Cancer Letters 604 (2024) 217269

Contents lists available at ScienceDirect

Cancer Letters

journal homepage: www.elsevier.com/locate/canlet

Review Articles

Histone acetyltransferases as promising therapeutic targets in glioblastoma resistance

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ARTICLE INFO

Keywords:
Glioblastoma
Histone acetyltransferases
Histone acetylation
HAT inhibitors
Therapy resistance

ABSTRACT

Glioblastoma (GBM) is a fatal adult brain tumor with an extremely poor prognosis. GBM poses significant challenges for targeted therapies due to its intra- and inter-tumoral heterogeneity, a highly immunosuppressive microenvironment, diffuse infiltration into normal brain parenchyma, protection by the blood-brain barrier and acquisition of therapeutic resistance. Recent studies have implicated epigenetic modifiers as key players driving tumorigenesis, resistance, and progression of GBM. While the vast majority of GBM research on epigenetic modifiers thus far has focused predominantly on elucidating the functional roles and targeting of DNA methyltransferases and histone deacetylases, emerging evidence indicates that histone acetyltransferases (HATs) also play a key role in mediating plasticity and therapeutic resistance in GBM. Here, we will provide an overview of HATs, their dual roles and functions in cancer as both tumor suppressors and oncogenes and focus specifically on their implications in GBM resistance. We also discuss the technical challenges in developing selective HAT inhibitors and highlight their promise as potential anti-cancer therapeutics for treating intractable cancers such as GBM.

1. Introduction

Glioblastoma (GBM) is a highly aggressive and malignant adult brain tumor with a dismal prognosis and a median overall survival of 15–20 months [1]. Despite extensive multi modal therapy including maximal surgical resection, fractionated radiation, and chemotherapy with Temozolomide (TMZ), virtually all GBM tumors recur as they acquire resistance [2]. Targeted molecular therapies and immunotherapies that have significantly improved the outcomes of other solid tumors have largely failed in providing any meaningful benefit for GBM patients mainly due to the acquisition of resistance and a highly immunosuppressive microenvironment [3]. Developing effective targeted molecular therapies is particularly challenging for GBM due to its extensive intra- and inter-tumoral heterogeneity and limited drug penetration across the blood-brain barrier [4,5].

Epigenetic therapies have emerged as a promising approach for treating recalcitrant solid tumors such as GBM [6]. Numerous studies have demonstrated the importance of epigenetic modifications such as DNA methylation and histone deacetylation in driving GBM tumorigenesis and resistance [7]. Drugs targeting these epigenetic modifiers are being evaluated as either monotherapies or as a combination therapy with radiation and TMZ for treating GBM and are currently in various phases of the clinical trials [8]. While the functional roles of histone deacetylases (HDACs) have been extensively investigated in GBM, their counterparts, histone acetyltransferases (HATs) have remained largely understudied.

HATs are epigenetic writers that catalyze the addition of acetyl groups to lysine residues on histone and non-histone proteins to regulate chromatin remodeling and gene expression [9]. HATs play key roles in various cellular processes including proliferation, differentiation, and DNA repair and their dysregulation leads to cancer development [7]. Several studies have indicated that HATs can act as both tumor suppressors and oncogenes depending on the cancer-type [10]. Emerging evidence suggests that HATs also play a key role in mediating treatment-induced plasticity and resistance to chemo-radiotherapy in GBM [11,12]. However, the underlying molecular mechanisms by which HATs promote tumorigenesis and therapy-resistance in GBM as well as other cancers are yet to be fully determined.

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https://doi.org/10.1016/j.canlet.2024.217269
Received 17 June 2024; Received in revised form 14 September 2024; Accepted 17 September 2024
Available online 24 September 2024

In this review, we will first briefly discuss the structure and types of HATs and elaborate on their functions in normal development and cancer with a specific focus on recent findings from GBM. We will also provide insights into their dual functions as oncogenes and tumor suppressors via regulation of histone and non-histone protein acetylation to drive cancer development and progression. Lastly, we will outline the challenges and opportunities in developing selective inhibitors of HATs for targeting GBM and other cancers.

2. Histone acetyltransferases (HATs): types, structure and substrates

HATs are enzymes that catalyze the transfer of acetyl groups from acetyl-CoA to specific lysine residues on histone and non-histone proteins resulting in their acetylation. Since the acetylation occurs specifically on lysine residues, they are also referred to as lysine acetyltransferases (KATs) [13–15]. Acetylation of the histone proteins alters the chromatin structure leading to a more relaxed state that is accessible to transcription factors and regulates gene expression (Fig. 1). Acetylation of non-histone proteins influences their stability, enzymatic activity, subcellular localization, and their interactions with DNA- and other proteins [16].

HATs are mainly classified into two types based on their cellular localization. Type A HATs are primarily nuclear enzymes that acetylate histone and non-histone proteins in the nucleus [9]. They are categorized into distinct families based on their sequence homology and include GNAT (General control non-repressible/GCN5-related N-acetyltransferases), MYST, and P300/CBP families [9]. The GNAT family consists of KAT2A (GCN5) and KAT2B (PCAF), the MYST family comprises KAT5 (TIP60), KAT6A (MOZ/MYST3), KAT6B (MORF/MYST4), KAT7 (HBO1/MYST2), and KAT8 (MOF/MYST1), while the P300/CBP family includes KAT3A (CBP) and KAT3B (P300). Type B HATs such as HAT1, HAT2, and HAT4 are cytoplasmic enzymes that modify free histones before they are transported to the nucleus and integrated into newly synthesized DNA [17,18]. These enzymes play an important role in acetylating newly synthesized histones prior to their assembly into nucleosomes.

Structurally, there are notable differences among the different HAT families, which contributes to their functional diversity and substrate specificity (Fig. 2). P300/CBP family of HATs consist of various

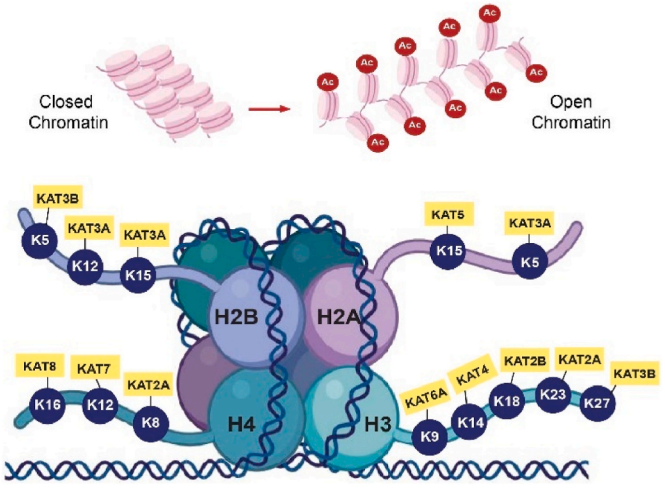

Fig. 1. HAT-mediated acetylation of lysine residues on histones alters the chromatin structure. Nucleosomes, the basic structural unit of chromatin, are made up of histone octamers containing two copies each of the histone proteins H2A, H2B, H3 and H4 that wrap around the DNA tightly. Histone acetyltransferases (HATs) acetylate specific lysine residues on the protruding tails of the histones to relax the chromatin structure that enables transcription factor binding and regulates gene expression.

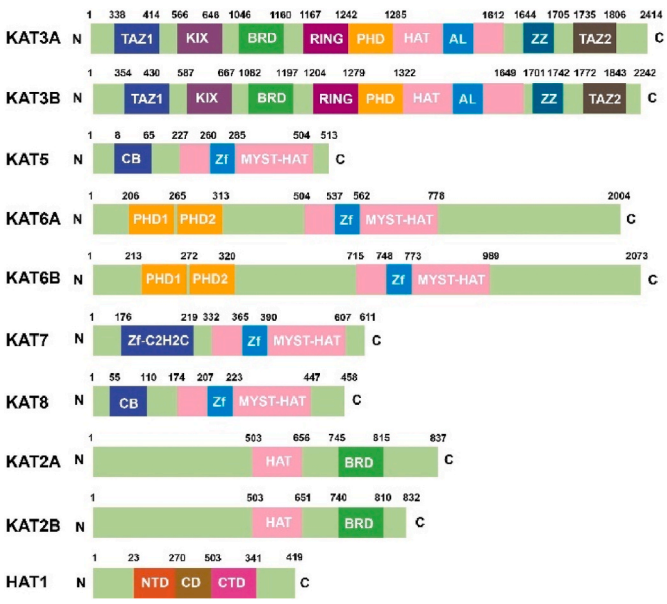

Fig. 2. Protein structure of HATs: HAT proteins contain several catalytic and substrate-binding domains such as TAZ1, KIX, BRD (Bromodomain), RING, PHD (Plant homeodomain), HAT (histone acetyltransferase domain), CB (Chromobarrel domain), N-terminal domain (NTD), CTD (C-terminal domain), AL domain (Autoinhibitory loop), CD (chromodomain) and ZZ (Zinc finger). These unique structural features determine their interactions with histone and non-histone protein substrates.

structured and unstructured domains including TAZ1/TAZ2, KIX, bromodomain (BRD), plant homeodomain (PHD), RING domain, HAT domain, ZZ-type zinc finger (ZZ) and autoinhibitory loop (AL), which regulate their interactions with various substrates [19–23]. MYST family members such as KAT5 and KAT6A/6 B are characterized by the MYST catalytic domain that includes zinc finger and core HAT domains [21]. KAT6A/6 B also contain tandem PHD domains that recognize specific acetylation marks on the histone tails [22]. Moreover, the unique structural domains of β-hairpins and conserved motifs in the MYST proteins regulates their catalytic activity and interactions with other substrates [23]. Members of the GNAT family including KAT2A/2 B exhibit selectivity for different acyl-CoA substrates such as acetyl-CoA, propionyl-CoA, and succinyl-CoA [24]. Type B HATs such as HAT1 lack a bromodomain, as their primary function is to recognize and acetylate core histones during the initial stages of histone synthesis [25].

HATs exhibit diverse substrate specificities for both histone and non-histone proteins. While KAT3A and KAT3B can acetylate all four core histones (H2A, H2B, H3, and H4), KAT6A specifically targets histone H3 and KAT8 acetylates lysine 16 on H4. KAT2A/2 B preferentially acetylates H3 and to a lesser extent H4 (Table 1) [26–28]. The substrate selection mechanisms also vary among the three HAT families. P300/CBP exhibit broad specificity influenced by their catalytic domain and interactions within multi-subunit complexes [29]. GCN5, PCAF, and P300 require only a few residues around the substrate lysine for efficient binding and catalysis, whereas KAT6A from the MYST family rely on interactions with more distal regions of the substrate for efficient acetylation [30,31]. Specific DNA interactions can also influence substrate selection as seen with KAT6A [30]. Thus, the complexity of HAT substrate specificity is shaped by interactions with accessory proteins, DNA, and the structural features of their catalytic domains.

2.1. *Functions of HATs in normal development*

HATs are essential for normal embryonic development as revealed by genetic perturbation studies in mice. Loss of *EP300* and *CBP* results in early embryonic lethality with neural tube closure, vascular and cardiac

Table 1
Histone and non-histone protein substrates of HATs.

HATs	Histone Substrates	Lysine residues	Non-histone substrates	References
KAT2A	H2B	K8	TFEB, E2F1 MYC, CDC6, CDK9, CCND1, CCNE1, HDM2, PTEN, TBX5, PLK4, CEBPB	[32–36]
	H3	K9, K11, K12, K14, K18, K23, K27, K36, K56		
	H4	K5, K16		
KAT2B	H3	K9, K14, K18, K23, K27, K125, K128, K36	P53, CDK9, MYC, FOXO1, AR, TBX5, PLK4, ACLY	[32,37,38]
KAT3B	H2A	K1, K7, K13, K15	P53, E2F1, NFKB, MYC, STAT3, CTNNB1, FOXO1, AR, SIRT2, HDAC1	[32,39–44]
	H2B	K7, K11		
	H3	K2, K3, K4, K9, K10, K14, K18, K23, K27, K36, K56, K20		
	H4	K5, K6, K8, K12, K16, K17		
KAT3A	H2A	K5, K9	P53, SNAI1 NFKB, c-MYB, FOXO1, PCAN, KLF1, IRF2	[9,32,40, 43,45]
	H2B	K5, K12		
	H3	K2, K3, K4, K9, K13, K14, K15, K18, K23, K27, K56		
	H4	K1, K5, K6, K7, K8, K10, K11, K12, K16, K17, K20		
KAT4	H3	K4, K9, K14, K373, K382	–	[46,47]
	H4	K5, K8, K12		
KAT5	H2A	K9	P53, ATM, E2F1, MYC, FOXP3, RAN	[32,39,48, 49]
	H3	K14		
	H4	K4, K5, K7, K8, K11, K12, K13, K15, K16		
KAT6A	H3	K4, K9, K14	SMAD3, P53	[32,50–53]
KAT6B	H3	K14, K23	RUNX2	[32,50,54]
KAT7	H2A	K5, K9	CDT1	[32,55–57]
	H3	K23		
	H4	K5, K8, K12, K14		
KAT8	H4	K16	P53	[32,58,59]
KAT13A	H3	K14	–	[42,60]
	H4	K9		
KAT13D	H3	K14, K537	–	[61,62]

defects [63,64]. Mice lacking either a HAT domain or harboring point mutations in the CREB interaction domain of *CBP* display defects in memory and synaptic plasticity [65]. *GCN5*-null embryos also exhibit embryonic lethality, whereas *PCAF* null mice do not display any overt phenotypes [65,66]. However, *PCAF*-null adult mice show defects in memory and learning [67]. In addition, point mutations affecting the HAT activity of GCN5 show cranial neural tube defects [65,66]. The defects observed in *GCN5*-null mice are not only due to its effect on histone acetylation, but also due to its regulation of the non-histone protein P53 [65,66]. Homozygous deletion of *TIP60* results in early embryonic lethality around the blastocyst stage of development [68]. In addition, *Tip60* is involved in regulation of neuronal plasticity and memory formation [69–71]. Mutations in the KIX domain of *EP300* results in disruption of its binding to c-MYB and CREB leading to multiple defects during hematopoietic development such as B-cell deficiency, thymic hypoplasia, megakaryocytosis, and thrombocytosis [17]. CBP and P300 also play opposing yet crucial roles in self-renewal and differentiation of hematopoietic stem/progenitor cells (HSPC) [72]. *KAT6A (MOZ)-deficient* mice display abnormalities in HSC numbers and disrupted B-cell development [73]. KAT6A acetylation activity is also essential for maintenance of normal hematopoiesis as it regulates the balance between proliferation and differentiation [73]. Furthermore, KAT6A controls neural and HSC proliferation by repressing the transcription of p16, which in the absence of KAT6A promotes replicative senescence [74]. *KAT7 (HBO1)* and BRD1 form a HAT complex that regulates fetal liver erythropoiesis [75]. KAT7 also controls HSC maintenance and self-renewal in adult hematopoiesis via H3K14 acetylation and regulation of a transcription factor network consisting of *GATA2*, *MPL*, *ERG*, *PBX1*, *MEIS1*, and *HOXA9* [76]. Similarly, *KAT8* (*MOF*) and its H4K16 acetylation activity is vital for adult, but not fetal hematopoiesis [77]. These studies illustrate the fundamental yet developmental-stage specific functional roles played by HATs and chromatin modifiers in embryonic development.

2.2. Dual roles of HATs as oncogenes and tumor suppressors in cancer

HATs are key drivers of tumorigenesis and exhibit dual yet context-specific roles as oncogenes and tumor suppressors. Overexpression often correlates with an oncogenic role, while loss of expression/function results in reduced acetylation capacity and a tumor-suppressive role (Table 2). The earliest observations of the tumor suppressor function of HATs were revealed by studies on *EP300/CBP*-deficient mouse models. Germline mutation of *CBP* results in Rubinstein-Tabyi syndrome, which is characterized by increased pre-disposition to childhood tumors of the neural crest origin. Inactivation of *CBP* and *P300* in mice also results in hematological malignancies such as thymic lymphoma and histiocytic

Table 2
HAT mutations in cancer.

HATs	Mutations	Types of Cancers	References
KAT2A	Deletion	Kidney	[10,83–88]
	Amplification	Breast, Colorectal, Prostrate, Lung	
KAT2B	Missense	Lung	[89–94]
	Deletion	Lung	
	Amplification	Esophageal squamous cell carcinoma, Cervical, Kidney	
KAT3A	Translocation	ALL, Diffuse large B-cell lymphoma	[19,95–98]
	Frameshift	AML	
	Missense	AML	
KAT3B	Frameshift	Pancreatic, Diffuse large B-cell lymphoma, AML	[10,99,100]
	Missense	Colorectal, Breast, Pancreatic	
KAT4	Missense	Colorectal, Gastric, Breast, AML, Kidney	[101–107]
	Splice	Ovarian	
KAT5	Missense	Colorectal	[79,108–110]
	Frameshift	Colorectal, Head and neck, Gastric	
	Nonsense	Colorectal, Head and neck	
KAT6A	Nonsense	Breast, AML	[111–114]
	Missense	Lung	
	Amplification	Colorectal, Lung, Breast	
	Deletion	Colorectal, Lung	
	Translocation	AML	
KAT6B	Nonsense	Colorectal	[55,115–119]
	Missense	GBM, Lung, Ovarian	
	Frameshift	AML	
KAT7	Amplification	Colorectal, Breast, Prostate, Ovarian	[120–125]
	Missense	Lung	
	Splice	Lung	
KAT8	Missense	Lung, Colorectal, Medulloblastoma, Ovarian, Gastric	[10,82, 126–129]
	Nonsense	Breast	
	Deletion	Colorectal	
KATI3A	Missense	Lung, Colorectal	[130–133]
	Deletion	Breast	
KATI3B	Nonsense	Colorectal	[10,45,120, 134–136]
	Missense	Ovarian, Lung	
	Amplification	Breast, Colorectal	
	In-frame insertion	Lung	
KATI3D	Missense	Colorectal, GBM, Lung	[10,137–140]
	Nonsense	Lung	

sarcomas [78]. Bi-allelic mutations in *TIP60* (*KAT5)* and gene silencing though CpG methylation has been identified in head and neck squamous carcinomas, ductal breast carcinomas, and low-grade B-cell lymphomas [79]. *TIP60* also regulates breast cancer progression by influencing cell cycle, invasion and metastasis, and reduced expression correlates with poor overall and relapse-free survival of breast cancer patients [80]. In cholangiocarcinoma, *TIP60* suppresses the proliferation and migration of tumor cells via regulation of the PI3K/AKT pathway [81]. Reduction of *MOF/KAT8* or mutations that lead to reduced H4K16ac levels occur in medulloblastoma and breast carcinomas [82].

P300/CBP family also possess oncogenic functions in many solid tumors and hematological malignancies. Overexpression of *P300* was observed in breast cancer and correlates with advanced clinical stage and tumor recurrence [161]. *P300* also promotes colon cancer growth by acetylating XRCC5 and regulating COX2 expression in mouse xenograft models [162]. Additionally, P300 overexpression is observed in hepatocellular carcinoma, non-small cell lung cancer (NSCLC), and prostate cancer [163–166]. Furthermore, chromosomal translocations involving *CBP and EP300* are common in hematological malignancies that creates fusion proteins such as *MLL-CBP*, *MLL-EP300*, *MOZ-EP300*, or *MOZ-CBP* and aberrantly acetylate genomic targets driving cancer development [167]. In acute myeloid leukaemia (AML), the *CBP* gene is involved in the t (8; 16) translocation (AML-M4). A point mutation at lysine 43 (K43) that converts to an unmodifiable arginine (K43R), but not the neighbouring lysine 24 (K24) in P300 significantly improve survival in mouse models of AML [168]. TAF1 (KAT4) functions as an oncogene by associating with K43 acetylated AE (AML1-ETO), which is crucial for AML tumor cell proliferation, chromatin binding, and gene regulation [169].

Acetylation of non-histone proteins by HATs also contributes to cancer development and progression [170]. Many non-histone proteins acetylated by HATs are involved in regulation of gene expression, DNA damage repair, cell division, signal transduction, protein folding, autophagy, and metabolism [171]. The tumor suppressor protein P53 was the first non-histone protein substrate whose acetylation by P300/CBP was shown to regulate its activation, stability and function [172,173]. Advances in proteomic technologies have expanded the non-histone protein acetylome that includes several tumor suppressor and oncogenes such as NF-κB, STAT3, and MYC that are acetylated by various HATs (Table 1). In breast cancers with *BRCA1* mutation, P300/CBP acetylate estrogen receptor α (ERα) to drive proliferation of tumor cells [174]. In prostate cancer, P300, and TIP60 acetylate the androgen receptor (AR) in a ligand-independent manner promoting cancer progression [175]. In human cell line models, PCAF acetylates the epigenetic regulator EZH2, increasing its stability and promotes migration and invasion of lung cancer cells [176]. Furthermore, TIP60 acetylates KDM2B, a histone demethylase to disrupts its activity and promote growth of osteosarcoma cells [177]. TIP60 also promotes radiation-resistance of prostate cancer by acetylating DNA repair proteins such as ATM, CHK2, and CDC25A [178].

HATs also promote cancer progression by reprogramming the tumor immune microenvironment to facilitate anti-tumor immune responses. In GBM, KAT13D is highly expressed in the glioblastoma stem-like cells (GSC) and promotes the infiltration of microglia and their polarization towards an immunosuppressive phenotype via regulation of HIF1a (hypoxia-inducible factor 1-alpha) signaling and transcription of the chemokines OLFML3 (olfactomedin-like 3) and LGMN (Legumain) [179,180]. Mutations in CREBBP/EP300 in diffuse large B-cell lymphoma (DLBCL) were associated with reduced ratios of peripheral lymphocyte to monocyte ratios and poor progression free survival. In B-cell lymphoma xenograft models with CREBBP or EP300 mutations, tumors displayed reduced histone acetylation and increased macrophage recruitment and their polarization towards an M2 phenotype via regulation of the FBWX7-NOTCH-CCL2/CSF1 axis, promoting tumor growth [181]. In lung cancer, the expression of M2 cytokine IL6 in macrophages is regulated by USP24 and P300-mediated histone acetylation of its promoter [182]. Furthermore, genetic and pharmacological inhibition of P300 in Forkhead box P3 (Foxp3+) T-regulatory cells (Treg) impaired their function and reduced mesothelioma tumor growth in immunocompetent mouse models without significantly affecting T effector cell responses or causing autoimmunity [183]. In liver cancer, P300/CBP drive the expression of PD-L1 by acetylating MEF2D, which impairs the ability of $CD8^+$ T cells to mount an effective anti-tumor response [184]. P300/CBP also modulate tumor cell immunogenicity via regulation of major histocompatibility class I (MHC-I) antigen processing and presentation and neoantigen amounts in various cancers [185]. GCN5 and PCAF also regulate Treg function through distinct yet partially overlapping mechanisms. Deletion of *Gcn5* prolonged allograft survival, whereas *Pcaf* abrogation enhanced anti-tumor immunity [186]. On the other hand, combined deletion of *GCN5* and *PCAF* resulted in reduced Treg stability and severe autoimmunity in mice [186]. In macrophages, particularly the M1 subtype, PCAF overexpression inhibited the expression of pro-inflammatory cytokines such as TNF-α, IL-6, and CXCL10 via transcriptional regulation of Kruppel-like transcription factors KLF2/KLF4 mediated by H3K9 acetylation [187]. In head and neck squamous cell carcinoma, GCN5 activates the transcription of immune checkpoint proteins PD-L1 and Galectin-9 through H3K27 acetylation enabling tumor cells to evade immune detection and destruction [188]. HAT1 upregulates PD-L1 expression in pancreatic tumor cells via acetylation of H4K5 and H4K12 that enables BRD4 binding to PD-L1 promoter to initiate its transcription and leads to immune evasion and enhanced tumor growth [189]. Taken together, these examples highlight a crucial role of HATs in driving tumor development and progression not only through their canonical function of histone acetylation to regulate gene expression but also by acetylating non-histone proteins involved in various cellular processes and regulating the function of immune cells and reprogramming the tumor immune microenvironment.

2.3. HATs in GBM tumorigenesis and resistance

Despite extensive research in other cancers, the functional role of HATs in GBM is critically understudied. The first study to implicate a role for HAT in GBM was by Malatesta et al., 2013, wherein PCAF/KAT2B was identified as a critical regulator of the Hedgehog (Hh) signaling pathway [190]. Depletion of *PCAF* impaired Hh activity and reduced the expression of Hh-target genes leading to decreased cell proliferation and increased apoptosis in medulloblastoma and GBM cells [191,192]. Another study reported that KAT6A was upregulated in GBM and correlated with patient survival [193]. Silencing *KAT6A* led to the suppression of GBM cell proliferation, migration, colony formation, and tumor growth in orthotopic xenograft models [193]. Mechanistically, KAT6A was shown to promote GBM tumorigenesis by upregulation of PI3K/AKT signaling via acetylation of H3K23 and recruitment of nuclear receptor binding protein TRIM24 to activate PIK3CA transcription [193]. Further, P300-interacting inhibitor of differentiation 3 (EID3), a member of the *EID* family has been implicated as a prognostic factor for GBM [194]. High *EID3* expression was shown to correlate with poor overall survival, and its expression was associated with MYC Targets, KRAS signaling, and DNA repair pathways [195]. A genome-wide CRISPR-Cas9 screening study identified TIP60/KAT5 histone acetyltransferase complex members as regulators of G0-like states in GBM. Inhibition of KAT5 activity led to cells arresting in a G0-like state, with implications for tumor growth [196].

Recent studies have implicated P300/CBP HAT family as key regulators of GSC plasticity and therapy resistance [11,12]. Tao et al., 2020, demonstrated that blocking CBP/SATB2 transcriptional activity using C646, a P300 inhibitor suppresses GSC proliferation and tumor growth and enhances the effects of TMZ and radiation therapy [197]. Importantly, C646 not only suppressed GSC proliferation on its own but also showed synergistic effects when combined with TMZ or radiation [197]. Muthukrishnan et al., 2022, discovered that radiation-induced

endothelial- and pericyte-like transdifferentiation of GSCs is mediated by increased chromatin accessibility and H3K27 acetylation in vascular gene regions. Blocking the HAT activity of P300 reversed the epigenetic changes and radiation-induced vascular conversion and reduced tumor growth following radiation. This study highlighted the critical role of P300 in regulating treatment-induced plasticity in GSC and radiation-resistance [11]. Mladek et al., 2022, demonstrated that P300 also interacts with RBBP4 and regulates the expression of pro-survival genes such as *c-MYC* [12]. Disrupting P300 activity with a small molecule inhibitor CPI-1612 effectively reduced H3 acetylation and sensitized GBM cells to TMZ chemotherapy [12]. In another study, RBBP4 was reported to mediate chemoradiotherapy resistance by promoting DNA repair via regulation of the expression of the Mre11-Rad50-NBS1 (MRN) complex [198]. Collectively, these studies emphasize an important role for P300/CBP HATs in mediating GSC phenotypic plasticity and chemo-radiation resistance, and their potential as promising therapeutic targets for mitigating GBM resistance.

3. HAT inhibitors currently being evaluated as potential mono- and combinatorial therapeutics to overcome resistance in GBM and other cancers

Given their dysregulation and critical functions in cancer development and resistance, several HAT inhibitors have been developed including natural derivatives, small molecule inhibitors and protein-protein interaction inhibitors that either target the bromodomain or acetyl-coA binding catalytic domain (Table 3). Specifically, numerous inhibitors targeting the P300/CBP family including Curcumin, Garcinol, PU141, and C646 have been extensively investigated in cell lines and mouse models in several cancers including neuroblastoma, gastric, esophageal, lung, breast, colorectal, prostate, and pancreatic cancers. Isothiazolone-based P300/PCAF inhibitors, CCT077791 and CCT077792 were reported to reduce acetylation and tumor growth in colon cancer [199]. TIP60 inhibitors such as TH1834 and NU9056 were shown to induce DNA damage and apoptosis in breast and prostate cancers [152,153]. PF-9363 (CTx-648) is a selective KAT6A/KAT6B inhibitor that targets H3K23 acetylation and showed potent anti-tumor activity in ER-positive breast cancer, particularly in models resistant to endocrine therapy [113]. The MOF inhibitor, DC-M01-7 reduces H4K16ac and inhibited the proliferation of human colon cancer cells [200].

Table 3
HAT inhibitors investigated in various cancer models.

Inhibitors	Targeted HAT	Cancers	References
Curcumin	P300	Prostate cancer, Breast cancer, AML	[141,142]
Garcinol	P300	Esophageal cancer, Lung cancer, Breast cancer	[143]
C646	P300/CBP	Gastric cancer, GBM, AML, NSCLC, Pancreatic cancer, Melanoma, Prostate cancer	[144,145]
HATi II	CBP/P300	Liver cancer, GBM, Melanoma, Prostate cancer	[146]
PU141	CBP/P300	Colorectal cancer, Neuroblastoma	[147]
Isothiazolones	P300/PCAF	Colon cancer, Hepatocellular carcinoma, Ovarian adenocarcinoma	[148,149]
Anacardic acid	GCN5, TIP60	Cervical cancer	[150,151]
TH1834	TIP60/KAT5	Breast cancer, NSCLC	[152]
NU9056	TIP60/KAT5	Prostate cancer, Neuroblastoma, Colon cancer	[153]
Carnosol	P300	Breast cancer	[154]
CPI-1612	P300/CBP	GBM, Lymphoma	[155]
PF-07248144	KAT6A/6B	Breast cancer	[156]
Inobrodib (CCS1477)	P300/CBP	Non-Hodgkin lymphoma, Multiple myeloma, AML, Breast cancer, NSCLC, Prostate cancer	[157]
FT-7051	P300/CBP	Prostate cancer	[157]
NEO2734	P300/CBP	Prostate cancer	[157]
WM3835	KAT7	Prostate cancer, Osteosarcoma,	[158,159]
CPTH2	KAT2A/P300	Kidney cancer, Colon cancer	[85,160]
PF9363	KAT6A/6B	Breast cancer	[113]

In pre-clinical models of GBM, several P300/CBP inhibitors have demonstrated significant effects in reducing tumor growth and sensitizing tumors to standard therapies like radiation and chemotherapy with TMZ. In early studies, HATi II was shown to be a potent and selective P300/CBP inhibitor that induced apoptosis and reduced proliferation of several GBM cell lines via regulation of the P53 signaling pathway [146]. Recent studies utilized C646 to inhibit CBP/SATB2 transcriptional activity which suppressed GSC proliferation, and tumor growth and synergized with TMZ and radiation [197]. C646 was also shown to reduce radiation-induced plasticity of GSC and tumor growth following radiation therapy [11]. Another P300/CBP inhibitor CPI-1612 significantly suppressed H3K27 acetylation and enhanced the sensitivity of GBM cells to TMZ [12]. Although these studies suggest that P300/CBP inhibitors like C646 and CPI-1612 are viable therapeutic targets that can penetrate the blood-brain barrier and effectively suppress tumor growth and therapeutic resistance, their exact mechanisms of action and clinical translational potential remain to be determined.

HAT inhibitors are also increasingly being combined with other chemotherapeutics and immunotherapies to increase their efficacy and overcome resistance in other solid tumors. In prostate and melanoma cancers, the combination of P300/CBP inhibitor CCS1477 with immune checkpoint inhibitors like anti-PD-L1 or anti-CTLA4 antibodies boosted the efficacy of immunotherapy [157]. CCS1477 is also being evaluated in Phase 1/2 trials for multiple cancers in combination with immunomodulatory and anti-neoplastic drugs such as pomalidomide, glucocorticoid dexamethasone, demethylating drug (azacitidine), and B-cell lymphoma-2 (BCL-2) inhibitor venetoclax for both hematologic and solid tumors [157]. The KAT6A/B inhibitor, PF-07248144 is currently in a Phase 1 clinical trials for metastatic ER+/HER2-breast cancer, castration-resistant prostate cancer, and metastatic NSCLC in combination with ER antagonist (fulvestrant), aromatase inhibitor (letrozole), CDK4 inhibitors (palbociclib and PF-07220060), cytochrome P-450c17 inhibitor (abiraterone acetate), AR antagonists (enzalutamide and darolutamide), PARP inhibitor (Olaparib), as well as an immune checkpoint inhibitor (atezolizumab) [157]. All these studies highlight the potential of HAT inhibitors as powerful anti-cancer therapeutics that can be combined with standard radiation-chemotherapy as well as immunotherapy to enhance their efficacy and improve patient outcomes.

3.1. Challenges and opportunities in developing HAT-based anti-cancer therapies

While it is evident that HATs are key mediators of cancer development and progression, the specific molecular mechanisms influenced by HATs are not well-defined, especially in the context of GBM [201]. The intra- and inter-tumoral molecular heterogeneity of GBM presents a significant hurdle for developing selective HAT inhibitors. Another major hurdle is the blood-brain-barrier (BBB) which prevents entry of chemotherapeutics into the brain. Furthermore, most studies in GBM have focused on the P300/CBP family and related inhibitors. However, there are several other HAT family members that may play essential roles in GBM tumorigenesis and progression and remain unexplored.

Identifying specific HAT dependencies of each cancer, elucidating their function in other cell types within the tumor microenvironment, and investigating the cross-talk between HATs and other chromatin modifiers can reveal critical insights for the development of substrate specific inhibitors and for designing rational combinatorial therapies to improve their clinical translation. However, developing such substrate-

specific inhibitors that target pathological acetylation without affecting normal cellular function remains a key challenge [17]. Current bi-substrate inhibitors mimicking the cofactor acetyl-coA and a lysine-like peptide provide selectivity but suffer from poor metabolic stability and cell permeability due to their peptide nature [9,29]. Recent advancements in proteolysis targeting chimera (PROTAC) technology have inspired newer strategies such as acetylation targeting chimera (AceTAC), regulated induced proximity targeting chimeras (RIPTACs) and transcriptional/epigenetic chemical inducers of proximity (TCIPs), which redirect HAT acetylation to selectively target cancer cells [157, 202]. Nanoparticles (NPs) are another promising approach to deliver chemotherapeutics like HAT inhibitors as they can improve bioavailability, solubility and distribution in the tissue, prolong the retention time of the drugs and significantly reduce cytotoxic effects [203]. Several types of NPs have been tested for systemic delivery of RNAi-based molecules and chemotherapeutics including liposomes, protein-based nanocarriers, dendrimers, silica and metal NPs, and quantum dots enabling drug delivery to the brain and other organs that could be harnessed to deliver and improve the efficacy and safety of HAT inhibitors for various cancers [203].

4. Conclusions

In this review, we have discussed the crucial role played by HATs in tumor development and progression with a special emphasis on GBM. Several small molecule inhibitors targeting the different HAT families are currently being evaluated in pre-clinical models and various phases of clinical trials as mono- or combinatorial therapies with standard chemo-radiation and immunotherapies to treat cancers. While challenges with drug delivery and cytotoxicity remain hurdles in realizing their full potential as anti-cancer therapeutics, newer drug delivery technologies such as PROTACs and nanoparticles can enhance their efficacy and improve treatment benefits for cancer patients.

CRediT authorship contribution statement

Spoorthy Pathikonda: Writing – review & editing, Writing – original draft, Investigation, Conceptualization. **Farzaneh Amirmahani:** Writing – review & editing. **Diya Mathew:** Writing – review & editing. **Sree Deepthi Muthukrishnan:** Writing – review & editing, Writing – original draft, Supervision, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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