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TOPIC REVIEW

Epigenetics and survivorship in pediatric brain tumor patients

Debanjan Bhattacharya[1] · Scott L. Pomeroy[2] · Daniel A. Pomeranz Krummel[1] · Soma Sengupta[1,3,4]

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Abstract

Introduction Brain tumors make up over a quarter of pediatric malignancies. Depending on the age of presentation and treatment, pediatric brain tumor survivors experience varying degrees of treatment induced morbidity and sequelae. Epigenetic mechanisms play a critical role in silencing of tumor suppressor genes and activation of driver genes involved in oncogenesis in different types of brain tumors. Epigenetic modifications in pediatric brain tumor patients may influence long-term survival and may refine the molecular response to treatment induced morbidity and sequelae. However, there is a dearth of studies on how epigenetics of pediatric brain tumors is connected with neurocognition and other treatment related sequelae in survivors.

Methods/Results In this review we explore epigenetic factors that may contribute to the survivorship and treatment of pediatric brain tumor patients. We focus on glioblastoma, medulloblastoma, and the neurocutaneous syndrome neurofibromatosis type-1 to highlight epigenetic biomarkers that can potentially serve not only as prognostic indicators of overall patient survival, but hopefully as indicators to the response to treatment neurocognitively and otherwise.

Conclusions Future studies will hopefully soon bridge the gap in our knowledge on how epigenetic modifications are linked to treatment related sequelae in pediatric brain tumor patients.

Keywords Survivorship · Pediatric brain tumors · CNS tumors · Treatment · Epigenetics

Introduction

Malignant and non-malignant tumors of the brain and central nervous system are the most common cancers in children (age 0–14 years) [1]. According to the Central Brain Tumor Registry of the United States, the 5-year survival following diagnosis of the malignant forms of brain and other CNS tumors (diagnosed between 2012 and 2016) was ~74% for ages 0–9 years, compared to ~21% for patients 40 and over [1]. In addition, the overall cancer mortality rate amongst children and adolescents is declining [2]. While the 5-year survival is better in children and mortality is decreasing, unfortunately pediatric brain tumor survivors experience significant neurocognitive deficits and other morbidities as a consequence of the tumor and/or treatment of the tumor [3, 4]. For pediatric brain tumor survivors who often undergo multi-modal standard therapy, the degree of neurocognitive dysfunction is impacted by the initial age of presentation and treatment factors. In the case of medulloblastoma survivors, for example, age at the time of radiotherapy, initial clinical stage, total dose of cranial radiotherapy, and the time of evaluation have significant impact on neurocognitive scores [5]. In addition, many medulloblastoma survivors will go on to develop new endocrine, neurological, or sensory complications several years after diagnosis and treatment [3]. Thus, the side effects encountered through survivorship start in the pediatric age range, but often continue into early adulthood. Pediatric brain tumor survivors also exhibit deficits in attention, processing speed and working memory along with reduced overall intellectual development and academic achievement [6]. Further, as a consequence of treatment, pediatric brain tumor patients have an increased probability of developing secondary tumors. In neurofibromatosis

✉ Soma Sengupta
soma.sengupta@uc.edu

1 Department of Neurology and Rehabilitation Medicine, University of Cincinnati College of Medicine, Cincinnati, OH, USA

2 F.M. Kirby Neurobiology Center, Boston Children's Hospital, Boston, MA, USA

3 University of Cincinnati Gardner Neuroscience Institute, Cincinnati, OH, USA

4 Department of Neurology and Rehabilitation Medicine, University of Cincinnati Academic Health Center, PO Box 670525, Cincinnati, OH 45267-0525, USA

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type-1 patients, for example, the incidence of secondary malignant neoplasms is 4–6 times the prevalence of the general population [7]. Neurofibromatosis type-1 patients have increased chances of developing cutaneous neurofibroma (> 99%), internal nerve sheath tumor (up to 60%), malignant glioma (0.8%), malignant schwannoma, and myelogenous leukemia [7]. In summary, pediatric brain tumor survivors require access to a multi-disciplinary and highly collaborative ("survivorship") team, consisting of pediatric and/or adult neuro-oncologists, neurologists, and endocrinologists, as well as psychologists, occupational therapists, speech therapists, and physical therapists.

Epigenetic regulations that may impact patient prognosis include state of DNA methylation, histone modification(s), nucleosome remodeling, and non-coding RNA-mediated targeting. DNA methylation, in particular, and its contribution to regulating expression of genes and influence on chromatin remodeling in pediatric brain tumors has been explored [8], including in glioblastoma, [9, 10], medulloblastoma [9], ependymoma, and diffuse midline glioma [11]. As a consequence, clinical trials for children with brain tumors are increasingly incorporating information on DNA methylation status and other epigenetic signatures as well as mutations of epigenetic players in their study design to evaluate survival outcomes [12] (Table 1). Still, how epigenetics influences pediatric brain tumor patient morbidity and sequela is poorly understood.

Epigenetics in the regulation of glioma survival

Gliomas are the most commonly observed malignant brain tumors in children, accounting for approximately 80% of all CNS pediatric tumors [24]. Pathologically, gliomas are graded as low- or high-grade [25, 26]. Low-grade gliomas (LGGs) include pilocytic astrocytomas, optic pathway gliomas, tectal gliomas, oligodendroglioma, ganglioglioma, and pleomorphic xanthoastrocytoma. High-grade gliomas (HGGs) (15–20% of all pediatric CNS tumors) are molecularly as well as spatially distinct [26–28], occurring in the brainstem (diffuse midline glioma), supratentorial (anaplastic astrocytoma), as well as anywhere in the brain or spinal cord in the case of glioblastoma multiforme (GBM). Amongst pediatric HGGs, the 5-year survival in diffuse midline glioma, is very poor (approximately 2%); while in pediatric patients with supratentorial HGG 5-year survival is less than 30%.

MGMT and survival

Initial genomic analysis of adult GBM proposed the existence of four molecular subtypes: proneural, neural, mesenchymal, and classical [27, 29]. However, more recent studies suggest that there may be less subtypes, possibly mesenchymal, proneural, and classical [30]. GBM patients within the mesenchymal subtype exhibit poorer survival than patients of other subtypes, when analysis is restricted to those with low transcriptional heterogeneity. DNA methylation has been reported as a dynamic parameter that can predict adult GBM patient survival and disease progression across subtypes [31]. For example, demethylation of

Table 1 Examples of mutations in genes involved in epigenetic machinery and implicated in pediatric brain tumors

Gene(s) mutated	Brain tumor type(s)	Reference(s)
H3F3A (encoding H3.3 with K27M)	High-grade glioma	[13]
H3K27M	DMG; high-grade glioma	[14–17]
H3.3 G34R/V mutations	Pediatric GBM	[18]
HIST1H3B (encoding H3.1 with K27M)	High-grade glioma	[19]
ATRX	Glioma in NF-1	[20]
SETD2	High-grade glioma	[21]
JMJD3	High-grade glioma	[22]
SET2 (KMT3A)	High-grade glioma	[19]
MLL2/KMT2C, MLL3/KMT2D	SHH and Group 4 MB	[14, 23]
LSD1 (KDM1A)	MB	[14, 19]
JARID1A (KDM5A)	MB	[19, 23]
UTX (KDM6A)	Groups 3 and 4 MB	[14, 23]
ARD1A	WNT and Groups 3 and 4 MB	[14]
SMARCA4	WNT, SHH, Group 3 MB	[14, 23]

DMG diffuse midline glioma, *MB* medulloblastoma, *NF-1* Neurofibromatosis-1

promoters of WNT signaling genes are noted in the subset of GBM patients who have the worst prognosis [31]. Overall, an increased alteration in patterns of DNA methylation or 'erosion' is positively associated with progression-free survival in primary GBM tumors [31]. In the case of proneural subtype patients, an advantage appears to be conferred by the 'glioma CpG island methylation phenotype' or G-CIMP [10]. While in the classical subtype, the methylation status of O^6-methylguanine DNA methyltransferase (*MGMT*) DNA may be a predictive biomarker for treatment response [10]. Indeed, for nearly 15-years, we have recognized the importance in particular of the methylation of the promoter of *MGMT* in adult GBM response to radiation and concomitant chemotherapy [32]. Specifically, the promoter methylation status of *MGMT* correlates with sensitivity to alkylating chemotherapy, where those patients with methylated *MGMT* promoter in recurring GBM tumors exhibit significantly better progression-free and overall survival compared to patients with unmethylated *MGMT* promoters [31] (Fig. 1a). Low *MGMT* expression as well as *MGMT* promoter methylation have been reported as markers that predict slower tumor progression in patients with GBM [33]. Turning to pediatric gliomas, *MGMT* methylation status appears to be more important in supratentorial gliomas, as discussed by Jalali et al. (2016) in a single institutional study of 66 patients, however, more studies need to be done to validate this observation [34]. In pediatric patients, *MGMT* expression correlates with outcomes in gliomas and *MGMT* promoter methylation status correlates with a survival benefit and sensitivity to Temozolomide in pediatric GBM, consistent with the earlier study on adult GBM patients of *MGMT* promoter methylation and Temozolomide [32, 35, 36].

Isocitrate dehydrogenase and survival in glioma patients

Clinically, adult glioma patients are commonly risk-stratified based on the methylation status of *MGMT* and mutation status of the enzyme isocitrate dehydrogenase 1 or 2 (*IDH1* or *IDH2*). IDH catalyzes the reduction of alpha-ketoglutarate to 2-hydroxyglutarate (2HG). Mutations in *IDH* results in the production of 2HG which is a competitive inhibitor of α-KG-dependent dioxygenases [37]. These groups of α-KG-dependent dioxygenases include the histone demethylases

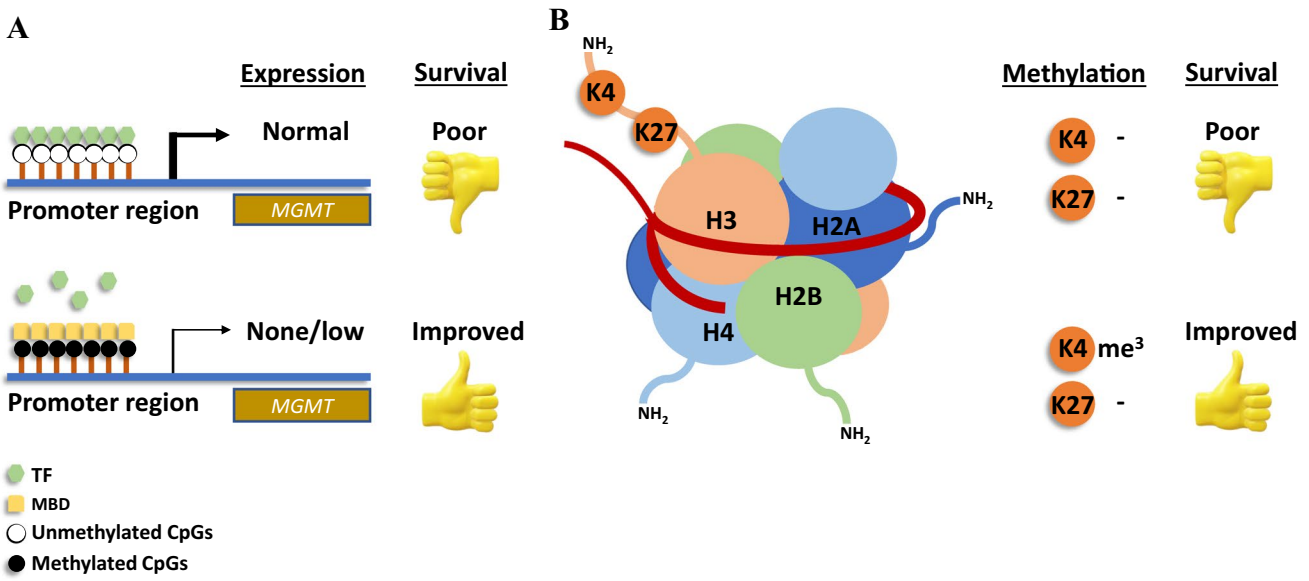

Fig. 1 Classic and recent examples where epigenetics may impact survival in pediatric brain tumors. **a** The promoter for O^6-methylguanine-DNA methyl-transferase (*MGMT;* chromosome 10q26.3) undergoes significant DNA methylation, which regulates this genes role in DNA repair. In the absence of *MGMT*, there is an accumulation of the alkylated adduct O^6-methylguanosine, leading to errors in DNA replication. This effect on DNA replication is compounded by exposure of cells to an alkylating agent. Top, there is poor overall and progression-free survival in adult GBM patients, including those 18 and over, who undergo alkylating chemotherapy, whose tumor exhibits *MGMT* unmethylated promoter. Bottom, there is improved overall and progression-free survival in *MGMT* methylated promoter in adult GBM patients, including those 18 and over, undergoing alkylating chemotherapy. **b** Methylation status of Histone H3 residues in non-WNT/non-SHH medulloblastomas. The N-terminal tail of histone H3 protein is modified at varied residues (R, S, E, K) with varied post-translational modification (acetylation, phosphorylation, methylation, etc.). These modifications contribute to differing responses in gene expression. Histone H3 methylation at lysine (K) 4 and K27 in populations of non-WNT/non-SHH medulloblastomas correlates with survival [46]. Top, In the absence of methylation of histone H3 K4 and K27, overall and progression-free survival is poor in WNT/non-SHH medulloblastomas. Bottom, if H3 K4 is methylated while K27 is not, overall and progression-free survival is improved in WNT/non-SHH medulloblastomas

JHDM1 and *KDM4* and the DNA demethylase *TET2* (Table 1). Hence, *IDH*-mutations in brain tumors result in significant dysregulation of epigenetic machinery, including DNA and histone hypermethylation, and *IDH* mutation could be a predictor of better survival for glioma patients [38]. Two different strategies could potentially be deployed to target *IDH*-mutant tumors: inactivation of *IDH* or inhibiting the effects of 2HG [39]. IDH mutant tumors are not common in the pediatric population, but are more common in young adults and adult population, therefore, will not be discussed further (see [40] and Table 1).

Epigenetics in survivorship of medulloblastoma patients

Medulloblastoma (MB) is a cerebellar brain tumor that is primarily pediatric. MB accounts for ~20% of all primary CNS tumors in children [6]. MB is classified per WHO (2016) into Wnt signaling pathway (WNT)-activated, sonic hedgehog signaling pathway (SHH)-activated and tumor suppressor protein p53 (*TP53*)-mutant, SHH-activated and *TP53*-wildtype, non-WNT/non-SHH Group 3, and non-WNT/non-SHH Group 4 [41]. MB tumors exhibit molecular heterogeneity, which is particularly pronounced in non-WNT/non-SHH or Group 3 and 4 subgroups. Large-cohort sequencing studies indicate that every subgroup of MB has altered epigenetic features.

Genomic characterization of MB has assisted in identifying subgroups with a poor, intermediate or good prognosis. Although risk stratification has been conducted for the MB molecular subgroups, based on mutations in molecular players and metastatic behavior and histopathology, there is a lack of studies relating epigenetic markers with MB survivorship in pediatric patients. In one significant study, Schwalbe et al.. investigated DNA methylation profiles along with molecular and clinical features from an extensive primary tumor cohort of 230 MB patients to predict better risk-survival stratification and prognostication [42]. This study identified the potential of epigenetics to advance the management of MB. They noted that DNA methylation biomarkers significantly improves survival prediction for non-WNT MBs arising in patients aged 3–16 at diagnosis. Inclusion of DNA methylation status of *MXI1* (a negative regulator of the *MYC* family of proteins) and *IL8* along with currently used molecular, pathological and clinical variables was found to improve risk stratification. In particular, inclusion of DNA methylation status of *MXI1* and *IL8* enabled ~46% of patients to be classified as favorable-risk, thereby implementing therapy de-escalation. On the other hand, methylation status of *MXI1* and *IL8* reduces the proportion of high-risk patients to ~16% who really require intensive therapies at the time of diagnosis [42].

In a landmark study on classification of MB subtypes based on molecular analysis, Cavalli et al. further subdivided the MB subgroups into distinct subtypes along with details on prognosis [43]. Regarding the SHH MB subgroup, they identified four subtypes (SHH-α, β, γ and δ) which included distinct somatic copy-number aberrations, activated pathways, and patient outcomes [43]. Frequency of mutations in the telomerase reverse transcriptase (*TERT*) gene promoter is highest in SHH subgroup of MB and *TERT* mutations define a favorable prognosis in a subgroup specific manner [44]. *TERT* promoter mutations define good prognosis in certain subtypes of SHH MB, but it also indicates poor prognosis in Group 4 MB [44]. Among the four molecular subtypes of SHH MB, SHH-γ (infants) and SHH-δ (adults), have a good prognosis, while SHH-β (infants) and SHH-α (children, 3–16 years) have worst prognosis [43, 45]. Interestingly, SHH-δ (adult) and SHH-γ (infants) MB subtypes are enriched with higher frequency of *TERT* promoter mutations and a better overall survival [43]. In contrast, SHH-β and SHH-α MB subtypes, bears lower frequency of *TERT* mutations have a worse prognosis and poor survival [43, 44].

Biology and behavior of Group 4 MB are the least understood among MB subgroups. The significant overlap of recurrent genetic mutations and copy number alterations has been observed with Group 3 tumors. Histone demethylases have been found to induce aberrant histone methylation of H3K4 and H3K27 in Groups 3 and 4 MB. Mutations in KDM-family members are extremely common in Group 4 [6]. *KDM6A*, a lysine demethylase regulating H3K27 methylation, is the most commonly mutated gene in Group 4 (13%) [6]. The biology of *KDM6A* and its role in determining Group 4 MB survivorship, however, is poorly understood.

It has been reported that specific tumor suppressor genes are silenced by DNA methylation in MB. *PTCH1*, the negative regulator of SHH signaling, is found to be repressed by CpG island hypermethylation leading to SHH MB [23] and hence, *PTCH1* expression levels could be an indicator of SHH prognosis. It has been reported that *OTX2* overexpression is common in Group 3 and Group 4. *OTX2* actually induces stem-cell like properties in tumor cells via epigenetic regulation and this in turn results in reduced survival in patients. Earlier studies found that H3K4me3 and H3K27me3, the chromatin effectors of *MLL2* and *KDM6A* activity respectively, carries alterations of the histone code in 24% of all MBs. H3K4me3 (depositing H3K4me3 marks) is typically associated with active promoters and it is deposited by the methyltransferase encoded by *MLL2*. An interesting study performed with a cohort of 175 patients reported a connection between these epigenetic marks H3K4me3 and H3K27me3 and survival in Groups 3 and 4 patients. They identified that a population of MB patients possessing H3K4me3+/H3K27me3−, has

improved outcome. In contrast, MB patients within Groups 3 and 4 with H3K4me3−/H3K27me3 − status showed abysmal overall survival [46] (Fig. 1b). *DAB2IP* (Disabled Homolog 2–Interacting Protein), a member of the RAS-GTPase activating protein family, is repressed in MB via EZH2-induced trimethylation. MB patient's expressing *DAB2IP* showed a history of improved survival and outcomes irrespective of subgroup, or patient's age [47]. In conclusion, these are clear examples of epigenetics impacting MB patient survival. However, there is clearly a dearth of studies linking epigenetics with the treatment induced long-term sequelae, a common problem in medulloblastoma survivors. The critical next step is to infer from these studies how best to treat patients once stratified in such a manner to avoid poor long-term morbidity and sequelae.

Epigenetics in survivorship of neurofibromatosis patients

Neurofibromatosis type-1 (NF-1) is an autosomal dominant inherited tumor predisposition syndrome, impacting 1 in 3000 individuals worldwide [48]. NF-1 results from a constitutional mutation of the gene *NF1*, which is located over a large locus (~ 350 kbp) on the long arm of chromosome 17 [49]. The product of *NF1*, neurofibromin, is a key regulator of the RAS/MAPK pathway [50]. As a negative regulator of the RAS pathway, its loss in function triggers increased RAS activity leading to the downstream activity of the MEK-ERK pathway as well as the PI3K-Akt-mTOR pathway. In NF-1 patients, mutations in *NF1* can lead to an acquisition of drug resistance to *BRAF* and *EGFR* inhibitors [51]. Biallelic inactivation of *NF1* is observed in a majority of NF-1 associated tumors. Individuals with NF-1 are at risk of developing CNS neoplasms, the most common being low-grade optic pathway glioma (OPG). OPGs are more common in children with NF-1, accounting for66–75% of all CNS tumors in NF-1 children [52]. OPGs in NF-1 patients, however, do not progress to high-grade [53]. NF-1 patients also develop pilocytic astrocytomas, WHO grade I gliomas, and are associated withloss of *NF1* expression [54]. A heterogenous variety of low- to high-grade gliomas is observed in NF-1 patients and a few epigenetic changes have been identified in gliomas associated with NF-1 patients. Loss of the *ATRX* gene that encodes a SWI/SNF family of histone chaperone proteins, has been shown to be associated with a chromatin remodeling gene expression signature in NF-1 glioma [20]. Loss of *ATRX* in glioma models and human samples was found to develop into a genetically unstable glioma that bears increased sensitivity to DNA damaging agents [55]. So, NF-1 glioma harboring the loss of chromatin remodeler *ATRX* could represent a novel group with an epigenetic signature that indicates increased sensitivity to DNA damaging agents but can have poor survival if left untreated. The same study reported that *ATRX* wild-type WHO grade III glioma associated with NF-1 has a significantly improved survival, as compared to *ATRX* mutant WHO grade III glioma [20]. This specific epigenetic signature of NF-1 glioma affecting overall survival and sensitivity to DNA damaging agents needs further investigation. The second most commonly encountered brain tumor arising in NF-1 patients are brain-stem gliomas (BSGs),which are indolent neoplasms. Prognosis of NF-1 patients with BSGis good [41, 56, 57]. BSGs occur in approximately 18% of NF-1 patients [56]. A retrospective study involving 133 NF-1 patients with BSG, showed that the mean age of diagnosis of a BSG is 7.2 years and 54% of children remain asymptomatic at diagnosis [56]. Unlike BSGs that occur sporadically, a good number of NF-1 children developing BSG are asymptomatic and the mortality rate is much lower from tumor-related complications [56]. BSGs that occur sporadically, like diffuse midline glioma, are progressive and typically fatal. Higher grade gliomas i.e., WHO grade IV, in NF-1 patients are rare ,accounting for approximately 2% of gliomas in NF-1 patients [20, 58, 59]. Epigenetic targeted therapy by inhibiting histone K27 demethylase *JMJD3* has been shown to reduce tumor growth and significantly improve survival in diffuse midline glioma orthotopic xenografts in mice [60]. However, the lack of precise information on *JMJD3* or other histone demethylase mutations in NF-1 BSGs presents a challenge and warrants further work to develop therapeutics to improve survival in pediatric patients.

Future directions

It is becoming increasingly evident that epigenetics in pediatric brain tumors is an important area dictating tumor progression. Findings may lead to prevention-intervention measures in pediatric brain tumors. Currently, apart from a few examples, data is scarce connecting epigenetics to survivorship. Thus, more research is needed to establish robust connections and to improve outcomes in pediatric brain tumor survivors whose neurological function is diminished or lost as a consequence of treatment or tumor. In addition, studies have been carried out in art and music therapy to improve the quality of life for pediatric brain tumor patients receiving chemotherapy, there is scope to do this kind of work for patients in survivorship [61, 62]. Further, cancer support groups provide counseling and assistance to brain tumor survivors and survivorship is a very important part of the National Cancer Institute's directives. It is critical that we move beyond addressing the disease and work to also address the long-term impact of treatment and hopefully our understanding of the epigenetics of pediatric brain cancers will provide approaches to do just that. Finally, it is our hope

and expectation that future studies will address the gap in our knowledge on how epigenetics and neurocognition are connected.

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Compliance with ethical standards

Conflict of interest Authors declare they have no conflict of interest with the present review.

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