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Histone acetylation and disease

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Abstract. Differential acetylation of histones and transcription factors plays an important regulatory role in developmental processes, proliferation and differentiation. Aberrant acetylation or deacetylation leads to such diverse disorders as leukemia, epithelial cancers, fragile X syndrome and Rubinstein-Taybi syndrome. The various groups of histone acetyltransferases (CBP/p300, GNAT, MYST, nuclear receptor coactivators and TAFII250) and histone deacetylases are surveyed with regard to their possible or known involvement in cancer progression and human developmental disorders. Current treatment strategies are discussed, which are still mostly limited to histone deacetylase inhibitors such as trichostatin A and butyrate.

Key words. HAT; HDAC; histone acetylation; butyrate; TSA; dietary fiber; leukemia; fragile X syndrome.

Introduction

In order to fit in the nucleus, chromosomal DNA has to be condensed about 10,000-fold. The DNA is first wound around a histone octamer core consisting of histones H2A, H2B, H3 and H4 [1]. Further compaction is achieved by assembling higher-order structures with the help of histone H1 [2] and other, nonhistone proteins. The N- and C-terminal tails of the nucleosomal core undergo post-translational modifications and help regulate chromatin assembly and/or DNA accessibility. Among these modifications, acetylation of nucleosomes has been extensively investigated in recent years, leading to a general model of how acetylation alters the transcriptional potential of nucleosomal DNA.

The N-terminal tails of the core histones are rich in lysines and are therefore positively charged under physiological conditions. It is assumed that this allows an intimate interaction with either the negatively charged backbone of the DNA and/or with adjacent nucleosomes, leading to a ‚tight‘ nucleosome formation and higher-order chromatin folding. Acetylation neutralizes this charge and may weaken interactions with the DNA, resulting in an ‘open’ chromatin conformation [3, 4]. Such a conformation facilitates access for transcriptional regulators [5, 6].

Generally, actively transcribed chromatin regions have been associated with hyperacetylation and histone acetyltransferase (HAT) recruitment, but histone deacetylases (HDACs) are recruited to accessible chromatin as well. HDAC-mediated deacetylation is thought to promote the return to a repressive, higher-order chromatin structure. This balance between acetylation and deacetylation is an important factor in regulating gene expression and is thus linked to the control of cell fate. As a consequence, hyperacetylation of normally silenced regions or deacetylation of normally actively transcribed regions can lead to various disorders, including developmental and proliferative diseases.

In this review, we will first investigate acetylation during development and differentiation and describe developmental abnormalities induced by germ-line acetylation defects. The much better understood and more widely investigated somatic mutations and their inherent implications in cancer development or progression will then be covered in more detail. The major groups of histone acetyltransferases and deacetylases are discussed and linked to current treatment strategies.

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Histone acetylation in development and differentiation

The significance of differential histone acetylation during development has been documented in a number of organisms. In *Tetrahymena,* histone acetylation is upregulated during macronuclear differentiation. Studies in the sea urchin revealed a correlation between histone acetylation and the degree of commitment to differentiation of specific cell types. Histone acetylation has also been associated with gastrulation in frogs and in *Xenopus.* Several reports have furthermore investigated the interplay between cell lineage differentiation and global histone acetylation. For example, estradiol treatment of immature chickens leads to increased liver histone acetylation, and histone acetyltransferase activity varies over time in differentiating chick myoblasts. Similarly, acetylation of chromosomal proteins in the rat skeletal muscle decreases as development progresses. Related to these reports are the numerous studies linking inhibition of deacetylases in human cancer cells to an increase in differentiation-associated markers. (Chromosomal modifications during development are reviewed in [7]).

In eutherian species, inactivation of the second X chromosome occurs in the cells of female progeny. While the exact mechanism of this inactivation is not yet clear, there is a compelling link between histone underacetylation and inactivation of the X chromosome (for a review see [8]). Interestingly, in patients containing aberrant copy numbers of the X chromosome (polysomy X), incomplete deacetylation of all X chromosomes was observed [9]. The syndrome of fragile X chromosome provides another link between histone acetylation and human hereditary disorders and will be discussed below.

Apart from these observations on the general acetylation state of chromosomal proteins, the role of specific histone acetyltransferases in development and differentiation has been investigated. In this context, it is important to note that HAT substrates are not limited to histones, but also include a range of transcription factors, such as p53, E2F-1 and MyoD [10–12]. Substrate specificity seems to be regulated by additional components of the large multimeric complexes containing HATs and HDACs. Inappropriate acetylation states of transcription factors may therefore contribute to diseases provoked by unbalanced enzymatic activities.

All HATs contain an acetyltransferase domain (proven or suspected), but sequence comparison allows the division into subfamilies according to additional shared domains.

CBP/P300

The CBP/p300 family of acetyltransferases consists of two highly homologous transcriptional coactivators, both of which are ubiquitously expressed and play critical roles in cell growth, differentiation, apoptosis and transformation [13]. CBP was originally identified as a coactivator for the transcription factor CREB (hence its name, CREB binding protein) [14], whereas p300 was isolated as a target of the adenoviral transforming protein E1A [15]. Although this family of proteins is considered a unique class of HATs, there are considerable homologies between the enzymatic domains of CBP/p300 and the GNAT family. Recombinant CBP/p300 has been shown to acetylate all four histones in free-histone form as well as in nucleosomes, demonstrating higher efficiency and less substrate specificity than the other HAT enzymes. Whereas the acetyltransferases of the GNAT family are found in vivo as subunits of multiprotein chromatin-remodeling complexes [16], the participation of CBP/p300 in such complexes has not been demonstrated to date. Apart from histones, CBP/p300 acetylates a wide variety of transcription regulatory proteins, such as p53, GATA-1, HIV-1 Tat, c-Myb, HNF1 and HNF4, and others ([17, 18], for a review see [19]).

Consistent with the role of CBP/p300 as broad transcriptional regulators, inactivation of CBP or p300 leads to a highly pleiotropic phenotype in *Drosophila* [20], *Caenorhabditis* [21] and mice [22–24]. Interestingly, the arrested endoderm differentiation of *cbp-1 C. elegans* mutants can be restored by repressing the *Caenorhabditis* histone deacetylase hda-1, arguing for the importance of a finely tuned HAT/HDAC balance. (For a review on developmental regulation by CBP/p300 see [25]).

Until recently, few significant differences in the activity of CBP and p300 had been identified in vivo [26, 27], which made it possible to refer to these two acetyltransferases as CBP/p300. However, recent evidence suggests that CBP, and not p300, might be critical for the normal development of the hematopoietic system, and for prevention of hematological malignancies [22]. The important role of CBP in cell transformation is further highlighted by the occurrence of human chromosomal translocations, which fuse CBP to MOZ (monocytic leukemia zinc-finger protein, see also below), or MLL (mixed lineage leukemia). These translocations can lead to leukemia in humans [28, 29].

The tumor-suppressor role of p300 in humans has been investigated as well. Spontaneously occurring mutations in the p300 gene have been associated with various human cancers in the analysis of two primary tumors and a number of cancer cell lines [30, 31]. Whereas CBP seems to be particularly important for the normal functioning of the hematopoietic system, p300 function has not been associated with any specific organ or tissue type, neither in the studies of knockout mice [24], nor in the analysis of tumors and cancer cell lines derived from humans.

Mutations in the human CBP gene were reported to be associated with Rubinstein-Taybi syndrome (RTS), a de-

velopmental haploinsufficiency disorder characterized by mental retardation, craniofacial defects, broad big toes and broad thumbs [32]. This syndrome is relatively common, accounting for 1 of 300 patients with mental retardation. Interestingly, RTS patients do not have a dramatically increased incidence of tumors, the estimate being in the range of 5%. Further evidence for the causal role of CBP in RTS is supported by the study of heterozygous mice lacking a single CBP allele, which demonstrate abnormal pattern formation with partial similarity to RTS [33]. However, it is not known whether diminished acetyltransferase activity of CBP is the cause of RTS.

The GNAT family

The family of Gcn5-related *N*-acetyltransferases (GNATs) contains proteins that share one or several conserved sequence motifs [34]. The first HAT shown to be involved in transcriptional regulation was HAT A from *Tetrahymena* [35], a homologue of yeast Gcn5. Meanwhile, Gcn5 homologues have been identified in a wide range of eukaryotes. Humans express two Gcn5-like proteins: Gcn5 and PCAF (p300/CBP associated factor). Both proteins can interact with p300/CBP [36, 37], participate in similar HAT complexes in the cell [16] and are involved in transcriptional regulation and cell cycle control.

Overexpression of PCAF can lead to growth arrest. This effect may, at least in part, be explained by an unbalanced interaction of PCAF with two important cell cycle regulators: E2F and p53. The transcription factor E2F is known to induce S-phase specific gene expression and is critically involved in promoting S-phase-entry. Acetylation of E2F by PCAF occurs in the DNA-binding region of E2F and increases the transcriptional activity of E2F in vivo. In addition, acetylation stabilized the E2F protein [38].

p53, on the contrary, acts as a tumor suppressor protein by inhibiting cell cycle progression and S-phase entry. Induction of p53 usually leads to posttranslational modifications of the protein; for example, phosphorylation of the C-terminal regulatory domain increases its DNA-binding capacity [39]. Recently, it was shown that acetylation of this domain is also involved in regulating the activity of p53 [40, 41]. Similar to E2F, acetylation of p53 by either PCAF or CBP/p300 increases its DNA-binding activity. Interestingly, acetylation of this site is observed after DNA damage in vivo, an event that leads to p53 induction and cell cycle arrest or apoptosis.

PCAF is therefore involved in two opposing scenarios: it can promote cell cycle progression by activating E2F or it can lead to cell cycle arrest by activating p53. Mutations in regions that control the HAT activity or specificity of PCAF (and possibly other HATs of the GNAT family) are thus expected to have significant effects on cellular proliferation and tumor formation. The first indications that PCAF might be involved in tumor suppression come from viral infection data: oncogenic viral proteins like human adenovirus E1A dissociate existing p300/CBP/PCAF complexes. This is accomplished by competition of the viral oncoproteins with PCAF for the same p300/CBP binding site [37, 42], and viral proteins that have lost the potential to bind to p300/CBP no longer induce transformation [43]. PCAF and GCN5 knockout mice have been described as well [44]. Whereas PCAF-null mice are viable and fertile, GCN5 null mice are embryonic lethal. Human mutations have not been described in either gene, however.

The MYST family

The human members of the MYST family of HAT enzymes currently include MOZ, MORF, HBO1 and Tip60. They all share a MYST homology domain with close sequence similarity; this domain contains an acetyl-coenzyme A (CoA) binding site (a motif shared with other HATs) preceded by an atypical zinc finger. Their known functions, however, differ widely among family members.

Tip60 was isolated in a screen for proteins interacting with the HIV-1 Tat transactivator protein and was subsequently shown to acetylate histones in vitro [45]. Since Tat represses Tip60 HAT activity in vivo, it is possible that Tat represses the transcription of genes normally activated by Tip60 acetylation [46]. Indeed, Tip60 was subsequently shown to be a coregulator for several nuclear hormone receptors [47] and for Bcl-3, a member of the IκB family of transcriptional regulators [48]. A recent publication, however, shows that at least one of Tip60‘s cellular functions, repression of the CREB protein, is independent of its acetyltransferase activity [49]. Tip60 can also presumably interact with a membrane receptor, the interleukin-9 receptor [50], whose deregulation is associated with asthma and T cell oncogenesis. Whether this cytoplasmatic interaction, apart from the known nuclear functions of Tip60, has physiological relevance remains to be shown. The different reports are highly suggestive of an involvement of Tip60 in differentiation and/or proliferation decisions, but the influence of its histone acetyltransferase activity on these processes remains to be shown conclusively.

The link between cancer and the MOZ protein (monocytic leukemia zinc finger protein) is better established. Several different types of translocations are observed in leukemia. In some cases, the N-terminal region of MOZ, containing its MYST domain, is fused to C-terminal portions (which include the HAT domain) of the acetyltransferases CBP or p300 [51–54]. In other cases, MOZ was

found to be fused to C-terminal portions of the transcription factor TIF2 [55–57], which itself interacts with CBP. This could essentially mimic a MOZ/CBP fusion. Furthermore, the TIF2 portion of MOZ/TIF2 fusion proteins contains its own acetyltransferase domain. These different fusions all lead to an association of the HAT and interaction domains of (at least) two different histone acetyltransferases. Therefore, it was hypothesized that the malignant conversion in this type of leukemia is brought about by a misdirection of HAT activity, either of the MOZ, the TIF2 or the CBP/p300 moiety.
The recently identified MORF protein (MOZ-related factor) [58] shows extensive sequence homology to the MOZ protein. However, the connection between cancer and MORF mutations has yet to be established, and the extent of functional similarities between MORF and MOZ is not known at this point.
Finally, a fourth identified human MYST family protein is HBO1, named for histone acetyltransferase bound to ORC1 (origin recognition complex) [59]. Its mechanism of action remains to be more fully investigated, and as of this writing, HBO1 mutations have not been linked to disease.

Nuclear Receptor Coactivators

Nuclear receptors and coactivator proteins are thought to stimulate gene expression by facilitating the assembly of basal transcription factors into a stable preinitiation complex [60]. The HAT activity presumably serves as one of the mechanisms by which these transcription factors gain access to transcriptionally silent chromatin. The human coactivators ACTR, SRC-1 and TIF2 [61–63], which interact with nuclear hormone receptors, are capable of acetylating free or nucleosomal histones H3 and H4. TIF2 is involved in certain types of leukemia, as it forms fusions with the MOZ protein (see MYST family above). Some of these cofactors interact with and are acetylated by CBP/p300 [64–67]. SRC-1 is capable of interacting with PCAF [62], suggesting that multiple HATs are required for the regulation of hormone-dependent transcription.
The role of steroid receptor overexpression in the genesis and progression of breast cancer has been investigated. Some reports suggest a possible correlation between the expression levels of SRC-1 and the clinical responses to the antiestrogen tamoxifen [68], since tamoxifen seems to be more effective in patients with increased levels of SRC-1 expression. Interestingly, in breast cancer, the expression levels of CBP seem to be increased in the intraductal carcinoma tissues as compared with normal mammary glands [69]. Taken together, these data suggest that steroid receptors and HAT coactivators may synergistically play a role in the occurrence and progression of breast cancer.

$TAF_{II}250$

$TAF_{II}250$ (TBP-associated factor) is a subunit of the general transcription factor TFIID. While human $TAF_{II}250$ contains an acetyl-CoA binding site and a bromodomain [70], its HAT region bears little similarity to other known acetyltransferases. In vitro, $TAF_{II}250$ also shows a notably weaker HAT activity than p300/CBP or PCAF [16, 71]. Whereas only a handful of genes have been found to require $TAF_{II}250$ for transcription [72, 73], a temperature-sensitive $TAF_{II}250$ mutant in the Syrian hamster cell line ts13 blocks cell-cycle progression at the nonpermissive temperature [74], clearly demonstrating that $TAF_{II}250$ is an essential gene. This may be the reason why no $TAF_{II}250$ mutations have been found in proliferative disorders.

Histone deacetylases and disease

The activating effect of histone acetyltransferases is counteracted by the presence of histone deacetylases. In humans, eight members of the HDAC family have been cloned so far. Depending on the sequence similarity to yeast proteins, they are grouped into RPD3-like (HDAC1-3,HDAC8) or HDA1-like (HDAC4-7) histone deacetylases. Consistent with the model of transcriptional activation through histone acetylation, HDACs are in general associated with transcriptional repression. Transcriptional repressors like YY1, Mad/Max or NCoR/Smart have been shown to form complexes with histone deacetylases in vitro and in vivo [75]. Similar to HATs, histone deacetylases seem to be organized in multisubunit complexes that are only beginning to be analyzed [75]. Recent findings on the importance of HDACs in cell cycle regulation and gene expression suggest a possible involvement in tumor formation.

HDACs and cell cycle regulation

HDACs are known to associate with two important cell cycle regulators: Mad/Max and RB. Mad/Max heterodimers are essential for the repression of E-box-containing growth stimulatory genes during cellular differentiation [76]. Transcriptional repression by Mad/Max requires the assembly of a multisubunit repressor complex that carries HDAC activity. Disruption of this repressor complex by overexpression of c-Myc or v-Ski results in reinduction of cell cycle progression and transformation [77, 78].
RB is critical for the regulation of S-phase entry in eukaryotic cells. It performs its function through association with the transcription factor E2F and repression of E2F-dependent promoters. In 1998, several laboratories demonstrated that the repressive function of RB is me-

Table 1. Histone acetylation in human diseases; further description in the text.

Disease	Acetylation defect	
Leukemia	HAT fusions MOZ/CBP MOZ/p300 MOZ/TIF-2 MLL/CBP MLL/p300	HDAC-mediated RARα/PML RARα/PLZF AML1 fusions
Epithelial cancers	p300 mutations in colorectal, gastric, breast, pancreatic carcinomas/cancer cell lines	
RTS (Rubinstein-Taybi syndrome)	CBP haploinsufficiency due to monoallelic CBP mutations	
Polysomy X	incomplete deacetylation of all X chromosomes	
Fragile X syndrome	FRM-1 mutations linked to deacetylation and hypermethylation of X chromosome	

diated by its interaction with a histone deacetylase [79–81]. Mutation or deletion of RB disbands this repressive complex and can lead to uncontrolled proliferation and tumor formation.

HDACs and translocations

Some chromosomal translocations result in the fusion of an HDAC-controlled repressor domain to the DNA-binding part of a transcription factor, as in the case of retinoic acid receptor-α (RARα). RARα is usually associated with the retinoid X receptor (RXR) and represses transcription by recruitment of an HDAC complex. Addition of retinoic acid releases the HDAC repressor complex and leads to retinoic acid-responsive gene expression. A variety of leukemias are associated with the expression of fusion proteins resulting from translocations of PML or PLZF to RARα. These fusion proteins are insensitive to physiological doses of retinoic acid, and it is hypothesized that, as a consequence, hematopoietic differentiation is blocked. Indeed, in leukemia patients, inhibition by RARα/PML fusion products can still be relieved by higher, therapeutical doses of retinoic acid. In the case of RARα/PLZF fusions, however, HDAC can also bind to the PLZF repressor domain. This second HDAC repressor complex is insensitive even to high doses of retinoic acid. Only a combination treatment of high levels of retinoic acid together with HDAC inhibitors was successful in overcoming the repressive function of the RARα/PLZF complex [82–84].

Similar to these translocations in leukemia, HDAC-mediated repression seems to block myeloid differentiation in patients in whom the DNA binding domain of AML-1-has been translocated to proteins that inhibit AML-1 dependent transcription, such as ETO, MTG16 and TEL [85]. Although the repressive effect of the translocation/fusion protein is likely to be mediated by HDAC complexes, the molecular mechanism of most AML fusions remains to be elucidated.

HDAC and promoter silencing

Increasing evidence demonstrates the association of histone deacetylase activity in chromatin-remodeling complexes such as NuRD [86, 87]. In addition to the HDAC subunit, NuRD contains components with helicase/ATPase activity, and proteins that specifically bind to methylated DNA [88, 89]. This intriguing finding of a connection between methylation and histone deacetylation allows speculations on the role of HDAC activity in promoter silencing. This link is further documented by the physical association between the methylated DNA-binding protein MeCP2 and HDACs [90, 91]. This transcriptional silencing by the coordinated action of methyltransferases and histone deacetylases is likely to be involved in a variety of transcriptional regulation processes and tumor formation. Transcriptional silencing due to hypermethylation of tumor suppressor genes such as RB, $p15^{ink4b}$ and $p16^{ink4a}$ has been observed in a wide variety of human tumors [92]. For the cdk inhibitor p21, a direct involvement of HDAC activity in promoter suppression has been documented. Treatment of colon cancer cells with HDAC inhibitors such as butyrate and TSA results in an upregulation of p21 expression and subsequent growth arrest [93]. The molecular mechanism of this effect, however, is not completely understood.

Fragile X syndrome

An example of a direct link between the levels of histone acetylation and a severe hereditary disorder in humans is the fragile X syndrome. This syndrome is the most frequently encountered form of inherited mental retardation in humans, characterized by mutations in the *FMR-1* gene on the X chromosome [94], which leads to hypermethylation and transcriptional silencing [95]. In a recent report, the mechanism of transcriptional silencing of the X chromosome through cytosine methylation and histone deacetylation was elucidated [96]. Considerable deacetylation of histones H3 and H4, and hypermethylation of the DNA was observed in the 5′-terminal end of *FMR-1* from fragile X-syndrome cells. Treatment of the cells with a methyltransferase inhibitor restored both methylation and histone acetylation of *FMR-1* to near wild-type levels, and reactivated transcription of the gene. However, treatment with TSA, an inhibitor of deacetylases, did not lead to any detectable transcription of the *FMR-1* locus, even though the acetylation of histone H4 was restored. Taken together, these data suggest a complex mechanism of transcriptional silencing in fragile X syndrome, in

which histone deacetylation may play an important role, albeit subordinate to DNA hypermethylation.

Modeling histone acetylation and cancer

On the basis of the available literature on acetylation and diseases, it is possible to differentiate between three different deregulation mechanisms. First, acetylation disorders may be due to hyperacetylation and concomitant derepression of normally repressed promoters, leading to the presence of a set of proteins at an inappropriate moment. Conversely, underacetylation of a set of promoters could have equally deleterious effects by repressing expression of genes necessary for maintenance of a certain phenotype. In each of these cases, the balance of acetylation and deacetylation is disturbed.

The actual situation encountered in vivo may be more complex, however, in that a misdirection of histone acetyltransferase or histone deacetylase activity to 'wrong targets' could be the disease-triggering process. Such a scenario is being discussed for certain types of leukemia, for instance, where two HAT enzymes are expressed as a fusion protein (see above).

Treatment of any acetylation defect, regardless of scenario, would ideally require an appropriately targeted and enzyme-specific (de)acetylase inhibitor.

Current treatment strategies

Today's treatment strategies are mostly limited to general histone deacetylase inhibitors, some of which have pleiotropic and/or unknown effects in addition to deacetylase repression. Several of these HDAC inhibitors are currently being investigated as potential drugs in leukemia management, since the characteristic translocations of certain leukemia forms ultimately lead to recruitment of an HDAC repressor. The potent deacetylase inhibitor TSA has been shown to release this transcriptional repression, demonstrating a possible treatment strategy for those cases of leukemia where mistargeting of histone deacetylase activity is suspected. Because of its toxicity, however, use of TSA as a treatment agent for leukemia is severely limited. (Other hydroxamates are available, though, and lead likewise to rapid histone acetylation [97]. Toxicity in patients has not yet been reported.) TSA is also effective in inhibiting squamous carcinoma cell proliferation and keratinocyte growth ex vivo. TSA-mediated arrest was found to be irreversible [98]. It is therefore possible to envision a topical application of TSA in skin cancer, limiting some of the toxic side effects.

Other deacetylase inhibitors are currently used in clinical trials of leukemia treatment [99], among them depsipeptide, hybrid polar compounds and sodium phenylbutyrate. The latter has a pleiotropic spectrum of action [100] and exerts only a weak repression of deacetylase activity, but has recently been used successfully in a combination therapy of promonocytic leukemia (PML). A related compound, arginine butyrate, was recently evaluated in a phase I trial on metastatic colorectal cancers in combination with interleukin-2, but induced severe liver damage [101]. Butyrate and its analogs are also currently being evaluated as differentiating agents in prostrate cancers.

Several groups furthermore report a link between dietary fiber uptake and histone acetylation. The protective effects of a high-fiber diet with regard to colon cancer development have been known for some time. A possible mechanism is the production of butyrate through colonic bacterial fermentation of fiber, which inhibits proliferation of colon cancer cell lines. However, although the concentration of butyrate in the colonic lumen exceeds levels that inhibit proliferation of colon cancer cells in tissue culture, these concentrations still allow growth in the colonic crypt (for a review, see [102]). Different dietary fibers may also vary in their efficacy of increasing butyrate production, as several groups found wheat bran superior to oat bran in this regard [103, 104]. A further complication for therapy may be the fact that the sensitivity of adenocarcinoma cells to butyrate can differ, at least in a tissue culture system [105].

The effects of butyrate also include apoptosis induction. Micromolar amounts of arsenic (As_2O_3) likewise lead to growth arrest and apoptosis induction, and, furthermore, can induce hyperacetylation of histones [106]. While active concentrations of arsenic can be achieved in clinical subjects, it is currently unclear if arsenic-induced histone acetylation is the cause of the observed apoptosis.

Other chemical compounds that may shift the balance of histone acetylation are certain cyclic dipeptides. Cyclo-(trp-trp) and cyclo(phe-pro), for example, have very recently been shown to increase histone acetylation in a tumor-derived cell line [107].

Future developments

We are beginning to understand how acetyltransferases and deacetylases work at the transcriptional and cellular level. However, much remains to be done to fully appreciate the involvement of HDACs and HATs in cancer and disease initiation and progression. One of the major challenges in the field of acetylation in the coming years will be to pinpoint the bona fide targets of each of these enzymes and to integrate our knowledge of histone and transcription factor acetylation into a broader context of cellular homeostasis. On the basis of this information, novel drugs and specific treatment strategies might be developed with less side effects than those currently available.

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