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Histone acetyl transferases as emerging drug targets

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Post-translational modifications, such as acetylation or phosphorylation, play a crucial role in the regulation of gene transcription in eukaryotes. Different subtypes of histone acetyl transferases (HATs) catalyze the acetylation of histones on specific lysine residues. A potential role of HATs in the pathology of cancer, asthma, COPD and viral infection has been described. This indicates that specific HAT inhibitors are potential tools for pharmacological research and might find therapeutic applications. This review focuses on the role of the HATs p300, CBP, PCAF and GCN5 in different diseases and the development of small-molecule inhibitors of these enzymes as potential drugs.

The nucleus of eukaryotic cells contains highly organized and tightly regulated machineries involved in the control of gene transcription [1]. Histones are the basic packaging units for DNA and they undergo post-translational modifications. Such modifications form distinct patterns that regulate the transcription of specific genes [2]. These patterns are referred to as 'the histone code' [3]. Normal and aberrant cell function depends not only on genetic properties encoded within the DNA sequence. There is increasing evidence that specific post-translational marks on the histones contribute to both normal and aberrant cell function. These post-translational marks are altered by histone-modifying enzymes, such as histone deacetylases (HDACs) and histone acetyl transferases (HATs). Reversible acetylation of histone and nonhistone targets can cause changes in conformation and/or molecular recognition of these proteins (Fig. 1). This review focuses on the HATs; general control of amino acid synthesis protein 5 (GCN5) and p300/CBP-associated factor (PCAF), which both belong to the GCN5-related *N*-acetyl transferase (GNAT) family HATs. Furthermore, the HATs p300 and CBP, which both belong to the p300/CBP family, are discussed. The discussion focuses on the role of these enzymes in different disease models like cancer, asthma, chronic obstructive pulmonary disease (COPD) and viral infection. We put particular emphasis on the development of small-molecule inhibitors for these enzymes as tools in reverse chemical genetics studies and for potential therapeutic applications.

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Histone acetylation is a key epigenetic modification

Epigenetic modifications

Epigenetic modifications have been defined as the structural alteration of chromosomal regions to register, signal or perpetuate altered activity states [4]. It has been shown that DNA-methylation can mediate heritage of properties that are not encoded in the DNA, and is therefore referred to as 'epigenetic modification' [4]. A comparable role has not been proven for post-translational modifications of the histones [4]. Nevertheless, both DNA-methylation and histone modifications are often referred to as 'epigentic modifications'. These modifications represent major contributors to the regulation of gene transcription [5]. Several histone modifications have been described, including acetylation, methylation, phosphorylation and ubiquitination (for a review see [2]). Histone modifications serve two main purposes. The first purpose is to provide or remove recruitment signals for nonhistone proteins involved in transcriptional activation and silencing. The second purpose is to change chromatin structure and, hence, the physical interactions between histones and DNA.

Action of histone acetyl transferases

The actions of HATs in gene transcription can be divided into gene-specific effects and global effects. Histone acetylation targeted to

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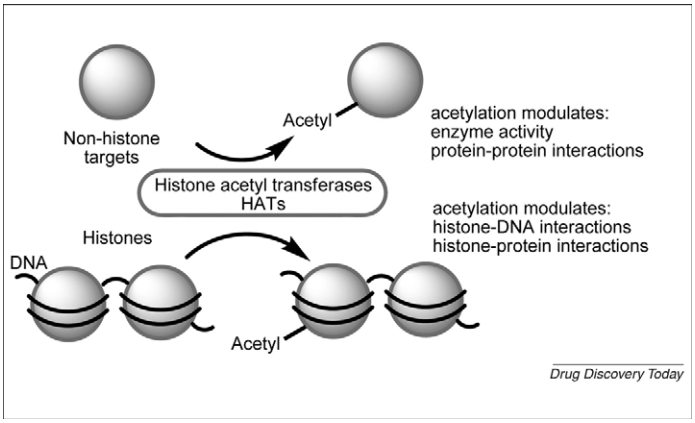

FIGURE 1

The disparate family of histone acetyl transferases (HATs) acetylates histones and nonhistone targets. Acetylation of nonhistone targets can lead to changes in enzyme activity and protein–protein interactions, which have consequences for signal transduction. Acetylation of histones can result in changes in histone–DNA and histone–protein interactions, which have consequences for the accessibility of the DNA and/or binding of transcription factors.

promoters mediates activation or repression of specific genes [6], whereas histone acetylation over large regions of chromatin, including coding regions and nonpromotor regions, affect global gene expression levels [7]. It has been shown that global histone modification levels are predictive of cancer recurrence [8]. This indicates that histone acetylation is a versatile regulatory event that plays a key role in multiple cellular processes.

Crosstalk between histone modifications

There is increasing evidence of crosstalk between histone modifications in the regulation of gene transcription [2,9]. Synergistic coupling within the same histone has been described between histone H3 serine 10 phosphorylation and lysine 14 acetylation in EGF-mediated signal transduction [10]. The enzyme GCN5 shows a tenfold increased K_m for acetylation of serine 10 in phosphorylated histone H3 compared to nonphosphorylated histone H3. It has been discovered that interaction of 14-3-3 proteins with histone H3 depends on the combined presence of both serine 10 phosphorylation and lysine 14 acetylation [11]. Recently, crosstalk between different histones in one nucleosome has been described. The GCN5 bromodomain of the Spt-Ada-Gcn5-acetyl transferase (SAGA) complex enhances histone H3 acetylation, when the other histone H3 tail in a nucleosome is already acetylated [12]. It also augments the acetylation of nucleosomes that are already acetylated on histone H4 lysine 16. These studies show how histone modifications can mutually affect each other and that combinations of histone modifications play a role in the regulation of gene transcription. Combined inhibition of different enzymes that influence different histone modifications could provide synergistic therapeutic effects, as demonstrated for the combination of the DNA demethylation inhibitor 5-aza-2′-deoxycytidine and the HDAC inhibitor trichostatin A (TSA) [13].

HAT families

HATs can be organized into families based on primary-structure homology. The four HAT families that have been studied extensively are: the GNAT family; the p300/CBP family; the MYST family and the Rtt109 family [6,14,15]. Several other HAT families have been identified, but they have been studied less extensively. The HATs, PCAF and GCN5, are the members of the GNAT family and share 73% sequence homology. The HAT PCAF acetylates histone H3 on lysine 14 and, less efficiently, histone H4 on lysine 8 [16]. It should be noted, however, that HATs are often part of multisubunit protein complexes that determine their binding preferences and catalytic activity [6]. The p300/CBP family HATs p300 (alternative name: E1A-associated protein p300; gene name: EP300) and CBP (alternative abbreviation: CREBBP) share 60% sequence homology. HAT p300 preferentially acetylates histone H2B lysine 12 and 15, H3 lysine 14 and 18 and H4 lysine 5 and 8 [16]. The MYST family HATs are closely linked to cancer (for a review see [17]). The enzymes p300 and PCAF show minimal sequence homology and rather modest structural homology [18]. The lack of homology suggests that these enzymes have different functions and that identification of subtype-specific HAT inhibitors is feasible.

The role of HATs in disease

p300 and CBP in cancer

The role of p300 and CBP in cancer is under debate. Some studies indicate a role as tumor suppressors, yet other studies suggest a role as tumor promoters. It has been reported that p300 behaves as a classical tumor suppressor gene [19]. Another study reported that the p300 gene and the CBP gene are mutated in >85% of microsatellite instable (MSI)+ colon cancer cell lines and primary tumors. p300 null MSI+ cancer cell lines that re-express exogenous p300 showed slower growth and a more flattened morphology. Despite the evidence that p300 acts as a tumor suppressor, other studies indicate that downregulation and inhibition of p300 inhibit the growth of tumor cells. It has been shown that downregulation of p300 activity resulted in growth inhibition and activation of a senescence checkpoint in human melanocytes [20] and that p300/CBP HAT activity is important for the G1/S transition [21,22]. These results indicate that the role of p300/CBP in cancer biology is versatile and context dependent. Interestingly, it has been found that the monocytic leukemia zinc finger protein (MOZ) forms fusion genes with the p300 HAT by chromosome translocation in myeloid leukemia [23,24]. This raises the idea that chromosomal translocations to histone acetyl transferases could lead to diseases like cancer and that small-molecule HAT inhibitors could be exploited therapeutically.

PCAF and GCN5 in cancer

The enzymes PCAF and GCN5 perform global histone acetylations and locus-specific histone acetylations, as well as acetylations of nonhistone proteins [6]. These enzymes are often part of large multiprotein complexes, which regulate their activity and specificity. It is, therefore, not surprising that studies on the roles of PCAF and GCN5 in cell proliferation and cancer biology provide contradictory results. The role of PCAF and GCN5 has been reviewed [6]. Mutations that result in elevated activity of the EGF signaling pathway are found in many cancer subtypes. Interestingly, GCN5 plays a key role in EGF-mediated gene transcription and provides a target for the downregulation of oncogenic EGF signaling [10]. Furthermore, it has been shown that GCN5 is

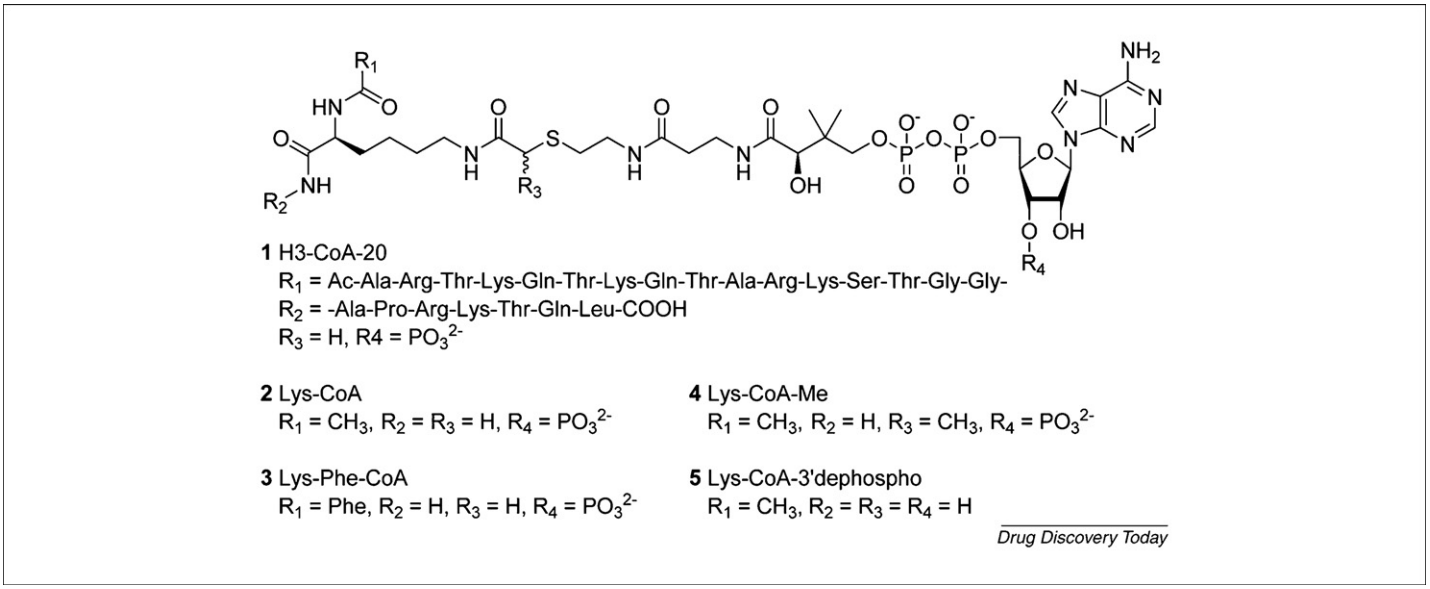

FIGURE 2

Bisubstrate inhibitors for the HATs p300 and PCAF.

crucial for cell cycle progression, which is also relevant for cancer therapy [25]. These results indicate that the HATs, PCAF and GCN5, might be exploited as anticancer targets.

Histone acetyl transferases in asthma and COPD

Inflammatory lung diseases, like asthma and COPD, are characterized by excessive expression of inflammatory genes. Nuclear factor κB (NF-κB) is an important regulator of gene transcription of several genes that are involved in airway inflammation. NF-κB requires cofactors, such as HDACs and HATs, for the activation of gene transcription [26,27]. The activities of HATs and HDACs are changed in asthma and COPD. Bronchial biopsies from asthmatic patients show increased HAT activity and reduced HDAC activity [27,28]. Similar changes have been found in alveolar macrophages from asthmatic patients [29]. Another study reported that tumor necrosis factor α (TNFα) induced NF-κB activity increases after overexpression of p300 and PCAF in human airway smooth muscle cells (HSAMs) [30]. All these findings suggest that HATs might represent potential drug targets for inflammatory lung diseases like asthma and COPD. The precise roles of different subtypes of HATs in inflammation remain, however, to be elucidated.

Histone acetyl transferases in learning and memory

Histone modifications participate in the development and maintenance of cellular differentiation, which determine synapse formation in nerve cells. Histone modifications, therefore, play an important role in learning and memory processes [31]. It has been discovered that PCAF knockout mice show an exaggerated response to stress and impaired learning capacity [32]. Knockdown of the HAT CBP in mice provides impaired long-term memory, whereas the short-term memory is unaffected. The detailed roles of the different subtypes of HATs in learning and memory, however, remain to be elucidated. These initial studies indicate that it would be interesting to explore the roles of histone-modifying enzymes in the central nervous system to find new drug targets.

Histone acetyl transferases in viral infections

The integration of HIV-1 virus into the human genome is catalyzed by a viral protein integrase. It has been demonstrated that the activity of the integrase is increased by p300-mediated acetylation [33,34]. A recent study showed that garcinol-derived molecules inhibit histone acetylation and HIV multiplication in T-cells at nontoxic concentrations [35]. This suggests that HAT inhibitors have potential for HIV treatment.

Small-molecule HAT inhibitors

Bisubstrate HAT inhibitors

The first inhibitor class to be described for the HATs p300 and PCAF were bisubstrate inhibitors (Fig. 2, Table 1) [36]. Bisubstrate inhibitors **1** and **2** show remarkable selectivity for the inhibition of the HATs PCAF and p300 [36]. Introduction of a phenyl group (inhibitor **3)** improves the inhibition fourfold [37]. An extra methyl on the linker between the lysine and Coenzyme A (CoA) **4** also improves the inhibition fourfold [37]. Another study revealed that dephosphorylation of the CoA moiety in the 3′-position **5** reduces the IC_{50} by 32-fold. The major limitation of bisubstrate inhibitors is their lack of cell-permeability. To address this problem, a construct has been reported in which a bisubstrate HAT inhibitor and an arginine-rich peptide sequence were linked to yield a cell-permeable molecule [38].

Structural information on the interaction between a bisubstrate inhibitor and the HAT GCN5 is available [39]. The crystal structure shows that the enzyme interacts with the pantothenic acid moiety, the pyrophosphate moiety and the 3′-phosphate of CoA. Furthermore, there are interactions with the linker and five amino acids of the histone peptide. This structural information could inspire structure-based inhibitor development.

The natural product curcumin

It has been discovered that histone H3 and histone H4 acetylation by p300/CBP is inhibited by curcumin **6** (IC_{50} 25 μM), whereas PCAF HAT activity is not affected (Fig. 3, Table 1) [40]. The enzyme

TABLE 1

Inhibitors of the HATs p300 and PCAF

Compound	p300 IC_{50} (μM)	PCAF IC_{50} (μM)	Refs
1, H3-CoA-20	200	0.3 (K_d 0.028)	[36,64]
2, Lys-CoA	0.5 (K_d 0.019)	200	[36,64]
2, Lys-CoA	3.2		[37]
3, Lys-Phe-CoA	0.7		[37]
4, Lys-CoA-Me	0.8		[37]
2, Lys-CoA	0.05		[65]
5, Lys-CoA-3′-dephospho	1.6		[65]
6, curcumin	>400		[41]
7	21		[41]
8	33		[41]
9	233		[41]
10	168		[41]
11	5		[41]
12, garcinol	7	5	[43]
13, isogarcinol	7	5	[35]
14, LTK-14	5–7	–	[35]
15, anacardic acid	8.5	5	[45]
20		100 (GCN5)	[49]
21	23	28	[53]
22		32	[53]
23		>200	[53]
24		>10	[52]
25		1.8	[52]
26		5.6	[52]

kinetics of p300/CBP inhibition by curcumin suggests that curcumin does not bind to the binding sites of either histone or acetyl CoA, but to some other site of the enzyme. Exposure of tumor cells to curcumin resulted in the inhibition of cell proliferation and induction of apoptosis. Curcumin also inhibited acetylation of HIV Tat by p300 *in vitro*. Another group reported small-molecule cinnamoyl-derivatives as inhibitors of the HAT p300 [41]. They identified derivative **11** (IC_{50} 5 μM) as a more potent inhibitor than curcumin. Recently, it has been described that curcumin **6** inhibits HAT activity *in vivo* and prevents heart failure in rats [42]. These findings indicate that the natural product curcumin **6** might be a useful tool to dissect the role of the HAT p300 in several disease models.

The natural product garcinol

The naturally occurring polyisoprenylated benzophenone garcinol **12** inhibits the HATs PCAF (IC_{50} 5 μM) and p300 (IC_{50} 5 μM) [43]. It has been shown that garcinol **12** inhibits histone acetylation in cells treated with the HDAC inhibitor, TSA. Furthermore, garcinol **12** induces apoptosis and predominantly downregulates global gene expression in HeLa cells. Another study has shown that garcinol **12** and isogarcinol **13** inhibit p300 and PCAF and exhibit high cytotoxicity [35]. The derivative LTK-14 **14** inhibits p300 and not PCAF in the concentration range studied. The garcinol derivatives are nontoxic to T-cells, inhibit histone acetylation in HIV-infected cells and also inhibit the multiplication of HIV. A recent study describes the mechanism of inhibition of garcinol **12**, isogarcinol **13** and LTK-14 **14** [44]. The stoichiometry for the inhibition of p300 by garcinol **12** and isogarcinol **13** was 1:2 and the stoichiometry for the inhibition of p300 by LTK-14 **14** was 1:1. Equilibrium-binding constants (K_d) for binding to p300 were 6.6 μM for garcinol **12**, 5.9 μM for isogarcinol **13** and 9.1 μM for LTK-14 **14**. The methyl group on the aromatic alcohol in LTK-14 **14** reduces binding to PCAF, but not to p300. Enzyme kinetics and mutagenesis studies suggest that the catechol moiety binds to the acetyl-CoA-binding site. Interpreting these studies, it can be concluded that garcinol is a valuable starting point for the development of p300 and PCAF inhibitors. The potency of the compound is relatively low, however, and the synthetic complexity of garcinol limits studies on structure activity relationships.

The natural product anacardic acid

It has been discovered that the natural product, anacardic acid **15**, inhibits the HATs p300 (IC_{50} 8.5 μM) and PCAF (IC_{50} 5 μM) [45]. The anacardic acid derivative, CTPB **16**, activates p300. CTPB derivatives **17** and **18** with different alkyl chain lengths and different substituents were studied for the inhibition of histone acetylation in cell lines [46]. It was discovered that derivatives **17** and **18** are as potent as anacardic acid. Recently, long-chain alkylidenemalonate **19** has been identified as a small-molecule modulator of the HATs p300 and CBP with potency approximately equal to anacardic acid **15** [47]. It has been shown that anacardic

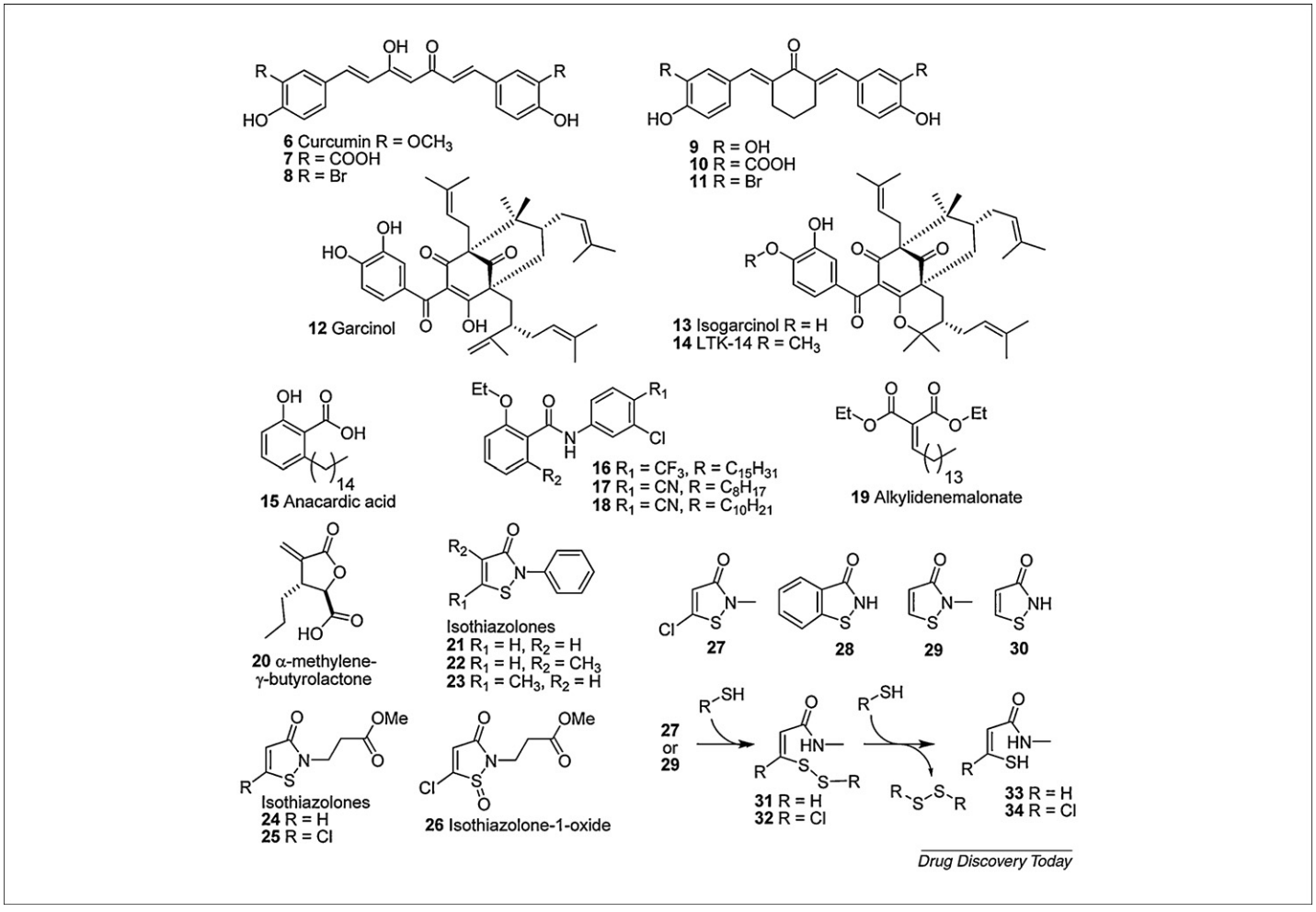

FIGURE 3

Inhibitors of the HATs p300 and PCAF.

acid **15** influences NF-κB activation in response to different stimuli [48]. It inhibits both inducible and constitutive NF-κB activation, without interfering with DNA binding. Furthermore, it inhibits the acetylation and nuclear localization of p65 and NF-κB reporter gene expression. Downregulation of p300 by RNA interference abrogated the effect of anacardic acid on NF-κB suppression. These results indicate that anacardic acid **15** is a promising starting point for further SAR development of HAT inhibitors. Unfortunately, only IC_{50} values and no equilibrium-binding constants (*K*) have been reported for the binding of anacardic acid **15** to HATs. It is, therefore, difficult to judge the relative potency of anacardic acid and related compounds. Another limitation is the absence of published structural information to enable structure-based optimization of the inhibitory potency.

α-Methylene-γ-butyrolactones as HAT inhibitors

Compounds with an α-methylene-γ-butyrolactone core structure (i.e. **20)** inhibit the HAT GCN5 [49]. This inhibitor class was developed, based on the catalytic mechanism of GCN5. This inhibitor class contains an α,β-unsaturated carbonyl that is prone to Michael-addition of the thiol in the enzyme active site. Remarkably, the authors found no time dependence for the inhibition, which is indicative of noncovalent binding.

Isothiazolones as HAT inhibitors

The isothiazolones have been identified as inhibitors of PCAF following high-throughput screening of a library of 69,000 compounds [50]. The isothiazolone functionality is readily available via organic synthesis [51] and can easily be modified with diverse substitutions to enhance binding to the enzyme active site. The isothiazolone core structure has been used as a starting point to explore PCAF inhibition (Fig. 3, Table 1) [52]. The *N*-aliphatic-substituted 5-chloroisothiazolone **25** shows an IC_{50} around 2–3 μM, whereas *N*-aliphatic-substituted isothiazolone **24** shows less than 50% inhibition at 10 μM. In the case of *N*-aromatic-substituted isothiazolones, the difference is much less pronounced. Oxidation of the isothiazolone core **26** is possible with the retention of PCAF inhibition. The 5-chloroisothiazolone **25** inhibits cell proliferation in micromolar concentrations, whereas isothiazolone **24** shows less than 50% growth inhibition at 10 μM. This indicates that the chlorine in the 5-position of *N*-aliphatic-substituted isothiazolones has a significant effect on their biological activity. Another study investigated the inhibition of the HATs p300 and PCAF by *N*-aromatic-substituted isothiazolones [53]. Increased PCAF and p300 inhibition were observed by changing the *N*-phenyl to an *N*-pyridyl substituent. Alkyl substitution in the 4-position had little effect on activity (**21** and **22**), whereas alkyl

substitution in the 5-position resulted in a significant reduction in potency (**21** and **23**). These findings indicate that reaction with the thiol of the enzyme active site is the main determinant of PCAF inhibition by isothiazolones.

Reactivity of isothiazolones

It is well known that *N*-substituted isothiazolones are biologically active. Several studies report antibacterial activity [54,55]. Some isothiazolone derivatives have been patented as biocides and have been used in shampoos and conditioners for over than 25 years under the name Kathon^{TM}CG, which is claimed to be safe and effective, although skin sensitization has been reported [56,57]. Morley *et al.* studied the antibacterial activity of a series of isothiazolones and found that those with the highest activities have chlorine at the 5-position [55]. They found a poor correlation between antibacterial activity and the electronic properties of the isothiazolone core. There is, however, a correlation between antibacterial activity and solvation energy, which suggests that diffusion plays an important role in their mode of action. Another study reported that the kinetic rate constants of the reaction of the isothiazolone core with 2-methyl-2-propanethiol lie in the order **27** > **28** > **29** > **30** (Fig. 3) [58]. It has been proposed that the sulfur of the isothiazolone core reacts with thiol nucleophiles, with concomitant cleavage of the S–N bond. A study on *N*-methylisothiazolone **29** with a thiol nucleophile shows formation of the intermediate **31** (Fig. 3) [57]. The reaction between 5-chloro-*N*-methyl chloroisothiazolone **27** is expected to proceed through a comparable intermediate **32**; however, this intermediate has not been identified. This might be because of the increased reactivity of intermediate **32** because of the presence of the chlorine atom.

Conclusions

Therapeutic relevance of HATs

Although many studies have been published on the roles of HATs in cell biology, many functions and interactions are yet to be investigated fully. There are, however, several factors complicating the analysis of HATs functions. HATs are often part of large multiprotein complexes that determine their specificity. HATs acetylate multiple targets and are regulated by autoacetylation. Furthermore, some HAT knockdowns are lethal. For these reasons, the validation of HATs as drug targets remains a challenge. Nevertheless, the currently published studies, the diverse role of HATs, the increasing numbers of HAT subtypes that are being discovered and the increasing evidence that the deregulation of epigenetic processes plays a key role in several diseases hold promise for future therapeutic strategies focused on HAT inhibition.

Reverse chemical genetics studies using small molecules as tools

Chemical genetics is an emerging strategy to overcome problems encountered in classical genetic studies by the application of small organic molecules that can selectively and temporarily alter protein function [59,60]. HATs can be targeted with small, cell-permeable molecules that bind to the enzyme active site. Small-molecule modulators of protein–protein interaction are also potentially promising tools for the modulation of gene transcription. They often suffer, however, from low cell-permeability because of their relatively large size [61–63]. Small-molecule HAT inhibitors are useful tools to unravel the functions of HATs, where classical genetic methods fail.

Future directions for the development of HAT inhibitors

Significant efforts have led to increased understanding of molecular recognition of substrates and small-molecule inhibitors of HATs. Nevertheless, the currently described inhibitor classes suffer from low potency, a lack of specificity or low cell-permeability. Future efforts should aim to solve these problems. The bisubstrate inhibitors in which the histone peptide is connected to CoA are subtype specific, but lack cell-permeability. Drug delivery strategies, such as covalent linkage to cell-permeable peptides, went some way to solving this problem, but did not result in druglike inhibitors [38]. The crystal structure of the HAT GCN5 in complex with a bisubstrate inhibitor has been published [39], which enables structure-based inhibitor design. Several naturally occurring HAT inhibitors have been reported, such as anacardic acid, garcinol and curcumin. Recently, the binding configuration of garcinol has been reported [44]. The design of improved HAT inhibitors remains a major challenge for the future.

References

1 Beckett, D. (2001) Regulated assembly of transcription factors and control of transcription initiation. *J. Mol. Biol.* 314, 335–352
2 Kouzarides, T. (2007) Chromatin modifications and their function. *Cell* 128, 693–705
3 Strahl, B.D. and Allis, C.D. (2000) The language of covalent histone modifications. *Nature* 403, 41–45
4 Bird, A. (2007) Perceptions of epigenetics. *Nature* 447, 396–398
5 Esteller, M. (2007) Cancer epigenomics: DNA methylomes and histone-modification maps. *Nat. Rev. Genet.* 8, 286–298
6 Nagy, Z. and Tora, L. (2007) Distinct GCN5/PCAF-containing complexes function as co-activators and are involved in transcription factor and global acetylation. *Oncogene* 26, 5341–5357
7 Vogelauer, M. *et al.* (2000) Global histone acetylation and deacetylation in yeast. *Nature* 408, 495–498
8 Seligson, D.B. *et al.* (2005) Global histone modification patterns predict risk of prostate cancer recurrence. *Nature* 435, 1262–1266
9 Suganuma, T. and Workman, J.L. (2008) Crosstalk among histone modifications. *Cell* 135, 604–607
10 Cheung, P. *et al.* (2000) Synergistic coupling of histone H3 phosphorylation and acetylation in response to epidermal growth factor stimulation. *Mol. Cell* 5, 905–915
11 Walter, W. *et al.* (2008) 14-3-3 interaction with histone H3 involves a dual modification pattern of phosphoacetylation. *Mol. Cell. Biol.* 28, 2840–2849
12 Li, S. and Shogren-Knaak, M.A. (2009) The Gcn5 bromodomain of the SAGA complex facilitates cooperative and cross-tail acetylation of nucleosomes. *J. Biol. Chem.* 284, 9411–9417
13 Cameron, E.E. *et al.* (1999) Synergy of demethylation and histone deacetylase inhibition in the re-expression of genes silenced in cancer. *Nat. Genet.* 21, 103–107
14 Hodawadekar, S.C. and Marmorstein, R. (2007) Chemistry of acetyl transfer by histone modifying enzymes: structure, mechanism and implications for effector design. *Oncogene* 26, 5528–5540
15 Marmorstein, R. and Trievel, R.C. (2009) Histone modifying enzymes: structures, mechanisms, and specificities. *Biochim. Biophys. Acta* 1789, 58–68
16 Schiltz, R.L. *et al.* (1999) Overlapping but distinct patterns of histone acetylation by the human coactivators p300 and PCAF within nucleosomal substrates. *J. Biol. Chem.* 274, 1189–1192
17 Avvakumov, N. and Cote, J. (2007) The MYST family of histone acetyltransferases and their intimate links to cancer. *Oncogene* 26, 5395–5407
18 Vetting, M.W. *et al.* (2005) Structure and functions of the GNAT superfamily of acetyltransferases. *Arch. Biochem. Biophys.* 433, 212–226

19 Gayther, S.A. *et al.* (2000) Mutations truncating the EP300 acetylase in human cancers. *Nat. Genet.* 24, 300–303
20 Bandyopadhyay, D. *et al.* (2002) Down-regulation of p300/CBP histone acetyltransferase activates a senescence checkpoint in human melanocytes. *Cancer Res.* 62, 6231–6239
21 Ait-Si-Ali, S. *et al.* (2000) CBP/p300 histone acetyl-transferase activity is important for the G1/S transition. *Oncogene* 19, 2430–2437
22 Iyer, N.G. *et al.* (2007) p300 is required for orderly G1/S transition in human cancer cells. *Oncogene* 26, 21–29
23 Kitabayashi, I. *et al.* (2001) Fusion of MOZ and p300 histone acetyltransferases in acute monocytic leukemia with a t(8;22)(p11;q13) chromosome translocation. *Leukemia* 15, 89–94
24 Katsumoto, T. *et al.* (2008) Roles of the histone acetyltransferase monocytic leukemia zinc finger protein in normal and malignant hematopoiesis. *Cancer Sci.* 99, 1523–1527
25 Howe, L. *et al.* (2001) Histone H3 specific acetyltransferases are essential for cell cycle progression. *Genes Dev.* 15, 3144–3154
26 Adcock, I.M. *et al.* (2007) Epigenetic regulation of airway inflammation. *Curr. Opin. Immunol.* 19, 694–700
27 Barnes, P.J. *et al.* (2005) Histone acetylation and deacetylation: importance in inflammatory lung diseases. *Eur. Respir. J.* 25, 552–563
28 Ito, K. *et al.* (2002) Expression and activity of histone deacetylases in human asthmatic airways. *Am. J. Respir. Crit. Care Med.* 166, 392–396
29 Cosío, B.G. *et al.* (2004) Histone acetylase and deacetylase activity in alveolar macrophages and blood monocytes in asthma. *Am. J. Respir. Crit. Care Med.* 170, 141–147
30 Clarke, D.L. *et al.* (2008) PKCbetaII augments NF-kappaB-dependent transcription at the CCL11 promoter via p300/CBP-associated factor recruitment and histone H4 acetylation. *J. Immunol.* 181, 3503–3514
31 Barrett, R.M. and Wood, M.A. (2008) Beyond transcription factors: the role of chromatin modifying enzymes in regulating transcription required for memory. *Learn. Mem.* 15, 460–467
32 Maurice, T. *et al.* (2008) Altered memory capacities and response to stress in p300/CBP-associated factor (PCAF) histone acetylase knockout mice. *Neurophychopharmacology* 33, 1584–1602
33 Cereseto, A. *et al.* (2005) Acetylation of HIV-1 integrase by p300 regulates viral integration. *EMBO J.* 24, 3070–3081
34 Stevens, M. *et al.* (2006) The regulation of HIV-1 transcription: molecular targets for chemotherapeutic intervention. *Med. Res. Rev.* 26, 595–625
35 Mantelingu, K. *et al.* (2007) Specific inhibition of p300-HAT alters global gene expression and represses HIV replication. *Chem. Biol.* 14, 645–657
36 Lau, O.D. *et al.* (2000) HATs off: selective synthetic inhibitors of the histone acetyltransferases p300 and PCAF. *Mol. Cell* 5, 589–595
37 Sagar, V. *et al.* (2004) Bisubstrate analogue structure–activity relationships for p300 histone acetyltransferase inhibitors. *Bioorg. Med. Chem.* 12, 3383–3390
38 Zheng, Y. *et al.* (2005) Synthesis and evaluation of a potent and selective cell-permeable p300 histone acetyltransferase inhibitor. *J. Am. Chem. Soc.* 127, 17182–17183
39 Poux, A.N. *et al.* (2002) Structure of the GCN5 histone acetyltransferase bound to a bisubstrate inhibitor. *Proc. Natl. Acad. Sci. U. S. A.* 99, 14065–14070
40 Balasubramanyam, K. *et al.* (2004) Curcumin, a novel p300/CREB-binding protein-specific inhibitor of acetyltransferase, represses the acetylation of histone/nonhistone proteins and histone acetyltransferase-dependent chromatin transcription. *J. Biol. Chem.* 279, 51163–51171
41 Costi, R. *et al.* (2007) Cinnamoyl compounds as simple molecules that inhibit p300 histone acetyltransferase. *J. Med. Chem.* 50, 1973–1977
42 Morimoto, T. *et al.* (2008) The dietary compound curcumin inhibits p300 histone acetyltransferase activity and prevents heart failure in rats. *J. Clin. Invest.* 118, 868–878
43 Balasubramanyam, K. *et al.* (2004) Polyisoprenylated benzophenone, garcinol, a natural histone acetyltransferase inhibitor, represses chromatin transcription and alters global gene expression. *J. Biol. Chem.* 279, 33716–33726
44 Arif, M. *et al.* (2009) Mechanism of p300 specific histone acetyltransferase inhibition by small molecules. *J. Med. Chem.* 52, 267–277
45 Balasubramanyam, K. *et al.* (2003) Small molecule modulators of histone acetyltransferase p300. *J. Biol. Chem.* 278, 19134–19140
46 Souto, J.A. *et al.* (2008) Synthesis of benzamides related to anacardic acid and their histone acetyltransferase HAT inhibitory activities. *ChemMedChem* 3, 1435–1442
47 Sbardella, G. *et al.* (2008) Identification of long alkylidenemalonates as novel small molecule modulators of histone acetyltransferases. *Bioorg. Med. Chem. Lett.* 18, 2788–2792
48 Sung, B. *et al.* (2008) Anacardic acid (6-nonadecyl salicylic acid), an inhibitor of histone acetyltransferase, suppresses expression of nuclear factor-kappaB-regulated gene products involved in cell survival, proliferation, invasion, and inflammation through inhibition of the inhibitory subunit of nuclear factor-kappaBalpha kinase, leading to potentiation of apoptosis. *Blood* 111, 4880–4891
49 Biel, M. *et al.* (2004) Design, synthesis and biological evaluation of a small-molecule inhibitor of the histone acetyltransferase Gcn5. *Angew. Chem. Int. Ed.* 43, 3974–3976
50 Stimson, L. *et al.* (2005) Isothiazolones as inhibitors of PCAF and p300 histone acetyltransferase activity. *Mol. Cancer Ther.* 4, 1521–1532
51 Clerici, F. *et al.* (2003) Isothiazoles. Part 14: new 3-aminosubstituted isothiazole dioxides and their mono- and dihalogeno derivatives. *Tetrahedron* 59, 9399–9408
52 Dekker, F.J. *et al.* (2009) Inhibition of the PCAF histone acetyl transferase and cell proliferation by isothiazolones. *Bioorg. Med. Chem.* 17, 460–466
53 Gorsuch, S. *et al.* (2009) Synthesis of isothiazol-3-one derivatives as inhibitors of histone acetyltransferases (HATs). *Bioorg. Med. Chem.* 17, 467–474
54 Khalaj, A. *et al.* (2004) Synthesis and antibacterial activity of 2-(4-substituted phenyl)-3(2*H*)-isothiazolones. *Eur. J. Med. Chem.* 39, 699–705
55 Morley, J.O. *et al.* (2005) Structure–activity relationships in 3-isothiazolones. *Org. Biomol. Chem.* 3, 3713–3719
56 Basketter, D. *et al.* (1999) Skin sensitization risk assessment: a comparative evaluation of 3 isothiazolinone biocides. *Contact Dermatitis* 40, 150–154
57 Alvarez-Sánchez, R. *et al.* (2003) Studies of chemical selectivity of haptens, reactivity, and skin sensitization potency. 3. Synthesis and studies on the reactivity towards model nucleophiles of the 13C labeled skin sensitizers, 5-chloro-2-methylisothiazol-3-one (MCI) and 2-methylisothiazol-3-one (MI). *Chem. Res. Toxicol.* 16, 627–638
58 Morley, J.O. *et al.* (2006) Kinetic studies on the reactions of 3-isothiazolones with 2-methyl-2-propanethiol. *Int. J. Chem. Kinet.* 39, 254–260
59 Dekker, F.J. *et al.* (2005) Protein structure similarity clustering (PSSC) and natural product structure as inspiration sources for drug development and chemical genomics. *Curr. Opin. Chem. Biol.* 9, 232–239
60 Balamurugan, R. *et al.* (2005) Design of compound libraries based on natural product scaffolds and protein structure similarity clustering (PSSC). *Mol. Biosyst.* 1, 36–45
61 Dekker, F.J. *et al.* (2003) Amino propynyl benzoic acid building block in rigid spacers of divalent ligands binding to the Syk SH2 domains with equally high affinity as the natural ligand. *Bioorg. Med. Chem. Lett.* 13, 1241–1244
62 Dekker, F.J. *et al.* (2003) Role of solution conformation and flexibility of short peptide ligands that bind to the p56(lck) SH2 domain. *Bioorg. Med. Chem.* 11, 941–949
63 Dekker, F.J. *et al.* (2002) Replacement of the intervening amino acid sequence of a Syk-binding diphosphopeptide by a nonpeptide spacer with preservation of high affinity. *Chembiochem* 3, 238–242
64 Lau, O.D. *et al.* (2000) p300/CBP-associated factor histone acetyltransferase processing of a peptide substrate. Kinetic analysis of the catalytic mechanism. *J. Biol. Chem.* 275, 21953–22159
65 Cebrat, M. *et al.* (2003) Synthesis and analysis of potential prodrugs of coenzyme A analogues for the inhibition of the histone acetyltransferase p300. *Bioorg. Med. Chem.* 11, 3307–3313