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Tuning acetylated chromatin with HAT inhibitors

A novel tool for therapy

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Epigenetics, the heritable changes that do not involve DNA sequences, give dynamic propulsion to a static genome and modulate genome accessibility by acting through multiple layers of regulation, ultimately ending with a variable organization of chromatin. The main player in chromatin reprograming is the nucleosome, which modifies its association to DNA depending on a variety of post-translational modifications (PTMs) on histone tails. PTMs act directly on higher order chromatin structures and affect the degree of DNA wrap around the histone octamer and the interaction and/or sequential recruitment of chromatin-associated proteins and transcription factors at defined regions.[1] Recently genomic approaches revealed a far more complex epigenome involving key proteins of cell signaling.

Key words: acetylation, chromatin, yeast, HAT inhibitors

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Overview

Histone tails affect the nucleosome structure via a number of active and inactive histone marks, inducing a closed, inaccessible silenced state or an open, decondensed and expressed chromatin. In this context, the hypothesis of a specific histone code[2] states that modification of a specific residue may affect a second on the same histone or a neighbouring one, so that the epigenome, i.e., the PTMs setting of the whole genome. Epigenome is effective in essential biological functions (e.g., development, maintenance of tissue specificity, genome integrity) converging in complex networks which constitute the sum of feedback mechanisms of multiple interlaced epigenetic layers. Decisive in this scenario are histone modifiers,[3] structural chromatin-associated proteins, and transcription factors that collectively contribute to regulate the epigenetic state, fixed and stable in somatic cells or dynamic in response to exogenous stimuli for rapid cell response. Epigenome dysfunction induced by mutations of chromatin regulators is one of the basic mechanisms of cancer. Histone acetylation and methylation concur to set an epigenetic pattern that can switch tumor suppressors and oncogenes on/off, thus becoming hallmark in human cancer.[4] DNA methylation is similarly recurrent in tumors, and increased methylation silences tumor suppressor genes.[5] Reversibility of epigenetic changes is a fundamental concept behind epigenetic drugs, some of which hold promise for cancer treatment. DNA demethylating agents like zebularine, for example, can reactivate genes and prevent further genome methylation.[6] Hypomethylating 5-azacitidine was found to promote complete remission in acute myeloid leukemia (AML) and the myelodysplastic syndrome (MDL).[7] Similarly, histone deacetylase (HDAC) inhibitors raise the acetylation level and prompt cells to undergo apoptosis.[8]

Acetylation and HATs

Acetylation of lysines is a bona fide positive activating mark. A rapidly growing body of evidence indicates that acetylation involves histone tails along with an increasing number of non histone proteins, thus providing a global cell signaling pathway. Histone acetyltransferases (HATs) are grouped into a few evolutionary conserved major families (**Table 1**): GNAT, Gcn5

Table 1. Classification of known lysine acetyltrasferases

Family	Alias	Yeast	Human	Histone	Auto-Ac	Non-histone	Complex
MYST	KAT5	Esa1	Tip60	H4K5, K8, K12, K16; Htz1K14		p53, ATM, myc, HIV-tat	NuA4/TIP60
	KAT8	Sas2	MOF/MYST1	H4K16			SAS/MAF2
	KAT6	Sas3/Ybf2		H3K14, K23			NuA3
	KAT6A		MOZ/MYST3	H3K14	X		
	KAT6B		MORF/MYST4	H3K14	X		
			Qkf				
	KAT7		Hbo1/MYST2	H4K5, K8, K12; H3			
GNAT	KAT1	Hat1	Hat1	H4K5, K12			HatB
	KAT2	Gcn5		H3K9, 14, 18, 23, 27, 36; H2B; yHtz1	X		SAGA, ADA, SLIK/SALSA
	KAT2A		hGcn5	H3K9, 14, 18; H2B	X		STAGA,TFTC
	KAT2B		P/CAF	H3K9, 14, 18; H2B	X	HMG17, HMG(Y), p53, Tal-1, E2F1, MyoD, DTCF, TFIIE, TFIIF, TAF(I), EVI1, HIV tat, Adenovirus E1A	PCAF
	KAT9	Elp3	Elp3	H3K14; H4K8			Elongator
	KAT10	Hpa2		H3K14; H4	X		
		Hpa3		H3; H4			
		Nut1		H3; H4			Mediator
P300/ CBP	KAT3B		P300	H2A-K5; H2B-K12, K15; H3; H4	X	Rb, p53, E2F1, MyoD, NFκB, HMG proteins, adenovirusE1A,	
	KAT3A		CBP	H2A-K5; H2B-K12, K15; H3; H4	X	MyoD, p53, NFκB, HMG proteins	
TFIIIC		TFIIIC		H3; H4			
	KAT12		TFIIIC90	H3; H4			
			TFIIIC110	H3; H4			
			TFIIIC220	H3; H4			
p160	KAT13A		SRC1	H3; H4			
			ACTR/pCIP	H3; H4			
			TIF2/GRIP1	H3; H4			
Orphans	KAT11	Rtt109		H3K9, 56		Asf1	
	KAT4	Taf1	Taf1	H3; H4			TFIID
			$TAF_{II}250$	H3; H4			TFIID
	KAT13C		CLOCK	H3; H4	X	BMAL1	
		TFIIB	TFIIB		X		

acetyltransferases (Gcn5p itself, PCAF, Elp3, Hat1, Hpa2 and Nut1), MYST (Esa1, Morf, Ybp2, Sas2, Sas3, Tip60, Hbo1) with additional domains: zinc fingers and chromodomain and p300/CBP with Taf1 and the nuclear coactivators (NR) component of a third "orphan" group.[9] Although GNAT and MYST are similar and are engaged in transcriptional activation, histone acetylation appears to influence other processes including cell cycle progression,[10] chromosome dynamics,[11] DNA recombination, repair[12] and double strand breaks.[13] Like Gcn5p, CBP/p300 are transcriptional coactivators and are recruited to specific promoters through interaction with transcription factors such as E1A, c-Jun, c-Myc, c-Fos, TFIID, MyoD, nuclear hormone receptor and E2F-1 through which they may integrate several signaling pathways with transcriptional responses. Gcn5p (classified as KAT2),[3,14] is highly conserved in evolution shows a global role in acetylation of histone H3 lysines on the N-terminal tail but also targets non histone transcription factors like Myc,[15] BRCA1,[16] and p53.[17]

Also recruited by Tat in HIV infection, it triggers chromatin remodeling at proviral genes.[18] Less detailed is the function of homologs Gcn5/2 (KAT2A) and PCAF (KAT2B) in mammals.[19-21] A recent study showed that Gcn5 is also involved in telomere maintenance and that its deletion leads to embryonic lethality, chromosomal fusions and dysfunctional telomeres.[22] Most HATs are the catalytic subunits of stoichiometric complexes characterized by substrate specificity. Gcn5p is a component of ADA and SAGA complexes which also contain conserved ubiquitin-specific protease (Ubp87/USP22) which removes ubiquitin from histone H2B-K123 to facilitate transcription.[23] In yeast, Gcn5p is required for the organization of centromeric chromatin assembly; its deletion causes mitosis defects and chromosome loss.[24]

HATs Inhibitors in Neoplasia

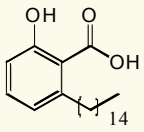
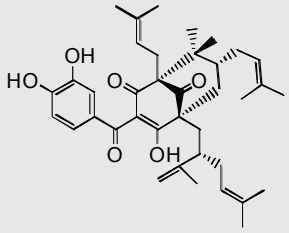
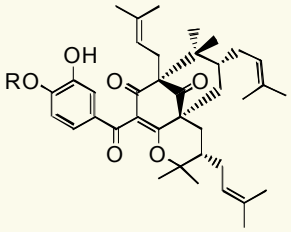
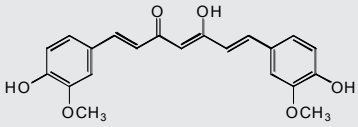
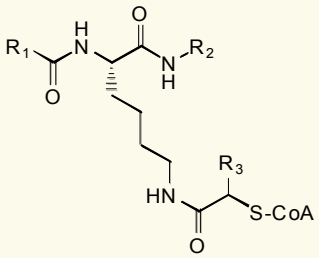
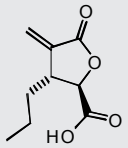
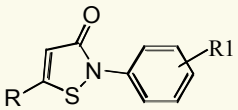
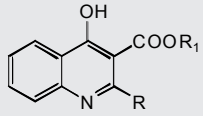
Misregulation of HATs induced by mutation, translocation and overexpression has been correlated with hematological malignancies and solid tumors. In AML, translocation of CBP leads to the formation of a chimeric protein fused with the monocytic leukemia zinc finger protein (MOZ), a transcriptional coactivator with intrinsic HAT activity. MOZ-CBP and MOZ-p300 cause aberrant gene expression, leading directly to malignant hematopoiesis.[25,26] Similarly, mutation or deletion of p300 correlates with solid tumors such as colorectal, gastric, breast, ovarian and epithelial cancer. Missense mutations and truncations in p300, leading to loss of critical domains (HAT and cys/his-rich domains) were found in both colorectal and gastric carcinoma.[27,28] Similarly, the role of steroid receptor coactivator AIB1 in breast cancer development and progression is one of the best-known association between cancer and a mutated HAT. AIB1 (amplified in breast cancer 1), also named SRC-3 (steroid receptor co-activator-3), promotes transcription of multiple nuclear receptors such as the estrogen receptor and others, its overexpression causes deregulation of AIB1 controlled pathway. HATs misregulation has been also shown to play an important role in other diseases like Rubinstein-Taybi syndrome (RTS), a complex genetic disease that includes a high incidence of neoplasia, where mutated CBP in germline inactivates the HAT catalytic domain.[30] Loss of CBP/P300 activity and hypoacetylation have also been correlated with other pathologies like neurodegenerative amyotrophic lateral sclerosis (ASL)[31] and, through inflammation to diabetes, asthma, chronic obstructive pulmonary disease (COPD) and cystic fibrosis. In the majority of these cases HDAC inhibitors have been successfully used in the clinic. While HDAC inhibitors have been intensively studied in the last decade and successfully assayed in cutaneous T cell lymphoma (CTCL) and Hodgkin's disease, poor results were obtained in solid tumors.[32] Some HDAC inhibitors in human trials (SAHA [Vorinostat]) received U.S. Food and Drug Administration approval for treating CTCL,[33] while others have not yet been approved.[31] Key to appreciating the relevance of HATs misregulation in pathology and understanding the implications of pleiotropic effects of acetylation are efforts to develop and identify a set of novel compounds that can modulate counteracting HATs-HDACs by reversing acetylation.

The HAT inhibitors (HATi) described so far can be classified in two groups: natural and synthetic compounds (**Table 2**). Anacardic acid and garcinol, natural compounds obtained from plant extracts, have been found to be potent inhibitors of both p300 and PCAF.[35,36] Also, curcumin, a natural polyphenolic compound extracted from the *Curcuma longa* rhizome, has been reported to be a HAT inhibitor highly specific for p300/CBP inhibition. Despite the many patents on anacardic acid and garcinol, curcumin is by far the most extensively studied and widely used compound in drugs that have demonstrated high efficacy in the prevention and treatment of several cancers including colorectal, prostate, kidney, lung, ovarian, breast, cervical and liver cancer.[37] Among synthetic inhibitors the first HATi group to be described was a class of bisubstrate analogues that mimic the Ac-CoA-lysine intermediate complex in HAT reactions. CoA conjugated peptides like Lys-CoA and H3-CoA-20 showed selectivity for p300 and PCAF.[38,39] Another group of synthetic HATi is composed of small molecules that can permeate the cell, thus overcoming the drug permeability problem with most HATi, including garcinol analogues (the LTK compound),[40] γbutyrolactone MB-3,[41] several quinoline and isothiazolone derivatives. A set of isothiazolone derivatives has been reported to inhibit the enzymatic activity of both PCAF and p300 and block cell proliferation in a panel of human colon and ovarian tumor cell lines.[42] Recently, a novel quinoline derivative was discovered after phenotypic screening in budding yeast: this small molecule is a global hypoacetylating drug that also reduces α-tubulin acetyation.[43] In light of the redundancy of epigenetic modifications and the modulation of opposing HATs/HDACs functions which might associate the effect of a test compound not merely with a single or a few targets but to cross-regulated gene pathways, the off-targets identification becomes crucial in drug discovery. Off-Target modulators bind to a different gene product that modulates the function of the therapeutic target, such as heterodimer or a distant interacting protein. Off-Target modulators are therefore promising for new indications of existing drugs or as substrates of novel molecules.

Reading Module Blocking Molecules

Every code needs to be deciphered. This is the case of protein modules invariably present and conserved in chimeric chromatin modifiers that "read" the epigenetic marks on histone tails. Histone tails constitute modified platforms responsible for integrating signaling cascades and regional recruitment.[44] High selectivity of PTMs recognition by chromatin reading modules is putatively linked to the recruitment of chromatin-associated complexes at defined regions of the genome. The first identified chromatin readout was the Gcn5p acetyl-lysine binding bromodomain[45] whose structure was solved in complex with the H4 AcK16 interacting peptide.[46] Bromodomain proteins belong to a conserved protein family composed of single (Gcn5,CBP, p300…), tandem (TAF250, Rsc4p) or polybromodomain (BAF180) repeats that invariably interact

Table 2. Known HAT inhibitors

Parental structures	Compounds	Specificity	References
	**Anacardic Acid**	p300, PCAF	35
	**Garcinol**	P300, PCAF	36
	**Isogarcinol:** (R = H) **LTK14:** (R = CH_3)	p300/PCAF p300	40 40
	**Curcumin**	p300/CBP	37
	**Lysyl-CoA**: (R_1 = CH_3; R_2 = R_3 = H) **H3-CoA-20**: (R_1 = G-G-T-S-K-R-A-T-Q-K-T-R-A-NH-$COCH_3$; R_2 = A-P-R-K-Q-L; R3 = H) **H3-(Me)-CoA**: (R_1 = CH_3CO-NH-A-R-T-A-R-K-S-T-G-G; R_2 = A-P-R-K-Q-L; R_3 = Me) **Lys-Phe-Coa**: (R_1 = Phe, R_2 = R_3 = H) **Lys-CoA-3'dephospho**: R_1 = (R_1 = Phe, R_2 = R_3 = H)	p300 PCAF p300 p300 p300	38 38 39 39 39
	**γ-Butyrolactone**	hGCN5	41
	**Isothiazolones**: (R = H, Cl; R_1 = NO_2, Cl, CF_3, OCH_3, COOEt)	p300/PCAF	42
	**Quinolines**		43

with acetyl-lysine. Interaction with acetyl-lysine may be more complex than a simple one-to-one residue interaction, and a combinatorial readout of PTMs can be encountered, as in the mouse TAF1 homolog Brdt which interacts cooperatively with hyperacetylated H4 tails to engage more than one mark.[47] Deciphering the roles for selectivity of

interaction among bromodomains (BRD) may therefore add insights into the specificity of interaction of histones and non histone proteins and lead to the discovery of novel tools for the control of acetylation.[48] In this connection, small chemical ligands specific for bromodomains may be considered suitable tools to modulate acetylation. Identification of molecules that could alter the binding and biological activity of bromodomains may aid in the development of efficient synthetic chemical switches. To do this, the solved 3-D macromolecular structure of bromodomains could lead to the development of molecular simulation approaches to identify br-interfering peptides, for example, CBP-br interaction with AcK538 of tumor suppressor p53.[49] Bromodomain protein expression is also recurrently misregulated in cancer, as in the overexpression of BRD8, a component of the hTRAPP/TIP60 complex associated with tumor progression in aggressive colorectal cancer.[50] These results highlight the importance of Br-proteins as putative targets for chemotherapy. Accordingly, BRD8 si-RNA mediated knock-down delayed cancer.

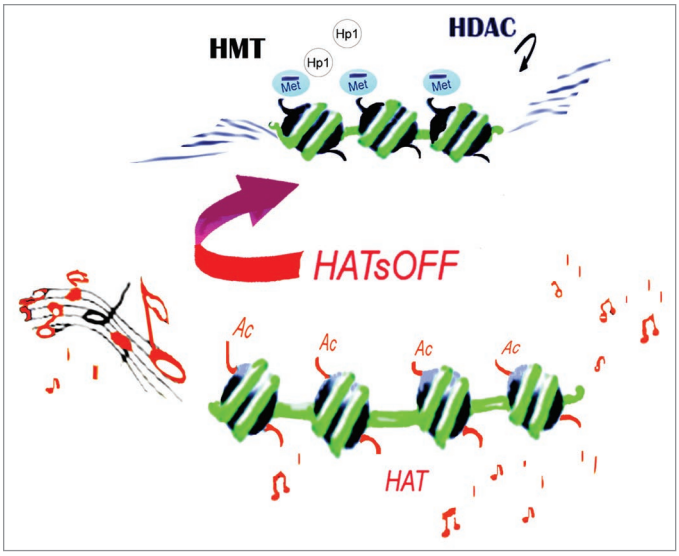


Figure 1. Modulating chromatin compaction. Notes and tempo rhythm music likewise acetylation of histone tails controls spatially and temporally gene transcription. HATs inhibitors induce a silent and inactive chromatin by changing histone epigenetic marks and recruitment of chromatin modifiers.

A Simple Yeast for Epistasis and Chemogenomics

Budding yeast *S. cerevisiae* is a very simple model for studying basic biological functions and shows high homology to humans. Its genome is compacted and few intergenic regions are found, accordingly, histone methylation is missing and silencing may therefore be studied only in part. Methylation may therefore be better investigated in the fission yeast *S. pombe* whose genome organization and methylation mediated silencing are similar to humans. *S.cerevisiae* genome is organized into 6466 open reading frames, at least 31% of which shows a human ortholog and almost 50% show a conserved yeast ortholog with a disease gene. Yeast offers a variety of combinations of OMICs approaches making this organisms one ideal candidate for drug discovery.[51] In yeast, synthetic enhancement genetics can be used to assay how mutations in two genes interact to modulate a phenotype.[52] The yeast gene-deletion set is a key resource for large-scale systematic genetics, it employs robotic procedures to create and systematically examine growth phenotypes of yeast haploid mutants incubated with a test compound. Global screening for anticancer and antifungal compounds carried out in yeast have frequently highlighted novel classes and known targets as well.[53] Some drugs are not developed for therapeutical application because of their unknown secondary mechanisms of action. Hence, yeast can be viewed as an ideal system to discover biochemical functions associated with a given compound. Haploinsufficiency profiling (HIP) in the heterozygous diploid leads to the identification of gene products which, if lowered for interaction with a drug, results in inhibition of cellular fitness, highlighting the primary target genes. Bar-coded integration cassettes allow the identification of strains hypersensitive to a drug.[54] Strains more sensitive to a drug often carry deletions in genes that interact directly with the test compounds and inhibit cell proliferation.[55] Alternatively, homozygous deletion profiling (HOP) or haploid deleted strain giving hypersensitive to a test compound means that the molecule targets a secondary gene sharing a back-up function with the deleted one and therefore represent putative off-target genes.[56] These methodologies have helped researchers to focus on molecular mechanisms for drugs of unknown function. For example, a compound inhibiting metastasis and angiogenesis turned out to be directed to sphingolipid metabolism.[57] In summary, applications of yeast chemogenomics may be of great help to investigate gene networks responding to a novel test compound and to unreveal site effects induced by modification of the acetylation state.

Future Directions

Epigenetic processes are buffered by environmental conditions that, in turn, affect the counterbalancing action of HDAC-HATs and gene expression. In addition, acetylation controls the expression of multiple genes involved in timing of differentiation and cell respons to signal molecules. Controlling the modulation of HATs ON-OFF is therefore a promising tool in the discovery of novel compounds that may extend their beneficial effect far behind already identified pathways. As a matter of fact, pre-clinical studies reported a reduced survival of cancer cells treated with HATs-OFF yet, the underlying mechanisms were not fully understood. Natural products like curcumin inhibited growth of oesophageal, breast and colon cancer cell lines.[58] The pleiotropic effects of HATs makes difficult to provide a

global compendium of possible effects of these drugs in vivo. Still, one important aspect to bear in mind deals with synergic effects of HAT inhibitors and the possibility to application coupled to known citotoxic agents, for this, the analysis and identification of secondary drug targets is of extreme importance. In this sense, yeast represents an awesome model where gene networks and chemogenomic effects of a test compound may be analysed and superimposed to a vast genetic and interactomic networks. Another important issue deals with the impressive growing examples of acetylated non histone proteins. Acetylation of cyclin A regulates its degradation,[59] in addition, acetylation of BubR1 by CBP activates the Spindle Associated Checkpoint thus blocking cells with unbalanced chromosome segregation.[60] Counteracting acetylation with specific inhibitors may therefore inactivate the checkpoint and force aberrant cells to duplicate and undergo apoptosis. Overall, epigenetic drugs represent a future challenge in the treatment of disease, their pleiotropic effects point for a use in combination with cytotoxic or radiation therapy.

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References

1. Mellor J. Dynamic nucleosomes and gene transcription. Trends Genet 2006; 22:320-9.
2. Jenewein T, Allis CD. Translating the histone code. Science 2001; 293:1074-80.
3. Allis CD, Berger SL, Cote J, Dent S, Jenuwien T, Kouzarides T, et al. New nomenclature for chromatin-modifying enzymes. Cell 2007; 131:633-6.
4. Fraga MF, Ballestar E, Villar-Garea A, Boix-Chornet M, Espada J, Schotta G, et al. Loss of acetylation at Lys16 and trimethylation at Lys20 of histone H4 is a common hallmark of human cancer. Nat Genet 2005; 37:391-400.
5. Esteller M. Epigentetic gene silencing in cancer: the DNA hypermethylome. Hum Mol Genet 2007; 16:50-9.
6. Yoo CB, Jones PA. Epigenetic therapy of cancer: past, present and future. Long-term epigenetic therapy with oral zebularine has minimal side effects and prevents intestinal tumors in mice. Nat Rev Drug Discov 2006; 5:37-50.
7. Ravandi F, Issa JP, Garcia-Manero G, O'Brien S, Pierce S, Shan J, et al. Superior outcome with hypomethylating therapy in patients with acute myeloid leukemia and high-risk myelodysplastic syndrome and chromosome 5 and 7 abnormalities. Cancer 2009; 115:5746-51.
8. Stimson L, Wood V, Khan O, Fotheringham S, La Thangue NB. HDAC inhibitor-based therapies and haematological malignancy. Ann Oncol 2009; 20:1293-302.
9. Roth SY, Denu JM, Allis CD. Histone acetyltransferases. Annu Rev Biochem 2001; 70:81-120. Review.
10. Howe L, Auston D, Grant P, John S, Cook RG, Workman JL, Pillus L. Histone H3 specific acetyltransferases are essential for cell cycle progression. Genes Dev 2001; 1:15.
11. Ha GH, Kim HS, Lee CG, Park HY, Kim EJ, Shin HJ, et al. Mitotic catastrophe is the predominant response to histone acetyltransferase depletion. Cell Death Differ 2009; 16:483-97.
12. Morrison AJ, Shen X. Chromatin modification in DNA repair. Results Probl Cell Differ 2006; 41:109-25.
13. Murr R, Loizou JI, Yang YG, Cuenin C, Li H, Wang ZQ, Herceg Z. Histone acetylation by Trapp-Tip60 modulates loading of repair proteins and repair fo DNA double-strand breaks. Nat Cell Biol 2006; 8:91-9.
14. Brownell JE, Zhou J, Ranalli T, Kobayashi R, Edmondson DG, Roth SY, Allis CD. Tetrahymena Histone Acetyltransferase A: a transcriptional coactivator linking gene expression to hystone acetylation. Cell 1996; 84:843-51.
15. Liu X, Vorontchikhina M, Wang YL, Faiola F, Martinez E. STAGA recruits Mediator to MYC oncoprotein to stimulate transcription and cell proliferation. Mol Cell Biol 2008; 28:108-21.
16. Oishi H, Kitagawa H, Wada O, Takezawa S, Tora L, Kouzu-Fujita M, et al. An hGCN5/TRRAP histone acetyltransferase complex co-activates BRCA1 transactivation function through histone modification. J Biol Chem 2006; 281:20-6.
17. Gamper AM, Roeder RG. Multivalent binding of p53 to the STAGA complex mediates coactivator recruitment after UV damage. Mol Cell Biol 2008; 28:2517-27.
18. Lusic M, Marcello A, Cereseto A, Giacca M. Regulation of HIV-1 gene expression by histone acetylation and factor recruitment at the LTR promoter. EMBO J 2003; 22:6550-61.
19. Grant PA, Duggan L, Cote J, Roberts SM, Brownell JE, Candau R, et al. Yeast Gcn5 functions in two multisubunit complexes to acetylate nucleosomal histones: characterization of an ADA complex and SAGA (Spt/Ada) complex. Genes Dev 1997; 111:640-50.
20. Trievel RC, Rojas JR, Sterner DE, Venkataramani RN, Wang L, Zhou J, et al. Crystal structure and mechanism of histone acetylation of the yeast GCN5 transcriptional coactivator 1999; 96:8931-6.
21. Zhang WZ, Bone JR, Edmondson DG, Turner BM, Roth SY. Essential and redundant functions of histone acetylation revealed by mutation of target lysines and loss of the Gcn5p acetyltransferase. EMBO J 1998; 17:3155-67.
22. Atanassov BS, Evrard YA, Multani AS, Zhang Z, Tora L, Devys D, et al. Gcn5 and SAGA regulate shelterin protein turnover and telomere maintenance. Mol Cell 2009; 35:352-64.
23. Daniel JA, Torok MS, Sun ZW, Schieltz D, Allis CD, Yates JR, 3rd, Grant PA. Deubiquitination of histone H2B by a yeast acetyltransferase complex regulates transcription. J Biol Chem 2004; 279:1867-71.
24. Vernarecci S, Ornaghi P, Bâgu A, Cundari E, Ballario P, Filetici P. Gcn5p plays an important role in centromere kinetochore function in budding yeast. Mol Cell Biol 2008; 28:988-96.
25. Kitabayashi I, Aikawa Y, Yokoyama A, Hosoda F, Nagai M, Kakazu N, et al. Fusion of MOZ and p300 histone acetyltrasferases in acute monocytic leukemia with a t(8;22)(p11;q13) chromosome traslocation. Leukemia 2001; 15:89-94.
26. Katsumoto T, Yoshida N, Kitabayashi I. Roles of the histone acetyltransferases monocytic leukemia zinc finger protein in normal and malignant hematopoiesis. CancerSci 2008; 99:1523-7.
27. Muraoka M, Konishi M, Kikuchi-Yanoshita R, Tanaka K, Shitara N, Chong JM, et al. p300 gene alterations in colorectal and gastric carcinomas. Oncogene 1996; 12:1565-9.
28. Gayther SA, Batley SJ, Linger L, Bannister A, Thorpe K, Chin SF, et al. Mutations truncating the EP300 acetylase in human cancers. Nat Genet 2000; 24:300-3.
29. Lahusen T, Henke RT, Kagan BL, Wellstein A, Riegel AT. The role and regulation of the nuclear receptor co-activator AIB1 in breast cancer. Breast Cancer Res Treat 2009; 116:225-37.
30. Murata T, Kurokawa R, Krones A, Tatsumi K, Ishii M, Taki T, et al. Defect of histone acetyl-transferase activity of the nuclear transcriptional coactivator CBP in Rubinstein-Taybi syndrome. Hum Mol Genet 2001; 10:1071-6.
31. Rouaux C, Jokic N, Mbebi C, Boutiller S, Loeffler JP, Boutiller AL. Critical loss of CBP/p300 histone acetylase activity by caspase-6 during neurodegeneration. EMBO J 2003; 22:6537-49.
32. Halili MA, Andrews MR, Sweet MJ, Fairlie DP. Histone deacetylase inhibitors in inflammatory disease. Curr Top Med Chem 2009; 9:309-19.
33. Richon VM, Zhou X, Rifkind RA, Marks PA. Histone deacetylase inhibitors: development of suberoylanilide hydroxamic acid (SAHA) for treatment in cancer. Blood Cells Mol Dis 2001; 27:260-4.
34. Bolden JE, Peart MJ, Johnstone RW. Anticancer activities of histone deacetylase inhibitors. Nat Rev Drug Discov 2006; 5:769-84.
35. Varier RA, Swaminathan V, BAlasubramanyam K, Kundu TK. Implications of small molecule activators and inhibitors of histone acetyltransferases in chromatin therapy. Biochem Pharmacol 2004; 68:1215-20.
36. Balasubramanyam K, Altaf M, Varier RA, Swaminathan V, Ravindran A, Sadhale PP, Kundu TK. Polyisoprenylated Benzophenone, Garcinol, a natural histone acetyltrasferase Inhibitor, represses chromatin trascription and alters global gene expression. J Biol Chem 2004; 279:33716-26.
37. Balasubramanyam K, Varier RA, Altaf M, Swaminathan V, Sidappa NB, Ranga U, Kundu TK. Curcumin, a novel p300/CREB-binding protein specific inhibitor of acetyltransferase, repress the acetylation of histone/nonhistone preotein and histone acetyltransferase-dependent chromatin transcription. J Biol Chem 2004; 279:51163-71.
38. Lau OD, Kundu TK, Soccio RE, et al. HATs Off: selective synthetic inhibitors of the histone acetyltransferases p300 and PCAF. Mol Cell 2000; 5:589-95.
39. Sagar V, Zheng W, Thomson PR, Cole PA. Bisubstrate analogue structure-activity relationships for p300 histone acetyltransferase inhibitors. Bioorg Med Chem 2004; 12:3383-90.
40. Mantelingu K, Reddy BA, Swaminathan V, Kishore AH, Siddappa NB, Kumar GV, et al. Specific inibition of p300-HAT alters gene expression and represses HIV replication. Chem Biol 2007; 645-57.
41. Biel M, Androniki K, Karatzali E, Papamatheakis J, Athanassios G. Design, synthesis and biological evaluation of a small-molecule inhibitor of the histone Acetylatrasferase Gcn5. Angew Chem Int Ed Engl 2004; 43:3974-6.
42. Stimson I, Rowlands MG, Newbatt YM, Smith NF, Raynaud FI, Rogers P, et al. Isothiazolones as inhibitors of PCAF and p300 histone acetyltransferase activity. Mol Cancer Ther 2005; 4:1521-32.

43. Mai A, Rotili D, Tarantino D, Ornaghi P, Tosi F, Vicidomini C, et al. Small-molecule inhibitors of histone acetyltransferase activity: identification and biological properties. J Med Chem 2006; 49:6897-907.
44. Taverna SD, Li H, Ruthenburg AJ, Allis CD, Patel DJ. How chromatin-binding modules interpret histone modifications: lessons from professional pocket pickers. Nat Struct Mol Biol 2007; 11:1025-40.
45. Filetici P, Ornaghi P, Ballario P. The bromodomain: a chromatin browser? Front Biosci 2001; 6:866-76.
46. Owen DJ, Ornaghi P, Yang JC, Lowe N, Evans PR, Ballario P, et al. The structural basis for the recognition of acetylated histone H4 by the bromodomain of histone acetyltransferase gcn5p. EMBO J 2000; 15:6141-9.
47. Morinière J, Rousseaux S, Steuerwald U, Soler-López M, Curtet S, Vitte AL, et al. Cooperative binding of two acetylation marks on a histone tail by a single bromodomain. Nature 2009; 46:664-8.
48. Sanchez R, Zhou MM. The role of human bromodomains in chromatin biology and gene transcription. Curr Opin Drug Discov Devel 2009; 12:659-65.
49. Eichenbaum KD, Rodríguez Y, Mezei M, Osman R. The energetics of the acetylation switch in p53-mediated transcriptional activation. Proteins 2009; Epub ahead of print.
50. Yamada HY, Rao CV. BRD8 is a potential chemosensitizing target for spindle poisons in colorectal cancer therapy. Int J Oncol 2009; 35:1101-9.
51. Menacho-Marquez M, Murgia JR. Yeast on drugs: *Saccharomyc cerevisiae* as a tool for anticancer drug research. Clin Transl Oncol 2007; 9:221-8.
52. Boone C, Bussey H, Andrews BJ. Exploring genetic interactions and networks with yeast. Nature Rev Genet 2007; 8:437-49.
53. Giaever G, Flaherty P, Kumm J, Proctor M, Nislow C, Jaramillo DF, et al. Chemogenomic profiling: identifying the functional interactions of small molecules in yeast. Proc Natl Acad Sci USA 2004; 101:793-8.
54. Pierce SE, Davis RW, Nislow C, Giaever G. Genome-wide analysis of barcoded *Saccharomyces cerevisiae* gene-deletion mutants in pooled cultures. Nat Protoc 2007; 2:2958-74.
55. Hillenmeyer ME, Fung E, Wildenhain J, Pierce SE, Hoon S, Lee W, et al. The chemical genomic portrait of yeast: uncovering a phenotype for all genes. Science 2008; 320:362-5.
56. Wuster A, Madan Babu M. Chemogenomics and biotechnology. Trends Biotechnol 2008; 5:252-8.
57. Baetz K, McHardy L, Gable K, Tarling T, Rebérioux D, Bryan J, et al. Yeast genome-wide drug-induced haploinsufficiency screen to determine drug mode of action. Proc Natl Acad Sci USA 2004; 10:4525-30.
58. Manzo F, Tambaro FP, Mai A, Altucci L. Histone acetyltrasferase inhibitors and preclinical studies. Expert Opin Ther Patents 2009; 19:761-74.
59. Mateo F, Vidal-Laliena M, Canela N, Busino L, Martinez-Balbas MA, Pagano M, et al. Degradation of cyclin A is regulated by acetylation. Oncogene 2009; 28:2654-66.
60. Choi E, Choe H, Min J, Choi JY, Kim J, Lee H. BubR1 acetylation at prometaphase is required for modulating APC/C activity and timing of mitosis. EMBO J 2009; 28:2077-89.