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REVIEW

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Histone acetyl transferases: a role in DNA repair and DNA replication

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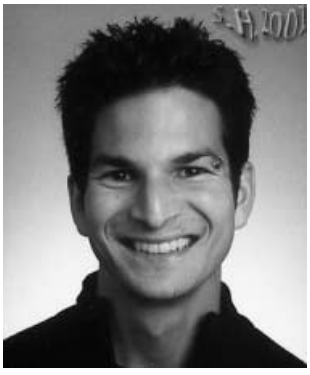
Abstract In eukaryotic cells DNA is associated with proteins to form a complex known as chromatin. The dominant proteins within this chromatin complex are the histones, which are subject to a wide variety of covalent and reversible posttranslational modifications such as acetylation. A specialized family of enzymes, the histone acetyl transferases, catalyzes the transfer of acetyl groups from their cosubstrate acetyl-coenzyme A to lysine residues of histones. Acetylation of histone N-terminal lysine residues induces chromosomal changes and results in the loss of chromosomal repression that allows the successful transcription of the underlying genes. Analogously, in DNA repair and also DNA replication the chromosomal repression is thought to be relieved by such mechanisms. Recently several publications have provided evidence that histone acetyl transferases also modify nonhistone proteins and thereby regulate their activities. This review discusses various aspects of histone acetyl transferases and summarizes recent findings which suggest a role for histone acetyl transferases in DNA repair and DNA replication.

Keywords Histone acetyl transferases · Chromatin · Transcription · DNA repair · DNA replication

Abbreviations *CAF:* Chromatin assembly factor · *FAT:* Factor acetyltransferase · *Fen:* Flap endonuclease · *GNAT:* GCN5-related *N*-acetyltransferase · *HAT:* HISTONE acetyl transferase · *HMG:* High-mobility group · *$TAF_{II}250$:* TATA binding protein associated factor · *PCNA:* Proliferating cell nuclear antigen · *SWI/SNF:* Mating type switch/sucrose nonfermenting · *TFTC:* TATA box binding protein free TAF_{II} complex



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Introduction

More than a quarter of a century has passed since the nucleosome was first recognized as the fundamental unit of chromatin in eukaryotic cells [1, 2]. The isolated nucleosome core particle consists of a histone octamer, two copies each of H2A, H2B, H3, and H4 around which is wrapped 146 bp of DNA (reviewed in [3]). This structure is extremely conserved and the same in virtually all eukaryotes. Nucleosomes are assembled with the assistance of chaperones such as the chromatin assembly factor (CAF) 1 soon after DNA is synthesized [4, 5]. It is important to note that individual nucleosomes do not exist in vivo, but they are rather folded into progressively higher-ordered structures. The current understanding is

that the next step of compaction leads to the so-called chromatosome, including the nucleosome core particle and an additional 20 bp of linker DNA associated with a linker histone (H1 or H5) [6, 7]. When chromatin structures are observed by electron microscopy, two types of higher order shapes can be seen: the so-called 10-nm fiber and the 30-nm fiber [8]. The 10-nm fiber is a string of nucleosomes which is obtained under conditions of low ionic strength and does not require the presence of H1. The 30-nm fiber seems to consist of an underlying coiled structure. It has around six nucleosomes for every turn; here the presence of H1 is absolutely required. This fiber is the basic constituent of both interphase chromatin and mitotic chromosomes [9, 10]. In addition to histones, the chromatin contains a set of nonhistone proteins, the high-mobility group (HMG) proteins (reviewed in [11]). The mammalian HMG proteins can be subdivided into three major families, named HMGA, HMGB, and HMGN, according to unique characteristic functional motifs [12]. All of these HMG proteins are thought to act as architectural elements that modify the structure of their binding site within chromatin.

It is important to note that chromatin folding is quite dynamic and is strongly influenced by multiple modifications of chromatin-associated proteins (e.g., histones) and remodeling activities. The degree of chromatin folding directly influences the behavior of DNA in all DNA metabolisms associated processes.

Chromatin, or the histone components, are subject to a wide variety of covalent reversible modifications which can directly influence the degree of compaction of the DNA and therefore also cellular processes (e.g., transcription). The modifications of histones include the addition of various chemical groups such as methyl, phosphate, acetyl, ribosyl, and/or ubiquitin groups [13]. One of the best-characterized posttranslational modifications of histones is the acetylation of lysine residues, an event with a tremendous impact on chromatin structure.

Histone acetylation can occur on all core histones and has usually been associated with transcriptional activation [14]. It occurs posttranslationally and reversibly, on the ε-$NH3^+$ groups of highly conserved lysine residues lying in the N-terminal tails of core histones (reviewed in [15]). Histone acetyl transferases (HATs) catalyze the transfer of the acetyl moiety from acetyl coenzyme A to these ε-$NH3^+$ groups of lysine residues. In the opposing deacetylation reaction, histone deacetylases remove the acetyl groups and thereby reestablish the positive charge in the histones (Fig. 1). Acetylation neutralizes the positive charge and thus increases the hydrophobicity of the histones, leading to a reduced affinity of acetylated N-terminal domains of histones to DNA thus "opening up" the chromatin structure. This change in nucleosomal structure is sought to play a causative role in activating transcription in vivo [14] (Fig. 2). As an alternative, or rather an additional effect, acetylation of histones might set a signal to serve as "flags" that are recognized by other molecules linked to transcriptional activation. Such a histone code model has recently been proposed by Allis and Jenuwein [16]. The histone code hypothesis predicts that the modification marks on the histone tails provide binding sites for effector proteins. In agreement with this hypothesis, one example of such a model is presented by a protein structure known as bromodomain that binds to acetylated lysine residues in the histone NH_2 terminal tail [17, 18]. The bromodomain is present in many transcriptional activators containing intrinsic HAT activity (e.g., p300, GCN5, P/CAF, see below). Similarly, chromodomains appear to be targeting modules for methylation marks within histones [19]. Proteins that recognize specifically ribosylated or phosphorylated histones have not yet been reported, although many pho-

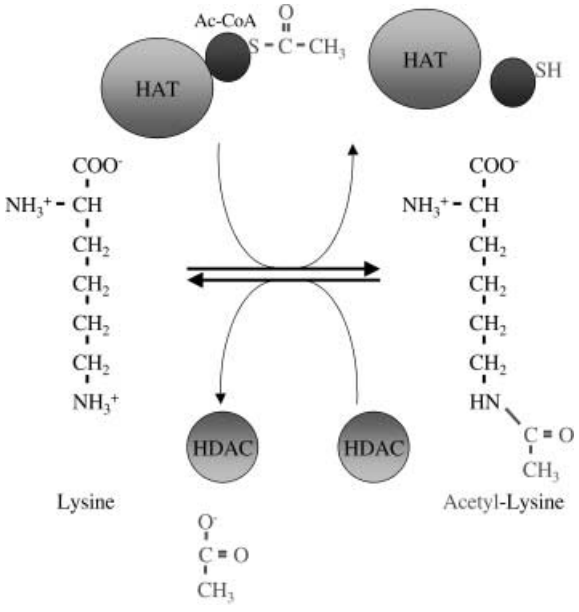

Fig. 1 Schematic diagram of the acetylation of a lysine residue (*left*) to an acetyl-lysine residue (*right*). The reaction is catalyzed by a histone acetyl transferase and its cofactor acetyl-coenzyme A (*Ac-CoA*). The deacetylation reaction is catalyzed by the activity of a histone deacetylase

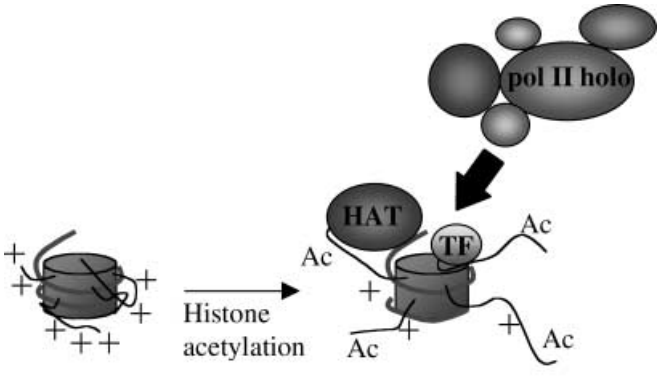

Fig. 2 Acetylation of a core nucleosome by a histone acetyl transferase leads to a loss of positive charges and a better accessibility of the associated DNA for transcription factors (*TF*) or other DNA binding proteins. Thereby, the transcription factor can bind and recruit the RNA-polymerase II holoenzyme (*pol II holo*) and enable transcription

Table 1 Known and putative mammalian type A HATs (for details see text)

Name	Size (kDa)	Target proteins
p300	300	H3, H4, H2A, H2B, nonhistone proteins
CBP	260	H3, H4, H2A, H2B, nonhistone proteins
P/CAF, GCN5	95	H3, H4, nonhistone proteins
TAFII250	250	H3, H4, nonhistone proteins
SRC-1, ACTR	150	H3, H4
TIP60	60	H3, H4, H2A
MORF	200	H3, H4, H2A
hMOF	50	H3, H4, H2A
HBO1	70	H3, H4
MOZ	225	Not determined
TFIIIC90	90	H3
TFIIIC110	110	H2A, H4?
TFIIIC220	220	H2A, H4?
ATF-2	50	H4, H2B

sphoserine binding motifs are known and are important in various signaling pathways [20, 21]. With the possibility of multiple histone modifications present at the same time, mainly at the N-terminal tails of the histones, the question arises as to how they influence each other. Could these modifications functionally regulate each other, and/or could they be used in combination to affect the function of nucleosomes and chromatin? There is evidence that one modification can affect, cooperatively or in an antagonistic manner, the establishment of another modification. Namely, lysine residue 9 of H3, which can either be methylated or acetylated. The mutually exclusive nature of modifying the same amino acid residue could develop into a reciprocal-regulatory mechanism by which the effects on chromatin alternate depending on the present modification [22].

Histone acetyl transferases

HATs can be grouped into at least two classes: type A HATs and type B HATs. While type A HATs are localized in the nuclei and most likely acetylate nucleosomal histones as well as nonhistone proteins, type B HATs can be found in cytoplasmic fractions and are responsible for acetylating newly synthesized histones before their translocation into the nucleus for chromatin assembly during DNA replication [23]. The later class are not discussed further here. To date several known transcriptional coactivators have been found to possess intrinsic class A HAT activity (Table 1). Class A HATs can be further grouped into different families based on amino acid sequence comparisons of homology regions and motifs [24]. Four members of three different HAT families are briefly presented below.

The best understood family of acetyltransferases is the Gcn5-related *N*-acetyltransferase (GNAT) family. This family includes GCN5 (see below), its relatives such as P/CAF (see below) and *Tetrahymena* p55, and at least three more distantly related HATs, namely Hat1, Elp3, and Hpa2. Four sequence motifs, the A, B, C, and D motifs, whose functions are not yet fully understood, characterize this family (reviewed in [13]). Of particular interest is the A motif, which is the most highly conserved region and can also be found in other HATs not belonging to this family [25]. The C motif is found in most of the GNAT family members but not in the majority of known HATs. The first member of the GNAT family type A HAT cloned was a 55-kDa polypeptide (p55) from the ciliated protozoan *Tetrahymena thermophila* [26]. Remarkably, p55 is highly similar to another known transcriptional coactivator, GCN5, in the budding yeast *Saccharomyces cerevisiae*. Homologues of GCN5 have recently been cloned from numerous divergent organisms: human [27], mouse [28], *Drosophila* [29], and even in plants such as *Arabidopsis thaliana* [30], suggesting that its function is highly conserved throughout eukaryotes. The HAT activity of GCN5 has been studied extensively in vitro [31]. It preferentially acetylates histone H3 under certain in vitro assay conditions, although H4 can also be acetylated when purified and presented separately to the enzyme. Protein sequence analysis of the reaction products revealed that the primary sites of acetylation were lysine residues 14 on H3 and lysine 8 and 16 on H4 [31]. Interestingly, only in the context of multisubunit native complexes such as SAGA and ADA allows GCN5 subsequently to acetylate nucleosomal histones, indicating that the influence of other proteins is required to confer this activity [32, 33]. As a coactivator of transcription GCN5 is required for the expression of several genes in vivo [34, 35, 36]. Serial deletion analyses have demonstrated that the minimal functional domain of GCN5 for the activation of target genes in vivo is the HAT catalytic domain and a motif for protein interaction [37]. GCN5 contains furthermore a bromodomain at its C-terminal part, which enables it to recognize acetylated lysine residues of histones and coordinate nucleosomal remodeling [38].

Another interesting member of the GNAT family is the p300/CBP-associating factor (P/CAF), which was identified via its homology to GCN5 and its ability to interact with p300/CBP [39]. Interestingly, this association is required for the transcriptional activation of many genes. The P/CAF HAT activity acetylates either free histones or nucleosomes (reviewed in [13]), primarily on

lysine residue 14 of histone H3, and less strongly on lysine 8 of H4 [40]. The carboxyl half of P/CAF is highly homologous to GCN5, and contains P/CAF's intrinsic HAT activity. It has been suggested that this HAT domain assists the GCN5-related HAT domain to recognize nucleosomal substrates [41]. Relevant to the P/CAF function is the fact that it binds to the same site on p300/CBP as the adenoviral oncoprotein E1A in a competitive manner [42]. In addition, E1A itself and another regulatory protein, namely Twist, reduce P/CAF-mediated in vivo transcription by binding to P/CAF, demonstrating that this HAT is tightly regulated [43]. Twist might function by inhibiting P/CAF's HAT activity; likewise a similar inhibition was found for E1A binding to P/CAF in two studies [42, 43] but not in another [44]. In transcription the requirement of P/CAF as a HAT and coactivator has been reported for myogenesis [45] and nuclear receptor-mediated activation [46].

Another very interesting HAT is $hTAF_{II}250$ (TATA binding protein associated factor, a subunit of the general transcription factor TFIID) which represents a unique family of HATs. The discovery that $hTAF_{II}250$ possesses intrinsic HAT activity in vitro [47] and has a preference to acetylate nucleosomal histones was another direct connection between acetylation and activation of transcription. TFIID is one of the general factors required for the assembly of the RNA polymerase II transcription preinitiation complex (reviewed in [48]). TFIID is in fact the first factor needed in the stepwise assembly model [49, 50]. The HAT activity of $TAF_{II}250$ and its homologues suggests a model for the initiation of transcription complex formation at chromatin-packaged promoters. Nucleosomes have been shown to inhibit binding of the TATA box binding protein to the TATA box [51], and this inhibition is apparently mediated by histone tails [52, 53]. As part of TFIID, $TAF_{II}250$ may well acetylate histones around the TATA box and thereby facilitate binding of the TATA box binding protein, which would allow the formation of the preinitiation complex. In vitro, $TAF_{II}250$ was found to acetylate H3, preferentially on lysine 14 as with GCN5, and H4 in a free histone mixture (additionally H2A as an individual histone, reviewed in [13]). $TAF_{II}250$ shares a structure similar to motif A found in GCN5 used for acetyl coenzyme A binding. Mutation of this motif leads to a reduced HAT activity [54]. As with GCN5, $hTAF_{II}250$ also contains a bromodomain to recognize acetylated histones.

As one last example of a unique HAT family, the transcriptional coactivator p300 and its close homologue CBP were identified as transcriptional coactivators, which are fundamentally important in various signal-modulated transcriptional events [55]. p300/CBP is a large protein of about 300 kDa in mass and is comprised of more than 2400 amino acid residues. Both proteins have been shown to interact with a diverse set of sequence-specific transcription factors that participate in a broad spectrum of biological activities [56]. The ability of p300/CBP to enhance transcription is believed to be accomplished in two modes. First, by acting as a bridging factor thus recruiting the RNA polymerase II holoenzyme via interaction with general transcription factors [57] and, second, by acetylation of histones via its HAT activity [58]. Nucleosomal histones H3 and H4 are preferred substrates. H2A and H2B are acetylated to a lower extent [40]. The HAT domain of p300/CBP lies within an interior region between the bromodomain and the E1A interaction region [59]. Sequence analysis identified regions with limited homology to the GNAT motifs A, B, and D, in addition to another short motif shared with P/CAF and GCN5 [60]. The HAT activity of p300/CBP is apparently regulated by other factors. As observed for P/CAF, E1A and Twist were shown to interact with p300 and inhibit its HAT activity [42, 61]. However, another report indicates that E1A has a stimulatory effect on CBP's HAT activity [62]. Furthermore cell cycle-dependent phosphorylation of p300 was first noted by Yaciuk and Moran [63] in 1991. Subsequently it has been shown that p300 can be phosphorylated by p34/Cdc2 and p33/Cdk2 [64]. Further understanding of the functional implications of this phosphorylation was provided by Snowden and coworkers [65], who showed that p300 is negatively regulated by cyclin E/Cdk2. This negative regulation was shown to be blocked by the cyclin-dependent kinase inhibitor p21. Further insight into the developmental importance of p300/CBP have been gained from studies of gene knock-outs [66]. Interestingly, homozygous p300 knockouts are embryonically lethal; the lethal phenotype occurs between E9 and E11.5 demonstrating the importance of p300 in murine development. The causes of lethality appear to be multifactorial, as the knockout mice display defects in neural tube closure, cardiac development and even in cell proliferation. Of note, these animals presumably express normal levels of CBP, indicating again that either CBP and p300 have nonoverlapping functions, such that both proteins are required, or that the total level of p300 and CBP is critical for normal development (dose effect).

Taken together, acetylation of histones by the above HATs seem to relieve chromosomal repression to facilitate transcriptional activation (Fig. 2). In the past few years it has become clear that there are several HATs with redundant functions in vitro. Genetic approaches will increase our understanding of the extent to which different HATs can complement for each other in vivo.

Nonhistone substrates for HATs

HATs are also able to acetylate nonhistone proteins and are then called factor acetyltransferases (FATs) accordingly. Several non-histone proteins serving as targets for acetylation mainly by p300/CBP and P/CAF have been identified in vivo. They include transcriptional activators such as E2F [67], p53 [68], EKLF [69], GATA1 [70], TCF [71] and other coactivators, other basal transcription factors such as TFIIF [72], and even structural proteins such as tubulin [73]. Generally, the consequence of this acetylation differs from target protein to target pro-

Table 2 Functional consequences of acetylation on selected protein targets

Target protein	Function	Acetylase	Effect of acetylation	Reference
E2F	Transcription factor	p300 (P/CAF)	Increases transcriptional activation and half life	76
p53	Transcription factor	p300/CBP, P/CAF	Increases DNA binding	68
GATA-1/3	Transcription factor	p300/CBP	Increases transcriptional activation	70
MyoD	Transcription factor	P/CAF	Increases DNA binding	45
EKLF	Transcription factor	P/CAF	Increases DNA binding	69
CIITA	Transcription factor	P/CAF	Increases nuclear accumulation	129
c-Myb	Transcription factor	p300/CBP, GCN5	Increases DNA binding	130
TCF	Transcription factor	CBP	Disrupts interaction with coactivator	71
Tat	HIV transactivator	p300/CBP, P/CAF	Modulates interaction with CDK9 and RNA	82
HMG-14	Chromatin-associated	p300/CBP protein	Decreases nucleosomal binding	131
HMG-17	Chromatin-associated	P/CAF protein	Decreases nucleosomal binding	132
HMG(Y)	Chromatin-associated	p300/CBP, P/CAF protein	Promotes enhanceosome assembly and disruption	133

tein and the functional role of the target protein's domain that is modified. The consequences for such an acetylation event are illustrated below for the p300 targets E2F, p53, and Tat. For an overview of other selected target proteins see Table 2.

As one of the key regulators in cell cycle progression, the ubiquitin-proteosome pathway, tightly regulates the cellular level of the E2F protein [74]. E2F is typically a heterodimer of an E2F family member and the DP1 protein and is known to regulate the expression of S-phase specific genes and is thus required for cell cycle progression (reviewed in [75]). Binding to Rb protects E2F from degradation. Remarkably, exogenous expression of wild-type P/CAF, but not the HAT-defective P/CAF mutant, results in an increase in E2F's half-life, indicating that acetylation stabilizes E2F. Furthermore, acetylation of E2F by p300 near its DNA binding domain increases its affinity to DNA, thereby enhancing the transcriptional activation of E2F in vivo [76]. This event leads then to cell cycle progression.

p53 is a tumor suppressor that responds to DNA damage by acting as a transcriptional activator of certain cell death related genes [77, 78, 79]. Because of its direct role in such processes as cell cycle arrest and apoptosis, p53 activity as a transcription factor must be tightly regulated. One possibility is to regulate p53 via acetylation. p53 interacts directly with p300, and two specific lysine residues in p53 (lysine residues 373 and 382) can be acetylated by p300. Increased DNA binding activity upon acetylation by p300 was observed and explained by a conformational change in the regulatory C-terminal domain of the protein upon acetylation [68]. Interestingly, an enhancement of p53's acetylation was observed upon stimulation of the cells with UV [80], and these results suggest that by acetylation of specific residues, p300/CBP (and also P/CAF) positively regulate the activity of p53 as part of the pathway of DNA damage response.

Taken together, factor-specific acetylation often facilitates transcription via a direct effect by the action of FATs. An opposite effect is observed when HIV Tat is acetylated. Tat is the transactivating protein of HIV, which has been shown to interact with and be acetylated by p300 [81, 82]. The consequence of this acetylation is not an increased nucleotide binding (as described for E2F and p53) and hence an activation of transcription, but a dissociation of Tat from the TAR RNA [82].

ATP-dependent chromatin remodeling and chromatin modifications

The packaging of DNA in eukaryotic organisms affects the accessibility and the action of DNA binding factors (e.g., transcription factors) as seen above for histone acetylation [83, 84]. The cells additionally make use of sophisticated chromatin-remodeling factors to open up the tight DNA-chromatin structure locally at sites of transcription. So called "open chromatin" is necessary for a successful transcription of a gene in vivo and allows the cell to regulate gene expression at a hierarchically higher level [84, 85]. Chromatin remodeling is an ambiguous term used to encompass a range of structural transitions that occur during gene regulation (reviewed in [86]). In many cases these include a combination of, first, posttranslational modifications (e.g., acetylation as discussed above), second, noncovalent alteration in chromatin structure mediated by the action of ATP-dependent remodeling activities, and, third, alterations in the non-core histone protein content of chromatin. The combined effect of these processes is to regulate the accessibility to DNA, and there is evidence that all of these processes act in concert in a highly organized manner. All eukaryotes appear to possess multiple forms of these ATP-dependent chromatin remodeling activities [87]. Their universally conserved feature is a catalytic ATP hydrolyzing core that shares a region of homology with a broad collection of proteins, several of which have helicase activity [88]. However, none of these have been found to possess the classic DNA helicase activity. Their function rather lies in altering the positions of nucleosomes along DNA, termed nucleosome mobilization, which even leads to disrupted chromatin fibers [89, 90, 91]. Examples for such activities are mating type switch/sucrose nonfermenting (SWI/SNF), RSC, NURF, CHRAC, ACF, RSF, and NuRD [92]. All these enzymes are highly con-

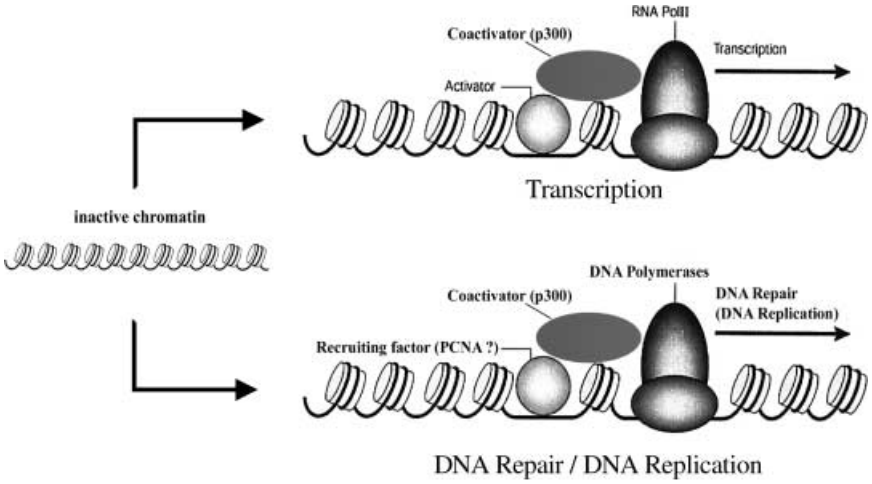

Fig. 3 Analogy between transcription and DNA repair/DNA replication. Within inactive chromatin (*left*) neither transcription nor DNA synthesis takes place. At sites of transcription or DNA synthesis the chromatin becomes acetylated by a histone acetyl transferase (e.g., the transcriptional coactivator p300) and the underlying DNA is thus accessible for transcription (*top*) or DNA synthesis (*bottom*)

served multiprotein complexes, and the probably best studied is SWI/SNF. The genes encoding for SWI/SNF, for example, were initially identified in yeast. SWI/SNF [93, 94] is a 2-MDa, multisubunit, DNA-dependent ATPase that has been shown genetically to regulate a subset of inducible genes in yeast and biochemically to facilitate the interaction of a variety of transcription factors to nucleosomal DNA (reviewed in [95]). Current studies support the view that SWI/SNF causes the partial unwrapping of DNA from the nucleosome without the actual loss of histones and can both promote nucleosome mobilization ("nucleosome sliding") and even transfer to neighboring DNA [96]. Interestingly, human SWI/SNF can additionally convert the nucleosomal structure from a basic state to remodeled structure in a reversible manner [97, 98]. Remarkably, not all chromatin-remodeling activities stimulate transcription, but rather can also cause transcriptional repression probably by pushing nucleosomes to activator binding sites. One example of such a protein is Isw2 which represses meiosis-specific genes in yeast [99].

A role of HATs in DNA repair

As for transcription, it is very likely that the accessibility of DNA for proteins involved in DNA metabolism (DNA repair and DNA replication) also depends on an open chromatin structure. The same chromatin-remodeling activities used in transcription, in particular the multiple HAT activities present in eukaryotic cells, could potentially confer to regulate DNA synthesis such as DNA repair and DNA replication. In this section we consider a role for HATs in DNA repair, and the next section presents a short summary of the current understanding on the effect of HATs on DNA replication.

In DNA repair damaged DNA must first be recognized, while subsequently the chromatin structure must be changed to allow proteins which are involved in repairing the damage to bind to or near the damaged site. It is conceivable that also in DNA repair the cell would regulated the accessibility of the DNA for proteins and the recruitment of the different proteins involved in the repair mechanisms by proteins such as HATs.

The first possible evidence for involvement of HATs in DNA repair synthesis was recently provided for the transcriptional coactivator p300 [100]. This study suggested that p300 interacts with proliferating cell nuclear antigen (PCNA). PCNA is a well-known key player in both DNA replication and DNA repair (reviewed in [101]). The function of PCNA is to act as a processivity factor for certain DNA polymerases such as DNA polymerase δ and DNA polymerase ε. The interaction between p300 and PCNA very likely allows PCNA to recruit p300, which cannot bind to DNA by itself, to damaged sites to allow acetylation of histones at or near damaged site [100]. Additionally, this event might also tether p300-associated HATs such as P/CAF to these sites and possibly enhance the acetylation of these histones. This acetylation event renders the chromatin to a more open state and very likely facilitates the binding of other repair proteins. Furthermore, gap-filling synthesis by DNA polymerases (for example, in NER or BER) would be facilitated as it has been proposed for DNA replication (see below) allowing a swift repair (Fig. 3), since the movement of polymerases through nucleosomal DNA is facilitated by acetylation of histone tails [102]. In a recent report Datta and coworkers [103] show that the p48 subunit of the damaged DNA-binding protein (DDB) associates with the p300/CBP family of histone acetyltransferases. DDB has been implicated both in DNA repair and in transcription. Mutations in DDB have been shown to be correlated with the repair-deficiency disease xeroderma pigmentosum group E. The authors propose that DDB participates in global genomic repair by recruiting p300/CBP to damaged chromatin as has been proposed to be the case for PCNA. A very recent work by Tini and coworkers [104] also links DNA repair and transcription. The authors provide evidence that p300/CBP interacts with thymine DNA glycosylase, an enzyme which initiates repair of G/T and G/U mismatches and propose that the consequence of this interaction is histone acetylation at or near the damaged site.

The second possibility for a cell to regulate DNA repair is, in analogy to transcription, to influence the activity of the repair proteins directly by acetylation through FATs. Indeed, heavy acetylation of human Flap endonuclease (Fen) 1 by p300 was seen in vitro and was significantly enhanced after UV radiation of the cells in vivo [105]. Fen1 is a structure-specific nuclease with a role both in DNA replication, where it is involved in Okazaki fragment processing, and in DNA repair, where it participates in base excision repair [106, 107]. The consequence of Fen1 acetylation is a down-regulation of its nuclease activity due to a decrease in the Fen1 DNA-binding activity. This at first glance paradoxical phenomenon was explained by an alternative route for Okazaki fragment processing in DNA replication as has recently been proposed by Bae and coworkers [106], which uses the nuclease activity of Dna2 instead that of Fen1. In DNA repair one could assume that the cells have a preference for an error-free repair pathway, namely recombination repair, and hence drive the repair reaction in such a direction by inhibiting the enzymatic activity of Fen1 by acetylation. This model raises the question of whether a deacetylase would activate Fen1 before DNA repair has occurred, supposing that Fen1 is an acetylated protein throughout the cell cycle. Moreover, the cells after being radiated with a high UV dose undergo apoptosis and would therefore tie down completely any repair activity by factor specific acetylation to allow complete degradation of its DNA. Together, these findings are first evidence that HATs/FATs directly influencing the efficiency of DNA repair by acetylation of a repair protein, a phenomenon otherwise restricted to transcription coupled processes. The question remains of whether acetylation of repair proteins (e.g., by p300) is a common phenomenon (as with phosphorylation of repair/replication proteins), or whether Fen1 is a just an unique example.

Also other HATs have been implied to be involved in DNA repair. A study by Brand and coworkers [108] demonstrated that the TATA box binding protein free TAF_{II} complex (TFTC) is able to bind UV-damaged DNA in vitro in both free and nucleosomal context, and that this binding is paralleled by recruitment of the repair factor XP-A. Moreover, the authors showed that, as a consequence of this increased binding, TFTC preferentially acetylates histone H3 in nucleosomes assembled on UV-irradiated DNA. In accordance, after UV radiation H3 acetylation was increased in vivo. The results of this study suggest that TFTC has a novel function in addition to its role in transcription, namely to facilitate DNA repair. Another HAT thought to be implicated in DNA repair is Tip60 [109]. Ectopically expressed TIP60 lacking HAT activity results in cells with defective double-strand break repair and impaired apoptotic competence. This finding indicates that the Tip60-associated HAT activity at least indirectly plays a role in DNA repair and apoptosis. Whether this effect takes place at the chromatin level or if factor specific acetylation is involved (see also above) is currently not known.

A role of HATs in DNA replication

Since DNA replication and DNA repair share the same chromatin DNA, a potential role of HATs in DNA replication can be foreseen. It is likely that HATs are involved in this process as well. Indeed there have been few reports which indicate a role for HATs in DNA replication.

In proliferating rat liver cells an increase in HAT activity is associated with the onset of DNA replication [110], and depression of histone acetylation by alkylating agents is correlated with an inhibition of thymidine incorporation [111], which is a marker for DNA synthesis in cells. These two reports provide first evidence that at least indirectly HAT activity is important for a successful replication of cellular DNA. Additionally, studies using Chinese hamster chromosomes demonstrate a close correlation between low levels of histone H4 acetylation and late DNA replication [112]. In a very recent work Burke et al. [113] provide evidence that the HAT HBO1 interacts with the replication factors MCM2 and ORC1, proteins involved in the early stage of DNA replication namely origin recognition and initiation complex formation. The reason of this interaction could lie in a regulation of either of these two proteins via acetylation by HBO1. Using the SV40 in vitro replication system, it has been shown that elongation of replication occurs with a higher efficiency in hyperacetylated minichromosomes, indicating that the movement of the replication machinery through nucleosomal DNA is facilitated by acetylation of histone tails [102]. Additionally, Aoki and Schultz [114] examined the temporal and spatial distribution of sites of DNA replication in one-cell mouse embryos. Treatment of these embryos with a specific inhibitor of histone deacetylase accelerated the completion of replication indicating that also in this case acetylation of histones is involved in the regulation of DNA replication. Work by Takei and colleagues [115] showed that the replication protein MCM3 is acetylated by MCM3AP, a novel acetyltransferase. MCM proteins form prereplication complexes in late G_1 (reviewed in [116]) after recruitment by the origin recognition complex and CDC6 where DNA replication is initiated upon activation of the complex by cyclin-CDK and CDC7 kinases [117]. Interestingly, overexpression of MCM3AP inhibited DNA replication, but it clearly demonstrates that acetylation of a nonhistone protein is a novel possibility for regulating DNA replication.

In summary, the presented evidence favors a functional relevance of HATs in the regulation of DNA replication. Remarkably, p300 as an example seems to be restricted to DNA repair, as experiments with UV treatments of human cells have indicated [100]. Also the function of other HATs presented seems to be restricted to either DNA repair or DNA replication. Therefore it seems that the cell distinguishes clearly between the replication and the repair event and very likely recruits specialized HATs for each purpose.

A role of HATs after DNA replication and DNA repair events

Once DNA replication has completed, the chromatin also requires the faithful inheritance of epigenetic chromatin marks to ensure appropriate gene expression patterns in the daughter cells. Hence the question arises of whether HATs are involved in this reprogramming process as well. Histone H3 and H4 are found to be posttranslationally modified in the cytoplasm even prior to their transport into the nucleus and assembly into chromatin, and that these modifications are removed again after assembly [118]. Indeed, diacetylation of two specific lysines in newly synthesized histone H4 (K5, K12) is observed in a wide range of organisms [23]. The HAT responsible for this acetylation is HAT B [119]. The reestablishment of parental acetylation patterns per se after chromatin replication likely involves the coordinated action of HATs. First, histones are deposited by the action of histone chaperones, such as CAF-1 [120]. CAF-1 is linked to replication through its interaction with PCNA [121]. Recently it has been found that the large subunit of yeast CAF-1, Cac1, interacts with a protein complex called SAS-1 that contains the HAT homologue Sas2 [122]. The authors proposed that Cac1 recruits HATs such as Sas2 to establish a parental acetylation pattern within fresh chromatin. Although these studies have been performed in yeast, similar mechanisms very likely exist in mammalian cells. The resetting mechanism for epigenetic information after DNA repair is probably dependent on the repair pathway that cell priory underwent. A repair pathway making use of extensive DNA synthesis very likely applies similar reestablishing mechanisms as in DNA replication (described above). However, in repair pathways with only little DNA synthesis (e.g., BER), additionally to potential acetylation resetting, the vast majority of epigenetic resetting involves deacetylation, since for DNA damage processing the chromatin is opened up previously through acetylation. Indeed, specialized NAD^+ dependent deacetylases are recruited in response to DNA damage [123]. Very likely these deacetlyases are involved in a resetting and additionally transcriptional silencing event.

Perspectives and conclusions

Taken together, several recent studies describe a novel role for HATs in the regulation of DNA repair and DNA replication. Hence the question arises of what would specify the HATs for DNA repair/replication rather than to transcription. One could imagine that the cell possesses different pools of HAT populations. One such population might be used for transcriptional regulation and another for the control of DNA repair. What distinguishes these hypothetical pools? It could be that certain HAT molecules become marked for repair control (or transcriptional) control by a posttranslational modification such as phosphorylation at distinct amino acid residues, or that HATs become specifically recruited to sites of DNA repair by protein-protein interactions, which might compete with transcriptional events. Another interesting question remains: whether other chromatin remodeling complexes (for example, the ATP-dependent ones such as the SWI/SNF complex) have a similar role in DNA replication and DNA repair. Recent data also suggest that this is indeed the case (reviewed in [124]). If acetylation of histones and nonhistone proteins are used to regulate DNA repair and DNA replication, it is conceivable that there must be a role for histone deacetylases. Indeed, recent findings by Luo et al. [125, 126] and Vaziri et al. [127] demonstrate that p53 is inactivated by the action of various deacetylases. It will be interesting to investigate, for example, whether putative Fen1 deacetylation can activate DNA repair.

Another relevant issue is whether the state of chromatin influences other DNA linked processes such as recombination. Indeed, a recent study has shown that the process of V(D)J recombination can be correlated with histone H3 acetylation [128]. There is growing interest to understand how a cell regulates its cellular metabolism processes associated with chromatin such as transcription, DNA replication, and DNA repair. At first glance these processes are highly organized and different. However, one could expect that nature shares similar features for common tasks in all these various processes. Considering the information available to date, we conclude that this is very likely the case – the HAT-associated chromatin remodeling and protein-specific acetylation serve as nice examples. It is now apparent that histone or protein specific acetylation as a regulatory mechanism is not restricted to transcription but is also a hallmark for all chromatin-based processes. Especially in DNA replication and DNA repair it seems likely that both HAT or FAT activities and specific FAT/target protein interactions seem to be required for a cell to regulate these complex processes. These interactions might open a new potential field of possibilities to develop new therapeutic compounds that would specifically inhibit one or the other cellular process. However, it remains a challenge to resolve the very exact mechanisms which regulate these various processes. Considering the complexity of life, the question remains unclear of whether this tremendous task will ever be solved. In the present era of functional genomics and proteomics new tools exist to obtain further insight into this questions. Clearly, this challenge will remain an active area of research in the rapidly developing field of transcription and genome DNA integrity.

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References

1. Kornberg RD (1974) Chromatin structure: a repeating unit of histones and DNA. Science 184:868–871
2. Kornberg RD, Klug A (1981) The nucleosome. Sci Am 244:52–64
3. Pruss D, Hayes JJ, Wolffe AP (1995) Nucleosomal anatomy-where are the histones? Bioessays 17:161–170
4. Verreault A (2000) De novo nucleosome assembly: new pieces in an old puzzle. Genes Dev 14:1430–1438
5. Ridgway P, Almouzni G (2000) CAF-1 and the inheritance of chromatin states: at the crossroads of DNA replication and repair. J Cell Sci 113:2647–2658
6. Meersseman G, Pennings S, Bradbury EM (1991) Chromatosome positioning on assembled long chromatin. Linker histones affect nucleosome placement on 5 S rDNA. J Mol Biol 220:89–100
7. Puigdomenech P, Jose M, Ruiz-Carrillo A, Crane-Robinson C (1983) Isolation of a 167 basepair chromatosome containing a partially digested histone H5. FEBS Lett 154:151–155
8. Harrington RE (1985) Optical model studies of the salt-induced 10–30-nm fiber transition in chromatin. Biochemistry 24:2011–2021
9. McGhee JD, Nickol JM, Felsenfeld G, Rau DC (1983) Higher order structure of chromatin: orientation of nucleosomes within the 30 nm chromatin solenoid is independent of species and spacer length. Cell 33:831–841
10. Allan J, Harborne N, Rau DC, Gould H (1982) Participation of core histone "tails" in the stabilization of the chromatin solenoid. J Cell Biol 93:285–297
11. Bustin M (2001) Chromatin unfolding and activation by HMGN(*) chromosomal proteins. Trends Biochem Sci 26: 431–437
12. Bustin M (2001) Revised nomenclature for high mobility group (HMG) chromosomal proteins. Trends Biochem Sci 26:152–153
13. Sterner DE, Berger SL (2000) Acetylation of histones and transcription-related factors. Microbiol Mol Biol Rev 64:435–459
14. Grunstein M (1997) Histone acetylation in chromatin structure and transcription. Nature 389:349–352
15. Kuo MH, Allis CD (1998) Roles of histone acetyltransferases and deacetylases in gene regulation. Bioessays 20:615–626
16. Jenuwein T, Allis CD (2001) Translating the histone code. Science 293:1074–1080
17. Dhalluin C, Carlson JE, Zeng L, He C, Aggarwal AK, Zhou MM (1999) Structure and ligand of a histone acetyltransferase bromodomain. Nature 399:491–496
18. Dyson MH, Rose S, Mahadevan LC (2001) Acetyllysine-binding and function of bromodomain-containing proteins in chromatin. Front Biosci 6D:853–865
19. Jones DO, Cowell IG, Singh PB (2000) Mammalian chromodomain proteins: their role in genome organisation and expression. Bioessays 22:124–137
20. Muslin AJ, Tanner JW, Allen PM, Shaw AS (1996) Interaction of 14-3-3 with signaling proteins is mediated by the recognition of phosphoserine. Cell 84:889–897
21. Weston CR, Davis RJ (2001) Signal transduction: signaling specificity – a complex affair. Science 292:2439–2340
22. Cheung P, Allis CD, Sassone-Corsi P (2000) Signaling to chromatin through histone modifications. Cell 103:263–271
23. Brownell JE, Allis CD (1996) Special HATs for special occasions: linking histone acetylation to chromatin assembly and gene activation. Curr Opin Genet Dev 6:176–184
24. Neuwald AF, Landsman D (1997) GCN5-related histone N-acetyltransferases belong to a diverse superfamily that includes the yeast SPT10 protein. Trends Biochem Sci 22:154–155
25. Dutnall RN, Tafrov ST, Sternglanz R, Ramakrishnan V (1998) Structure of the histone acetyltransferase Hat1: a paradigm for the GCN5-related N-acetyltransferase superfamily. Cell 94: 427–438
26. Brownell JE, Zhou J, Ranalli T, Kobayashi R, Edmondson DG, Roth SY, Allis CD (1996) Tetrahymena histone acetyltransferase A: a homolog to yeast Gcn5p linking histone acetylation to gene activation. Cell 84:843–851
27. Candau R, Moore PA, Wang L, Barlev N, Ying CY, Rosen CA, Berger SL (1996) Identification of human proteins functionally conserved with the yeast putative adaptors ADA2 and GCN5. Mol Cell Biol 16:593–602
28. Driessen CA, Winkens HJ, Kuhlmann LD, Janssen BP, van Vugt AH, Deutman AF, Janssen JJ (1997) Cloning and structural analysis of the murine GCN5L1 gene. Gene 203:27–31
29. Smith ER, Belote JM, Schiltz RL, Yang XL, Moore PA, Berger SL, Nakatani Y, Allis CD (1998) Cloning of Drosophila GCN5: conserved features among metazoan GCN5 family members. Nucleic Acids Res 26:2948–2954
30. Stockinger EJ, Mao Y, Regier MK, Triezenberg SJ, Thomashow MF (2001) Transcriptional adaptor and histone acetyltransferase proteins in Arabidopsis and their interactions with CBF1, a transcriptional activator involved in cold-regulated gene expression. Nucleic Acids Res 29:1524–1533
31. Kuo MH, Brownell JE, Sobel RE, Ranalli TA, Cook RG, Edmondson DG, Roth SY, Allis CD (1996) Transcription-linked acetylation by Gcn5p of histones H3 and H4 at specific lysines. Nature 383:269–272
32. Grant PA, Duggan L, Cote J, Roberts SM, Brownell JE, Candau R, Ohba R, Owen-Hughes T, Allis CD, Winston F, Berger SL, Workman JL (1997) Yeast Gcn5 functions in two multisubunit complexes to acetylate nucleosomal histones: characterization of an Ada complex and the SAGA (Spt/Ada) complex. Genes Dev 11:1640–1650
33. Pollard KJ, Peterson CL (1997) Role for ADA/GCN5 products in antagonizing chromatin-mediated transcriptional repression. Mol Cell Biol 17:6212–6222
34. Georgakopoulos, Thireos G (1992) Two distinct yeast transcriptional activators require the function of the GCN5 protein to promote normal levels of transcription. EMBO J 11:4145–4152
35. Martens JA, Genereaux J, Saleh A, Brandl CJ (1996) Transcriptional activation by yeast PDR1p is inhibited by its association with NGG1p/ADA3p. J Biol Chem 271:15884–15890
36. Chiang YC, Komarnitsky P, Chase D, Denis CL (1996) ADR1 activation domains contact the histone acetyltransferase GCN5 and the core transcriptional factor TFIIB. J Biol Chem 271: 32359–32365
37. Candau R, Zhou JX, Allis CD, Berger SL (1997) Histone acetyltransferase activity and interaction with ADA2 are critical for GCN5 function in vivo. EMBO J 16:555–565
38. Syntichaki P, Topalidou I, Thireos G (2000) The Gcn5 bromodomain co-ordinates nucleosome remodelling. Nature 404: 414–417
39. Yang XJ, Ogryzko VV, Nishikawa J, Howard BH, Nakatani Y (1996) A p300/CBP-associated factor that competes with the adenoviral oncoprotein E1A. Nature 382:319–324
40. Schiltz RL, Mizzen CA, Vassilev A, Cook RG, Allis CD, Nakatani Y (1999) Overlapping but distinct patterns of histone acetylation by the human coactivators p300 and PCAF within nucleosomal substrates. J Biol Chem 274:1189–1192
41. Utley RT, Ikeda K, Grant PA, Cote J, Steger DJ, Eberharter A, John S, Workman JL (1998) Transcriptional activators direct histone acetyltransferase complexes to nucleosomes. Nature 394:498–502
42. Chakravarti D, Ogryzko V, Kao HY, Nash A, Chen H, Nakatani Y, Evans M (1999) A viral mechanism for inhibition of p300 and PCAF acetyltransferase activity. Cell 96:393–403
43. Hamamori Y, Sartorelli V, Ogryzko V, Puri PL, Wu HY, Wang JY, Nakatani Y, Kedes L (1999) Regulation of histone acetyltransferases p300 and PCAF by the bHLH protein twist and adenoviral oncoprotein E1A. Cell 96:405–413
44. Reid JL, Bannister AJ, Zegerman P, Martinez-Balbas MA, Kouzarides T (1998) E1A directly binds and regulates the P/CAF acetyltransferase. EMBO J 17:4469–4477

45. Sartorelli V, Puri PL, Hamamori Y, Ogryzko Y, Chung G, Nakatani Y, Wang JY, Kedes L (1999) Acetylation of MyoD directed by PCAF is necessary for the execution of the muscle program. Mol Cell 4:725–734
46. Blanco JC, Minucci S, Lu J, Yang XJ, Walker KK, Chen H, Evans RM, Nakatani Y, Ozato K (1998) The histone acetylase PCAF is a nuclear receptor coactivator. Genes Dev 12:1638–1651
47. Mizzen CA, Yang XJ, Kokubo T, Brownell JE, Bannister AJ, Owen-Hughes T, Workman J, Wang L, Berger SL, Kouzarides T, Nakatani Y, Allis CD (1996) The TAF(II)250 subunit of TFIID has histone acetyltransferase activity. Cell 87:1261–1270
48. Dvir A, Conaway JW, Conaway RC (2001) Mechanism of transcription initiation and promoter escape by RNA polymerase II. Curr Opin Genet Dev 11:209–214
49. Workman JL, Roeder RG (1987) Binding of transcription factor TFIID to the major late promoter during in vitro nucleosome assembly potentiates subsequent initiation by RNA polymerase II. Cell 51:613–622
50. Furukawa T, Tanese N (2000) Assembly of partial TFIID complexes in mammalian cells reveals distinct activities associated with individual TATA box-binding protein-associated factors. J Biol Chem 275:29847–29856
51. Meisterernst M, Horikoshi M, Roeder RG (1990) Recombinant yeast TFIID, a general transcription factor, mediates activation by the gene-specific factor USF in a chromatin assembly assay. Proc Natl Acad Sci U S A 87:9153–9157
52. Godde JS, Nakatani Y, Wolffe AP (1995) The amino-terminal tails of the core histones and the translational position of the TATA box determine TBP/TFIIA association with nucleosomal DNA. Nucleic Acids Res 23:4557–4564
53. Imbalzano AN (1998) Energy-dependent chromatin remodelers: complex complexes and their components. Crit Rev Eukaryot Gene Expr 8:225–255
54. Dunphy EL, Johnson T, Auerbach SS, Wang EH (2000) Requirement for TAF(II)250 acetyltransferase activity in cell cycle progression. Mol Cell Biol 20:1134–1139
55. Eckner R, Ewen ME, Newsome D, Gerdes M, DeCaprio JA, Lawrence JB, Livingston DM (1994) Molecular cloning and functional analysis of the adenovirus E1A-associated 300-kD protein (p300) reveals a protein with properties of a transcriptional adaptor. Genes Dev 8:869–884
56. Snowden AW, Perkins ND (1998) Cell cycle regulation of the transcriptional coactivators p300 and CREB binding protein. Biochem Pharmacol 55:1947–1954
57. Manteuffel-Cymborowska M (1999) Nuclear receptors, their coactivators and modulation of transcription. Acta Biochim Pol 46:77–89
58. Ogryzko VV, Schiltz RL, Russanova V, Howard RH, Nakatani Y (1996) The transcriptional coactivators p300 and CBP are histone acetyltransferases. Cell 87:953–959
59. Bannister AJ, Kouzarides T (1996) The CBP co-activator is a histone acetyltransferase. Nature 384:641–643
60. Martinez-Balbas MA, Bannister AJ, Martin K, Haus-Seuffert P, Meisterernst M, Kouzarides T (1998) The acetyltransferase activity of CBP stimulates transcription. EMBO J 17:2886–2893
61. Perissi V, Dasen JS, Kurokawa R, Wang Z, Korzus E, Rose DW, Glass CK, Rosenfeld MG (1999) Factor-specific modulation of CREB-binding protein acetyltransferase activity. Proc Natl Acad Sci U S A 96:3652–3657
62. Ait-Si-Ali S, Ramirez S, Barre FX, Dkhissi F, Magnaghi-Jaulin L, Girault JA, Robin P, Knibiehler M, Pritchard LI, Ducommun B, Trouche D, Harel-Bellan a (1998) Histone acetyltransferase activity of CBP is controlled by cycle-dependent kinases and oncoprotein E1A. Nature 396:184–186
63. Yaciuk P, Moran E (1991) Analysis with specific polyclonal antiserum indicates that the E1A-associated 300-kDa product is a stable nuclear phosphoprotein that undergoes cell cycle phase-specific modification. Mol Cell Biol 11:5389–5397
64. Banerjee AC, Recupero AJ, Mal A, Piotrkowski AM, Wang DM, Harter ML (1994) The adenovirus E1A 289R and 243R proteins inhibit the phosphorylation of p300. Oncogene 9:1733–1737
65. Snowden AW, Anderson LA, Webster GA, Perkins ND (2000) A novel transcriptional repression domain mediates p21 (WAF1/CIP1) induction of p300 transactivation. Mol Cell Biol 20:2676–2686
66. Yao TP, Oh SP, Fuchs M, Zhou ND, Ch'ng LE, Newsome D, Bronson RT, Li E, Livingston DM, Eckner R (1998) Gene dosage-dependent embryonic development and proliferation defects in mice lacking the transcriptional integrator p300. Cell 93:361–3672
67. Marzio G, Wagener C, Gutierrez MI, Cartwright P, Helin K, Giacca M (2000) E2F family members are differentially regulated by reversible acetylation. J Biol Chem 275:10887–10892
68. Gu W, Roeder RG (1997) Activation of p53 sequence-specific DNA binding by acetylation of the p53 C-terminal domain. Cell 90:595–606
69. Zhang W, Bieker JJ (1998) Acetylation and modulation of erythroid Kruppel-like factor (EKLF) activity by interaction with histone acetyltransferases. Proc Natl Acad Sci USA 95:9855–9860
70. Boyes J, Byfield P, Nakatani Y, Ogryzko V (1998) Regulation of activity of the transcription factor GATA-1 by acetylation. Nature 396:594–598
71. Waltzer L, Bienz M (1998) Drosophila CBP represses the transcription factor TCF to antagonize Wingless signalling. Nature 395:521–525
72. Imhof A, Yang XJ, Ogryzko VV, Nakatani Y, Wolffe AP, Ge H (1997) Acetylation of general transcription factors by histone acetyltransferases. Curr Biol 7:689–692
73. Shea TB, Beermann ML, Nixon RA (1990) Post-translational modification of alpha-tubulin by acetylation and detyrosination in NB2a/d1 neuroblastoma cells. Brain Res Dev Brain Res 51:195–204
74. Hateboer G, Kerkhoven RM, Shvarts A, Bernards R, Beijersbergen RL (1996) Degradation of E2F by the ubiquitin-proteasome pathway: regulation by retinoblastoma family proteins and adenovirus transforming proteins. Genes Dev 10:2960–2970
75. Frolov MV, Huen DS, Stevaux O, Dimova D, Balczarek-Strang K, Elsdon M, Dyson NJ (2001) Functional antagonism between E2F family members. Genes Dev 15:2146–2160
76. Martinez-Balbas MA, Bauer UM, Nielsen SJ, Brehm, Kouzarides T (2000) Regulation of E2F1 activity by acetylation. EMBO J 19:662–671
77. Gottlieb TM, Oren M (1996) p53 in growth control and neoplasia. Biochim Biophys Acta 1287:77–102
78. Ko LJ, Prives C (1996) p53: puzzle and paradigm. Genes Dev 10:1054–1072
79. Levine AJ (1997) p53, the cellular gatekeeper for growth and division. Cell 88:323–331
80. Liu L, Scolnick DM, Trievel RC, Zhang HB, Marmorstein R, Halazonetis TD, Berger SL (1999) p53 sites acetylated in vitro by PCAF and p300 are acetylated in vivo in response to DNA damage. Mol Cell Biol 19:1202–1209
81. Hottiger MO, Nabel GJ (1998) Interaction of human immunodeficiency virus type 1 Tat with the transcriptional coactivators p300 and CREB binding protein. J Virol 72:8252–8256
82. Kiernan RE, Vanhulle C, Schiltz L, Adam E, Xiao H, Maudoux F, Calomme C, Burny A, Nakatani Y, Jeang KT, Benkirane M, Van Lint C (1999) HIV-1 tat transcriptional activity is regulated by acetylation. EMBO J 18:6106–6118
83. Workman JL, Kingston RE (1998) Alteration of nucleosome structure as a mechanism of transcriptional regulation. Annu Rev Biochem 67545–79
84. Wolffe AP, Hayes JJ (1999) Chromatin disruption and modification. Nucleic Acids Res 27:711–720

85. Kuo MH, Zhou J, Jambeck P, Churchill, Allis CD (1998) Histone acetyltransferase activity of yeast Gcn5p is required for the activation of target genes in vivo. Genes Dev 12:627–639
86. Flaus A, Owen-Hughes T (2001) Mechanisms for ATP-dependent chromatin remodelling. Curr Opin Genet Dev 11:148–154
87. Vignali M, Hassan AH, Neely KE, Workman JL (2000) ATP-dependent chromatin-remodeling complexes. Mol Cell Biol 20:1899–1910
88. Eisen JA, Sweder KS, Hanawalt PC (1995) Evolution of the SNF2 family of proteins: subfamilies with distinct sequences and functions. Nucleic Acids Res 23:2715–2723
89. Hamiche A, Sandaltzopoulos R, Gdula DA, Wu C (1999) ATP-dependent histone octamer sliding mediated by the chromatin remodeling complex NURF. Cell 97:833–842
90. Langst G, Bonte EJ, Corona DF, Becker PB (1999) Nucleosome movement by CHRAC and ISWI without disruption or trans-displacement of the histone octamer. Cell 97:843–852
91. Jaskelioff M, Gavin IM, Peterson CL, Logie C (2000) SWI-SNF-mediated nucleosome remodeling: role of histone octamer mobility in the persistence of the remodeled state. Mol Cell Biol 20:3058–3068
92. Muchardt C, Yaniv M (1999) ATP-dependent chromatin remodelling: SWI/SNF and Co. are on the job. J Mol Biol 293: 187–198
93. Laurent BC, Treitel MA, Carlson M (1991) Functional interdependence of the yeast SNF2, SNF5, and SNF6 proteins in transcriptional activation. Proc Natl Acad Sci USA 88:2687–2691
94. Peterson CL, Herskowitz I (1992) Characterization of the yeast SWI1, SWI2, and SWI3 genes, which encode a global activator of transcription. Cell 68:573–583
95. Winston F, Carlson M (1992) Yeast SNF/SWI transcriptional activators and the SPT/SIN chromatin connection. Trends Genet 8:387–391
96. Peterson CL, Workman JL (2000) Promoter targeting and chromatin remodeling by the SWI/SNF complex. Curr Opin Genet Dev 10:187–192
97. Cote J, Peterson CL, Workman JL (1998) Perturbation of nucleosome core structure by the SWI/SNF complex persists after its detachment, enhancing subsequent transcription factor binding. Proc Natl Acad Sci U S A 95:4947–4952
98. Schnitzler G, Sif S, Kingston RE (1998) Human SWI/SNF interconverts a nucleosome between its base state and a stable remodeled state. Cell 94:17–27
99. Goldmark JP, Fazzio TG, Estep PW, Church GM, Tsukiyama T (2000) The Isw2 chromatin remodeling complex represses early meiotic genes upon recruitment by Ume6p. Cell 103: 423–433
100. Hasan S, Hassa PO, Imhof R, Hottiger MO (2001) Transcription coactivator p300 binds PCNA and may have a role in DNA repair synthesis. Nature 410:387–391
101. Jonsson ZO, Hübscher U (1997) Proliferating cell nuclear antigen: more than a clamp for DNA polymerases. Bioessays 19:967–975
102. Alexiadis V, Halmer L, Gruss C (1997) Influence of core histone acetylation on SV40 minichromosome replication in vitro. Chromosoma 105:324–331
103. Datta A, Bagchi S, Nag A, Shiyanov P, Adami GR, Yoon T, Raychaudhuri P (2001) The p48 subunit of the damaged-DNA binding protein DDB associates with the CBP/p300 family of histone acetyltransferase. Mutat Res 486: 89–97
104. Tini M, Benecke A, Um SJ, Torchia J, Evans RM, Chambon P (2002) Association of CBP/p300 acetylase and thymine DNA glycosylase links DNA repair and transcription. Mol Cell 9:265–277
105. Hasan S, Stucki M, Hassa PO, Imhof R, Gehrig P, Hunziker P, Hubscher U, Hottiger HO (2001) Regulation of human flap endonuclease-1 activity by acetylation through the transcriptional coactivator p300. Mol Cell 7:1221–1231
106. Bae SH, Bae KH, Kim JA, Seo YS (2001) RPA governs endonuclease switching during processing of Okazaki fragments in eukaryotes. Nature 412:456–461
107. Kim K, Biade S, Matsumoto (1998) Involvement of flap endonuclease 1 in base excision DNA repair. J Biol Chem 273: 8842–8848
108. Brand M, Moggs JG, Oulad-Abdelghani M, Lejeune F, Dilworth FJ, Stevenin J, Almouzni G, Tora L (2001) UV-damaged DNA-binding protein in the TFTC complex links DNA damage recognition to nucleosome acetylation. EMBO J 20:3187–3196
109. Ikura T, Ogryzko VV, Grigoriev M, Groisman R, Wang J, Horikoshi M, Scully R, Qin J, Nakatani Y (2000) Involvement of the TIP60 histone acetylase complex in DNA repair and apoptosis. Cell 102:463–473
110. Weiss G, Puschendorf B (1988) The maximum of the histone acetyltransferase activity precedes DNA-synthesis in regenerating rat liver. FEBS Lett 238:205–210
111. Talasz H, Weiss G, Puschendorf B (1990) Replication-linked histone acetylation in rat liver tissue is sensitive to alkylating agents. FEBS Lett 264:141–144
112. Belyaev ND, Keohane AM, Turner BM (1996) Histone H4 acetylation and replication timing in Chinese hamster chromosomes. Exp Cell Res 225:277–285
113. Burke TW, Cook JG, Asano M, Nevins JR (2001) Replication factors MCM2 and ORC1 interact with the histone acetyltransferase HBO1. J Biol Chem 276:15397–15408
114. Aoki E, Schultz RM (1999) DNA replication in the 1-cell mouse embryo: stimulatory effect of histone acetylation. Zygote 7:165–172
115. Takei Y, Swietlik M, Tanoue A, Tsujimoto G, Kouzarides T, Laskey R (2001) MCM3AP, a novel acetyltransferase that acetylates replication protein MCM3. EMBO Rep 2:119–123
116. Ritzi M, Knippers R (2000) Initiation of genome replication: assembly and disassembly of replication-competent chromatin. Gene 245:13–20
117. Bousset K, Diffley JF (1998) The Cdc7 protein kinase is required for origin firing during S phase. Genes Dev 12:480–490
118. Jackson V, Shires A, Tanphaichitr N, Chalkley R (1976) Modifications to histones immediately after synthesis. J Mol Biol 104:471–483
119. Parthun MR, Widom J, Gottschling DE (1996) The major cytoplasmic histone acetyltransferase in yeast: links to chromatin replication and histone metabolism. Cell 87:85–94
120. Verreault A, Kaufman PD, Kobayashi R, Stillman B (1996) Nucleosome assembly by a complex of CAF-1 and acetylated histones H3/H4. Cell 87:95–104
121. Shibahara K, Stillman B (1999) Replication-dependent marking of DNA by PCNA facilitates CAF-1-coupled inheritance of chromatin. Cell 96:575–585
122. Meijsing SH, Ehrenhofer-Murray AE (2001) The silencing complex SAS-I links histone acetylation to the assembly of repressed chromatin by CAF-I and Asf1 in Saccharomyces cerevisiae. Genes Dev 15:3169–3182
123. Martin SG, Laroche T, Suka N, Grunstein M, Gasser SM (1999) Relocalization of telomeric Ku and SIR proteins in response to DNA strand breaks in yeast. Cell 97:621–633
124. Fyodorov DV, Kadonaga JT (2001) The many faces of chromatin remodeling: SWItching beyond transcription. Cell 106:523–525
125. Luo J, Su F, Chen D, Shiloh A, Gu W (2000) Deacetylation of p53 modulates its effect on cell growth and apoptosis. Nature 408:377–381
126. Luo J, Nikolaev AY, Imai S, Chen D, Su F, Shiloh A, Guarente A, Gu W (2001) Negative control of p53 by Sir2alpha promotes cell survival under stress. Cell 107:137–148
127. Vaziri H, Dessain SK, Eaton EN, Imai SI, Frye RA, Pandita TK, Guarente L, Weinberg RA (2001) hSIR2 (SIRT1) Functions as an NAD-dependent p53 deacetylase. Cell 107:149–159

128. McMurry MT, Krangel MS (2000) A role for histone acetylation in the developmental regulation of VDJ recombination. Science 287:495–498
129. Spilianakis C, Papamatheakis J, Kretsovali A (2000) Acetylation by PCAF enhances CIITA nuclear accumulation and transactivation of major histocompatibility complex class II genes. Mol Cell Biol 20:8489–8498
130. Tomita A, Towatari M, Tsuzuki S, Hayakawa F, Kosugi H, Tamai K, Miyazaki T, Kinoshita T, Saito H (2000) c-Myb acetylation at the carboxyl-terminal conserved domain by transcriptional co-activator p300. Oncogene 19: 444–451
131. Bergel M, Herrera JE, Thatcher BJ, Prymakowska-Bosak M, Vassilev A, Nakatani Y, Martin B, Bustin M (2000) Acetylation of novel sites in the nucleosomal binding domain of chromosomal protein HMG-14 by p300 alters its interaction with nucleosomes. J Biol Chem 275:11514–11520
132. Herrera JE, Sakaguchi K, Bergel M, Trieschmann L, Nakatani Y, Bustin M (1999) Specific acetylation of chromosomal protein HMG-17 by PCAF alters its interaction with nucleosomes. Mol Cell Biol 19:3466–3473
133. Munshi N, Merika M, Yie J, Senger K, Chen G, Thanos D (1998) Acetylation of HMG I (Y) by CBP turns off IFN beta expression by disrupting the enhanceosome. Mol Cell 2:457–467