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Mammalian histone acetyltransferases and their complexes

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Abstract. One of the key questions in the current molecular genetics of eukaryotes is how genetic information is retrieved from tightly packed chromatin. Acetylation of core histone N-termini is implicated in the regulation of chromatin function, and I summarize what is known about the mammalian enzymes that promote this post-translational histone modification. Chromatin is important in gene expression not only because of the accessibility problem that it poses for the transcriptional machinery but also with regard to the phenomenon of chromatin memory, i.e. the ability of alternative chromatin states to be maintained through many cell divisions. This phenomenon is believed to be central to epigenetic inheritance [1], an important concept in developmental biology, which is also emerging as a contributing factor in cancer and other health disorders. Analyses of the composition of large multiprotein acetyltransferase complexes suggest their role in the mechanisms of epigenetic inheritance. The review will discuss some models pertinent to this function of histone acetyltransferases.

Key words. Transcription; gene expression; histone acetylation; chromatin; epigenetic inheritance; multiprotein complexes; histone-like proteins.

Introduction

A key distinguishing characteristic of the eukaryotic genome is its tight packaging into chromatin, a hierarchically organized complex of DNA and histone and non-histone proteins. The past several years have seen substantial progress in elucidating how the eukaryotic genome operates in the chromatin context. Of the different ways to modify chromatin, one of the most extensively studied is acetylation of lysine residues of the core histone N-termini. Its relation to the regulation of gene activity was suggested more than 30 years ago [2]. Following the groundbreaking work of the Allis group [3], many previously known coactivators of transcription were found to be histone acetyltransferases (HATs). Conversely, many histone deacetylases (HDACs) have been identified as corepressors of transcription. A convincing mechanistic link between this histone modification and regulation of gene expression has been established [4, 5]. These findings provide us with necessary tools to address further questions of the precise role of histone acetylation in the regulation of chromatin function. They also promise to provide us with new therapeutic targets for a variety of health disorders.

This review will focus on mammalian HATs and emphasize what the study of their interaction partners tells us about the physiological role of these enzymes. In particular, we will review data that implicate some of these acetyltransferases in epigenetic inheritance. For a more general perspective on the subject of acetylation, the reader is referred to recent reviews [6–8].

Mammalian acetyltransferases and their targets

Known and putative mammalian HATs and their targets are listed in table 1. Recent developments implicate these enzymes in an expanding number of cellular activities, from transcription regulation to replication to apoptosis. Although histone acetylation is acknowledged to play an important role in function of chromatin, little is known yet about its exact mechanistic role. The functional consequences of acetylation are likely to differ from one histone type to another, and even between different lysine positions on the same histone molecule [9]. One argument in favor of this possibility is often a narrow and non-overlapping substrate specificity of different HATs. The extreme examples are yGCN5 and PCAF, which acetylate

Table 1. Known and putative mammalian histone acetyltransferases.

Name	Size, kDa	Targets	Structural features	Function	Medical significance	First HAT references
PCAF GCN5	95	H3/H4; H3[a] [15], nonhistone proteins[b]	bromodomain, N-terminal p300/CBP interacting domain	coactivator of transcription	regulation of cell cycle [76; 77], target of viral oncoproteins [76; 78–80]	[76]
TAFII250	250	H3/H4; non-histone proteins[b]	bromodomain, Kinase domains [81], TBP-binding repressive domain [82]	coactivator of transcription (subunit of TFIID)	regulation of cell cycle [83, 84], target of HIV Tat [85]	[86]
p300 CBP	260	H3, H4, H2A, H2B; nonhistone proteins[b]	bromodomain, PHD finger, zinc fingers	coactivator of transcription	fusions in leukemia, Rubinstein-Taybi syndrome [87]	[88, 89]
SRC-1 ACTR	150	H3/H4	LXXLL motifs PAS/bHLH domain	nuclear receptor coactivator	ACTR amplification in breast and other cancers [90; 91; 92]	[93, 94]
TIP60	60	H3/H4/H2A; H4/H2A[a]	chromodomain	coactivator of transcription, Repair	cellular response to DNA damage [16], target of HIV Tat [95]	[95]
MORF	2000	H3/H4/H2A	C-terminal activator and n-terminal repressor domains	activator/repressor	neurogenesis[d] [97]	[98]
hMOF	50[c]	H3/H4/H2A	chromodomain	dosage compensation?		[99]
HBO1	70	H3/H4		replication/silencing?		[100]
MOZ	225	ND[e]	zinc finger, acidic domain	regulation of transcription?	fusion with CBP or TIF2 correlate with AML [101]	[70, 102]
TFIIIC90 TFIIIC110 TFIIIC220	90 110 220	H3 H2A/H4? H2A/H4?	zinc fingers	relieving chromatin repression of Pol III transcription		[53, 54]
ATF-2	50	H4/H2B	bZIP DNA binding domain	activation of transcription		[17]

[a] Targets of the corresponding HAT complexes on nucleosome substrates.
[b] See review [8] for more information.
[c] Molecular weight of the C-terminal part of the protein.
[d] Based on analysis of *Querkopf* mutant in the probable mouse homologue of MORF.
[e] The HAT activity has not been determined.

preferentially lysine 14 of H3 [10–12]; and *Drosophila* MOF, which targets mainly lysine 16 of H4 [13]. Additional evidence is distinct genome-wide acetylation patterns often observed for different histones and lysine positions [14]. Complicating the analysis of HAT function is the finding of nonhistone substrates of the acetyltransferases [8].

More clues to the physiological role and in vivo targets of particular acetyltransferases will be provided by analyzing their interaction partners, as most of the acetylation in vivo appears to be done by large multiprotein complexes, reaching megadaltons in size. Examples from humans are PCAF and TIP60 HAT complexes. The HATs themselves serve as the catalytic subunits of these complexes, with their substrate specificity depending on the interactions with other proteins [15, 16].

Current models of transcription regulation involving chromatin modifiers rely on their recruitment by transcriptional activators (or repressors) that recognize specific DNA sequences and bring the chromatin-modifying activities to the sites of transcription. In the case of transcription-related HATs, the only known exception to date is ATF-2 [17], a transcription factor that recognizes a specific DNA sequence, and at the same time has an intrinsic HAT activity. Due to their comparatively weak and transient nature, we will not consider the interactions between transcription factors and HATs (or other coactivators) as a subject of this review. We will focus on more stable multiprotein complexes that are believed to be recruited as functional entities to the chromatin targets and have been biochemically characterized.

Complexes containing histonelike proteins

This family of HAT complexes comprises TFIID [18], PCAF/GCN5 [15], STAGA [19] and TFTC [20]. These complexes share number of identical subunits (table 2), most notably, H3 histone-like TAF31 and H2B-like TAF20/15, whereas others are very similar: PCAF/GCN5 have a PAF65α and PAF65β, similar to WD40-containing hTAFII100 and H4-like hTAFII80, correspondingly. In addition, both complexes possess a bromodomain containing acetyltransferase (PCAF/GCN5 or TAFII250). Unique for TFIID is the TATA-binding protein TBP and some additional TAFs (table 2). GCN5/PCAF complexes contain Ada2, Ada3, Spt3 and TRRAP proteins, absent in TFIID.

The function of TFIID, the most extensively studied of these complexes, was originally investigated in the chromatin-independent context [18, 21]. It plays an essential role in the preinitiation complex assembly, with TBP and TAFs involved in recognition of core promoter sequences [18]. It is also believed to contribute to the communication between transcriptional activators and the basal transcriptional machinery [21].

The parallel between TFIID and PCAF/GCN5-containing complexes suggests that their functions are similar. Accordingly, it was shown that TFTC can mediate activation of transcription in vitro, although it does not contain TBP, previously considered necessary for transcription activation [20]. Furthermore, genome-wide studies confirm that yTFIID and SAGA (yeast GCN5-containing complex) can in many cases compensate for each other in vivo. Approximately 25% of yeast genes require either TAF145 or GCN5 (the acetyltransferase subunits of the yTFIID and SAGA complexes, correspondingly) for normal expression [22].

As expected from the differences in yTFIID and SAGA composition, the genome-wide analysis demonstrates that these complexes have unique functions as well. Thirty percent of the yeast genome is dependent on TFIID-specific subunits only, whereas 12% of the genome depends on SAGA-specific subunits [22]. Interestingly, some genes require both TFIID and SAGA for normal levels of expression.

Table 2. Composition of the HAT complexes containing histone-like proteins.

	TFIID [18]	PCAF/ GCN5 [15]	STAGA [19]	TFTC [20, 103]
TATA binding	TBP	–	–	–
HAT	TAFII250	PCAF/ GCN5-S[a]	GCN5-L	GCN5-L
WD40 repeats	TAFII100	PAF65α	ND[b]	TAFII100 and PAF65α
H3-like	TAFII31	TAFII31	TAFII31	TAFII31
H4-like	TAFII80	PAF65β	ND[b]	TAFII80 and PAF65β
H2A-like	TAFII135	–	–	TAFII135
H2B-like	TAFII20/15	TAFII20/15	ND	TAFII20/15
Histone fold[c]	TAFII 28	hSPT3	hSPT3	hSPT3
Histone fold[c]	TAFII18	hSPT3	hSPT3	hSPT3
ATM-like	–	TRRAP/ PAF400	ND	TRRAP/ PAF400
Initiator interaction	TAFII150	ND	ND	TAFII150
	TAFII55	ND	ND	TAFII55
	TAFII30	TAFII30	ND	TAFII30
	–	hADA3	ND	hADA3
	–	hADA2	ND	ND

[a] Epitope-tagged PCAF or GCN5-S were used in purification of these complexes from HeLa cells.

[b] TAFII100 and TAFII80 are not present in the STAGA complex [19]; however, the presence of PAF65α and PAF65β remains to be determined.

[c] The TAF(II)18 and TAF(II)28 atypical histone fold motifs are also present in the N- and C-terminal regions of the SPT3 proteins [104].

Histone octamer-like structure

Structural and biochemical studies strongly suggest that a histone octamer-like substructure exists in TFIID [23–25] and, by extension, in the PCAF/GCN5-containing complexes [15]. Genetic evidence from yeast also supports that the histone-like TAFs form a functional entity [26]. More recent identification of the H2A-homologous subunits of TFIID and SAGA complexes, previously unaccounted for, demonstrates the predictive power of the octamer structure model [27, 28].

The octamer-like structure in TFIID might simply reflect an evolutionary relation between histones and TAFs [29]. Histone fold is an ancient protein-protein interaction motif [30–32], identified in a number of proteins functioning mostly in DNA metabolism. Aside from the protein-protein interactions, the TAF-histone similarity might not have any other functional significance.

Alternatively, the histone octamer-like structure could recapitulate some additional functions of the regular histone octamer. Based on the interactions between TFIID and promoters in vitro, it was suggested the TAFs organize DNA in the nucleosome-like structure [33–35]. An intriguing consequence of this idea is that upon transcriptional activation, the octamer-like structure could replace the regular histone octamer and therefore have an architectural role in the establishment of the active state of a gene. In this respect, the absence of regions corresponding to histone amino-terminal tails in the TAFs might be essential to the function of the octamer structures. Dynamic acetylation of the histone tails relieves their repres-

Table 3. Characterized and putative mammalian histone acetyltransferase complexes.

HAT complex	General reference	Histone targets	Function
TFIID [86]	[18]	H3	coactivator of transcription
PCAF/GCN5 [15, 19, 103]	[15, 19, 103]	H3	coactivator of transcription
TFIIIC [53, 54]	[105]	H3/H4/ H2A	pol III transcription
TIP60 [16]	[16]	H4/H2A	coactivator of transcription, Repair, apoptosis
HBO1 [100]	[100]	H3/H4	replication? Silencing?
Mediator?[a] [106]	[107]	H3?[a]	coactivator of transcription
MSL?[b]	[13]	H4?[b]	dosage compensation?[b]
Elongator?[b] [108]	[109]	H3/H4/ H2A/ H2B?[b]	transcription elongation[b]

[a] HAT activity of the human mediator might be expected on the basis of HAT activity of the yeast mediator complex.

[b] Existence of these complexes might be expected on the basis of human homologues of MOF [61] and Epl3 (V.O.), the HAT subunits of corresponding *Drosophila* and yeast complexes.

sive role in chromatin function [36, 37]. Their abolishment in the octamer-like structure would lead to a 'permanently activated nucleosome', unable to recruit corepressors or participate in formation of repressive higher-order chromatin structure. Compared with acetylation, this might be an alternative, more suitable for the constitutively active genes such as housekeeping or lineage-specific genes [15].

Despite the esthetic power of the nucleosome-like hypothesis, direct evidence to support it is scarce. Moreover, crystallographic analysis of the nucleosome structure at the 2.8 Å resolution [38] does not favor the nucleosome-like model. The arginine residues in the histone-fold domains, contributing significantly to histone-DNA interactions within the nucleosome, are poorly conserved in the TAFs and PCAF-associated factors (PAFs). Thus, the mode of interaction between TAF/PAFs and DNA might be different from that in the nucleosome [39].

It could be argued, however, that these arginine residues might serve to accommodate almost any DNA sequence wrapped into a nucleosome. On the other hand, the TAFs recognize a particular DNA sequence [40, 41], and the change of arginines into other residues could better serve this specialized interaction. Alternatively, other subunits in the TFIID/PCAF complexes could also contribute to the stability of the nucleosome-like structure.

Regardless of the ability to wrap DNA into a nucleosome-like structure, the cell can still recognize and utilize the octamer-like structure just as it recognizes the regular histone octamer. In this respect, it is noteworthy that the WD40-repeat subunits of the TFIID and PCAF/GCN5 complexes are associated with the histone-like subunits both functionally [26] and structurally [15, 42]. They might play a role analogous to the WD40-repeat RbAp46/48 proteins, known to interact with core histones and participate in chromatin replication and remodeling [43, 44]. A number of other nuclear proteins shown to bind core histones, such as lamins [45, 46], might also recognize the histone-like TAFs instead of histones.

The possible functional significance of the octamer-like structure might be also related to TFIID interaction with the downstream promoter sequences via the histone-like TAFs [40, 41]. A protein bound to DNA is generally expected to roadblock the RNA polymerase progression along the template. On the other hand, such phenomena as nucleosome remodeling [47, 48] or chromatin disruption during Pol II elongation [49] illustrate that the regular histone octamer structure allows the tight packaging of DNA to be compatible with the dynamic nature of chromatin. One might speculate that some octamer-like properties of the TAFs (either intrinsic to the octamer structure or recognizable by external proteins) can serve a similar function and make the stable binding of TFIID with downstream promoter DNA compatible with transcription. Consistent with this interpretation, comparison of single- and multiple-round transcription assays in vitro indicates that TAFs play a role in facilitating reinitiation events [50].

Thus, although evidences towards the nucleosome-like structure formed by the histone-like factors are limited, the structural similarity between the histone octamer and the octamer-like structures in the TFIID and PCAF complexes could have an additional functional significance beyond their (in)ability to wrap DNA. In this respect, it is noteworthy that protein fusion events, a common occurrence in the evolution of interacting proteins [51], have not been observed between H3 and H4 (or H2A and H2B) histones or corresponding TAFs, suggesting that in all of these cases the histone folds do not serve only to mediate protein-protein interactions.

TFIIIC

Many small non-protein-coding RNAs, such as tRNAs, 5S RNA, U6 snRNA and others are synthesized by RNA polymerase III [52]. The short size of Pol III genes and the highly efficient nature of Pol III-dependent transcription makes it likely that the Pol III-dependent genes, when transcribed, are not organized into a nucleosome structure, as they are maintained in transcriptional complexes undergoing multiple rounds of reinitiation. Thus, once established, Pol III-dependent transcription

may not have to deal with chromatin. Nevertheless, during activation (and replication) of the Pol III-dependent gene, the nucleosomes would still pose a problem. TFIIIC, a general transcription factor in the RNA polymerase III basal machinery, has been reported to alleviate chromatin-mediated transcriptional repression in vitro [53]. Not surprisingly, human TFIIIC possess HAT activity, essential for its chromatin-combating role. Moreover, three different components in hTFIIIC were shown to possesses independent HAT activity in an in-gel assay [53, 54] and are distinct with regard to acetylation profile.

Comparing Pol II- and Pol III-dependent systems, TFIIIC appears to be similar to TFIID. It has HAT activity, presumably needed to overcome the chromatin repression. It is the first factor to be bound to the promoter. It has contacts with DNA downstream of transcription initiation start, which does not interfere with transcription [55, 56]. As suggested in the previous section, the octamer-like properties of TAFs might be utilized to make the binding of TFIID to downstream promoter sequences compatible with RNA polymerase progression along the DNA template. To serve the same purpose, much stricter constraints on the sequences of Pol III-transcribed genes might have forced the corresponding proteins to diverge beyond recognition.

TIP60 complex

TIP60 complex is another multiprotein acetyltransferase recently purified by the Nakatani group [16]. Its specificity is distinct and nonoverlapping with the PCAF and TFIID complexes: whereas the main target of the PCAF complex is the lysine 14 of H3 histone, the TIP60 complex prefers H4 and H2A histones. Intriguingly, the PCAF/GCN5 complex subunit PAF400/TRRAP is also present in the TIP60 complex. However, no traces of other PCAF complex subunits are found in the TIP60 complex and vice versa [V. V. Ogryzko, Y. Nakatani, unpublished]. Overall, this complex appears to be the human counterpart of the NuA4 complex [57, 58], as it has homologues of all subunits present in the NuA4. A notable exception is TAP54α and TAP54β. The yeast homologues of these proteins are not found in the NuA4 complex.

TAP54α,β are human homologues of the bacterial ATPase/helicase RuvB [59], involved in recombination and recombination-dependent repair. RuvB acts as a motor protein that catalyzes migration of the Holliday junction during recombination and repair. Its similarity to TAP54 α,β, together with the association of TIP60 with ATM-like PAF400/TRRAP, implicates TIP60 acetyltransferase in DNA repair. Consistent with this idea, a dominant-negative HAT mutation of TIP60, introduced into HeLa cells, negatively interferes with cellular response to DNA damage [16].

Intriguingly, the 100-kDa protein in the TIP60 complex is a human homologue of *Drosophila* E(Pc) (enhancer of polycomb) gene product. E(Pc) is known to affect both polycomb group (PcG) regulation and position effect variegation (PEV), and is the only gene known so far that links these two distinct cases of gene silencing in fruit flies [60]. All other genes involved in PcG regulation and PEV are different; nevertheless, both of these phenomena rely on higher-order chromatin structure in their mechanism of silencing. This implicates E(Pc) protein and thus TIP60 complex, which contains E(Pc), in a more general aspect of higher-order chromatin functioning, crucial for both PcG- and PEV-dependent gene silencing. Supporting the idea of TIP60 complex involvement in higher-order chromatin structure is the presence of a chromodomain in TIP60 itself and its close homology to *Drosophila* MOF, the HAT subunit of the dosage compensation complex [61].

HAT complexes and epigenetic inheritance

In addition to their roles in activation and/or repression of gene activity, HATs are likely to play a role in the maintenance of a particular state of a gene. Namely, they might be involved in the mechanisms of epigenetic inheritance [62], an important concept in developmental biology [1, 63] which is also emerging as a contributing factor to oncogenesis and other health disorders [64, 65].

Acetylation of histone tails was proposed to serve as an epigenetic code that marks alternative transcriptional states of a gene and can be propagated with generations of cell divisions independently from the genetic sequence [14, 66]. Although any HAT could contribute to this epigenetic coding, the composition of TFIID/PCAF and TIP60 HAT complexes suggests alternative mechanisms of epigenetic inheritance involving these HATs.

Based on the potential for the histone-like factors to form a nucleosome-like structure on DNA, it was suggested that TFIID might serve as a specialized chromatin component that fulfills the topological requirements necessary to mediate and maintain the inducibility of genes [35]. The model of how the octamer-like structure in the TFIID and PCAF/GCN5 complexes can contribute to the maintenance of an active state of chromatin through generations of cell divisions is shown in figure 1 A. It also incorporates the finding of a specific interaction between the PCAF/GCN5 and TAFII250 bromodomains and acetylated lysines or histone tails [67, 68]. Regardless of its ability to wrap DNA into a nucleosome-like structure, the remarkable stability of TFIID association with promoter DNA in vitro [18] and the fact that a significant portion of TFIID (as judged by analysis of TBP and

TAFII20, which is also a part of PCAF/GCN5 complexes) remains associated with mitotic chromosomes in the cell cycle [69], strongly suggests its involvement in the maintenance of a particular chromatin state. Some octamer-like properties of the histone-like TAF subcomplex in TFIID (and PCAF/GCN5 complexes) might remain significant in this regard.

Unlike TFIID and PCAF, the TIP60 complex appears not to contain histone-like factors. On the other hand, the TIP60 relatives in yeast (SAS2 and SAS3) and *Drosophila* (MOF), have been implicated in epigenetic regulation of gene expression [61, 70]. The model for an epigenetic role of TIP60 is based on its possible involvement in the higher-order aspects of chromatin structure and functioning (see previous section). According to the idea proposed here (fig. 1 B), the newly replicated chromatin exists in a 'ground state' which is neither transcriptionally active nor silenced, with the histone tails engaged in the interactions between the neighboring nucleosomes. In order for chromatin to recruit corepressors or coactivators

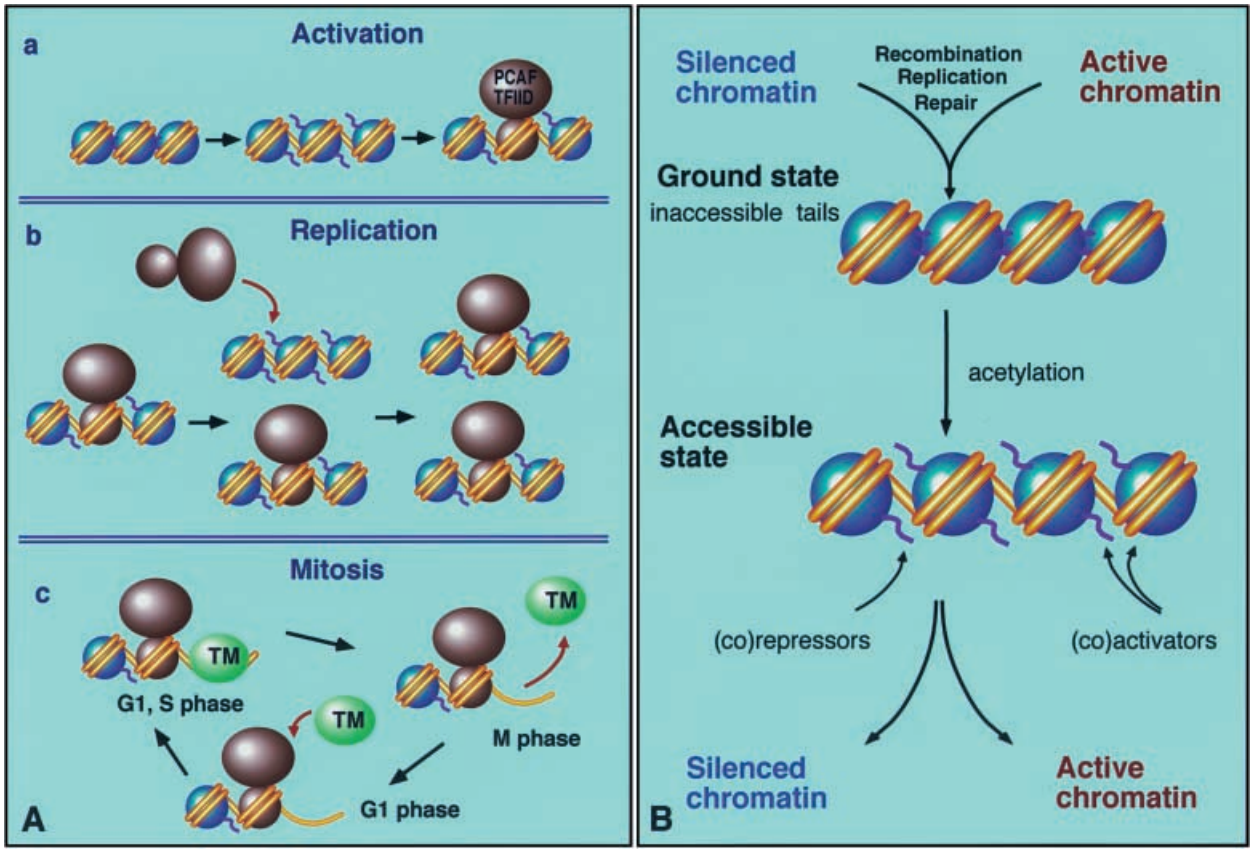

Figure 1. Histone acetyltransferases in epigenetic inheritance. (*A*) Role of histone octamer-like structure and PCAF/TAFII250 bromodomains in establishment and maintenance of an active state of chromatin. (*a*) After acetylation of a nucleosome, PCAF/TFIID complexes can replace it with the histone octamer-like structure. Given that the histone-like factors in the PCAF/TFIID complexes do not have the N-terminal tails, this will create 'permanently activated' nucleosome, resistant to deacetylation. (*b*) During replication, the PCAF/TFIID complexes remain associated with one of the daughter strands. A second complex can be recruited to the sister strand via interaction of the PCAF/TAFII250 bromodomain with an acetylated nucleosome on this strand. (For the sake of space, the 'ground state' step (see fig. 2) is skipped.) This recruitment via bromodomain can contribute to replication of the active chromatin state. (*c*) During mitosis, most of the transcription factors and other components of transcriptional machinery (TM) are displaced from DNA [111]. The nucleosomes, and presumably, nucleosome-like structure in the PCAF/TFIID complexes remain on the DNA. After completion of mitosis, the PCAF/TFIID complex can facilitate recruitment of transcriptional machinery back to the site of active transcription. Thus, these complexes can provide a molecular bookmark that helps to reestablish transcription after mitosis [112]. (*B*) Transient histone acetylation in the mechanisms of epigenetic inheritance. Newly deposited acetylated histones H3 and H4 are deacetylated after their assembly into nucleosome (for review see [113]. On other hand, histone tails have been suggested to be involved in internucleosome interactions [38, 110]. Accordingly, we propose that the newly synthesized chromatin is in a 'ground state', with deacetylated histone tails engaged in the interactions between the neighboring nucleosomes. The ground state is neither transcriptionally active or silenced, and in order to be converted to either of these states it has to recruit silencing or activating factors, which could be accomplished through interaction of the histone tails with such repressors as Tup1, Sir3 or Sir4 [114, 115], or a bromodomain of some coactivators [67, 68]. For this recruitment to occur, the histone tails have to be made accessible and liberated from their interaction with the neighboring nucleosome, which is accomplished via their acetylation by TIP60 or other acetylases. In this way histone acetylation may be required for epigenetic inheritance. Whether the resulting chromatin state is silenced or active could depend on the replication timing or/and the environment of the particular gene.

and mature into either a silenced or active state, these tails have to be liberated from the internucleosome interactions, which is accomplished by their acetylation by the TIP60 complex (or other MYST acetylases). In contrast to the idea of an epigenetic code, which relies on stable propagation of a modified histone state through generations of cell divisions, the model proposed here allows for a transient acetylation of histones, sufficient to provide a window of opportunity for cofactor recruitment. The hypothesis of TIP60 acetylating newly synthesized chromatin is consistent with the specific binding of TIP60 complex to alternative DNA structures, which would direct it to the sites of DNA metabolism [M. Grigoriev, personal communication]. In agreement with the proposed role of TIP60 in epigenetic inheritance, mutations in the yeast NuA4 complex subunit Act3/Arp4 (and, probably, its catalytic subunit Esa1 as well [58]) cause variegated expression of some genes [71], reminiscent of the phenomena of position effect variegation [72, 73].

Importantly, the concept of maintaining a particular state of gene activity is more general than that of epigenetic inheritance. Even in nondividing cells, a particular state of chromatin faces such challenges as, for example, DNA repair [74, 75]. Links to DNA damage response, seen in the case of TIP60 acetyltransferase complex [16], might reflect its role in the maintenance of chromatin states in processes other than replication.

Conclusion

Study of histone acetylation is helping us to understand how the human genome operates in the context of chromatin. New insights into the function of histone acetyltransferases come with identification of interaction partners of these enzymes. Future studies will show the relevance of models for the role of PCAF/TFIID and TIP60 in epigenetic inheritance, discussed in this review.

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