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Review Article

Biological functions and therapeutic potential of acylation by histone acetyltransferases

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ABSTRACT

Histone lysine acylation is a major class of histone post-translational modifications involved in essential biological activities, such as transcriptional regulation, DNA-damage repair, and cell-cycle progression. Abnormal acylation is strongly associated with various diseases, such as cancer. Thus, histone acetyltransferases (HATs), the "writers" that catalyze histone acylation, are promising targets for cancer treatment. Rapid developments in structural biology and artificial intelligence have facilitated the development of drugs targeting HATs. To provide new ideas for exploring novel HAT modifiers with high efficiency and selectivity, this article reviews the relationships between acylation and diseases, illustrates HAT catalytic mechanisms through structural biology, and summarizes research progress in HAT modifiers.

Keywords: Acylation, Histone acetyltransferase, Drug target, Structural biology

1. INTRODUCTION

Post-translational modifications (PTMs) are important regulators of protein functions. More than 460 types of PTMs have been identified, among which phosphorylation, methylation, acylation, glycosylation, and ubiquitination are the most common [1]. Nucleosomes are the basic functional units of chromatin. Nucleosome core particles are made of 146 bp of DNA wrapped 1.75 turns around a histone octamer [2]. During histone packaging, the N-terminal lysine and arginine-rich "tails" of histones protrude from the nucleosome ends and are the most prevalent sites of histone PTMs (HPTMs) [3]. HPTMs are essential in the epigenetic regulation of gene transcription, chromatin dynamics, DNA-damage repair, oxidative stress, cell metabolism, the cell cycle, cellular senescence, angiogenesis, and other key biological processes [4]. Consequently, HPTMs are closely associated with the development of various diseases.

Histone acetylation is among the earliest discovered and best-studied HPTMs (**Figure 1**). Classical histone lysine acetylation (Kac) promotes gene transcription by neutralizing the positive charge at the end of the lysine side chain or by recruiting its corresponding "reader" enzyme, which recognizes and binds the modified lysine residue and triggers downstream effects, usually an increase of gene transcription [5]. In the past decade, with the development of mass-spectrometry-based proteomics, more than a dozen novel histone or non-histone lysine acylation modifications have been characterized, including propionylation (Kpr), butyrylation (Kbu),

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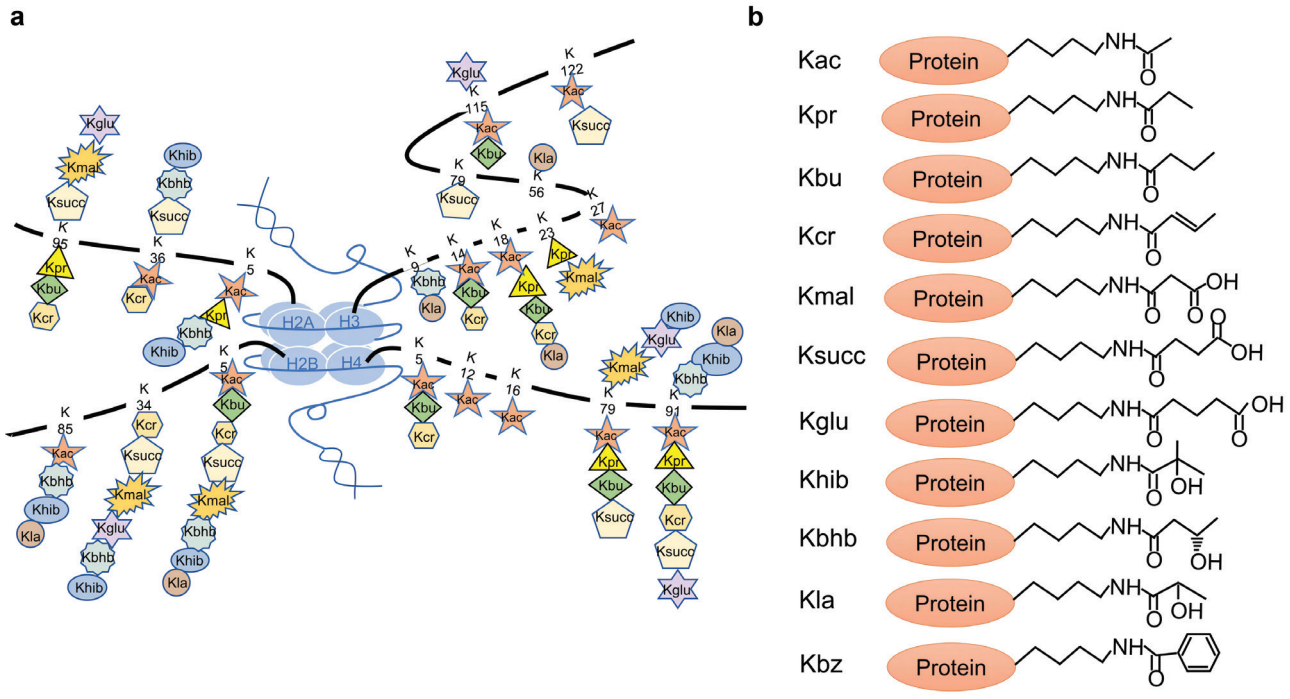

Figure 1 | Histone acylation modifications.
(a) Examples of histone acylation sites. Histone tails are shown in black. Acylation modifications are indicated by different shapes. (b) Chemical structures of lysine acylation.

succinylation (Ksucc), crotonylation (Kcr), malonylation (Kmal), glutarylation (Kglu), 2-hydroxyisobutyrylation (Khib), β-hydroxybutyrylation (Kbhb), lactylation (Kla), and benzoylation (Kbz). Acylation affects protein functions through multiple mechanisms, including the regulation of protein stability, enzymatic activity, subcellular localization, crosstalk with other PTMs, and control of protein-protein and protein-DNA interactions [6]. Histone acylation epigenetically regulates gene transcription, whereas non-histone acylation plays crucial roles in protein stability, activity, and protein-protein interactions. Both are critical for cellular processes relevant to physiology and pathology [6].

Acylation is a broad and reversible HPTM class regulated by lysine acyltransferases (writers) and deacylases ("erasers"). All writers and erasers of novel protein acylation identified to date are histone acetyltransferases (HATs) and histone deacetylases (HDACs; **Table 1**). HATs are divided into the following three subclasses according to structural homology. (1) The p300/CBP family consists of two highly homologous HATs: adenoviral E1A binding protein of 300 kDa (p300, also known as EP300) and the cyclic adenosine monophosphate response element binding protein (CREB binding protein, CBP). (2) The MYST family consists of tat interacting protein 60 kD (TIP60), monocytic leukemia zinc finger protein (MOZ) and MOZ related factor (MORF), HAT binding ORC1 (HBO1), and males absent on the first (MOF). These MYST family proteins are also known as KAT5, KAT6A, KAT6B, KAT7, and KAT8, respectively. (3) The GCN5-associated N-acetyltransferase (GNAT) family contains mainly HAT 1 (HAT1), general control nonderepressible 5 (GCN5, also known as GCN5), and p300/CBP-associated factor (PCAF, also known as KAT2B) [29, 30].

In this article, we focus on HATs and reviews recent findings on the 11 types of acylation. We discuss biological functions and medical relevance, the structural basis for catalytic mechanisms, and potential therapeutic targets, primarily for histone acylation (as well as acylation of several non-histone proteins). Drug development targeting HATs provides new insights into treating related diseases and thus has great potential basic-science and clinical value. Further analysis of histone acylation is expected to lead to breakthroughs in research on HATs-targeting drugs.

2. ACYLATION IN DISEASES

2.1 Cancer

Acylation plays a key role in the tumorigenesis and pathogenesis of various cancers (**Table 2**). Alterations in the same acylation modification have been found to be involved in the development of multiple types of cancer. Meanwhile, multiple acylation alterations could been detected in the same type of cancer. Here, we describe possible carcinogenesis mechanisms involving the dysregulation of 11 novel acylation modifications.

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Table 1 | Writers, readers, and erasers of acylation modifications.

Acylation modification	Metabolite sources	Writers	Readers	Erasers	References
Kac	Acetyl-CoA	p300/CBP, GNATs (GCN5, PCAF), MYSTs (TIP60, MOZ, MORF, HBO1, MOF)	Bromodomain, YEATS domain, DPF domain	HDAC1–10, SIRT1–7	[7, 8]
Kpr	Propionyl-CoA, propionate	p300/CBP, GNATs (GCN5, PCAF), MYSTs (MOF, MOZ, HBO1)	Bromodomain (BRD4, BRPF1), YEATS domain	SIRT1–3	[9-13]
Kbu	Butyryl-CoA, butyrate	p300/CBP, HBO1	Bromodomain (BRD4, BRD9, CECR2, TAF1, Brdt, BRPF1), YEATS domain	SIRT1–3	[7, 14, 15]
Ksucc	Succinyl-CoA, Succinate	GNATs (GCN5, HAT1), CPT1A, KGDHC	YEATS domain (GAS41)	SIRT5, SIRT7	[15-17]
Kcr	Crotonyl-CoA, crotonate	p300/CBP, HBO1	YEATS domain (AF9, Taf14, YEATS2, ENL), DPF (DPF2, MOZ, TAF1)	HDAC1–3, SIRT1–3	[7, 18-20]
Kmal	Malonyl-CoA, malonate	NA	NA	SIRT5	[21]
Kglu	Glutaryl-CoA, glutarate	p300, GCN5	NA	SIRT5, SIRT7	[7, 22]
Khib	2-hydroxyisobutyryl-CoA, 2-hydroxyisobutyrate	p300, TIP60	NA	HDAC1–3	[7, 14, 23]
Kbhb	β-hydroxybutyryl-CoA, β-hydroxybutyrate	p300	NA	HDAC1–3, SIRT3	[24, 25]
Kla	Lactyl-CoA, LGSH	p300	NA	HDAC1–3	[14, 26, 27]
Kbz	Benzoyl-CoA, sodium benzoate	HBO1	YEATS, DPF	SIRT2	[7, 26, 28]

Abbreviations: CPT1A, carnitine palmitoyltransferase 1A; KGDHC, ketoglutarate dehydrogenase complex; LGSH, lactoylglutathione; NA, not available.

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Table 2 | Biological functions of acylation modifications in cancers.

Acylation modifications	Deviant modifications	Related cancers	Mechanism/interaction	Ref.
Acetylation	H4K16ac (↓)	Breast cancer, medulloblastoma, colorectal cancer, gastric cancer, liver cancer, renal cell carcinoma, ovarian cancer	H4K16ac regulates higher-order chromatin structure and protein-histone interactions. hMOF is the primary writer of H4K16ac and is down-regulated in a variety of cancers.	[31-38]
	H4K16ac (↑)	Non-small cell lung cancer	hMOF mediates the expression of the oncogene Skp2 by regulating H4K16ac in the promoter region.	[39]
Propionylation	H3K23pr (↓)	Medulloblastoma, leukemia, glioma, colorectal cancer	The tetrameric BRPF1-KAT6 complex is a functional histone propionyl-transferase, and deficiency in H3K23pr caused by BRPF1 mutations may be a potential mechanism for the development of various cancers.	[40]
Succinylation	H3K79succ (↑)	Glioma	The complex of GCN5 and α-KGDH acts as an H3 succinyl-transferase, and H3K79succ promotes the proliferation and development of glioma cells.	[41]
	PGAM1-K99succ (↑)	Pancreatic cancer, hepatocellular carcinoma	HAT1-mediated succinylation of PGAM1 is critical for the glycolysis of tumor cells and contributes to tumor growth.	[42]
Crotonylation	Overall histone Kcr (↑)	Prostate cancer	Histone crotonylation promotes proliferation, migration, and invasion of PCa cell lines.	[43]
	Kcr (↓)	Hepatocellular carcinoma	Rescued Kcr levels inhibit the progression of HCC.	[44]
Malonylation	SDHA-Kmal (↓)	Wild-type KRAS colorectal cancer	Sirt5-mediated demalonylation of SDHA leads to its inactivation. The accumulation of succinic acid caused by the inactivation of SDHA enhances the activity of TrxR2, thus resulting in chemotherapy resistance.	[45]
Glutarylation	GLUD1-K545glu (↓)	Colorectal cancer	SIRT5 activates GLUD1 in a deglutarylation-dependent manner, enhances glutamine synthesis and metabolism, and promotes the progression of CRC.	[46]
2-hydroxyisobutyrylation	Total protein Khib (↑)	Pancreatic cancer	Suppression of Khib levels inhibits proliferation, migration, and invasion of PC cells	[47]
	Khib (↑)	Oral squamous cell carcinoma	Khib alters the actin aggregation and stabilization state, thereby affecting and regulating the actin cytoskeleton in OSCC.	[48]
β-hydroxybutyrylation	H3K9bhb (↑)	Hepatocellular carcinoma	The MTA2-HDAC2-CHD4 complex transcriptionally represses BDH1 via R-loops, thus leading to βHB accumulation, elevated levels of H3K9bhb, and ultimately tumorigenesis and progression of HCC	[49]
Lactylation	H3K18la (↑)	Ocular melanoma	Histone Kla promotes expression of YTHDF2, which recognizes N6-methyladenosine-modified mRNA of the tumor suppressors PER1 and TP53, and promotes their degradation, thereby accelerating tumorigenesis in ocular melanoma.	[50]
	H3K9la and H3K56la (↑)	Hepatocellular carcinoma	Demethylase decreases lactate levels and inhibits histone H3K9la and H3K56la formation, thereby inhibiting the proliferation and migration of liver cancer stem cells.	[51]
	Kla (↑)	Non-small cell lung cancer	Kla regulates the expression of metabolic genes in NSCLC cells, thus resulting in cell proliferation and tumor progression.	[52]
Benzoylation	Histone Kbz (↑)	Hepatocellular carcinoma	Kbz is enriched around transcription start sites, and may be involved in cancer progression through transcriptional regulation.	[26]

Abbreviations: CPT1A, carnitine palmitoyltransferase 1A; KGDHC, ketoglutarate dehydrogenase complex; LGSH, lactoylglutathione; NA, not available.

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2.1.1 Acetylation. Kac is among the most widely studied acylation modifications, and it plays a major role in cancer development. Breast cancer is the most prevalent cancer among women worldwide and is responsible for more deaths than any other single cancer [53]. Elsheikh et al. have found that loss of H4K16ac might be an early hallmark of invasive breast cancer [31], possibly because of H4K16ac's role in regulating higher-order chromatin structure and protein-histone interactions [32]. MOF is the primary writer of H4K16ac, and the level of H4K16ac is closely associated with the expression of MOF. In breast cancer [33], medulloblastoma [33], colorectal cancer (CRC) [34], gastric cancer [35], hepatocellular carcinoma (HCC) [36], renal cell carcinoma [37], and ovarian cancer [38], patients with down-regulated MOF expression have been demonstrated to have poorer overall survival. However, Zhao et al. have shown that MOF is expressed at high levels in non-small cell lung cancer (NSCLC) [39]. S-phase kinase-associated protein 2 (Skp2) facilitates tumorigenic activity. MOF promotes the expression of Skp2 by acetylating H4K16 at the promoter region [39]. In addition, MOF-mediated NF-E2-related factor 2 (Nrf2) acetylation is essential for antioxidant and drug resistance in NSCLC cells *in vitro* [54]. The function of non-histone acetylation (on targets such as p53, NF-κB, and heat shock protein 90) and its potential as a therapeutic target for cancer has been well described in previous reviews [4, 6, 55]. Herein, only the most recent studies are discussed. In ovarian cancer, upregulated KAT6A acetylates the K294 residue of constitutive photomorphogenic 1 (COP1). Acetylation of COP1 impairs its E3 ubiquitin ligase function, thereby leading to the accumulation and increased activity of β-catenin [56]. Thus, novel strategies targeting the KAT6A/COP1/β-catenin signaling axis in ovarian cancer are promising.

2.1.2 Propionylation and butyrylation. In early 2007, Chen et al. found that the acetyltransferase p300/CBP catalyzes propionylation and butyrylation of H4 *in vitro*; however, the enzyme(s) catalyzing this novel acylation *in vivo* remained to be determined [57]. Recently, Yan et al. have shown that the tetrameric BRPF1-KAT6 complex is a genuine histone propionyltransferase *in vitro* and *in vivo*, which catalyzes H2K23pr formation [40]. Deficiency in H3K23pr caused by bromodomain- and PHD finger-containing protein 1 (BRPF1) mutations may be a potential mechanism underlying the occurrence of cancers such as medulloblastoma, leukemia, glioma, and CRC [40].

2.1.3 Succinylation. Ksucc is a newly discovered PTM that is extensive and conserved. The complex of GCN5 and α-ketoglutarate dehydrogenase (α-KGDH) acts as a histone H3 succinyltransferase, and H3K79succ promotes the proliferation of glioma cells [41]. A novel histone succinyltransferase, HAT1, has been found to be significantly overexpressed in HCC, pancreatic cancer (PC), and cholangiocarcinoma tissues. HAT1 enhances epigenetic regulation and gene expression by catalyzing the formation of histone H3K122succ as well as K99succ in phosphoglycerate metastase 1 (PGAM1), a prominent glycolytic enzyme in cancer cells, thus enhancing cancer cell glycolysis and promoting tumor growth [42].

2.1.4 Crotonylation. Tan et al. have identified 28 Kcr sites on human histones [58]. Studies have indicated that levels of Kcr are diminished in liver, gastric, and kidney cancers, but up-regulated in thyroid, esophageal, colon, pancreatic, and lung cancers; moreover, elevated Kcr levels inhibit the motility and proliferation of HCC cells [44]. These findings have suggested that Kcr may play multiple roles in cancer progression by regulating various important oncoproteins. However, its exact mechanism remains unclear. In prostate cancer (PCa) cell lines, the histone acetylation effector protein BRD4 regulates Kcr by modulating the expression of the HATs GCN5 and p300; Kcr in turn promotes the proliferation, migration, and invasion of PCa cell lines [43].

2.1.5 Malonylation and glutarylation. Sirtuin5 catalyzes lysine demalonylation and deglutarylation *in vitro* and *in vivo* [59]. SIRT5-mediated succinate dehydrogenase complex subunit A (SDHA) demalonylation and inactivation are crucial factors leading to multi-drug resistance in $SIRT5^{+}$ WT-KRAS CRC [45]. SDHA-inactivation-induced succinate accumulation enhances thioredoxin reductase 2 (TrxR2) activity and renders cancers resistant to chemotherapy resistant [45]. Glutamine is an essential nutrient in the growth of diverse cancer cells. Wang et al. have shown that SIRT5 activates GLUD1 through deglutarylation-dependent mechanisms, thereby enhancing glutamine anabolism, and promoting the proliferation of CRC cells and the growth of xenografts [46].

2.1.6 2-hydroxyisobutyrylation. In mammalian cells, TIP60, a member of the MYST family, is believed to have lysine 2-hydroxyisobutyryl-transferase activity [23]. In seven patients with PC, Lu et al. have identified 10367 Khib sites on more than 2300 modified proteins, and have shown that decreasing Khib levels inhibits PC cell proliferation, migration, and invasion [47]. The most common malignant carcinoma in the oral cavity is oral squamous cell carcinoma (OSCC), which is highly aggressive and prone to recurrence. Zhang et al., through combined proteomics and bioinformatics analysis, have revealed that Khib alters the state of actin aggregation and stability in OSCC and consequently may contribute to the progression of OSCC [60].

2.1.7 β-hydroxybutyrylation. Xie et al. have reported Kbhb as a novel HPTM [48]. Abnormalities in metabolism and the tumor microenvironment contribute to tumorigenesis and progression. Metastasis-associated protein 2 (MTA2), a component of the NuRD deacetylase complex, interacts with HDAC2/CHD4, thereby forming the MTA2-HDAC2-CHD4 complex. The complex inhibits 3-hydroxybutyrate dehydrogenase 1 (BDH1) via R-loop transcription, thus leading to the accumulation of β-hydroxybutyrate (βHB) and increased H3K9bhb levels,

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and a subsequent cascade of effects on HCC tumorigenesis and progression [49]. p53 is a well-known tumor suppressor. βHB-mediated formation of Kbhb on p53 has recently been found to inhibit p53 acetylation levels and to decrease the transcriptional activity of p53 target genes (including p21 and PUMA), thereby diminishing p53 mediated apoptosis [50].

2.1.8 Lactylation. Histone Kla is a metabolic stress-associated HPTM. A positive H3K18la signal in ocular melanoma induces YTHDF2 expression, an enzyme that facilitates the degradation of N6-methyladenosine-modified PER1 and TP53 mRNAs, thereby driving tumorigenesis [61]. Pan et al. have demonstrated that demethylzeylasteral, a compound with anti-tumor activity, inhibits histone H3K9la and H3K56la formation, and consequently cell proliferation and migration, and promotes apoptosis, of liver cancer stem cells [51]. In addition, Kla promotes cell proliferation and tumor development by regulating metabolic genes in NSCLC cells [52].

2.1.9 Benzoylation. Sodium benzoate, a widely used food preservative, stimulates histone Kbz formation by producing benzoyl-CoA [28]. Genome-wide analysis of histone Kbz in HepG2 cells has indicated that Kbz is enriched around transcription start sites and therefore is likely to be involved in cancer progression through transcriptional regulation [26]. B-cell lymphoma-2-associated transcription factor 1 (BCLAF1) is an apoptosis and transcriptional regulator. In addition to participating in autophagy and the DNA-damage response, BCLAF1 is strongly associated with tumor growth and drug resistance [62]. Interestingly, whether it acts as a tumor promoter or suppressor depends on the cellular context. Eight Kbz sites are present within BCLAF1, but further research is required to determine whether the Kbz of BCLAF1 is associated with tumor progression [62].

2.2 Cardiovascular diseases

The incidence of cardiovascular diseases (CVDs), such as hypertension, stroke, coronary heart disease, heart failure, pulmonary heart disease, arrhythmias, and rheumatic heart disease, is increasing each year [63, 64]. Short-chain fatty acids (SCFAs) are fatty acids with one to six carbon atoms that supply intracellular short-chain acyl-CoA. A growing number of studies suggest that SCFAs and short-chain fatty acylation contribute to CVD pathophysiology. Propionate, an SCFA, has been found to slow the progression of CVDs, in a manner potentially associated with enhanced protein propionylation [3]. Propionylation of H3K14 is enriched specifically in the gene active promoter region and significantly affects lipid metabolism in mice. Consequently, H3K14pr is likely to be involved in the physiological and pathological progression of CVDs [9]. As described above, the BRPF1-KAT6 complex catalyzes H3K23pr formation [40]. Yan et al. have also found that BRPF1 mutant patients have cardiac anomalies, such as ascending aortic dilation, which might be caused by H3K23pr deficiency [40]. Thus, histone propionylation may be critical in cardiovascular homeostasis and disease. Elevated malonylation of mitochondrial proteins contributes to oxidative stress and cardiac hypertrophy, thus resulting in cardiac damage [65]. In addition, malonylation impairs the kinase activity of the mammalian target of rapamycin complex 1 (mTORC1) and leads to angiogenesis defects [66]. H3K18cr and H2BK12cr are significantly elevated in hypertrophied hearts in humans and mice. Increased histone crotonylation may be a mechanism underlying human and mouse ECHS1 mutation-mediated cardiac defects [67]. The SCFA butyrate inhibits oxidative stress and inflammation, and has cardioprotective, atherosclerosis-preventive, and anti-hypertensive effects [68]. However, the functional mechanism of butyrate and protein Kbu in CVDs requires further investigation. SIRT5 is a lysine desuccinylase whose deficiency leads to elevated succinylation in cardiac myocytes, thus enhancing succinate dehydrogenase (SDH) activity and in turn increasing ischemia-reperfusion injury [69]. The compound d-β-hydroxybutyrate (βOHB) is a major energy source in mammals during starvation [70]. Shimazu et al. have found that βOHB is an endogenous HDAC inhibitor that increases histone acetylation at the promoters of the oxidative stress resistance genes Foxo3a and Mt2, promotes gene transcription, and ultimately inhibits oxidative stress [71]. The cardioprotective factor SIRT3 has histone de-β-hydroxybutyrylation activity, which may contribute to cardiac protection. Moreover, β-hydroxybutyrylation impairs the activity of p53 and ultimately delays vascular cell senescence [50]. The functions and underlying mechanisms of protein SCFA acylation in CVDs are complicated and warrant further study.

2.3 Neurological disorders

Alzheimer's disease (AD) is the most prevalent neurodegenerative pathology featuring progressive impairment of synaptic plasticity and memory function. Histone acetylation is a major modulator of plasticity and memory formation [72]. Aging is the strongest risk factor for AD, and H4K16ac is associated with aging in mammals [73]. Nativio et al. have found that, whereas normal aging leads to H4K16ac enrichment, AD leads to a dramatic loss of H4K16ac near genes associated with aging and AD, through a mechanism not well understood [74]. Tau inclusions are the hallmark lesion of AD. p300 mediates acetylation of tau, and acetylated tau may promote tau-mediated neurodegeneration by decreasing solubility and microtubule assembly, and increasing tau fibrillation [75].

Parkinson's disease (PD) is the second most prevalent chronic neurodegenerative disorder after AD. In patients with PD, the substantia nigra pars compacta in the brain undergoes a progressive loss of dopaminergic neurons, thus decreasing dopamine neurotransmission in the striatum and resulting in motor dysfunction

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[76]. By activating the Smad signaling pathway, HDAC inhibitors help midbrain dopamine neurons survive and grow [77].

Increasing evidence indicates that Kac is crucial for the persistence of long-term memory. HDAC inhibitors enhance memory and synaptic plasticity by activating genes regulated by the CREB/CBP transcriptional complex [78]. Guan et al. have shown that HDAC2 deficiency increases synapse number and memory facilitation, thus suggesting that HDAC2 negatively regulates memory formation and synaptic plasticity [79]. Both CBP and p300 mutations can lead to Rubinstein-Taybi syndrome [80], a congenital neurodevelopmental disorder. Brain-derived neurotrophic factor (BDNF) is essential for synaptic plasticity and long-term memory maintenance. Bredy et al. have found that the loss of conditioned fear is accompanied by a considerable increase in H4Kac around the promoter of BDNF [81]. However, the expression of BDNF is downregulated in patients with major depressive disorder [82]. Chen et al. have found that treatment of depressed mice with the antidepressant βHB alleviates symptoms while attenuating the downregulation of BDNF and H3k9bhb, but not increasing H3k9ac levels. Thus, H3k9bhb may be a new potential target for depression treatment [82].

2.4 Metabolic diseases

Growing evidence indicates that PTMs of proteins are closely associated with metabolic disorders, which can be caused by genetic and environmental factors [83]. Acetyl-CoA is the acetyl donor for histone acetylation and the central metabolite in eukaryotic cells, thus acting as a hub linking catabolism, anabolism, and energy production. Histone acetylation and deacetylation are controlled by HATs and HDACs, which are essential players in the regulation of metabolism-associated gene expression [83]. HDACs also affect the deacetylation of signal transducers and transcription activator 3 (STAT3). Kimura et al. reported that the classical HDAC inhibitor trichostatin A attenuated the endoplasmic reticulum stress-induced inhibition of STAT3 acetylation and phosphorylation, thereby inhibiting hepatic gluconeogenic enzymes (phosphoenolpyruvate carboxylase-1 (PCK-1) and glucose 6-phosphatase (G6PC)) expression, ultimately ameliorating high blood glucose in obese and diabetic mice [84]. Therefore, HDAC regulates hepatic gluconeogenesis and may be a novel target for diabetes treatment.

Novel histone acylation exerts crucial functions in metabolic diseases. Kebede et al. have proposed that histone Kpr, together with Kac and Kbu, promotes higher transcriptional output and couples the cellular metabolic state to chromatin structure and functions [9]. Therefore, dysregulation of short-chain CoA (e.g., malonyl-CoA) homeostasis contributes to the development of metabolic diseases such as diabetes. Bandyopadhyay et al. have analyzed HPTMs in the liver in a mouse model of prediabetic obesity induced by a high-fat diet, and have observed downregulated levels of H3K23mal, H3K122ac, H3K18bu, and H3K23pr [85]. Xie et al. have found significantly elevated levels of histone H3K9bhb in the liver in mice during starvation or streptozocin-induced diabetic ketosis, together with upregulation of genes involved in the starvation response pathway [48]. Although these studies provide a possible link between cellular metabolism and novel histone acylation, further investigation of the molecular mechanisms involved is needed.

2.5 Kidney diseases

Renal diseases can be divided into acute kidney injury (AKI) and chronic kidney disease, both of which can progress to end-stage renal disease (ESRD). Short-chain lysine acylation has been demonstrated to be involved in the pathophysiological processes of kidney diseases. Andres et al. have reported that crotonic acid increases levels of histone Kcr and expression of peroxisome proliferator-activated receptor-gamma co-activator-1α (PGC-1α) in the renal tissue in AKI mice, thus protecting against AKI [86]. SIRT3-deficient mice have elevated Khib phosphofructokinase (PFK) levels in the adrenal glands and enhanced glycolytic pathways. This metabolic change ultimately leads to altered differentiation of renal progenitor cells, delayed nephrogenesis, and fewer nephrons in the mice [87]. Renal fibrosis progression is the final pathological stage of ESRD. Bioinformatic analysis has revealed that Khib regulates the Rho/ROCK signaling pathway and may contribute to renal fibrosis in patients with ESRD [88]. Treatment with βHB increases H3K9bhb levels at the promoter, thus resulting in the upregulation of matrix metalloproteinase-2 (MMP-2), which antagonizes glomerulosclerosis in diabetic rats [89]. Other novel acylation modifications may be involved in the pathogenesis of renal diseases, a topic warranting further research.

2.6 Autoimmune diseases

HPTMs affect the pathogenesis of several inflammatory and autoimmune diseases. Elevated histone acetylation is associated with several chronic inflammatory lung diseases, including asthma. Hyperacetylation of H3 and H4 at the TGF-β1 promoter may lead to transcriptional activation of the inflammatory transcription factors NF-κB and AP-1 [90]. Xie et al. have suggested that Kcr and Khib may promote antigen presentation and co-regulate leukocyte migration-mediated tissue damage in patients with systemic lupus erythematosus [91]. Acquired immunodeficiency syndrome is a lethal infectious disease that is caused by infection with HIV and characterized by impaired or lost immune function. Jiang et al. have reported that acyl-CoA synthetase short-chain family member 2 (ACSS2)-driven histone Kcr reverses HIV latency [92]. Further studies on the mechanisms of histone acylation in regulating immune and autoimmune diseases are expected to enable novel treatments.

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2.7 Reproductive disease

Impaired spermatogenesis can lead to azoospermia and severe oligospermia, thus causing male infertility. HPTMs are involved in regulating multiple stages of spermatogenesis [58]. Chromodomain Y-like transcription corepressor (CDYL) has crotonyl-CoA hydratase activity and catalyzes the conversion of crotonyl-CoA to β-hydroxybutyric-CoA. Liu et al. have revealed that CDYL negatively regulates histone crotonylation, thus decreasing the number and motility of sperm cells in *Cdyl* transgenic mice [93]. No studies have reported the relationship between HPTMs and oocytes and female infertility.

3. STRUCTURAL STUDIES AND RELATED CATALYTIC MECHANISMS

The regulatory mechanism of histone short-chain acylation is sophisticated and complex. The rapid development of structural biology has contributed to epigenetics research, e.g., by providing the atomic coordinates of biological macromolecules, details of interactions, and information on conformational changes between functional states. The combination of such data not only promotes the understanding of molecular mechanisms and answers major biological questions, but also enables exploration of the pathogenesis of diseases associated with molecular dysfunction. More importantly, structural studies can provide a basis for rational drug design.

3.1 p300/CBP

The p300/CBP protein contains structured and unstructured regions. The structured regions include transcriptional adapter zinc finger domain 1 (TAZ1), kinase inducible domain of CREB interacting (KIX) domain, bromodomain (BRD), plant homeodomain (PHD), really interesting new gene (RING)domain, histone acetyltransferase (HAT) domain, ZZ-type zinc finger (ZZ) domain, and transcriptional adapter zinc finger domain 2 (TAZ2; **Figure 2a**, **2b**) [94]. Liu et al. have generated a high-resolution X-ray crystal structure of the p300 HAT domain in complex with the dual-substrate inhibitor Lys-CoA. They have proposed a "Theorell-Chance" catalytic mechanism for p300/CBP, in which the peptide substrate weakly binds the p300 surface after acetyl-CoA binding, thus allowing the lysine residue to tunnel through p300 and react with the acetyl group, similar to the catalytic mechanism proposed for *E. coli* KAT and Tetrahymena GCN5 (**Figure 3**). In addition, they have structurally confirmed several disease-associated mutations [58]. The tyrosine residue Y1467 is critical for mediating the acetyl transfer reaction of p300 (**Figure 2a**) [95], whereas a similar catalysis mechanism has been found for GCN5 (**Figure 2b,2c**) [96, 97]. Ortega et al. have demonstrated that transcription factor dimerization can activate p300 HAT activity by p300 trans-autoacetylation in the intrinsic auto-inhibitory loop (AIL) of the HAT domain [98]. Their findings have provided insights into the correlation between chromatin acetylation and gene transcription. Delvecchio et al. have published a 2.8-Å crystal structure of the human p300 catalytic core and have shown that the RING domain has a repressive effect on HAT activity. The RING domain alters the steric hindrance of HAT domain active sites, thus modulating enzymatic activity [99]. Zhang et al. have suggested that acetyl-lysine binding to the BRD is necessary for p300 to catalyze almost all lysine acetylation in H3 and H4. In addition, the authors have found that the selectivity of the p300 HAT domain for H3 lysine acetylation sites, such as H3K27 and H3K18, is due to the ZZ domain binding the N terminus of H3 [100]. Park et al. demonstrated that the BRD of p300/CBP was essential for histone H3 acetylation. The autoregulatory loop (AL) is located in the HAT domain of CBP (**Figure 2a**). After K1596 in AL is auto-acetylated by the HAT domain, acetyl-K1596 acts as a negative regulator of histone H3 acetylation by binding intramolecularly to the BRD [101]. This intramolecular interaction negatively regulates histone acetylation and may facilitate the dissociation of CBP from chromatin, which is necessary for transcription initiation. The cryo-electron microscopy structure of the p300-NCP complex has revealed multiple binding modes of p300 to nucleosome core particle (NCP), which correspond to the various sites on nucleosomes that can be acetylated by p300 [102]. Lasko et al. have presented a 1.95-Å co-crystal structure of the small molecule A-485 bound to the p300 HAT domain, and have demonstrated that A-485 is a potent and selective p300/CBP catalytic inhibitor that competes with acetyl CoA (**Figure 4a**) [103]. Their findings have confirmed the feasibility of selectively targeting HATs with small-molecule inhibitors, which might be effective in treating malignancies and diseases driven by transcriptional activators.

3.2 MYSTs

The main feature of MYST family members is the MYST catalytic domain, containing the zinc finger and the core HAT domain (**Figure 2a**). TIP60 consists of an N-terminal chromo barrel domain (TIP60-CB) and a C-terminal MYST domain (**Figure 2a**). As revealed by the crystal structure of TIP60-CB, the putative peptide binding site may be blocked by a unique β-hairpin, thus resulting in failure of TIP60-CB to recognize the histone tail [104]. The 1.47-Å crystal structure of the tandem PHD finger (PHD12) of hMOZ in complex with the H3K14ac peptide has revealed the structural basis for H3K14ac recognition [105]. Structures of the double plant homology domain finger (DPF) of hMOZ in complex with H3K14cr (**Figure 2c**), H3K14bu, and H3K14pr have indicated that the DPF is adapted to extensive histone acylation, with a preference for Kcr [106]. Dreveny et al. first revealed a unique recognition pattern of H3K4-T11 induced by MOZ DPF. Furthermore, they have shown that conserved double glycine hinges on both sides of the H3 tail helix are necessary for the change in conformation allowing H3K14ac to dock with DPF [107]. High-resolution crystal structures of $MORF_{DPF}$-H3K14cr (**Figure 2c**) and $MORF_{DPF}$-H3K14bu, together with mutagenesis experiments, have confirmed that F218 is the main driver

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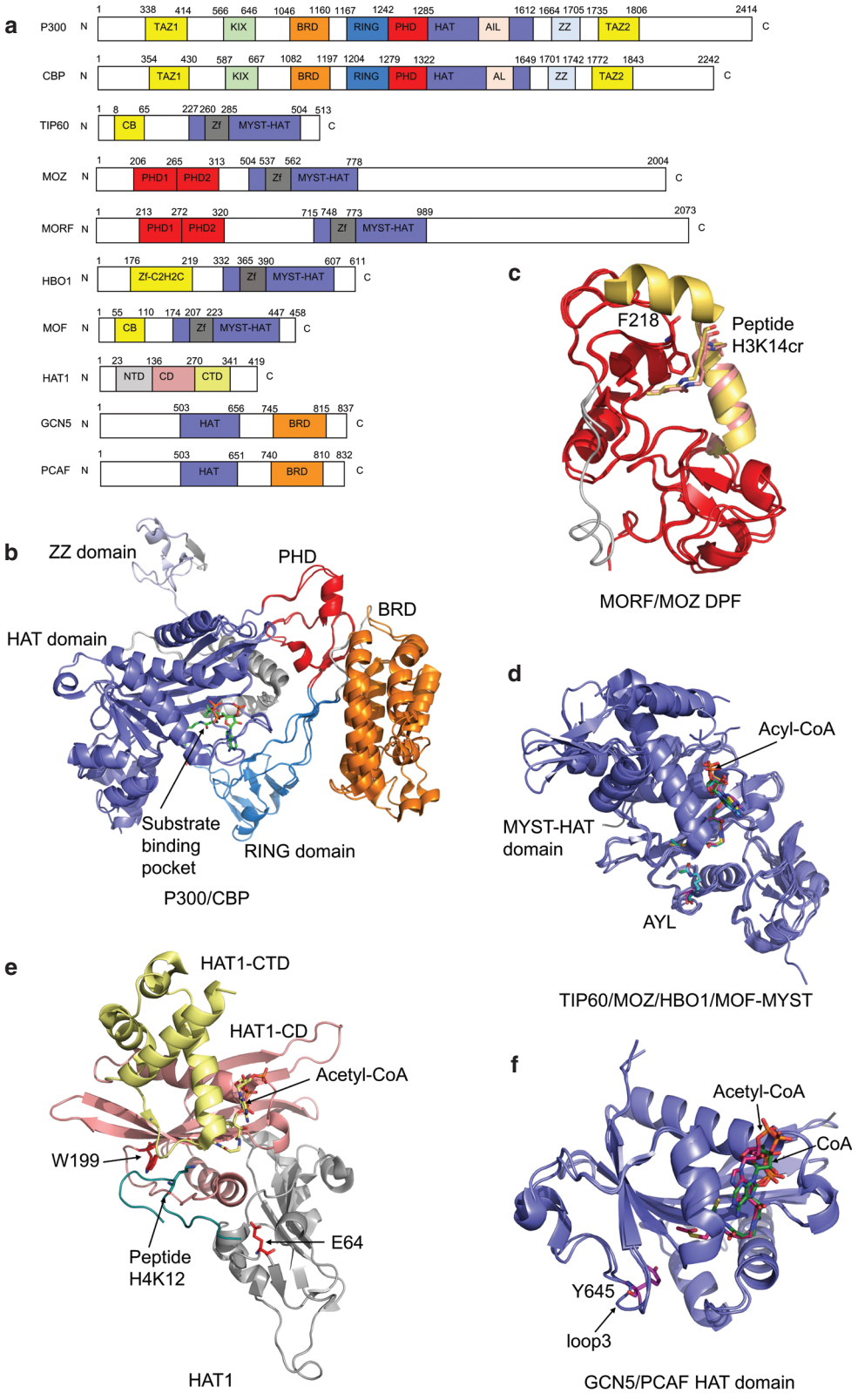

Figure 2 | Functional domains and structures of HATs.
(a) The functional domains of human HATs. (b) Superposition of the p300 (PDB ID 4BHW) and CBP (PDB ID 5U7G) structures. The structural domains are in different colors (BRD: orange; RING domain: marine; DPF: red; ZZ domain: light blue; HAT domain: slate). The substrate

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binding pocket of the HAT domain is indicated by arrows. The Lys-CoA binding p300 is shown as green sticks. (c) Superposition of the structures of the MYST-HAT domain. The substrates binding TIP60-HAT domain (PDB ID: 2UO2, acetyl-CoA, green), MOZ-HAT domain (PDB ID: 2OZU, acetyl-CoA, cyan), HBO1-HAT domain (PDB ID: 5GK9, acetyl-CoA, yellow), and MOF-HAT domain (PDB ID: 5WCI, glutaryl-CoA, magenta) are shown as sticks in different colors. The acetylated lysine (AYL) of TIP60, MOZ, and MOF is also indicated. (d) Superposition of the DPF structures of MOZ and MORF (magenta, PDB ID: 5B76), and MORF (salmon, PDB ID: 2OZU). The peptide H3K14cr binding MOZ (PDB ID: 5B76) and MORF (PDB ID: 2OZU) is displayed in yellow and salmon. The F218 of MORF is also shown as sticks. (e) The structure of the HAT1 functional domain (PDB ID: 2P0W). The NTD is in gray, the CD is in pink, and the CTD is in yellow. The peptide H4K12 is in deep teal, and the acetyl-CoA is in pale yellow. The key residues are displayed as red sticks. (f) Superposition of the HAT domain structures of GCN5 and PCAF. The acetyl-CoA binding GCN5 is shown in blue sticks (PDB ID: 1Z4R). The CoA binding PCAF is shown in forest sticks (PDB ID: 1CM0). The Y645 and loop 3 are also marked.

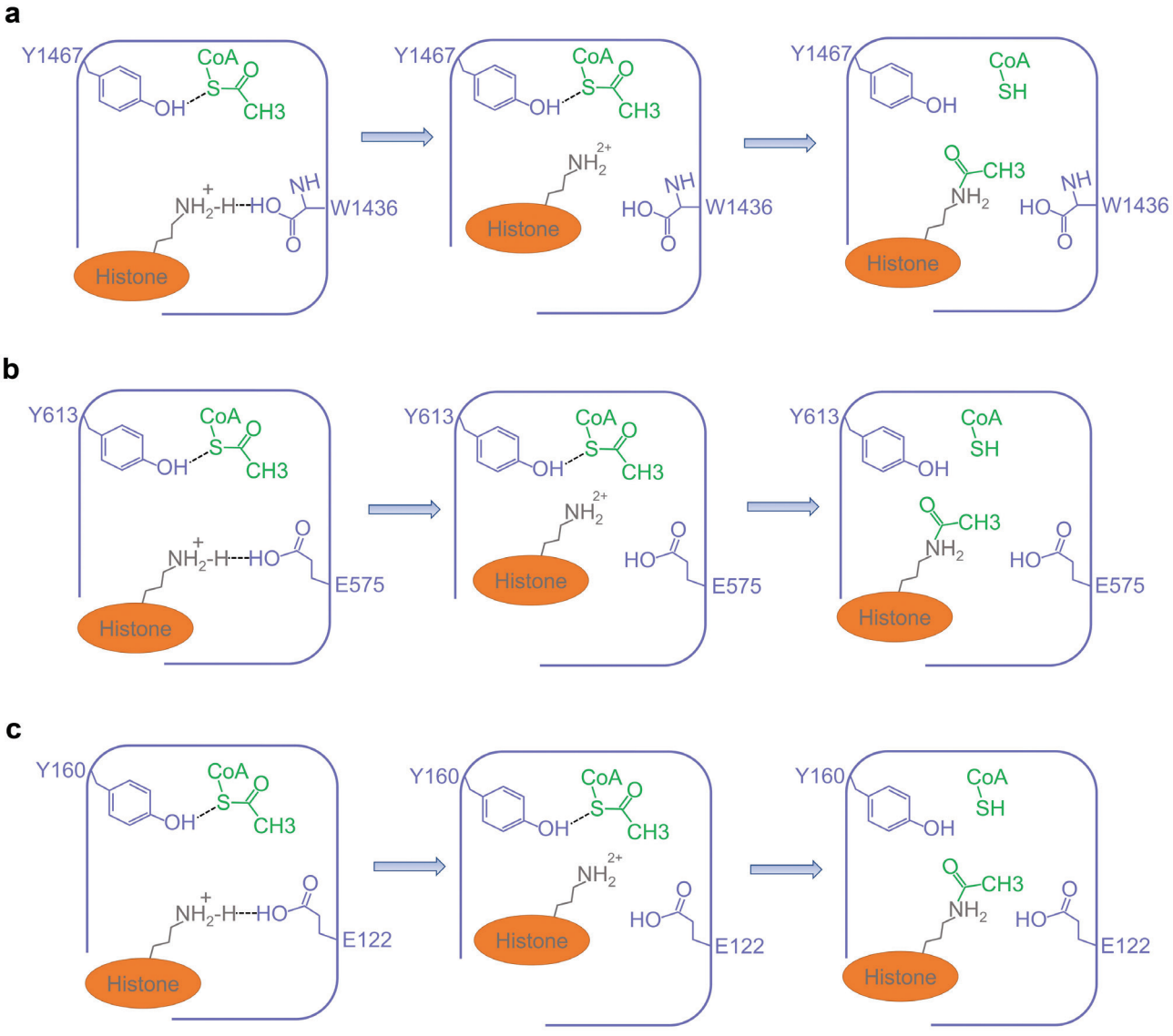

Figure 3 | Catalytic mechanism of acetylation by histone acetyltransferases.
(a) Human p300. (b) *E. coli* KAT [96]. (c) *Tetrahymena* GCN5 [97]. The histone acetyltransferases are simplified to purple outlines, the histones are in the orange ellipses, and the acetyl-CoA is in green chemical formula. Crucial residues are also marked.

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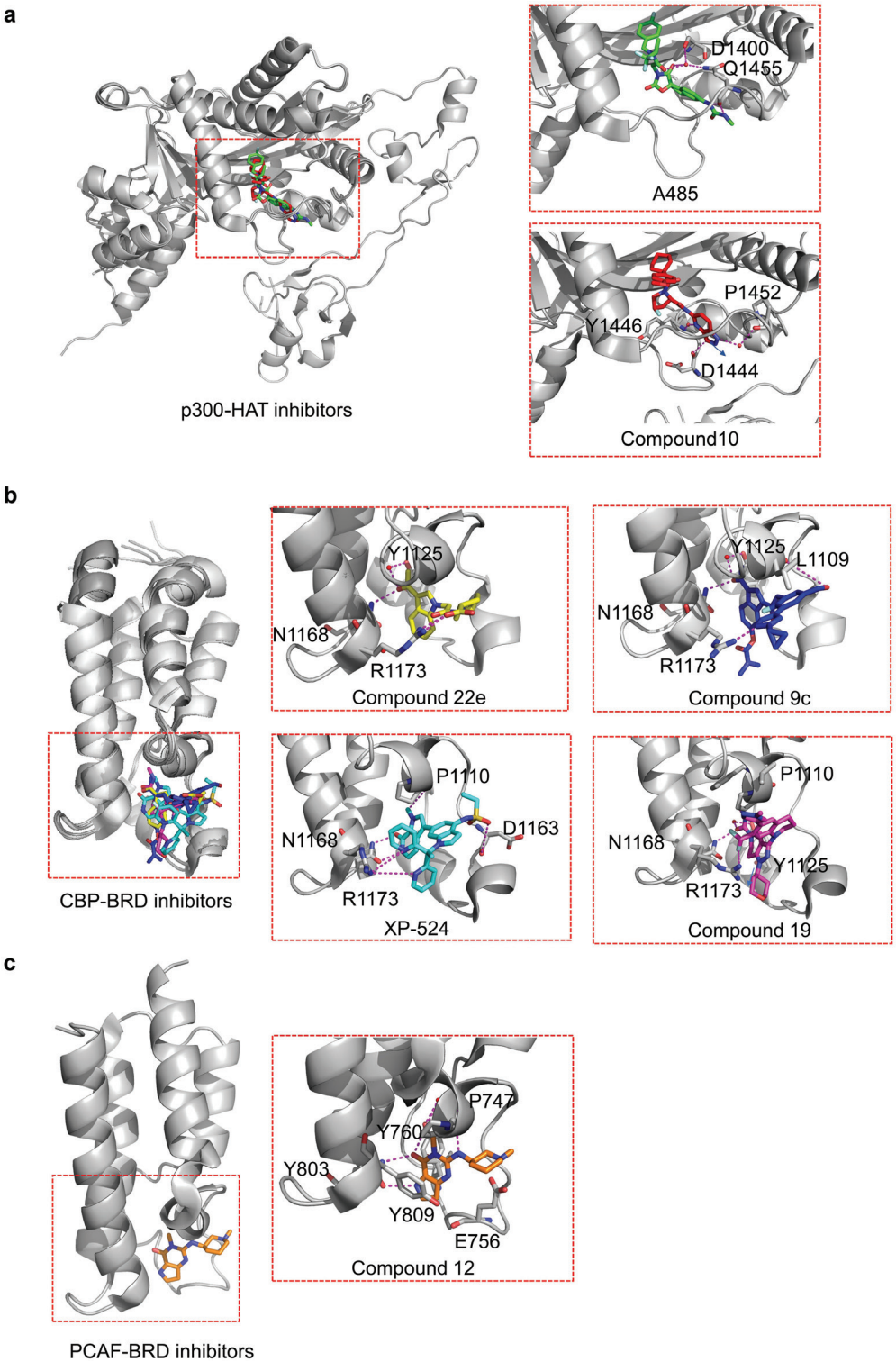

Figure 4 | Interactions between inhibitors and histone acetyltransferases.
(a) Superposition of A-485 (green, PDB ID: 5KJ2) and compound 10 (red, PDB ID: 8GZC) binding p300 HAT domain (gray) structures. (b) Superposition of compound 22e (yellow, PDB ID: 5XXH), compound 9c (blue, PDB ID: 7EVJ), XP-524 (cyan, PDB ID: 7JUO), and compound 19 (magenta, PDB ID: 5W0E) binding the CBP bromodomain (gray) structures. (c) The structure of compound 12 (orange, PDB ID: 6J3O) binding the PCAF BRD (gray). All inhibitors are shown as sticks. The zoomed-in view of interaction details are shown at right. Key water molecules are indicated by red dots, and hydrogen bonds are indicated with a magenta dotted arrow.

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of MORF selectivity for short-chain acyl-groups [108]. Human HBO1 consists of two main structural domains: the N-terminal domain (NTD), which contains a short zf-C2HC DNA binding motif, and the C-terminal MYST domain (**Figure 2a**), which is responsible for acyl-CoA binding and acylation reaction [109]. Structural and functional experiments on the HBO1 MYST domain in complex with the scaffold protein BRPF2 fragment have suggested that the N-terminal region of BRPF2 plays a critical role in HBO1 binding and a secondary role in nucleosome binding. Their studies have provided a possible mechanism for the regulation of HBO1 HAT activity by BRPF2 [110]. Sun et al. have shown that hMOF auto-acetylation at K274 significantly enhances the catalytic activity of the enzyme, thus providing a structural basis for the regulation of enzymatic activity by hMOF intramolecular auto-acetylation (**Figure 2d**) [111].

3.3 GNATs

HAT1 consists of N-terminal, central, and C-terminal domains. The structure of the HAT1-AcCoA-H4 ternary complex shows that acetyl-CoA and the side chain of H4K12 are located in a canyon between the central and C-terminal domains. The highly conserved residues E64 and W199 together determine the substrate binding specificity of HAT1 (**Figure 2e**) [112]. Both GCN5 and PCAF consist of a PCAF N-terminal domain (PCAF_N), the HAT domain, and the BRD. The structure of hGCN5 HAT domain (residues 496–658) in complex with acetyl-CoA suggests that the coenzyme forms hydrogen bonds with V587, G589, G591, and T592 and fits in the crack in the protein surface [113]. The co-crystal structure of the catalytic domain of GCN5 (residues 497–662) with succinyl-CoA suggests that succinyl-CoA binds the same deep cleft of GCN5 with the succinyl groups indicating the end of loop 3 [41]. Further analysis has confirmed that Tyr645 of loop 3 is crucial for the selectivity between succinyl-CoA and acetyl-CoA (**Figure 2f**) [41]. A novel supramolecular assembly of GCN5 catalytic domain has been observed by Wang et al. in the crystal structure of GCN5-succinyl-CoA complexes. The authors have found that 24 molecules of GCN5 form a spherical, octahedral complex with a hollow center characterized by four-fold, three-fold, and two-fold symmetry, which is believed to enhance enzymatic efficiency [114]. GCN5 selectively acylates histones by using acetyl-CoA, propionyl-CoA, butyryl-CoA, and succinyl-CoA [115]. Acyl-CoA molecules with long, charged, or branched acyl chains were believed to be inefficient or non-reactive substrates of HATs [116]. However, a recent study by Li et al. has shown that the alternative substrate binding pocket of GCN5, as well as the length and electrostatic characteristics of the acyl chain, together contribute to GCN5's selection of acyl-CoA substrates [115]. The PCAF protein contains a structurally dispersed N-terminal region, a central HAT domain, and a C-terminal BRD [117]. The HAT domain of PCAF shows high structural homology to GCN5 (**Figure 2f**).

4. HISTONE ACYL TRANSFERASES AS EMERGING DRUG TARGETS

HATs are among the most prominent potential targets for HAT-related disease therapies. Some achievements have been made in discovering and optimizing modifiers targeting HATs. A summary of current research progress in HAT inhibitors (**Table 3**) and activators is provided below.

5. INHIBITORS

5.1 p300/CBP

Inhibition of the p300/CBP HAT domain is a potential treatment for some cancers. Various estrogen receptor (ER) targets, including MYC and CCND1, are regulated by the p300/CBP HAT inhibitor A-485 (**Figure 4a**), which decreases H3K27ac at their enhancers, inhibits their expression, and suppresses the proliferation of breast cancer cells [118]. A-485 exhibits similar anticancer activity in acute myeloid leukemia (AML), multiple myeloma (MM), and non-Hodgkin's lymphoma (NHL) cell lines [118]. Ding et al. have optimized the structure of A-485 to identify compound 13f, which inhibits ovarian cancer cell proliferation and tumor progression [119]. B029-2 inhibits the progression of HCC *in vitro* and *in vivo*, probably through decreasing the expression of genes associated with nucleotide synthesis, amino acid metabolism, and glycolysis; consequently, HCC cell proliferation, migration, and invasion are inhibited [120]. Compound 29, a competitive inhibitor of p300 HAT domain against substrate histones, inhibits H3K27ac and H3K9ac and exhibits favorable anti-tumor activity in a variety of solid tumors and blood cancers [121]. Compound 12 is known as an inhibitor of p300 HAT domain and PCAF BRD (**Figure 4c**) which decreases levels of H3K9ac, H3K18ac, and H3K27ac in cells [122]. Compound 12 exhibits strong anti-proliferative activity against tamoxifen-resistant breast cancer cell lines (e.g., MCF-7) and thus has potential therapeutic value in the treatment of endocrine-resistant breast cancer [115]. In addition, compound 12 suppresses the proliferation of PC cells and leukemia cells [122].

DCH36_06, a potent inhibitor of p300/CBP, decreases H3K18ac levels and inhibits proliferation in leukemia cells [125]. DCH36_06 also induces cell-cycle arrest and apoptosis in a caspase-dependent pathway in leukemia cells [125]. The p300/CBP HAT domain inhibitor C646 downregulates oncogene expression, decreases AML cells cloning potential, and induces AML cell-cycle arrest and apoptosis [153]. Both lung and hematopoietic cancer cells with CBP deletion mutations are more sensitive to C646 treatment than wild-type cancer cells [154]. In addition, C646 inhibits H3 acetylation in melanoma cells and arrest the cell cycle at G1-S phase, thus blocking cell growth [155]. The p300/CBP HAT inhibitor B026 downregulates MYC oncogene expression, and consequently blocks AML cells proliferation and leukemia progression [123]. I-CBP112

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Table 3 | Drugs targeting HATs.

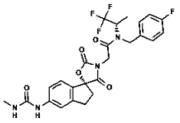
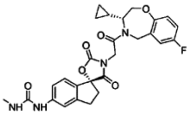
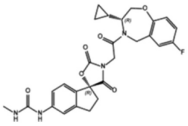
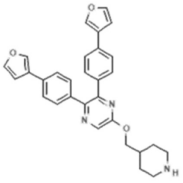
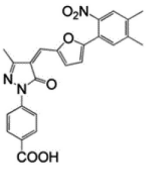
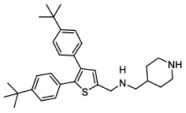
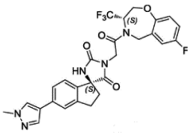
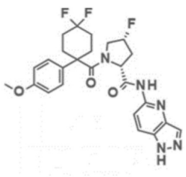
HAT family	Drug target	Potential drug	Model system	Mechanism/outcome/ advantage	References
p300/CBP	p300/CBP HAT domain inhibitor	A-485 	CRPC cell lines, BC cell lines, AML cell lines, MM cell lines, NHL cell lines	Decrease histone acetylation; downregulate expression of estrogen receptor/ androgen receptor target genes; inhibit proliferation of BC/ CRPC cells	[103, 118]
		Compound 13f 	OC cell lines	Inhibit ovarian cancer cell proliferation and tumor progression	[119]
		B029-2 	Hepatoma cell lines	Decrease nucleotide synthesis and amino acid metabolism gene expression; decrease nucleotide synthesis and glycolysis; inhibit HCC cell proliferation, migration, and invasion	[120]
		Compound 29 	BC cell lines, PC cell lines, AML cell lines, MM cell lines	Inhibit H3K27ac and H3K9ac; exhibit good antitumor activity in a variety of solid tumors and blood cancers	[121]
		C646 	AML cell lines, lung cancer cell lines, hematopoietic cancer cell lines, melanoma cell lines	Down-regulate oncogene expression; induce AML cell cycle arrest and apoptosis; inhibit H3 acetylation in melanoma cells, arrest the cell cycle at G1-S phase, thus blocking cell growth	[118, 119]
		Compound 12 	Tamoxifen-resistant breast cancer cell lines, pancreatic cancer cells, leukemia cells	Decrease levels of H3K9ac, H3K18ac, and H3K27ac; suppress cancer cell proliferation	[122]
		B026 	AML cell lines	Downregulate expression of the oncogene MYC; block the proliferation of AML cells	[123]
		DSC-9300 	AR-positive prostate cancer cell lines, mouse models	Inhibit cell growth against AR-positive prostate cancer cell lines by suppressing histone acetylation and downregulating prostate-specific antigen (PSA) expression	[124]

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Table 3 | Continued

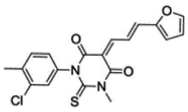
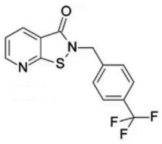
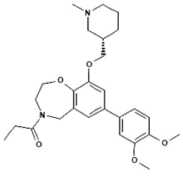
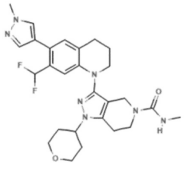
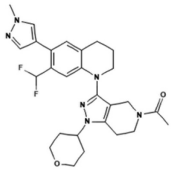
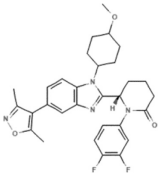
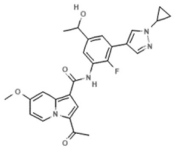
HAT family	Drug target	Potential drug	Model system	Mechanism/outcome/ advantage	References
	p300/CBP inhibitor	DCH36_06 	Leukemia cell lines, mouse models	Decrease H3K18ac in leukemia cells, thereby inhibiting cell proliferation, inducing cell cycle arrest, and activating apoptotic signaling pathways	[125]
		PU141 	Neuroblastoma cell lines, mouse models	Decrease H3K14ac and H4K8ac	[126]
	p300/CBP BRD inhibitor	I-CBP112 	AML cell lines	Impair abnormal self-renewal of leukemia cells, thus leading to severely impaired colony formation, induction of cell differentiation, and significantly decreased potential of AML cells to initiate leukemia	[127]
		GNE-781 	AML xenograft mouse models	Suppress tumor growth	[128]
		GNE-049 	CRPC cell lines, mouse models	Decrease histone acetylation; inhibit transcription of androgen receptor target genes	[129]
		CCS1477 	CRCP, metastatic breast cancer, NSCLC, AML, NHL, MM	Phase I/II clinical trials	[130, 131]
		Compound 9g (Y08284) 	PC cell lines, mouse models	Show significant anti-prostate cancer efficacy *in vitro* and *in vivo*, with good metabolic stability	[132]
		FT-7051 (structure of FT-7051 not reported)	CRPC	Phase I clinical trials	[133]

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Table 3 | Continued

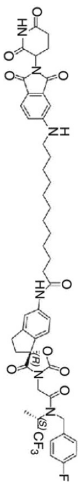
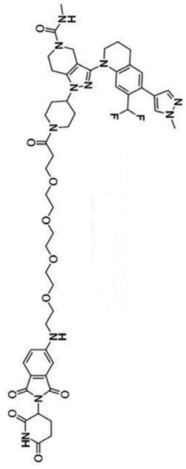
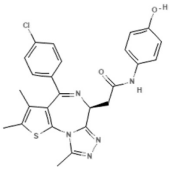
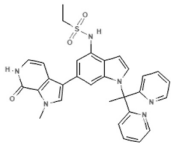
HAT family	Drug target	Potential drug	Model system	Mechanism/outcome/ advantage	References
	PROTAC p300 protein degrader	JQAD1 	Neuroblastoma cell lines, mouse models	Selectively target p300 protein for degradation; decrease transcription of key oncogenes such as MYCN; induce apoptosis in cancer cells	[134]
		dCBP-1 	MM cell lines	Inhibit proliferation of multiple myeloma cells; ablate oncogene MYC enhancer-mediated transcription	[135]
	p300/CBP and BET BRD dual inhibitors	NEO1132, NEO2734 	Leukemia cell lines, lymphoma cell lines, PC cell lines	Induce transcriptional changes in cancer cells; inhibit cancer cell proliferation	[136]
		XP-524 (YF2-23) 	PDAC mouse models	Suppress oncogenic KRAS signaling and enhance immune checkpoint inhibition, thus prolonging survival in PDAC mice	[137]

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Table 3 | Continued

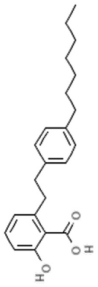
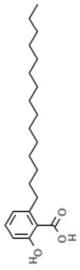
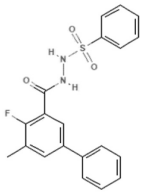
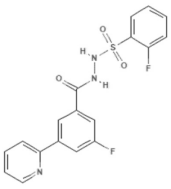
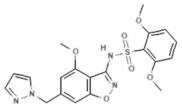
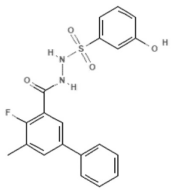
HAT family	Drug target	Potential drug	Model system	Mechanism/outcome/ advantage	References
MYSTs	TIP60 inhibitor	MG149 	PC cell lines	Significantly decrease total Khib levels in PC; strongly inhibit the proliferation and invasive ability of PC cells	[47]
			HCC cell lines, mouse models	Enhance the efficacy of sorafenib in advanced HCC by upregulating cytotoxic endoplasmic reticulum stress	[138]
		Anacardic acid 	HeLa cells	Inhibit TIP60-dependent acetylation and activation of the ATM protein kinase in HeLa cells; sensitize the cells to the cytotoxic effects of radiation	[139]
	MOZ and MORF inhibitor	WM-8014 	Hepatoma cell lines, zebrafish model	Enhance oncogene-induced senescence and tumor growth arrest	[140]
		WM-1119 	Lymphoma cell lines, mouse model	Arrest tumor growth	[140]
			Ovarian cancer cells	Induce apoptosis in ovarian cancer cells, and increase their sensitivity to cisplatin treatment	[56]
		CTx-648 (PF-9363) 	BC	Phase I clinical trials	[141]
	HBO1 inhibitor	WM-3835 	AML cell lines, osteosarcoma cell lines, NSCLC cell lines	Downregulate L genes by decreasing H3K14ac levels; induce AML cell apoptosis and G0/G1 cell cycle arrest; inhibit the proliferation and migration of osteosarcoma cells and NSCLC cells, and lead to apoptosis activation	[142-144]

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Table 3 | Continued

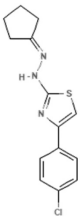
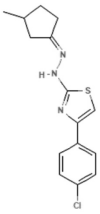
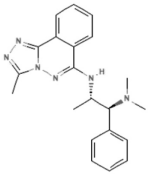
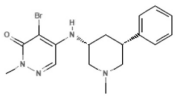
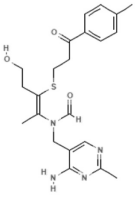
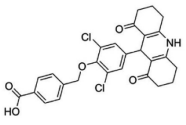
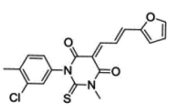
HAT family	Drug target	Potential drug	Model system	Mechanism/outcome/ advantage	References
GNATs	GCN5 HAT domain inhibitor	CPTH2, 	Leukemia cell lines, CRC cell lines	Induce apoptosis of cancer cells	[145]
		CPTH6 			
	PCAF BRD inhibitors	L-45 (L-Moses) 	Peripheral blood mononuclear cells, mouse liver microsomes	Show high selectivity and metabolic stability, without clear cytotoxicity	[146]
	PCAF/GCN5 BRD inhibitors	GSK4027 	NR	Show high efficiency, solubility, and selectivity for the BET family	[147]
	GCN5 inhibitor	MB-3 	ALL cell lines	Decrease acetylation and expression of the oncoprotein E2A-PBX1 in ALL cells	[148]
		DC_G16-1, 	Leukemia cell lines	Occupy the H3 substrate binding pocket; decrease H3K14ac levels; inhibit leukemia cell growth	[149]
		DCH36_06 			

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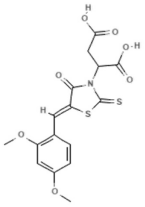
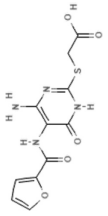
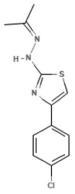
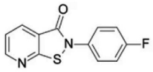
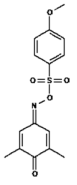
Table 3 | Continued

HAT family	Drug target	Potential drug	Model system	Mechanism/outcome/ advantage	References
	PCAF/GCN5 inhibitor	BTB09406 (structure of BTB09406 not available), F1418-0051,  F1880-1727 	MDS mouse model	Show potent dual inhibitory properties	[150]
Pan-HAT inhibitor	GCN5 and p300 inhibitor	BF1 	Neuroblastoma cell lines, glioblastoma cell lines	Decrease the overall acetylation of H3 and H3K18ac in neuroblastoma and glioblastoma cells	[151]
	GCN5, PCAF, and p300/CBP inhibitor	PU139 	Neuroblastoma cell lines, mouse model	Decrease H3K14ac and H4K8ac; show doxorubicin synergy	[126]
		L002 	Leukemia cells, lymphoma cells, triple-negative breast cancer cell lines	Decrease overall H4 acetylation; induce growth arrest and apoptosis in cancer cells	[152]

Abbreviations: castration-resistant prostate cancer, CRPC; breast cancer, BC; acute myeloid leukemia, AML; multiple myeloma, MM; non-Hodgkin's lymphoma, NHL; colorectal cancer, CRC; gastric cancer, GC; hepatocellular carcinoma, HCC; renal cell carcinoma, RCC; ovarian cancer, OC; non-small cell lung cancer, NSCLC; pancreatic cancer, PC; pancreatic ductal carcinoma, PDAC; myelodysplastic syndrome, MDS; NR, not reported.
Note: all structures of compounds are from PubChem (https://pubchem.ncbi.nlm.nih.gov/).

and GNE-781 are both selective small-molecule inhibitors of the p300/CBP BRD. I-CBP112 prevents aberrant self-renewal of leukemia cells, thus leading to severely impaired colony formation and cell differentiation, and significantly decreasing the potential of AML cells to initiate leukemia [127]. GNE-781 has also been shown to potentially suppress tumor growth in AML xenograft mouse models [128].

p300/CBP is a potential target of PCa therapy. In mouse models, A-485 and the p300/CBP BRD inhibitors GNE-049 and CCS1477 (**Table 4**) exhibit therapeutic effects against castration-resistant prostate cancer

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Table 4 | Summary of clinical candidates.

Drug	Target	ClinicalTrials. gov identifier	Sponsor	Indication	Phase
CCS1477	p300/CBP BRD inhibitor	NCT03568656	CellCentric Ltd.	Advanced solid tumors	Phase I/II
CCS1477	p300/CBP BRD inhibitor	NCT04068597	CellCentric Ltd.	Hematological malignancies	Phase I/II
FT-7051	p300/CBP BRD inhibitor	NCT04575766	Forma Therapeutics, Inc.	Metastatic CRPC	Phase I
PF-07248144	KAT6A/KAT6B inhibitor	NCT04606446	Pfizer	Locally advanced or metastatic CRPC/NSCLC/ER^{+} HER2^{-} breast cancer	Phase I

Note: All clinical trial details are from the ClinicalTrials.gov database (https://clinicaltrials.gov/).

(CRPC). CCS1477 inhibits androgen receptor (AR) target gene transcription by decreasing histone acetylation [103, 129, 130]. GNE-049 significantly inhibits cell proliferation and AR expression in androgen-resistant CRPC mutant cell lines [129]. The 1-(indolizin-3-yl)ethan-1-one derivatives are a group of novel CBP BRD inhibitors. Xiang et al. have optimized drugs based on the high-resolution crystal structures of CBP and inhibitor 9c complex, and have synthesized compound 9g (Y08284), which shows substantial anti-PCa efficacy *in vitro* and *in vivo*, and good metabolic stability (**Figure 4b**) [132]. Kanada et al. have identified a novel, potent, selective, orally available p300/CBP HAT inhibitor, DS-9300, which also exhibits excellent antitumor activity in PC cell lines and mouse tumor models. DS-9300 is a potential candidate for the treatment of CRPC [124].

p300/CBP inhibitors also have promising applications in cancer immunotherapy. FOXP3 is a principal transcription factor required for Treg cell development and function. p300/CBP HAT inhibitors and BRD inhibitors impair FOXP3 expression and Treg cell function, and promote anti-tumor immunity, thereby inhibiting tumor growth [128, 156].

In human neuroblastoma tissue, high p300 expression is associated with poor patient prognosis. Durbin et al. have developed a PROTAC compound, JQAD1, which targets p300 for degradation [134]. In mice, JQAD1 inhibits transcription of oncogenes, such as *MYCN*, a member of the MYC family of basic helix–loop–helix transcription factors, and induces apoptosis and suppresses tumor growth in neuroblastoma cells *in vitro* [134]. dCBP-1 is a p300/CBP heterobifunctional degrader that significantly inhibits the proliferation of multiple myeloma cells and ablates oncogene *MYC* enhancer-mediated transcription [135].

NEO1132 and NEO2734, dual inhibitors of p300/CBP and BET BRD, have shown potent anti-proliferative effects in cells from cancers including leukemia, lymphoma, and PCa [136]. NEO2374 has been found to inhibit lymphoma progression in mice more effectively than either a CBP/p300 inhibitor or a BET BRD inhibitor alone [136]. Another multispecific BET inhibitor targeting the BRD4 and p300/CBP BRDs is XP-524 (**Figure 4b**). In pancreatic ductal carcinoma (PDAC) mouse models, XP-524 has been found to suppress oncogenic KRAS signaling and enhance immune checkpoint inhibition, thus prolonging the survival of PDAC mice [137].

CCS1477 is a novel inhibitor targeting the p300/CBP BRD. In preclinical models of AML and lymphoma, CCS1477 has been found to improve the effectiveness of azacitidine and venetoclax [157]. Phase I/II clinical trials on CCS1477 are currently underway for AML, NHL (including B-cell lymphoma), and MM (**Table 4**) [131]. Although no published preclinical information is available, FT-7051, a potent and selective inhibitor of CBP/p300 BRD, is orally active and is entering a multicenter phase I clinical trial in patients with CRPC (**Table 4**) [133].

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5.2 MYSTs

MG149, a highly selective inhibitor of TIP60, markedly decreases total Khib levels in PC, and strongly inhibits PC cell proliferation and invasion [47]. Moon et al. have shown that MG149 enhances the efficacy of sorafenib in advanced HCC, probably through upregulating cytotoxic endoplasmic reticulum stress [138]. The small-molecule compound anacardic acid has been shown to inhibit the HAT activity of p300 and PCAF [158]. Sun et al. have demonstrated that anacardic acid inhibits TIP60-dependent acetylation and activation of ATM protein kinase in HeLa cells, thereby sensitizing them to radiation cytotoxicity [139]. In contrast, WM-8014 and WM-1119 are highly selective inhibitors of MOZ and MORF that induce cell-cycle arrest and cellular senescence. WM-8014 has been found to enhance oncogene-induced senescence in an HCC zebrafish model, and WM-1119 has been found to effectively prevent the progression of lymphoma in mice [140]. WM-1119-mediated inhibition of KAT6A induces apoptosis in ovarian cancer cells and increases their sensitivity to cisplatin treatment [56]. CTx-648, an effective and highly selective KAT6A/KAT6B inhibitor, has strong anti-tumor activity in ER^+ breast cancer cell lines and patient-derived xenograft models, thus highlighting the promising potential of this new therapy in patients with ER^+ breast cancer [141]. On the basis of the strength of preclinical data, a selective KAT6 inhibitor (PF-07248144) is under phase 1 clinical study in advanced or metastatic solid tumors (**Table 4**) [141]. HBO1 is required for the maintenance of leukemic stem cells. MacPherson et al. have developed an HBO1 inhibitor, WM-3835, which effectively inhibits the growth of AML cells [142]. Moreover, WM-3835 also inhibits the proliferation and migration of osteosarcoma and NSCLC cells, and leads to activation of apoptosis [143, 144].

5.3 GNATs

Inhibition of the PCAF/GCN5 HAT domain and BRD are promising strategies for cancer treatment. The GCN5 HAT inhibitors CPTH2 and CPTH6 induce apoptosis in human leukemia and CRC cells [145]. The compound L-45 (also called L-Moses) is the first potent PCAF BRD inhibitor. L-45 has good metabolic stability and no apparent cytotoxicity, thus supporting its potential for *in vivo* use [146]. Humphreys et al. have reported a highly selective PCAF/GCN5 BRD inhibitor, GSK4027, which has great potential in cancer therapies [147]. The GCN5 inhibitor α-methylene-γ-butyrolactone 3 (MB-3) decreases acetylation and expression of the oncoprotein E2A-PBX1 in ALL cells, and thus has potential value for ALL treatment [148]. DC_G16-11, a novel inhibitor of GCN5, inhibits proliferation, and induces cell-cycle arrest and apoptosis in leukemic cells, but has minimal effects on normal cells [149].

BTB09406, F1418-0051, and F1880-1727 are dual inhibitors of PCAF and GCN5 that suppress the progression of myelodysplastic syndrome (MDS) [150]. H3K18ac plays an essential role in driving tumorigenesis [159]. BF1 primarily inhibits the catalytic activity of GCN5 and p300, thus decreasing the overall acetylation of H3 and specific H3K18ac in neuroblastoma and glioblastoma cells [151]; consequently further pharmacological research is warranted. PU139 and PU141 also block the growth of neuroblastoma cells in mice. PU139 is an inhibitor of pan-HATs that inhibits the activity of GCN5, PCAF, and p300/CBP, whereas PU141 has a selective inhibitory effect on CBP and p300 [126]. Compound L002 inhibits p300/CBP, PCAF, and GCN5; moreover, leukemia, lymphoma, and triple-negative breast cancer cell lines are extremely sensitive to L002 [152].

The HATs inhibitors introduced above are used primarily for cancer treatment, but some inhibitors have also shown therapeutic potential in other diseases. Tannic acid and 3,4-dihydroxytoluene are novel p300 inhibitors. Both decrease the levels of H3K9ac and H3K36ac, thereby preventing the progression of non-alcoholic fatty liver disease in mice [160, 161]. Garcinol inhibits GCN5 activity and effectively prevents replication of *Toxoplasma gondii* [162]. C14, a selective inhibitor of PfGCN5, has been shown to decrease H3K9ac in *Plasmodium falciparum*, inhibit *Plasmodium* growth, and serve as a potential antimalarial drug [163]. Research on such inhibitors is expected to accelerate the development of therapies targeting histone acylation.

6. ACTIVATORS

CTPB is a selective p300/CBP HAT domain activator that increases histone acetylation in SH-SY5Y cells (a PD cell model), promotes neurite growth, and protects SH-SY5Y cells against cell death induced by the dopamine neurotoxin 6-OHDA [76]. The conjugation of TTK21, a small-molecule activator of p300/CBP, with glucose-based carbon nanospheres (CSP) enhances the cell permeability and tissue specificity of TTK21 [164]. After intraperitoneal administration in mice, a significant increase in histone acetylation has been detected in the hippocampus and frontal cortex [164]. Chatterjee et al. have found that CSP-TTK21 promotes neurogenesis and extends memory duration in adult mice [165]. The authors have also shown that CSP-TTK21 restores neuronal activity, synaptic plasticity, and spatial memory in AD-like Tauopathy mouse models, thus further confirming the therapeutic potential of HAT activators [165].

Cardiac mesenchymal cells from patients with type 2 diabetes (D-CMSC) show a diminished proliferation rate and differentiation potential, and premature cell senescence [166]. Treatment with the GNAT activator pentadecylenolate 1b (SPV106) restores normal H3K9ac and H3K14ac levels, decreases DNA CpG hypermethylation, and results in resumption of proliferation and differentiation of D-CMSC [166].

Although current inhibitors and activators of HATs target primarily the HAT domain and/or the BRD, other

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domains may also potentially be therapeutic targets. The KIX domain of the transcriptional co-activator p300/CBP acts as a docking site for transcription factors [167]. Modell et al. have developed a combined computational-experimental approach to optimize a peptidomimetic for KIX. The peptide has extremely high affinity for the KIX domain of p300/CBP, thus blocking binding of KIX to transcription factors and inhibiting gene transcription [168]. In conclusion, comprehensive studies on other domains of HATs are necessary to advance their development as drug targets.

7. CONCLUSION AND FUTURE PROSPECTS

Protein lysine acylation, a class of PTMs, regulates many important biological processes. Major diseases, such as cancer, neurological disorders, and metabolic diseases, are closely associated with aberrant acylation (**Figure 5**). Thus, HATs have attracted the attention of many scientists, and small-molecule modifiers targeting HATs have been developed. HAT inhibitors not only suppress the proliferation and metastasis of cancer cells, but also synergistically enhance the effects of chemotherapy and radiotherapy. Consequently, HAT inhibitors and activators are promising and emerging anticancer therapies.

Unfortunately, the investigation of HAT modifiers and disease-associated mechanisms has been limited. Low oral activity and poor tissue specificity are the primary difficulties in the development of HAT inhibitors and activators. In recent years, rapid advances in medicinal chemistry, structural biology, molecular biology, artificial intelligence (AI), and targeted drug delivery have provided a strong foundation for developing and applying HAT modifiers. AI techniques are an important and powerful data mining tool in various drug design-associated fields, such as high-performance screening, activity scoring, and *de novo* drug design [169]. Machine learning and deep learning are branches of AI that can be used to build quantitative structure–activity relationship models, predict molecular pharmacokinetic properties, and improve and generate desired molecules, thus greatly facilitating the development of new drugs [170]. Advances in nanomedicines and micro-nano-robots have led to a new paradigm for drug delivery, thus markedly increasing drug specificity and efficacy [171]. Although very few HATs modifiers are currently in clinical trials, with the development of related fields and advances in the study of HATs, breakthroughs in HAT-based disease research and drug development are likely to be achieved.

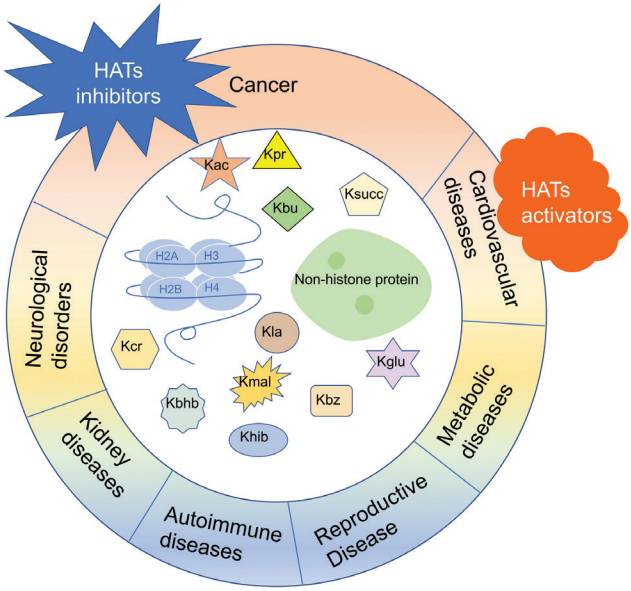

Figure 5 | Summary of this review.
The center of the graph contains histone and non-histone proteins, as well as 11 acylation modifications, with associated diseases surrounding them.

ABBREVIATIONS

HPTMs, Histone post-translational modifications; HATs, Histone acetyltransferases; HDACs, Histone deacetylases; PTMs, Post-translational modifications; Kac, Lysine acetylation; Kpr, Lysine propionylation; Kbu, Lysine butyrylation; Ksucc, Lysine succinylation; Kcr, Lysine crotonylation; Kmal, Lysine malonylation; Kglu, Lysine glutarylation; Khib, Lysine 2-hydroxyisobutyrylation; Kbhb, Lysine β-hydroxybutyrylation; Kla, Lysine lactylation; Kbz, Lysine benzoylation; p300, Adenoviral E1A binding protein of 300 kD/KAT3A; CBP, CREB binding protein/KAT3B; TIP60, Tat interacting protein 60 kD/KAT5; MOZ, Monocytic leukemia zinc finger protein/KAT6A; MORF, MOZ-related factor/KAT6B; HBO1, Histone acetyltransferase binding to ORC1/KAT7; MOF, Males absent on the first/KAT8; GNAT, GCN5-related N-acetyltransferases; HAT1, Histone acetyltransferase 1/KAT1; GCN5, General control non-repressed protein 5/KAT2A; PCAF, p300/CBP-associated factor/KAT2B; NSCLC, Non-small cell lung cancer; PCa, Prostate cancer; SIRT5, Sirtuin 5; CRC, Colorectal cancer; PC, Pancreatic cancer; OSCC, Oral squamous cell carcinoma; βHB, β-hydroxybutyrate; CVD, Cardiovascular diseases; SCFAs, Short-chain fatty acids; AD, Alzheimer's disease; PD, Parkinson's disease; BDNF, Brain-derived neurotrophic factor; AKI, Acute kidney injury; ESRD, End-stage renal disease; CDYL, Chromodomain Y-like transcription corepressor; TAZ1/2, Transcriptional adapter zinc finger domain 1/2; KIX, Kinase inducible domain of CREB interacting domain; BRD, Bromodomain; PHD, Plant homeodomain; HAT, Histone acetyltransferase domain; ZZ, ZZ-type zinc finger domain; AIL, Auto-inhibitory loop; AL, Autoregulatory loop; TIP60-CB, N-terminal chromo barrel domain of TIP60; NTD, N-terminal domain; AML, Acute myeloid leukemia; MM, Multiple myeloma; NHL, Non-Hodgkin's lymphoma; HCC, Hepatocellular carcinoma; CRPC, Castration-resistant prostate cancer; AR, Androgen receptor; PDAC, Pancreatic ductal carcinoma; AI, Artificial intelligence; BC, Breast cancer; OC, Ovarian cancer; RCC, Renal cell carcinoma; MDS, Myelodysplastic syndrome.

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CONFLICTS OF INTEREST

The authors declare that they have no competing financial interests.

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