Oncology and Translational Medicine
DOI 10.1007/s10330-016-0165-5

October 2016, Vol. 2, No. 5, P216–P226

REVIEW ARTICLE

Histone modification as a drug resistance driver in brain tumors*

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Abstract

Patients with brain tumors, specifically, malignant forms such as glioblastoma, medulloblastoma and ependymoma, exhibit dismal survival rates despite advances in treatment strategies. Chemotherapeutics, the primary adjuvant treatment for human brain tumors following surgery, commonly lack efficacy due to either intrinsic or acquired drug resistance. New treatments targeting epigenetic factors are being explored. Post-translational histone modification provides a critical regulatory platform for processes such as chromosome condensation and segregation, apoptosis, gene transcription, and DNA replication and repair. This work reviews how aberrant histone modifications and alterations in histone-modifying enzymes can drive the acquisition of drug resistance in brain tumors. Elucidating these mechanisms should lead to new treatments for overcoming drug resistance.

Key words: histone modification; drug resistance; brain tumor

Received: 16 June 2016
Revised: 15 July 2016
Accepted: 25 August 2016

Brain tumors are among the most formidable and devastating cancers in children and adults. Over 30,000 new malignant or benign brain tumors are diagnosed annually, accounting for 1.4% of all tumors and 2.3% of cancer-related deaths [1–2]. The overall 5-year survival following diagnosis and treatment of a primary malignant brain tumor is approximately 30% [2].

Tumor treatment generally consists of surgical resection in conjunction with radiotherapy and/or treatment with one or more chemotherapeutic agents. Irrespective of the chemotherapeutic agent employed, acquisition of multidrug resistance (MDR) is a major challenge [3]. Mechanisms of MDR acquisition differ in response to reagents and genetic factors, and these mechanisms have been comprehensively studied in recent decades. However, understanding the role epigenetics plays in MDR acquisition is limited and continues to be an active area of research.

Higher order chromatin structure is an important regulator of gene expression [4–5]. Chromatin is the condensed combination of DNA and histones within the nucleus of a cell. The structural and functional unit of chromatin is the nucleosome, which consists of a disc-shaped octamer composed of two copies of each histone protein (H2A, H2B, H3, and H4) wrapped twice by –147 base-pairs of DNA [6]. Nucleosomal arrays are visualized with electron microscopy as a series of 'beads on a string'; the 'beads' are the individual nucleosomes and the 'string' is the linker DNA. Linker histones, such as histone H1, and other non-histone proteins interact with the nucleosomal arrays to

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*Supported by the Rory David Deutsch Foundation, the Surgical Neuro-oncology Research Fund of Ann & Robert H Lurie Children's Hospital (A&RLCH) of Chicago, and the Dr. Ralph and Marian C. Falk Medical Research Trust.

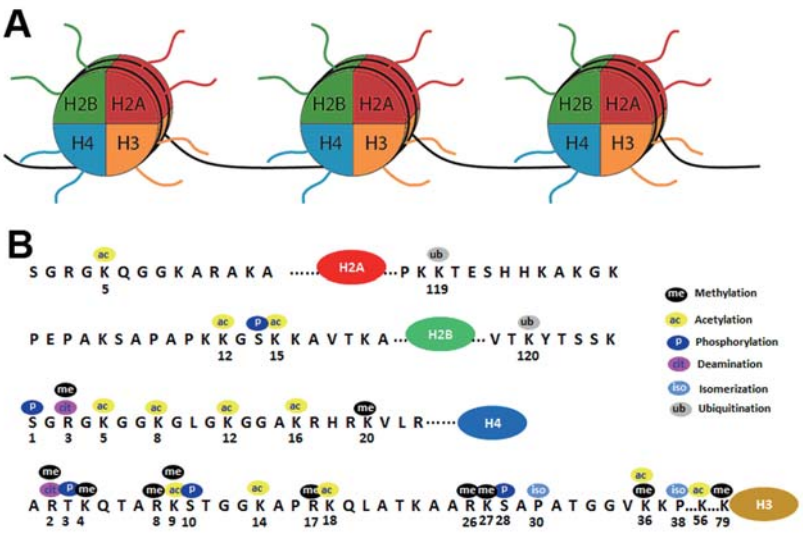

Fig. 1 Nucleosome structure. (a) The core protein of the nucleosome: disc-shaped octamer composed of two copies each of histones H2A, H2B, H3, and H4 wrapped twice by DNA; (b) Amino-terminal tails of core histones showing potential modifications

further package the nucleosomes into higher-order chromatin structures (Fig. 1a).

Histones, the key protein components of chromatin, are regulators of chromatin dynamics. These proteins are subject to a wide variety of post-translational modifications including acetylation, methylation, ubiquitylation, or glycosylation on lysine; methylation on arginine; phosphorylation on serine or threonine (Fig. 1b); and diphosphate ribosylation or carbonylation on adenosine. All of these modifications are catalyzed by histone-modifying enzyme complexes in a dynamic manner [7]. Modifications occur primarily within histone amino-terminal tails protruding from the surface of the nucleosome, but may also be present on the globular core region [8]. Recent studies have observed differential histone modification in adult and pediatric brain tumors compared to normal tissue as summarized in Table 1.

Histone modification in brain tumors

Histone modification has significant roles in brain tumorigenesis, proliferation, invasiveness, therapeutic response, and clinical outcome. Global histone modification patterns are prognostic markers in glioma patients [20]. Increased histone H3 acetylation is observed more frequently in glioblastomas than in low-grade astrocytomas and normal brain tissue [21]. Increased trimethylation of lysine 4 on H3 (H3K4me3) alters the transcriptional landscape and leads to oncogenic protein overexpression in glioblastomas [9]. Genes associated with H3K4me3 and H3K27me3 are potential therapeutic targets for inducing differentiation in glioblastomas [22]. Decreased H3K27me3 has been found in glioblastomas expressing the K27M mutation in the *H3F3A* gene, which codes for the replacement histone H3.3 [13]. H3K4me3 and H3K27me3 [11], as well as monomethylation of lysine 9 on H3 (H3K9me) [17] also play critical roles in the pathogenesis of medulloblastomas (MBs). H3K27 methylation is a therapeutic target for CpG island methylator-positive hindbrain ependymomas [14]. H3K9Ac inversely correlates with ependymoma prognosis [23]. Enhanced H3 acetylation and diminished H3 methylation control the balance between FGF7/FGFR2-IIIb signals in pituitary neoplasia [19, 24–25].

As expected, enzymes targeting histones are also altered in brain tumors. Class II and IV histone deacetylases (HDACs) are downregulated in glioblastomas [21]. HDACs 1, 2, 3, and 9, histone demethylases (JMJD1A and JMJD1B), and histone methyltransferases (SET7, SETD7, MLL3, and MLL4) also have altered expression patterns in gliomas [25–26], and have been linked to tumor recurrence and progression [26]. Inhibition of the lysine demethylase, KDM1, is associated with increased H3K4me2 and H3K9Ac and decreased H3K9me2, leading to apoptosis of glioma xenograft tumors [16]. The gene encoding BMI-1, a member of the polycomb group complex that regulates histone H3K27 methylation, is frequently subjected to copy number alterations in gliomas, and BMI-1 deletions are associated with poor prognosis in these tumors [21]. In MB, restoration of genes controlling H3K9 methylation diminishes proliferation *in vitro* [17]. HDAC2 is upregulated in primary MB subgroups with poor prognosis (Sonic hedgehog, Groups 3 and 4) compared to normal brain and MB of the WNT subgroup, and inhibition of HDAC2 is a valid target in patients with myelocytomatosis gene-amplified MBs [27].

Finally, mutations in genes coding for histones or histone-modifying enzymes can bring about gene dysregulation in brain tumors. For example, mutations in H3F3A are observed in pediatric and young adult gliomas, and the presence of these mutations is associated with alternative lengthening of telomeres and specific gene expression profiles [28]. Mutations for genes coding for MLL2,

Table 1 Histone modification, histone modifying enzymes and target genes deregulated in brain tumors

Histone modification	Enzymes	Genes affected	Gene function	Brain tumor	References
H3K4me3	Unknown	hTERT	Limitless replication potential	Glioblastoma	Nagarajan RP, *et al* [9]
		GLI3	Cell growth, cell specialization, and patterning of structures		
		TP73	Cell cycle arrest, apoptosis		
	MLL2	MLL2 mutation	Histone lysine methyltransferase	MB	Parsons DW, *et al* [10]
	MLL3	MLL3 mutation			
	ZMYM3	KDM1A			Robinson G, *et al* [11]
H3K27me3	N/A	$H3F3A^{G34/RV}$ mutation	Coding histone H3.3	Glioblastoma	Costa BM, *et al* [12]
	EZH2	HOXA9	Apoptosis		Venneti S, *et al* [13]
	EZH2	PRC2	Polycomb group	Ependymoma	Mack SC, *et al* [14]
	KDM6A	KDM6A mutation	Histone methyltransferase	MB	Dubuc AM, *et al* [15]
	KDM6B	KDM6B mutation			Parsons DW, *et al* [10]
H3K4me2, H3K9Ac	KDM1	P21, PUMA	Proliferation, apoptosis	Glioblastoma	Sareddy GR, *et al* [16]
H3K9me2	EHMT1	EHMT1 amplification	Histone lysine methyltransferase	MB	Northcott PA, *et al* [17]
	SMYD4	SMYD4 amplification			
	L3MBTL2	L3MBTL2 deletion	Polycomb group		
	L3MBTL3	L3MBTL3 deletion			
	SCML2	SCML2 deletion			
	JMJD2B	JMJD2B amplification	Histone lysine demethyltransferase		
	JMJD2C	JMJD2C amplification			
	MYST3	MYST3 amplification	Histone lysine acetyltransferase		
	KDM1	P21, PUMA	Proliferation, apoptosis	Glioblastoma	Sareddy GR, *et al* [16]
H4K20me, H3K36me	NSD1	MEIS1	Homeobox gene, normal development	NB, glioma	Berdasco M, *et al* [18]
H3Ac, H3me	N/A	MAGE-A3	Enhanced ubiquitin ligase activity	Pituitary tumor	Zhu X, *et al* [19]

Abbreviations: me, methylation; Ac, acetylation; MB, medulloblastoma; NB, neuroblastoma

MLL3, KDM6A, and ZMYM3, enzymes for H3K27 and H3K4 trimethylation, are defined novel targets for subgroup 3 and 4 MBs [11, 15, 29–30].

As illustrated, histone modifications are key regulators of gene expression in brain tumors. Increasing evidence indicates cell-specific and spatiotemporal histone marks related to brain tumor chemo- and radio-sensitivity. MDR is a major clinical challenge that hampers the success of brain tumor pharmacotherapy. This review summarizes major MDR mechanisms in brain tumors, and presents an overview of the current findings on the role of histone modifications in MDR in pediatric and adult brain tumors. Future directions to further elucidate how epigenetic changes impact these mechanisms will also be discussed.

Classic MDR mechanisms in brain tumors

Mechanisms of MDR include increased drug efflux by ATP-binding cassette (ABC) transporters, perturbed DNA damage repair, inactivation of pro-apoptotic genes, activation of parallel or downstream signal transduction pathways and secondary mutations in drug targets, as summarized in Table 2. This section will review MDR mechanisms, with the following section outlining current knowledge of epigenetic modifications associated with these mechanisms.

ABC transporters

ATP-dependent efflux pumps impair chemotherapeutic efficacy by lowering intracellular drug concentrations. These pumps belong to a family of ABC transporters that share sequence and structural homology. Presently, 48 human ABC genes have been identified and divided into seven distinct subfamilies (ABCA-ABCG) [31] [refer to Gottesman PA, *et al* (2002) for a complete review on the role of these molecules in cancer [32]].

P-glycoprotein (P-gp), also known as multi-drug resistance protein 1 (MDR1), mediates drug resistance and is the most extensively characterized brain tumor MDR mechanism. P-gp is an ATP-driven transmembrane drug transporter that decreases intracellular drug accumulation bidirectionally by both decreasing drug uptake and increasing drug efflux. High expression of P-gp, encoded by the ABCB1 or MDR1 gene is associated with chemoresistance and poor outcome in brain tumors including MBs [33–34], gliomas [35] and ependymomas [36–38].

Regulatory mechanisms that induce the overexpression of P-gp in brain tumors remain largely undefined, however there is growing evidence that protein kinase C, the RAS oncogene, the TP53 tumor-suppressor gene, and the murine double minute 2 (MDM2) gene are involved

Table 2 Chemotherapy drugs are currently in use for brain tumors and their potential relevant mechanisms of resistance

Mode of action	Drugs	Mechanism of resistance	Brain tumor
DNA crosslink	Nimustine (ACNU)	MGMT, PKC, DNA repair	Glioblastoma, anaplastic astrocytoma
	Carmustine (BCNU)	MGMT, GST/GSH, PKC, DNA repair	Glioblastoma, anaplastic astrocytoma
	Lomustine (CCNU)	MGMT, PKC, DNA repair	Glioblastoma, anaplastic astrocytoma, anaplastic oligodendroglioma, PNET, MBs
	Fotemustine	MGMT, DNA repair	Glioblastoma, anaplastic astrocytoma
	Cisplatin, carboplatin	Metallothioneins, GST/GSH, MRP, PKC, cell cycle arrest	PNET, MBs, anaplastic ependymoma
	Ifosfamide	DNA alkylation by attachment at the N-7 guanine	PNET, MBs, anaplastic ependymoma
	Cyclophosphamide	DNA alkylation	PNET, MBs, anaplastic ependymoma
Topoisomerase II interference	Teniposide	Topoisomerase Iiα, P-gp *, MRP, PKC	Glioblastoma, anaplastic astrocytoma
	Etoposide (VP-16)	Topoisomerase Iiα, P-gp, MRP, PKC	PNET, MBs, anaplastic ependymoma
MGMT	Temozolomide	MGMT, DNA repair	Recurrent of progressive high grade glioma
	Procarbazine	MGMT, DNA repair	Glioblastoma, anaplastic astrocytoma, anaplastic oligodendroglioma, PNET, MBs
	Dacarbazine	MGMT, DNA repair	PNET, MBs
Inhibition of microtubule formation	Vincristine	P-gp, MRP, PKC	Anaplastic oligodendroglioma, progressive high grade glioma, PNET, MBs
Folate pathway interference	Methotrexate	DHFR	PNET, MBs, anaplastic ependymoma

Abbreviations: MGMT, O6-methylguanine-DNA methyltransferase; PKC, protein kinase C; GSH, reduced glutathione; GST, glutathione-s-transferase; MRP, multidrug resistant-associated protein; DHFR, dihydrofolate reductase; MB, medulloblastoma; PNET, primitive neuroectodermal tumors. * ABCG2 may work with P-gp in this process

in modulating MDR1 expression and P-gp phosphorylation [39]. Our laboratory has demonstrated that ABCB1 is overexpressed in glioblastoma cells following prolonged chemotherapy, and this process is regulated by CD133 and DNA dependent protein kinase (DNA-PK) via the PI3K- or Akt-NF-κB signaling pathway [40].

In addition to P-gp, multidrug-resistance-related proteins (MRPs), which belong to ABC transporter subfamily C, may also be a factor in the formation of intrinsic or acquired MDR in brain tumors [41–44]. MRP-mediated drug transport is influenced by intracellular glutathione levels [45]; the details of this interaction are still being elucidated. The mechanism of MRP induction in brain tumors remains unclear, however post-transcriptional regulation is likely the primary mode of MRP upregulation [45]. A link between MRP overexpression and decreased patient survival has been shown for neuroblastomas [46].

A number of additional drug transporters, ABCG2 (breast cancer resistance protein, BCRP) [47–49], ABCA1 [50-51], and ABCB6 [52], are overexpressed in brain tumors and are involved in the formation of either intrinsic or acquired MDR. For instance, ABCG2 is a dominant drug transporter in brain tumors [53], and its expression and activity are upregulated in neuroepithelial tumors such as ependymomas and in glioma tumor stem-like cells [54]. However, ABCG2 protein expression and transport activity are downregulated in primary CNS lymphoma [55]. ABCG2 is highly expressed in the plasma membrane of human neural stem cells and tumor stem cells [56–57]. At a functional level, ABCG2 significantly overlaps with P-gp [58–59]. Anticancer drugs transported by ABCG2 include tyrosine kinase inhibitors [60–65], topotecan, irinotecan, epirubicin, doxorubicin, daunorubicin, and mitoxantrone [66–67]. ABCG2 restricts brain tumor penetration by these chemotherapeutics.

Overall, enhanced ABC transporter activity is a primary mechanism for drug resistance and a significant impediment to successful brain tumor treatment.

DNA repair

DNA repair is another crucial mechanism associated with chemotherapeutic resistance in human brain tumors. The majority of chemotherapeutic agents used to treat brain tumors, including chloroethylnitrosourea (CENU), carmustine (BCNU), cisplatin, carboplatin, and temozolomide (TMZ), target rapidly dividing cancer cells directly or indirectly, which in turn induces DNA damage. Upon recognizing DNA damage, cells initiate a complex variety of signaling pathways collectively referred to as the DNA damage response. Some repair mechanisms target specific lesions, such as mismatch repair, excision repair, double-strand break repair, and the addition of

poly-ADP ribose, while other more general mechanisms can act on a wide range of lesions. Enhanced DNA repair capability has been implicated as a cause of increased chemoresistance in brain tumors including gliomas [40, 68–70], ependymomas [71], MBs [36, 71–72], primitive neuroectodermal tumors (PNET) [71], and pituitary carcinoma [73].

Alkylating agent-based chemotherapy increases response rates and survival times for glioma patients. The most frequently used alkylating agent, TMZ, crosses the blood-brain barrier, and exhibits schedule-dependent antitumor activity. The efficacy of TMZ for glioblastoma treatment is influenced by the expression of the ubiquitous DNA repair enzyme O^6-methylguanine-DNA-methyl-transferase (MGMT). MGMT is overexpressed in gliomas and is the primary mechanism for TMZ resistance. TMZ induces cytotoxic O^6-guanine methyl adducts that are removed by functional MGMT. MGMT promoter methylation lowers MGMT protein expression, improves clinical outcomes in adults and children with high grade gliomas, and is thus a predictor for TMZ response [74]. Deficiencies in DNA mismatch repair (MMR) are also linked with resistance to alkylating agents like TMZ [74], as are elevated levels of Ape1/Ref-1, a major component of the base excision repair (BER) system [75]. Attempts to enhance TMZ-induced cytotoxicity by disrupting BER via poly-(ADP-ribose)-polymerase inhibition has been proposed as a treatment for malignant gliomas, particularly in tumors deficient in DNA mismatch repair [76].

Other DNA damage repair factors also contribute to drug resistance in brain tumors. For example, functional alterations of the MMR system, such as overexpression of the MMR gene *hMSH2*, are associated with drug resistance in gliomas [77]. The double strand break (DSB) DNA repair enzyme DNA-dependent protein kinase catalytic subunit (DNA-PKcs), a critical enzyme for DSB repair via non-homogeneous end joining, is overexpressed and regulates drug resistance in glioblastoma cells [40]. PARP1, which is essential in single strand break DNA repair through BER, is overexpressed in malignant pediatric brain tumors including ependymomas, atypical teratoid/rhabdoid tumors, MBs, choroid plexus papillomas, and PNET [78]. Rad51-mediated homologous recombination directed DNA repair contributes to cisplatin resistance in MB cells [79] and oligodendrogliomas [80]. ARTD-5, a poly ADP-ribose enzyme (PARP) involved in non-homologous end-joining the major pathway for DSB repair, enhances DNA damage repair through DNA-PKcs activation in MB cells [81].

Additional mechanisms of drug resistance in brain tumors

In addition to efflux pumps and DNA repair mechanisms, apoptosis, cell cycle, and cell transduction pathways are also factors in drug resistance. For instance, anti-apoptotic BCL2 proteins such as BCL2, BCL-XL, MCL1, and BCL2A1 are overexpressed and appear to be involved in MDR of various cancer types, including glioma [82–83] and MB [84–86]. The tumor suppressor p53, which can limit cell proliferation through several mechanisms, is also associated with drug resistance. Artificial expression of wild-type p53 curtails MGMT transcription in human tumor cells and enhances their sensitivity to alkylating agents [87]. Mutant TP53 enhances glioblastoma cell resistance to TMZ by upregulating MGMT [88], while abrogation of wild-type p53 function strongly attenuates TMZ cytotoxicity [70]. The oncogenes RB [89], c-Myc, c-Jun [90] and Ras [91], the cell cycle regulators p21 and p27 [92], the MDM2 gene [93], signal transduction elements such as protein kinase C [94–95] and NF-κB [40], and tyrosine kinase receptors such as EGFR [96–97] and c-Met [98–99] also demonstrate critical roles in the genesis of drug resistance in brain tumors.

Histone modifications and drug resistance in brain tumors

Drug resistance mechanisms were initially associated with genetic alterations, however, recent studies indicate that histone modifications also play a role in drug efflux, perturbed DNA repair, and silencing of apoptotic genes. Post-translational histone modification provides an important regulatory platform for biological processes such as chromosome condensation and segregation, gene expression, proliferation, apoptosis, and DNA replication and repair. Recent studies demonstrated that histone modifications also contribute to brain tumorigenesis [11, 14, 25, 28–30, 100–104]. These studies established a critical role for epigenetics as a driving force in tumorigenesis and provide a rationale for epigenetic changes and non-genetic heterogeneity observed in brain tumors. The establishment of tumor epigenomes further allows for the determination of additional epigenetic changes that regulate biological processes, including MDR.

Histone modification of ABC transporters

Histone modification has not yet been shown to directly affect ABCB1 expression in brain tumors, however, histone modification and changes in activity of key chromatin remodeling complexes do alter ABCB1 promoter methylation, and thus ABCB1 expression. Chemotherapeutic drugs can actively induce H3 and H4 acetylation, H3K4 methylation [105], and H3K9 acetylation [106] within discrete regions of the ABCB1 locus. Acetylated histone H3, H3K4me3, H3S10 phosphorylation, and H3K9me3 are associated with the ABCG2 promoter following selection for drug resistance [107]. Overall, it is highly likely that histone modification regulates ABC transporter expression in brain tumors.

In addition to global aberrations at the histone level, enzymes for histone modification and their effects on drug tolerance have been studied. Trimethylation of H3K4 at the ABCB1 promoter is dependent on the methyltransferase MLL1. MLL1 knockdown decreases constitutive ABCB1 expression and sensitizes cancer cells to chemotherapeutic agents [108]. HDAC inhibition enhances global histone acetylation, and results in upregulation of several members of the ABC transporter family, MDR1, ABCG2, and MRP8 [45, 107, 109–112]. MeCP2, a methyl-CpG-binding protein [113], binds to hypermethylated DNA at the ABCB1 promoter [114] and provides a docking platform for nucleosome modifiers and remodelers, such as SWI/SNF, HDAC1, HDAC2, and mSIN3, thereby altering the chromatin state of gene promoters and subsequent transcription [115–117]. Although a direct interaction of these corepressors with ABCB1 promoter-bound MeCP2 has not been described, ABCB1 expression is induced upon inhibition of HDAC activity or by overexpression of the p300/CREB lysine acetyltransferase, KAT3B [105, 118–119]. The MeCP2/HDAC complex represses ABCB1 expression [114], however, removal of HDAC inhibition dramatically reduces ABCB1 protein levels, suggesting that other factors may also regulate ABCB1 expression [120]. Overall, the data indicate that ABC transporter expression is regulated by promoter histone modification, and these changes can contribute to acquisition of drug resistance in response to chemotherapy.

Histone modification and DNA repair in brain tumors

Eukaryotic cells encounter numerous endogenous and exogenous genotoxic stresses that trigger DNA damage, including DNA DSBs. To overcome these threats, cells have evolved mechanisms of DNA damage repair to maintain genomic stability and prevent oncogenic transformation or disease. Compacted chromatin is a major obstacle in the orchestration of DNA repair. For efficient DNA repair, chromatin must first be relaxed to give repair proteins access to the break sites, thus chromatin remodeling is an early event in the DNA repair process [121].

Histone modifications, such as acetylation, methylation, phosphorylation, and ubiquitylation, as well as histone dynamics promoted by histone chaperones and remodeling factors, play critical regulatory roles in response to DNA damage. H4K16Ac and an intact acidic pocket at H2AX are required for recruitment of the DNA repair complex adapter protein Mdc1 to DNA damage sites [122]. H3K56Ac and H3K9Ac are downregulated by DNA damage [123], while H3K56Ac accumulates in response to DNA damage [124–125]. H3K36me3 is involved in MMR [126] and H4K20me1/2 is recognized by the checkpoint mediator 53BP1, which targets it to DNA damage sites [127]. H2AX phosphorylation is required for the recruitment of HATs to DNA break sites; this recruitment is mediated by Arp4 and leads to acetylation of the chromatin surrounding the breaks, thereby relaxing the chromatin and facilitating access for repair proteins [128]. Mono-ubiquitylation of H2A at lysine 119 (H2AK119Ub) mediated by BMI-1 occurs at DNA double-strand breaks [129]. Histone loss, enhanced histone mobility/turnover, histone chaperones and enrichment of histone variants are also associated with DNA repair, as recently reviewed by Adam S *et al* [130] and House NC *et al* [131]. Finally, crosstalk between histone modifications during the DNA damage response is also crucial for DNA repair [132].

Histone modification is involved in the DNA damage response in brain tumors. Phosphorylation of H2AX at serine 139 (Ser139), termed γH2AX, accumulates at DNA damage sites in glioblastoma cells [133]. Acetylated H3, along with the γH2AX/53BP1 complex increase following DNA damage induced by radiation in glioblastoma cells [134]. Inhibition of LSD1 (also known as KDM1A), a demethyltransferase of H3K4me2, sensitizes glioblastoma cells to DNA damage induced by HDAC inhibitors [135]. Overexpression of γH2AX following valproic acid and pyrimethamine treatment sensitizes meningioma cells to radiotherapy [136] and pituitary adenomas cells to TMZ [137], respectively. Accumulation of γH2AX occurs in MBs following DNA damage induced by irradiation and SPARC, a putative radioresistance-reversal gene, increases γH2AX levels [138]. These studies indicate that chromatin remodeling, including histone modification, is involved in DNA repair induced by irradiation or DNA-damaging pharmacotherapy in brain tumors.

Histone modification and other drug resistance mechanisms in brain tumors

Epigenetic perturbations, including histone modification, may result in defective apoptotic response, cell cycle arrest, and/or cell signal transduction, which may in turn produce drug-resistant tumor cells.

The tumor suppressor gene TP53 promotes cell-cycle arrest or apoptosis in response to chemotherapy. TP53 loss or inhibition can induce drug resistance [70]. Inhibition of LSD1 increases H3K4me2 and H3K9Ac, reduces H3K9me2, and promotes p53 target genes p21 and PUMA, leading to apoptosis of glioma xenograft tumors [16]. Treatment of glioma cells with the HDAC inhibitor vorinostat enhances H3 and H4 acetylation, increases p21 levels in a p53-independent manner, and decreases cyclin B1, resulting in G2 phase cell cycle arrest followed by apoptosis [139]. HDAC4 suppresses the expression of the cell cycle regulator $p21^{WAF1/CIP1}$ in tumor cells by reducing H3 acetylation at the proximal promoter of the CDKN1A gene (cyclin dependent kinase inhibitor 1A). Silencing HDAC4 induces $p21^{WAF1/CIP1}$ expression and decreases tumor growth of glioblastoma cells independently of p53 [140].

Histone modifications regulate a number of other apoptotic genes. For example, CHI3L1 (chitinase-3-like protein 1, also known as YKL-40) is overexpressed in glioma cells, where it affects chemo- and radio-sensitivity [141]. TNF-α (tumor necrosis factor-alpha)-mediated recruitment of NF-κB subunits p65 and p50 to the YKL-40 promoter suppresses its expression. Recruitment of HDAC1 and HDAC2 deacetylates H3 at the YKL-40 promoter region, preventing NF-κB binding [142]. RASL10A (RAS-like family 10, member A, also named RRP22), a novel neural tumor suppressor that induces caspase-independent cell death [143], is downregulated in astrocytomas [144]. RASL10A is repressed by H3K9me3 and reduced pan-Ac-H3 in its promoter region [145]. Apoptosis has been observed in response to HDAC inhibition in PNET [146], atypical teratoid/rhabdoid tumors [147], and MBs [148]. Histone modification regulates the expression of NEURL1, thereby downregulating Notch target genes [149], which are potentially associated with drug resistance [150]. The oncogenic PI3K–AKT pathway, frequently altered in malignant gliomas, upregulates expression of the transcription factor HOXA9 (homeobox A9) through histone modification. Pro-proliferative, anti-apoptotic properties of HOXA9 are associated with poor glioma prognosis. These modifications could possibly be initiated by AKT-induced EZH2 histone methyltransferase activity [12].

Histone modification: therapeutic targets for treating brain tumors

Four epigenome-targeted anticancer drugs have been approved by the U.S. Food and Drug Administration: two DNA methyltransferase inhibitors, azacitidine and decitabine, and two HDAC inhibitors: vorinostat and romidepsin. Only HDAC inhibitors are being tested in glioblastomas, as reviewed by Spyropoulou A *et al* [151]. HDACs cooperate with LSD1 to regulate key cell death pathways in glioblastoma cell lines but not in normal cells, therefore a combination of LSD1 and HDAC inhibitors is being investigated as a therapeutic approach for glioblastoma [135].

A major challenge for cancer treatment via epigenetic therapy is target specificity. For instance, genes that are normally inactive due to histone deacetylation may become activated in response to HDAC inhibitors. Moreover, HDACs not only catalyze deacetylation of lysine residues in core histones but also in non-histone proteins, and as a result, they exhibit complex, unpredictable effects. In addition, interactions between histone modification, DNA methylation, and DNA binding proteins are crucial in DNA repair and cellular signaling and function [132, 152]. These interactions have yet to be fully elucidated. Overall, molecular mechanisms that bring about histone modifications and their outcomes should be further studied to get an overall understanding of their role in these biological processes.

Conclusion

Histone modifications described in this review and their roles in development of drug resistance are only the tip of the iceberg. With advances in high throughput studies, including methylated DNA immuno-precipitation and sequencing, RNA-seq, and chromatin immunoprecipitation and sequencing (ChIP-seq), new patterns of histone modifications as well as their interactions with DNA methylation and non-coding RNAs are likely to be uncovered in brain tumors and other tissues. Gaining insight into the causes and consequences of aberrant histone modifications will extend our understanding of brain tumor carcinogenesis, adaption, and survival in response to environmental factors such as drug treatment. This knowledge will accelerate the development of "epigenetic drugs" for prevention or treatment of drug-resistant cells.

Conflict of interest

The authors declare no conflict of interest.

Acknowledgement

We are grateful to Dr. Ben Yang for his assistance in the preparation of figure for this review. We apologize to authors whose primary references could not be cited due to space limitation.

Conflicts of interest

The authors indicated no potential conflicts of interest.

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DOI 10.1007/s10330-016-0165-5
Cite this article as: Xi GF, Barbara Mania-Farnell, Lei T, *et al*. Histone modification as a mechanism drives drug resistance driver in brain tumors. Oncol Transl Med, 2016, 2: 216–226.