Balancing Histone/Protein Acetylation: Gene Regulation and Cancer Therapy

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A highly sophisticated mechanism organizes the 2-meter long human genome within a 6-µm wide nucleus. Up to 10,000-fold of compaction of the chromatin is achieved during mitosis, allowing faithful segregation of mitotic chromosomes to daughter cells. Conversely, the interphase chromatin is much less compacted, more dynamic, and amenable for a variety of chromatin-based functions. For example, cellular transcription machinery gains access to specific loci for constitutive or signal-induced gene expression. When committed to differentiation, those transcription programs designed for cellular proliferation are repressed, or uncontrolled division and malignancies may occur. Damage of DNA, hence potentially deleterious mutations, caused by such factors as UV, free radicals, and active transcription, needs to be repaired before these mutations are passed to daughter cells. Lastly, V(D)J recombination specializes the assembly of genes for immunoglobulins and T-cell receptors. Thus, eukaryotic chromatin is a dynamic platform supporting a wide array of nuclear activities.

The fundamental repeating units of chromatin are nucleosomes. Each nucleosome consists of about 150 basepairs of DNA and a histone octamer containing two of each core histones H2A, H2B, H3, and H4. Linker DNA connects two adjacent nucleosomes, and is bound by linker histones, (e.g. H1) that organize the 10-nm nucleosomal array into a 30-nm fiber. This 30-nm fiber is the predominant structure of interphase chromatin, but permits low accessibility and processivity for regulator proteins and enzymes. Conserved mechanisms regulate the structure and biophysical behaviors of chromatin in a way that selective loci become amenable for the activities of specific macromolecular assemblies. During development, and in different tissues, the profile of transcription is inherited epigenetically. The genetic code per se remains unchanged; whereas, locus-specific chromatin structures specifying the transcription status are inherited. These epigenetic regulatory mechanisms include covalent modifications of histones, ATP hydrolysis-dependent chromatin remodeling activities, substitutions of the core (major) histones with their related variant (minor) histones, and DNA methylation. There are many excellent reviews for different aspects of epigenetic control that are beyond the scope of this article [1-5]. This essay focuses on one well-studied epigenetic control, histone (de)acylation, and the recent development of cancer therapy aiming at altering the balance of histone and protein acetylation.

Acetylation of histones occurs at the ε-amino group of lysine residues within the peptide chain. This is different from the co-translational acetylation at the ε-amino group of the first amino acid [6]. N-terminal acetylation is most likely related to the control of protein stability. The internal ε-acytlation of histones (henceforth simply referred to as histone acetylation) exerts several functions. First, adding an acetyl moiety to the ε-amino group neutralizes the positive charge. The already bulky lysine side chain becomes bulkier. Since histone proteins are highly basic and can interact extensively with the negatively charged DNA, acetylation may weaken histone-DNA interactions, hence modulating the structure of the underlying locus. Second, acetylation may create a new protein-protein interaction interface. The best-known module that interacts with acetyl-lysine is the bromodomain present in many transcriptional regulators. Furthermore, a recent genetic screen identified novel acetylated histone-binding proteins without the bromodomain [7], suggesting a broader repertoire of possible interaction targets for acetylated histones. Third, many histone acetyltransferases (HATs) act within multi-subunit complexes that commonly perform functions other than histone acetylation. For example, the yeast SAGA complex recruits TATA-binding proteins to the promoter, and also contains a ubiquitin hydrolase that facilitates the cycling of protein (de)ubiquitination [8-10]. Thus, histone acetylation may simply be a by-product of anchoring the multi-functional HAT complexes to the target loci. Fourth, acetylation is cleared by histone deacetylases (HDACs). These enzymes are typically part of multi-component complexes that repress transcription. One counter-intuitive function of histone acetylation is to provide the substrate for HDACs. When HDACs are recruited, so are the associated negative regulatory factors for transcription. Furthermore, the acetylation-deacetylation cycle may be the basis for cyclic transcriptional (re)initiation that permits a swift response to the oscillation of environmental stimuli [11]. Finally, HATs and HDACs also use non-histone protein substrates [12]. An increasing number of transcriptional regulators, chromatin components, and signaling factors have been shown to be regulated by acetylation, adding yet another level of control.

Histone Acetyltransferases
Several families of HATs have been recognized: GNAT (Gcn5-related N-acetyltransferases); MYST (MOZ-Ybf2/Sas3-Sas2-Tip60); p300/CBP, although the catalytic domains of p300 and CBP are very similar to those of the GNAT family HATs; nuclear hormone receptor coactivators; and TAF1 (formerly TAFI230 in human and TAFI250 in Drosophila) [13,14]. Structural and kinetic studies of GNAT and MYST families have been thoroughly investigated [15]. An array of point mutations with highly specific effects on catalysis are available for molecular and functional studies of Gcn5, the founding member of the GNAT family HATs [16,17].

From yeast to mammals, many HATs form complexes with other proteins. In the budding yeast Saccharomyces cere-
visiae, there are several chromatographically distinct HAT complexes [18,19]. The SAGA (Spt-Ada-Gcn5 acetylase) and NuA3 complexes prefer H3, while NuA4 uses nucleosomal H4 as the predominant substrate. Mammalian HAT complexes are less thoroughly characterized. PCAF is closely related to the yeast Gcn5 protein in many aspects. PCAF is also part of a complex whose composition is quite similar to that of SAGA [20]. Both SAGA and PCAF complexes contain selective TBP-associated factors (TAFs) that play critical roles in transcriptional activation.

Figure 1. Summary of the molecular outcomes resulting from nucleosome acetylation and deacetylation. Histone acetylation may weaken the electrostatic interactions between DNA and histones and recruit bromodomain-containing transcriptional co-activators and other chromatin modulating proteins/activities. When histones are acetylated, the lysine residues become refractory to other modifications such as methylation and ubiquitinylation. Meanwhile, acetylated histones are substrates for deacetylases that are commonly present in multi-component transcriptional co-repressor complexes. When HDACs are recruited to the acetylated loci, deacetylation occurs and consequently renders the unacetylated lysine residues available for other modifications, including re-acetylation, and binding of transcriptional repressor proteins. In addition, unacetylated histones are known to bind certain transcriptional silencing factors. Thus, the cycle of histone acetylation/deacetylation provides a means for cells to rapidly control gene activities.

p300 and CBP are highly similar to each other throughout the entire length as both are about 2,400 amino acids long [21]. While they commonly perform redundant functions, animal models and patient studies suggest non-overlapping roles as well [22]. These two HATs are targets of many cellular and viral proteins [23]. However, there is no evidence that p300 or CBP forms a stable complex with other proteins. SAGA, PCAF, and p300/CBP HATs are recruited to the target promoters by interacting with selective transcriptional activators [13].

In their catalytic domain, the MYST family of HATs possess an acetyl coA binding motif, and a C2HC zinc finger [24]. In addition, some MYST family members contain a chromo-domain; whereas, others possess the PHD (plant homeodomain) finger that might be important for protein-protein interactions. The chromodomains interact with methylated lysines for transcriptional repression and silencing. Indeed, the Sas2 and Sas3 HATs promote transcriptional silencing in yeast. Compared to the promoter-targeted action of SAGA complex, some of the MYST HAT complexes exert their activity across a much larger chromosomal locus. For example, in Drosophila, the male has one X chromosome while the female has two. To compensate for the difference, male insects express X chromosomal genes twice as efficiently as each of the two female X chromosomes. This dosage compensation is achieved by MOF-mediated H4 Lys16 acetylation coating the entire male X chromosome [25].

HDACs are best known for their ability to repress transcription. Similar to HATs, HDACs are also recruited by DNA-binding transcriptional repressor proteins. Microarray and chromatin immunoprecipitation studies have shown that different enzymes function at selective loci [32]. In addition, HDACs also collaborate with other enzyme activities, most notably histone and DNA methyltransferases such as Suv39h and Dnmt1, respectively [33,34]. For example, the NURD/Mi2/MeCP1 complex contains both HDAC and methylated DNA-binding activities [35]. DNA methylation is an important epigenetic mark for imprinting [1]. The prevalent model suggests that HDACs are attracted to DNA methylated loci and deacetylate the local histones. Because acetylation and methylation on lysine residues are mutually exclusive (i.e., competing for the same ε-amino group), the action of HDACs generates a suitable substrate for subsequent histone methyltransferase activity. Methylated lysine residues then recruit and anchor repressors such as HP1 (heterochromatin protein 1) that create long-range transcriptional silencing.

Histone Deacetylases

Histone deacetylases are also grouped into different families [27]. Each family is represented by a yeast HDAC: Class I, II, and III members are homologous to Rpd3, Hda1, and Sir2, respectively. Class I and II HDACs require a zinc ion and a water molecule at the active center for catalysis; whereas, Class III HDACs use NAD as the cofactor and are insensitive to many chemicals that effectively inhibit the activities of Classes I and II enzymes [28,29]. The Sir2-related Class III HDACs, because of their obligatory need of NAD for catalysis, have been linked to intracellular sensing of nutrient/energy status and senescence [30,31].

Non-Histone Proteins Controlled by Acetylation

In addition to histones, a growing number of non-histone proteins have been shown to be controlled by acetylation. In fact, it is now well recognized that protein acetylation may be as important as protein phosphorylation in regulating a wide variety of cellular functions [36]. Interested readers are directed to an excellent review article by Sterner and Berger [12].
p53 is probably the best-known acetylated, non-histone protein. Mutations of p53 are found in 50% of all human cancers. p53 acetylation is induced by DNA damage and has been shown to recruit other transcriptional co-activators [37]. The acetylation of p53 is also enhanced by phosphorylation at certain residues [38]. In addition, acetylation at the nuclear localization sequence of p53 may be a regulatory mechanism, determining the intracellular distribution of p53 [39].

The key activator determining muscle differentiation is MyoD [40]. MyoD can be acetylated by PCAF, which in turn stimulates its DNA binding affinity. In addition to being a target for acetylation, MyoD interacts with p300/CBP and CARM1, an arginine methyltransferase and transcriptional co-activator [41]. Class I HDACs also target their action on MyoD to inhibit myogenesis [42]. Signaling mechanisms cause hypophosphorylation of Rb, which in turn strips HDACs from MyoD. Consequently, myogenesis is permitted.

E2F is required for cell cycle progression [43]. PCAF-acetylated E2F shows stronger DNA binding affinity. Thus, acetylation has a positive role on E2F. Similarly, the function of the GATA-1 blood cell differentiation factor is also enhanced by p300/CBP-mediated acetylation.

Recent data suggest that the replication factor, PCNA (proliferating cell nuclear antigen), may be acetylated by p300, and that the acetylated PCNA may participate in DNA replication; whereas, its unacetylated counterpart may play a role in termination [44].

**HATs and HDACs in Diseases and Development**

Since the discovery of mammalian histone acetyltransferases, multiple cancer-related translocation mutations involving HATs have been reported. The most notable example of these is the MOZ protein, a MYST family HAT, that has been shown to be fused to the HATs including CBP, p300, and TIF-2, resulting in a variety of leukemias [45,46]. Furthermore, the MLL (mixed lineage leukemia) protein was also found to be fused to CBP and p300 [47]. It is possible that these translocations produce unregulated or misregulated HATs, which then alter the expression pattern of genes involved in cellular growth or differentiation, resulting in tumorigenesis [48]. A variety of epithelial cancers, including breast, colorectal, gastric, and pancreatic carcinomas are linked to missense mutations of p300 [48]. Similarly, Rubinstein-Taybi syndrome is a developmental disorder associated with CBP mutations [49]. Patients with the Rubinstein-Taybi Syndrome have a 350-fold increased risk of developing cancer.

There are very few pathogenic mutations of HDACs. Aberrant activities of HDACs are, instead, caused by mutations of key transcriptional repressors that rely on HDACs for their functions, e.g. translocation and fusion of RARα (retinoic acid receptor-α) to PML or PLZF causes leukemia [50,51]. RARα represses transcription by recruiting HDAC complexes. Retinoic acid displaces HDACs and, thus, relieves the repression created by RARα. When fused to PML or PLZF, the remnant RARα becomes insensitive to retinoic acid, leading to persistent repression of retinoic acid-responsive gene expression and blockage of hematopoietic differentiation [52].

Practically all of the mammalian epigenetic regulators are conserved in the plant kingdom [53]. The Gcn5 homolog in Arabidopsis, AtGcn5, and one of its interacting partners, Ada2b, are important for plant development, and appear to be involved in cold acclimation, an important trait of plants that enables them to deal with sub-freezing environments [54]. Knocking down the expression of several Arabidopsis deacetylases by antisense RNA leads to developmental defects such as early senescence, delayed flowering and seed abortion [55,56].

Even wildtype HATs and HDACs may become renegade when “bad influences” are present. Many viral proteins target their pathogenic actions at HATs and HDACs [23]. The adenovirus E1A oncprotein competes with PCAF for p300 and CBP. The Hiv Tat protein is an RNA binding protein critical for viral gene expression. Tip60, TAF1, p300, CBP, and PCAF all are direct interaction targets for Tat. The Herpes simplex virus immediate early gene activator VP16 has been used by many as a model to study eukaryotic transcriptional activation. VP16 hijacks p300, CBP, and PCAF to activate viral transcription. HDACs are also targeted by viral regulators. For example, the Papilloma virus E7 oncprotein interacts with the NURD/Mi-2 complex to promote cell growth. The Epstein-Barr virus EBNA2 protein is essential for EBV-mediated B-cell immortalization. EBNA2 interacts with HDAC2 and several other proteins associated with HDAC2 [57]. Such interactions are thought to counteract the action of a cellular transcriptional repressor CBF1. Similar scenarios are also seen in plants. For example, the fungus Cochliobolus Carbonum produces HC-toxin, a cyclic tetrapeptide that selectively inhibits the host (maize) but not its own HDACs during infection [58]. In fact, the production of HC-toxin is an indicator of virulence of this pathogenic fungus.

In summary, perturbation of the balanced action of HATs and HDACs, arising either from germline or somatic mutations, or from pathogenic infection, may lead to deleterious consequences in different organisms. Indeed, the close link between cancers and dysregulation of histone acetylation led to the exciting discoveries that a variety of HDAC inhibitors have therapeutic potential in the treatment of cancer. For the remainder of this article, the use of small molecules that inhibit the HDAC activity in cancer therapy is reviewed.
Cancer Therapy with HDAC Inhibitors

One of the recurring mechanisms underlying the immortality of cancer cells is the repression of genes encoding tumor suppressors and apoptotic factors [48]. Meanwhile, proteins that promote cell division are up-regulated. Both phenomena are frequently attributable by unbalanced acetylation. Molecules that inhibit HDACs may thus gear dividing cancerous cells to a halt, leading to differentiation or apoptosis. Indeed, in the 1970s, several reports showed that butyric acid, commonly produced by anaerobic bacteria, can stop DNA synthesis and cell proliferation [59]. Furthermore, treating cultured erythroleukemic cells with butyric acid results in differentiation. Later, butyric acid was found able to induce histone hyperacetylation in HeLa and Friend erythroleukemic cells [60], marking the dawn of cancer treatment with HDAC inhibitors. The studies of HAT inhibitors are comparatively less advanced. Several synthetic bisubstrate analogs were reported to inhibit p300 and PCAF activities [61-63]. However, cells have very low permeability to these potential drugs. Two recent reports showed promising anti-p300 activity of curcumin, a major curcumanoid present in the spice trumeric [64,65], raising the hope that HAT inhibitors may soon catch up with their HDAC inhibitor counterparts.

To date, many naturally occurring and synthetic HDAC inhibitors have been shown to possess anti-cancer activity and are in clinical trials (see Figures 2 and 3 for representative compounds). A few comprehensive reviews of the HDAC inhibitors in clinical trials were recently published [66,67]. A brief summary is included herein.

Different HDAC inhibitors are able to change transcription, both positively and negatively, for about 2% of total human genes. While this number seems to be small, common genes affected by these inhibitors are known to exert critical functions in controlling cell cycle and apoptosis [68]. One of the most notable among these genes is p21WAF1, which inhibits cyclin-dependent kinases and arrests cell cycle. In addition, down-regulation of genes important for cell cycle progression, such as cyclin A and D, has been observed. Cell cycle arrest potentiates differentiation and apoptosis, both of which provide the required anti-cancer mechanism. For apoptosis, both intrinsic and extrinsic pathways have been shown to be affected by HDAC inhibitors. Mitochondrial permeability can be increased by certain HDAC inhibitors, in particular the hydroxamic acid derivatives (see Figures 2 and 3), resulting in the release of molecules such as cytochrome c, Smac, and Omi, and leads to caspase-dependent apoptosis.
For the extrinsic death signal-triggered apoptosis, Fas and the Apo-2L/TRAIL receptors DR4 and DR5 have been shown to be up-regulated by these inhibitors [69].

The potent effects on cell cycle arrest and apoptosis induced by HDAC inhibitors make them promising anti-cancer drugs. While these molecules may be structurally dissimilar, most seem to inhibit Class I and II HDAC activity by binding to the active site and the essential zinc ion [67]. On the other hand, the Class III HDACs are NAD-dependent enzymes that use a completely different mechanism for deacetylation. New activators and inhibitors for these HDACs (a.k.a. sirtuins) were recently reported [72-75]. Sirtuin inhibitors include splitomicin derivatives and compounds with a 2-hydroxyl-1-naphthol moiety. Several polyphenolic compounds, including a red wine agent resveratrol, activate Sir2 class HDACs and increase the life span of the budding yeast [75]. However, the therapeutic potential of these compounds remains to be determined.

Chemically, inhibitors of Class I and II HDACs can be divided into five major and one hybrid groups [67]. These include short-chain fatty acids (e.g. butyric acid, phenylacetate, and phenylbutyrate), hydroxamic acids (e.g. Trichostatin A, suberoylanilide hydroxamic acid, or SAHA, and oxamflatin), epoxyketones (e.g. Trapoxin, HC-toxin, amino-8-oxo-9,10-epoxydecenoic acid, or AOE), cyclic polyphenolic compounds, including a red wine agent resveratrol, activate Sir2 class HDACs and increase the life span of the budding yeast [75]. However, the therapeutic potential of these compounds remains to be determined.

Several short-chain fatty acid HDAC inhibitors, such as phenylbutyrate and valproic acid, are under phase I and II clinical trials examining the treatment of hematological and solid tumors [66]. Effects of these inhibitors on cancer cells include proteosomal degradation of HDAC2, antiangiogenesis, induction of p21\textsuperscript{WAF1/CIP1}, apoptosis, and telomerase inhibition. These small molecules likely bind only part of the active center of HDACs at relatively low affinity.

The hydroxamate derivatives are the broadest class of HDAC inhibitors with high affinity for the targets (sub-micromolar range). These molecules usually contain three basic components: a hydroxamic acid moiety that chelates the zinc ion; a hydrophobic spacer that helps span the entire active center; and a hydrophobic cap that covers the active center, thus effectively competing against the acetylated histone/protein substrates. Other than butyrate [70], trichostatin was one of the first HDAC inhibitors to be identified [71], and has since been a highly valuable tool in studies of transcription and other acetylation-related molecular functions. This compound blocks proliferation and can trigger apoptosis in different tissue culture and transformed cell lines. Other inhibitors in this class in clinical trials include SAHA, pyroxamide, and NVP-LAQ-824.

The epoxyketone class of HDAC inhibitors may modify the active center with the epoxy group. The ketone group may also hydrogen bond with the target residues. Several hybrid molecules are derived from the combination of epoxyketone and a cyclic peptide. Trapoxin and HC-toxin fall into this group. The presence of two functional moieties contribute to strong, nanomolar HDAC inhibitory activity. Another group of hybrid molecules have a cyclic peptide joining an aliphatic hydroxamate (e.g. CHAP31 and CHAP50). Strong binding affinities are displayed by these inhibitors.

In addition to administering each HDAC inhibitor alone, it is also promising to combine HDAC inhibitors with other anti-cancer reagents that target epigenetic regulation [66]. For example, long-term transcriptional repression (i.e. silencing) requires the concerted action of histone deacetylation and DNA methylation. 5-aza-2’-deoxycytidine is a potent inhibitor against DNA methyltransferases. Combining trichostatin A with this DNA methylation inhibitor restores transcription of several key factors such as MLH1, TIMP3, maspin, and gelsolin [71], leading to anti-neoplastic effects.

**Summary**

Maintaining the balance of histone and non-histone protein acetylation is of tremendous importance for regulating transcription and cellular development and differentiation. Mutations that cause dysregulation of HAT activities or recruitment of HDAC complexes result in devastating phenotypes in animals and plants. Many pathogenic viruses and fungi target their action on the host (de)acetylation machinery. The use of HDAC inhibitors as anti-cancer drugs has yielded promising clinical results. Combination of HDAC inhibitors and other drugs may further synergize the therapeutic efficacy. It is anticipated that the use of specific HDAC, and possibly HAT, modulators in the future will not only offer an effective cancer therapeutic strategy, but also critical insights into the molecular mechanisms underlying tumorigenesis.

**About the Author**

Min-Hao Kuo received his Ph.D. from the University of Rochester. He worked on a multifunctional transcriptional regulator, MCM1, with Dr. Elizabeth Grayhack. He then did his postdoctoral research with Dr. David Allis, during which time he began his studies on histone acetylation and chromatin dynamics. He joined the Department of Biochemistry and Molecular Biology, Michigan State University in 1999 as an Assistant Professor. Current research carried out in Dr. Kuo’s lab focuses on genetic and biochemical studies of yeast histone acetyltransferases and kinases, as well as pro-
teomic identification of protein-protein interactions modulated by specific post-translational modifications.

References

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