al., 2018; Takahashi et al., 2018; Houzelstein et al., 2002; Lee et al., 2017; Penas et al., 2019; Li et al., 2016). BRD4 has become an attractive target in brain cancers for its role in stem-cell signaling and sustaining SONIC HEDGEHOG (SHH) signaling in MB, as well as its regulation of proliferation in GBM (Henssen et al., 2013; Long et al., 2014; Tang et al., 2014; Pastori et al., 2015; Pastori et al., 2014). In addition to BRD4's role in transcription initiation, a role in genomic stability through modulation of DNA damage repair and telomere maintenance has also been proposed (Donati et al., 2018; Li et al., 2018; Stanlie et al., 2014). While BRD4 has become an attractive target for the treatment of GBM due to its regulation of the transcription of oncogenic drivers, BRD4 recruitment of DNA damage response complexes implicate the protein in potential radiosensitization and bring new light to potential mechanisms of cancer cell cytotoxicity. BET inhibition has also been shown to attenuate adaptive reprogramming in response to kinase inhibition in other cancers (Timothy et al., 2015; Kurimchak et al., 2019), and showed synergistic effects in reducing GBM growth when combined with other inhibitors such as the AURORA KINASE inhibitor alisertib (Stathias et al., 2018). However, a major challenge is identifying brain penetrant compounds that act synergistically and are safe for use in GBM.

2.7. EZH2 in GBM

EZH2 has been implicated in oncogenesis as the catalytic methyltransferase within PRC2. EZH2 is also over-expressed in a number of cancers, and is correlated with poor survival in GBM (Zhang et al., 2017). During normal development, EZH2 modulates stem-cell trajectory as part of the C-MYC/HBXIP/HOTAIR/LSD1 complex (Zhang et al., 20120). Although the mechanism is not entirely known, pharmacological inhibition of EZH2 activity eventually leads to a reduction in C-MYC expression and tumorigenicity in GBM (Suva et al., 2009). In addition to C-MYC regulation, EZH2 can be phosphorylated by MELK, facilitating EZH2 mediated methylation of NF-κB and downstream oncogenic transcription (Liu et al., 2019). Interestingly, the formation of the MELK/EZH2 complex and its interactions with NF-κB appeared to preferentially occur in tumor cells that were more stem-like. Considering theplasticity of the GBM transcriptional landscape, it is important that ablation of this axis promoted stem-like glioma cells to a more differentiated phenotype and reduced overall tumor burden *in vivo*. This suggests that targeting EZH2 could address the presence of the mesenchymal-like cell population within these tumors, driven by loss of *NF1* and increased NF-κB activity (Yamini, 2018; Neftel et al., 2019) (Fig. 1). Interestingly, mechanistic studies have identified an indirect dual-role for mTOR in catalyzing H3K27 hypermethylation by increasing the expression of EZH2, and the availability of key substrates (Harachi et al., 2018). Importantly, this provides an opportunity to indirectly target EZH2's catalytic activity through the inhibition of mTOR.

2.8. HDACs in GBM

Acetylation and deacetylation of histone lysine residues is a major means of regulating chromatin accessibility, which is tightly controlled by a balance of the activities of HISTONE ACETYLTRANSFERASES (HATs) and HISTONE DEACETYLTRANSFERASES (HDACs). The removal of acetyl groups by HDACs promotes closed chromatin conformation, reduced transcription factor accessibility and transcription of certain tumor suppressors. Pharmacological inhibition of HDACs leads to increased acetylation and open chromatin. HDAC overexpression has been reported in GBM (Rundle-Thiele et al., 2016) (Tan et al., 2018). The improved chromatin accessibility leads to increased expression of tumor suppressors, and reduced expression of other

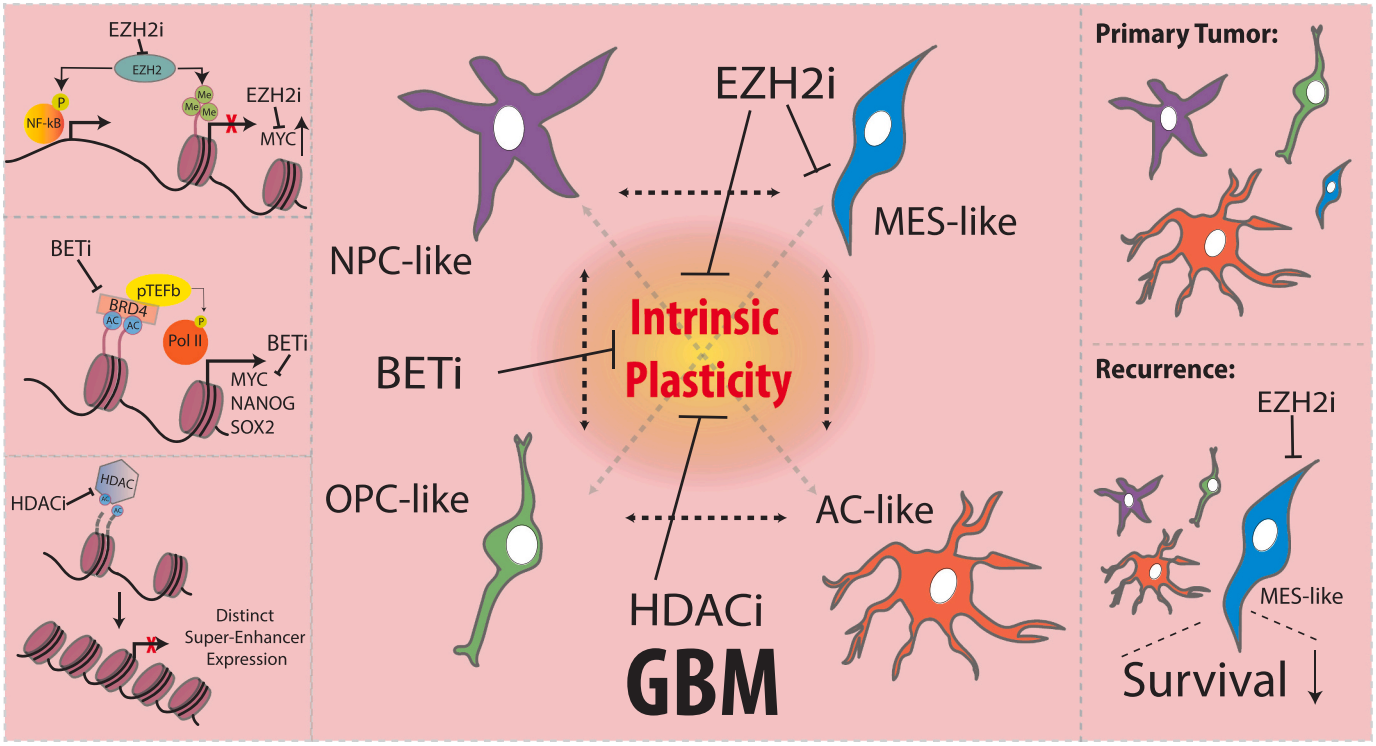

Fig. 1. Targeting epigenetic pathways and plasticity in GBM. In the case of GBM, transcriptionally NPC-like, OPC-like, AC-like, and MES-like cells have been described through single-cell sequencing analyses. Studies have shown that there could be cell type plasticity – a single purified cell-type can recapitulate all other transcriptional states found within the original tumor. We propose here that epigenetic regulators like EZH2, BET, or HDAC inhibitors may be able to reduce this plasticity.

regulators such as *MGMT* in GBM. Treatment of glioma-derived stem cells with the HDAC inhibitors trichostatin A or valproic acid resulted in a loss of stemness (Alvarez et al., 2015). Not surprisingly, HDAC1 and HDAC2 are essential in neuro-glial development, with HDAC1 expression localizing to neural and glial progenitors while HDAC2 expression occurs in more differentiated neural cells (Macdonald and Jane Roskams, 2008). It is possible that HDAC inhibition could also be used as part of combination therapies for GBM to reduce transcriptional state plasticity through targeting of the least differentiated tumor cells.

3. Medulloblastoma

As is the case for GBM, targeting epigenetic pathways may be an attractive therapeutic strategy for treating MB, the most common pediatric brain tumor (Siegel et al., 2017). MB standard of care includes surgery, followed by radiation of the brain and spinal cord, and adjuvant chemotherapy (Martin et al., 2014). Although survival benefit occurs for some patients after standard-of-care treatment(Northcott et al., 2017; Parsons et al., 2011), several deficits persist. Treatment sequalae include neurocognitive impairments, mutism, and hearing loss as well as secondary malignancies that arise (Crawford et al., 2007; Neglia et al., 2006). Importantly, some patients are resistant to conventional therapy (Zhukova et al., 2013; Tabori et al., 2010; Schwalbe et al., 2017). Thus, there is considerable interest in identifying new therapies for treating MB patients. MB has been classified into four major subgroups: WNT, SHH, Group 3 and Group 4, each with its own histology, molecular drivers and prognoses (Taylor et al., 2012; Northcott et al., 2017). WNT subgroup represent 10% of MB cases, is characterized by nuclear accumulation of β-CATENIN and mutations in several components of WNT signaling including genes encoding β-CATENIN and APC (Gajjar and Robinson, 2014). SHH subgroup represents 30% of MB cases where several components of the SHH signaling pathway such as *PTCH1, SMO, SUFU, and GLI2 or MYCN* are either mutated or amplified (Thompson et al., 2005). Group 3 MB is mostly characterized by *MYC* amplifications and has the worst overall prognosis (Northcott et al., 2017). Group 4 is less well characterized with amplifications in *MYCN* and *CDK4 (*Gajjar et al., 2015*)*. Interestingly, recent studies have further subdivided these classes of MB, suggesting that there is greater intertumor heterogeneity than previously thought (Cavalli et al., 2017). However, in almost all MB tumors epigenetic pathways control key developmental or cell cycle transitions, making them attractive therapeutic targets.

3.1. Epigenetic pathway mutations in MB

6% of the mutations found in MB are germline and linked to hereditary syndromes such as Li-Fraumeni (*TP53*), Gorlin (*PTCH1*), Turcot (*APC*) and the Fanconi anemia (*BRCA2*) (De et al., 2008). Many other MB tumors are driven by *de novo* somatic mutations mostly in genes encoding components of the WNT and SHH pathways (Northcott et al., 2017). In addition to components of these or similar developmental pathways, a number of epigenetic regulators have been consistently found mutated in MB samples. Gene sequencing analyses found inactivating mutations of the genes encoding the histone-lysine *N*-methyltransferases MLL2 (KMT2D)(or MLL3 (KMT2C) in 1% of MB patients. Moreover, a smaller percentage of sequenced tumors also displayed mutations in *SMARCA4*, *ARID1A,* or the histone lysine demethylase *KDMB* (Parsons et al., 2011). The list of epigenetic regulators mutated in MB tissues was further completed by using subgroup specific sequencing analyses in a larger cohort of MB samples. This sequencing effort found a number of mutations in chromatin marking genes such as *EZH2*, *KDMA, CHD7* and *ZMYM3,* which were specific to Group 3 and 4 tumors. In addition, alterations in chromatin remodelers such as *SMARCA4*, *TRRAP*, *MED13* and *CREBBP*, and in the DEAD-box RNA helicase *DDX3X* were observed only in WNT MB (Robinson et al., 2012). Some of these alterations are unlikely to be tumor drivers, but

may cooperate with other oncogenic mutations such as those in *CTNNB1* to induce tumor growth.

3.2. Epigenetic pathways in MB tumorigenesis

The absence of driver mutations in some MB samples suggests that dysregulation of oncogenic drivers may occur epigenetically. An example of this is *TP53*. In human MB only ~1% of tumors harbor a *TP53* mutation (Tabori et al., 2010), although approximately half of the mouse MB models used in preclinical studies require loss of P53 activity to allow tumor growth (Wu et al., 2011). Indeed, loss of P53 activity *via* somatic mutations has been shown to be a key step in evading senescence in pre-neoplastic MB lesions (Tamayo-Orrego et al., 2016). In addition to *de novo* mutations in *TP53*, loss of the activity of this tumor suppressor in MB might be explained by epigenetically reducing its levels. Consistent with this notion, the methyl-CpG binding protein MBD2 represses the expression of BAI1, which drives MDM2-mediated P53 degradation to trigger tumor formation (Zhu et al., 2018). Similar epigenetic modulations might be required to trigger neoplasia in *SMO* mutant adult MB. In these patients, inactivating mutations in the chromatin reader *BRPF1* are able to induce massive chromatin remodeling (Aiello et al., 2019). Therefore, it is important to incorporate epigenetic studies with proteomic analysis to define therapeutic targets in MB.

Most of the tumors lacking gene mutations cluster as group 4 MB. Moreover, pathway analysis of recurrent genetic events in these tumors shows an enrichment for genes linked to chromatin modification (Northcott et al., 2017). This suggests that aberrant activity of epigenetic regulators is likely to be critical in this particular set of tumors. Accordingly, analysis of somatic structural variants in MB tissues found enhancer hijacking events resulting in overexpression of epigenetic modulators such as the histone methyltransferase *PRDM* family in Group 4 MB (Northcott et al., 2017). Similar enhancer hijacking activities inducing high levels of expression of the GROWTH FACTOR INDEPENDENT proto-oncogenes *GFI1* and *GFI1B*, have been observed in both group 3 and 4 MB (Northcott et al., 2014). Specifically, in group 3 MB high levels of *GFI1* collaborate with *MYC* amplifications to allow tumor formation. Importantly, as recruitment of the enzyme LYSINE DEMETHYLASE 1 (LSD1) is essential for GFI1 activity, eliminating LSD1 expression in a *MYC* amplified mouse MB model abrogates the growth of Group 3 MB (Lee et al., 2019). Lastly, repression and inhibition of EZH2 reduced proliferation and self-renewal in SHH MB cells (Miele et al., 2017). Thus, aberrant activation of epigenic pathways might play a key role in triggering MB growth, and further validate the use of small-molecule epigenetic modulators for the treatment of these tumors.

3.3. MB at single cell resolution

Single-cell analysis of medulloblastoma has confirmed previous reports that these tumors utilize transcriptional programs present during fetal neurodevelopment (Vladoiu et al., 2019; Jessa et al., 2019; Packer et al., 1984). However, the MB cell-of-origin, or MB progenitor cell, seems to be different in the 4 major subgroups (Gibson et al., 2010). Accordingly, canonical correlation analysis of subgroup specific transcriptomic analyses identified distinct glutamatergic cell populations as putative cells-of-origin for SHH and group 4 MB (Hovestadt et al., 2019). In the case of the SHH subgroup, these tumors are known to arise from granule cell progenitors (GCPs) in the developing cerebellum (Hatten and Roussel, 2011), which was further confirmed by single-cell transcriptomic analyses (Hovestadt et al., 2019). However, other studies suggest that there may be more than one cell-of-origin for SHH MB (Zhang et al., 2019, 2020; Ocasio et al., 2019) (Selvadurai et al., 2020). Single cell transcriptomic analyses in this subgroup of MB identified an OPC-like progenitor population of cells positive for the oligodendrocyte transcription factor OLIG2. These cells, are actively dividing in the initial phases of tumor development, functioning as a transit-amplifying cell reservoir. Gene expression profile comparison demonstrates that tumors lacking *OLIG2* downregulate cell proliferation, and upregulate neuronal differentiation pathways. Indeed, the expression of several components of these pathways is controlled by OLIG2, which binds to *de novo* enhancers (highly enriched for the activating histone mark H3K27ac) to regulate the chromatin landscape during neoplasia formation. Importantly some of these H3K27ac marks localize to known tumor pathways, such as *HIPPO* and *MYCN*, whose combined inhibition reduces tumor growth and increase survival in SHH MB bearing mice. Moreover, by contrast to GCPs, these OPC-like progenitor cells do not only foster tumor initiation and further growth, but are responsible for tumor resistance, as they are enriched in residual mouse MB tumors exposed to chemotherapeutics, and in relapsed and metastatic MB samples (Zhang et al., 2019). All together these data suggest that OLIG2 acts as an activator of those signaling pathways driving tumor growth and relapse, and the importance of targeting OPC-like progenitor cells for the clinical management of SHH MB patients (Fig. 2).

OPC-like propagating cells were also identified by single-cell transcriptomic analysis performed to identify cell types resistant to SHH pathway inhibitors. These studies describe the existence of a cell reservoir that remains proliferative upon vismodegib treatment and displays either a SHH ($MYOD1^+$) or a stemness-like gene signature ($SOX2^+$). Interestingly, within this $SOX2^+$ cell population two different subpopulations were identified: one GCP-like that does respond to SHH inhibition, and another OPC-like that persists upon treatment (Ocasio et al., 2019) (Fig. 2). These results are consistent with the above findings (Zhang et al., 2019), suggesting that OLIG2 labeled cells constitute the cancer stem-like MB cell niche responsible for tumor relapse.

By contrast to the above referenced studies where small populations of OPC-like propagating cells were suggested to be the MB cell-of-origin (Ocasio et al., 2019; Zhang et al., 2019), other studies suggest that SHH MB arises from the continuous hierarchical growth of a rare population of stem-like $SOX2^+$ cells (Selvadurai et al., 2020; Vanner et al., 2014). These studies reveal no substantial presence of OLIG2 cells in the cerebella of P0 mice. Moreover, single-cell transcriptomic analyses identified a sub-cluster of quiescent GCPs expressing SOX2. Similar to what was previously described for OPC-like propagating cells (Zhang et al., 2019), this pool of $SOX2^+$ cells are temporally present during cerebellar development, and give rise to GCPs (Selvadurai et al., 2020). Results from these analyses are consistent with a model in which a population of $SOX2^+$ propagating cells contributes to cerebellar development and yield a more differentiated progeny. Interestingly, in pathological conditions in which constitutive activation of SHH signaling leads to MB formation, this population of $SOX2^+$ cells persists in the cerebella and allows the transition from pre-neoplastic lesions to hyperplasia (Selvadurai et al., 2020). Future studies are needed to determine whether SOX2 and OLIG2 collaborate during cerebellar development and tumor initiation. Moreover, more extensive analysis of rare cell populations routinely detected by single-cell RNA sequencing analyses should be performed in order to define the epigenetic pathways allowing persistent hierarchical expansion under pathological conditions.

4. Diffuse intrinsic pontine glioma

Recent studies suggest that epigenetic pathways in GBM and MB are also active and targetable in DIPG, a devastating childhood brain tumor that is almost entirely lethal within 10 months after diagnosis (Mackay et al., 2017; Nagaraja et al., 2019). The current standard of care is radiation but this is thought to only reduce symptoms and not increase survival. Therefore, as with GBM and treatment resistant MB, novel therapies are desperately needed. Epigenetic pathways offer therapeutic targets in DIPG as most DIPG tumors harbor mutation in the gene encoding HISTONE H3.3/3.1 (K27M) (Maury and Hashizume, 2017). There is global hypomethylation of chromatin, which leads to

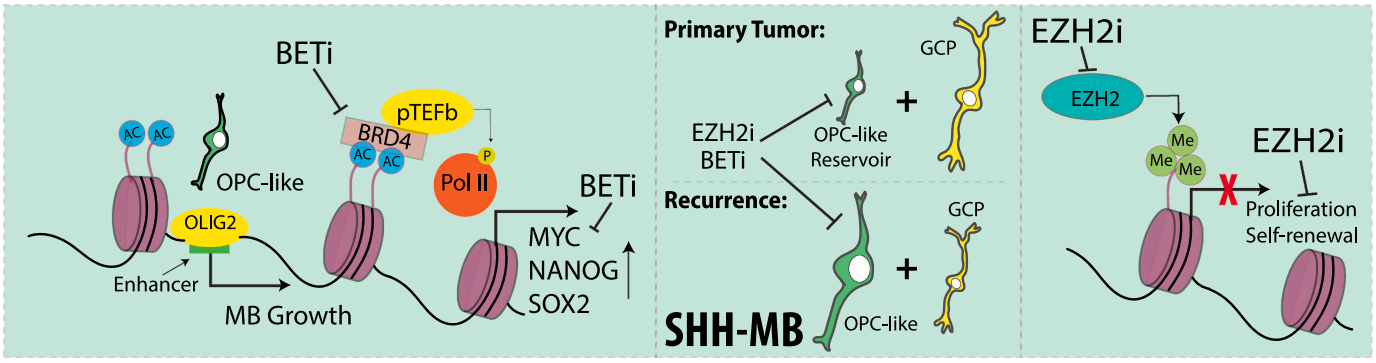

Fig. 2. Targeting epigenetic pathways and plasticity in MB. For MB, single-cell RNA-sequencing experiments have shown that in addition to the putative cell-of-origin, the granule cell progenitor (GCP), MB tumors may also contain a reservoir of OPC-like cells. Within these OLIG2+ OPC-like cells, OLIG2 is found at enhancer regions characterized by H3K27ac activating marks, and drives MB tumor growth. BET inhibition could reduce OLIG2 mediated transcription by blocking BRD4's binding to acetylated histones, and thus recruitment of key transcriptional machinery. Pharmacologic inhibition of EZH2 has also been shown to attenuate self-renewal and proliferation in SHH MB cells.

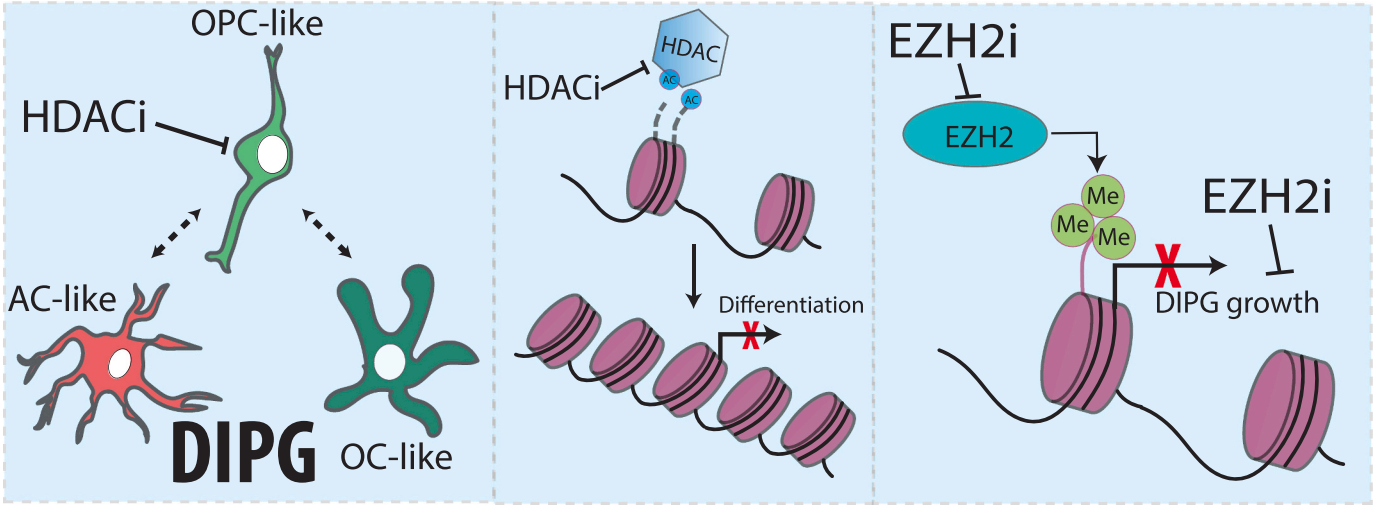

Fig. 3. Targeting epigenetic pathways and plasticity in DIPG. For DIPG, OPC-like cells have been described as possible cells of origin and therefore targeting this population with epigenetic pathway inhibitors may be therapeutically efficacious. Epigenetic inhibitors such as HDACis and EZH2is have been proposed to indirectly reverse global hypomethylation and attenuate tumor growth through the increased expression of tumor supressors. EZH2's role in chromatin remodeling and compaction may target the putative cells of origin through promoting differentiation.

the decreased expression of some tumor suppressor genes. There has been considerable effort to utilize small molecule inhibitors of epigenetic enzymes including HDACs, EZH2, LSD1, and Jumonji proteins to reverse this hypomethylation and increase expression of these tumor suppressor proteins. In addition, co-targeting molecules such as Corin that simultaneously inhibit HDACs and LSD1 have been developed and have shown efficacy in preclinical models of DIPG (Anastas et al., 2019). Another compound co-targeting HDACs and PI3K exerts radiosensitizing effects by inhibiting transcription factor recruitment to promoters of key components of the DNA damage response pathways (Pal et al., 2018). Interestingly, HDAC inhibitors have also been shown to induce differentiation of cells into neurons, which may be an attractive therapeutic approach. As is the case for GBM and MB, one putative cell-of-origin for DIPG are OPC-like and therefore, small molecules that favor a neuronal lineage over an OPC-like lineage would likely yield favorable outcomes in DIPG (Fig. 3). As with GBM and MB, DIPG can also be grouped into at least two transcriptional profiles. Depending on whether H3.1 or H3.3 is mutated, it is possible to stratify these DIPG tumors into two distinct transcriptional subgroups, driven by H3K27me3 in primarily either intronic (H3.1) or intergenic (H3.3) regions, respectively (Castel et al., 2018). Further analysis of the effects that these unique mutations have on the single cell landscape of DIPG will be interesting and important.

5. Single cell analysis in DIPG

Investigating DIPG at the single cell level revealed similar trends in developmental transcriptional programs across tumors to those found in GBM (Filbin et al., 2018). A proliferative, dedifferentiated, OPC-like transcriptional state driven by *PDGFRA* expression is dominant across the DIPG single cell landscape. Together with *PDGFRA* overexpression and *TP53* loss, mutations of histone H3 lysine27 to methionine can transform neural precursor cells (Larson et al., 2019). These mutations can be repressors of EZH2's activity in regards to PRC2, and likely lead to dysregulation of cell differentiation. Histone H3 lysine 27 trimethylation (H3K27me3) marks regulate neural progenitor subtypes in the developing mouse brain (Zhang et al., 2020). Along with an OPC-like transcriptional program within DIPG, Filbin et al.'s study revealed the presence of other transcriptional programs, namely an astrocyte-like program driven by the expression of *APOE* and *GFAP* and a more differentiated oligodendrocyte-like program driven by the expression of markers such as *MBP* that appear to fit within a developmental

Table 1
Table summarizing clinical trials for epigenetic modulators in MB, DIPG and MB patients.

	MB	DIPG	GBM
HDACi's	**Vorinostat** Phase 1: NCT00867178 Phase 1: NCT00994500 Phase 1: NCT00217412 Phase 1: NCT01076530 **MS-275**	**Vorinostat** Phase1, Phase 2: NCT01189266 Phase 1: NCT02420613 **Valproic Acid** Phase 3: NCT03243461	**Vorinostat** Phase 1: NCT03426891 Phase 1: NCT01378481 Phase 1: NCT00762255 Phase 1: NCT00268385
	Phase 1: NCT00020579	**Panobinostat** Phase 1: NCT04341311 Phase 2: NCT03632317 **Panobinostat - MTX110** Phase 1-2: NCT03566199 **Panobinostat - LBH589** Phase 1: NCT02717455	Phase 1: NCT01076530 Phase 1-2: NCT00731731 Phase 1-2: NCT01110876 Phase 1-2: NCT00555399 Phase 1-2: NCT01266031 Phase 1-2: NCT00939991 Phase 1-2: NCT01189266 Phase 1-2: NCT01983969 Phase 2: NCT00641706 Phase 2: NCT00238303 Phase 2: NCT01738646 Phase N/A: NCT01342757 **Valproic Acid** Phase 2: NCT00302159 Phase 3: NCT03243461 **Panobinostat** Phase 2: NCT01115036 Phase 2: NCT00848523 **Belinostat** Phase 2: NCT02137759
BETi's	**BMS-986158** Phase 1: NCT03936465		**MK-8628** Phase 2: NCT02296476 **INCB057643** Phase 1-2: NCT02711137
EZHi's	**Tazemetostat** Phase 2: NCT03213665 Phase 2: NCT03155620		
DNMTi's			**Ibrutinib** Phase 1: NCT03535350 **Nivolumab** Phase 3: NCT02667587 Phase 3: NCT02617589

Color Code: RED: Terminated, Cancelled, Completed or Withdrawn. GREEN: Active, recruiting or not recruiting yet. PURPLE: Active, but not recruiting.

hierarchy and arise from the predominant, proliferative OPC-like population of malignant DIPG cells. Potentially, this could mean that the cells within an OPC-like transcriptional state should be the primary therapeutic target, as these appear to be the cells-of-origin, and the cells driving the aggressive nature of these tumors. Combination therapies including inhibitors of EZH2 become attractive for reducing transcriptional plasticity, and the developmental hierarchy that complicates the druggable landscape across these tumors (Fig. 3).

6. Comparisons of cell types in GBM, MB, and DIPG

Although GBM, MB, and DIPG may present in different locations of the brain and arise during different times of development, it is possible that therapeutic opportunities may become evident after comparing all three cancers at the single-cell level. As the intrinsic plasticity within cells capable of self-renewal, proliferation, and differentiation has long been recognized in numerous brain cancers, it will be important to understand mechanisms regulating brain tumor cell identity as a whole (Singh et al., 2003). We have already discussed that OPC-like cells seem to be a common cell type to target in all three cancers. Interestingly, we compared single-cell analysis of GBM, MB, and DIPG from the published literature and found that small molecule inhibitors of EZH2 and HDACs would successfully target OPC-like cells (our unpublished observations). Therefore, it will be important to determine if safe brain penetrant inhibitors can modulate these enzymes and their associated pathways in all three brain tumors (Figs. 1, 2, & 3).

7. Epigenetic pathway inhibitors in brain cancer

As mentioned above there is considerable interest in targeting HDACs, BET proteins, EZH2, LSD1, and other epigenetic regulators in GBM, MB, and DIPG (Table 1). However, the failure of many single agent clinical trials may indicate we need to consider combination therapies. We recently developed a computational pipeline to identify combinations for GBM in a patient specific manner. We first searched for compounds to combine with BET inhibitors in GBM cells using the L1000 assay. The L1000 assay is a high-throughput assay that has been utilized to describe the transcriptional response of cells treated with different perturbagens, including small molecules (Subramanian et al., 2017). The steady-state levels of 978 transcripts are determined in cells using a bead-based fluorescence assay performed at the Broad Institute (Duan et al., 2014). Here, dimension reduction methods were applied to identify candidate transcripts that were co-regulated based on the DSGEO dataset. Subsequently, from every cluster of co-regulated genes, one gene was selected as a candidate landmark gene. These landmark genes (978) were found to be key signaling nodes in various important cell regulatory pathways. We recently demonstrated that combining disease signature along with compound transcriptional signatures *via* L1000 profiling identifies synergistic combinations in GBM (Stathias et al., 2018). Although we developed this computational pipeline (SynergySeq.com) to identify combinations in GBM, we posit that this method can be used for both MB and DIPG. Indeed, our recent studies suggest that we can identify distinct combinations for each of these childhood cancers using this pipeline (our unpublished observations). In addition, we are working on using single-cell sequencing RNA-sequencing information in conjuction with SynergySeq in order to identify compounds that selectively target certain cell populations (Suter et al., in preparation).

Thus far in all approaches we have focused on coding RNAs although several studies have linked noncoding RNAs to brain cancer progression. For example, there are extensive reports on the importance of long noncoding RNAs (lncRNAs) and microRNAs (miRNAs) in the epigenetic regulation and maintenance of GBM (Banelli et al., 2017; Zeng et al., 2018; Lu et al., 2020), medulloblastoma (Mollashahi et al., 2019; Laneve and Caffarelli, 2020; Po et al., 2018), DIPG and other brain cancers (Pezuk et al., 2019). Additionally, miRNAs and lncRNAs could represent additional targets for the treatment of these tumors. (Disney et al., 2018). Future studies are required to determine the potential utility of small molecules targeting noncoding RNAs in brain tumors.

8. Brain tumor models

To investigate epigenetics and cell plasticity in these and other brain tumors, representative models are essential. Transcriptional heterogeneity is not unique to human tumors, but is also found in genetically engineered and orthotopic mouse models. (Neftel et al., 2019, {Ocasio, 2019 #108)}. Importantly, syngeneic models could permit the analysis of the effect of epigenetic pathways and plasticity on the immune response (Pham et al., 2016), and transgenic mouse models can further permit mechanistic studies of epigenetic regulators (Dobson et al., 2019). Further, *ex vivo* models wherein tumor cells are cultured with iPSC-derived brain organoids are also emerging as an attractive means to explore the dynamics of these tumors in a potentially more relevant micro-environment, and to shed light on regulation of key brain tumor characteristics such as infiltration (Goranci-Buzhala et al., 2020). Potentially, recent insight from medulloblastoma models may translate to other brain cancer models as well (Roussel and Stripay, 2020).

10. Conclusions and future directions

The last decade has yielded a wealth of information on the genetic and epigenetic basis of GBM, MB, and DIPG. The last three years have added remarkable advances in understanding these tumors at the single-cell level. A comparison of cell types within these three tumors suggests that there are common targetable epigenetic pathways in putative cells-of-origin such as OPCs. Future studies will illuminate whether small molecule inhibitors of HDACs, EZH2, or BET proteins can be utilized effectively to eliminate OPCs or OPC-like cells in these tumors and whether this yields favorable clinical outcomes. Likely combination therapies will be needed to achieve the greatest benefit. Emerging technologies that incorporate multi-omics approaches that accurately describe the epigenome, transcriptome, and proteome of cells-of-origin will need to be utilized to identify safe and effective combinations for treating GBM, MB, and DIPG. Furthermore, mechanisms of resistance driven by epigenetics and plasticity in these and other brain cancers are likely conserved in many other cancers as well.

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