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Histone acetylation in gene regulation

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Abstract

Genetic information is packaged in the highly dynamic nucleoprotein structure called chromatin. Many biological processes are regulated via post-translational modifications of key proteins. Acetylation of lysine residues at the N-terminal histone tails is one of the most studied covalent modifications influencing gene regulation in eukaryotic cells.

This review focuses on the role of enzymes involved in controlling both histone and non-histone proteins acetylation levels in the cell, with particular emphasis on their effects on cancer.

Keywords: *nucleosomes; gene expression; acetylation; deacetylation; cancer*

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INTRODUCTION

Eukaryotic chromosomes are highly organized. Chromatin consists of DNA, histones and a plethora of different protein complexes that assist the dynamic changes occurring during DNA replication, cell-cycle progression, regulated-transcriptional and post-transcriptional events, DNA repair and recombination.

Histone proteins play structural and functional roles in all nuclear processes. Nucleosomes are the basic structural units of chromatin and are evolutionarily conserved in all eukaryotes. The nucleosome core particles consist of two copies each of H2A, H2B, H3 and H4 histones, around which 146 base pairs of DNA are wrapped. The H1 linker histone stabilizes the assembly of the octameric core into chromatin-specific higher-order structures [1]. In addition to nucleosomes, the chromatin fiber contains a large variety of additional accessory proteins and numerous histone variants that are not randomly distributed in chromatin but are expressed in developmentally restricted and cell type specific patterns [2]. The yeast and mammalian centromeres contain a variant of histone H3, Cse4/CENP-A, that was found to be essential for centromere assembly and function [3–4]. Likewise, H2A.Z, a variant of histone H2A, is shown to be required for one or more essential roles in chromatin structure that cannot be replaced by bona fide histone H2A [5]. Studies in *Drosophila* and budding yeast showed that H2A.Z is widely and uniformly distributed along chromosomes [6]. In yeast, H2A.Z is required for both transcriptional repression and activation, and is also relevant in the regulation of progression through the cell cycle [7–9]. The variant histone H2A.Z is uniformly localized on the promoters of inactive yeast genes and regulates nucleosome positioning [10–13]. In most cases, how histone variants alter nucleosome structure or change the folding properties of nucleosomal arrays remain poorly defined.

The amino-terminal portion of the core histones contains a flexible and highly basic tail region, the target of several types of post-translational modifications. Histone modifications, including lysine

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acetylation and methylation, serine phosphorylation and arginine methylation, play major regulatory roles in many genetic events such as transcriptional activation and elongation, silencing and epigenetic cellular memory [14–16]. Such modifications, singly or in combination, provide a source of information that can be used for signal transduction during ongoing processes or as epigenetic marks.

All the changes in chromatin that do not involve a change in DNA sequence are defined as epigenetics.

Beyond the genetic code itself, chromatin function and gene expression are under epigenetic histone-code control. Histone modifications can be considered as letters of the histone alphabet. Different combinations of modifications formulate different words endowed with different biological meanings [17].

A possible link between chromatin modifications and genetic regulation was identified in early studies [18]. Evidence was reported that altered levels of histone acetylation and methylation are associated with changes of transcription rates [19].

What appears to be safely established is that the various histone modifications have distinct functional effects and are mediated and recognized by conserved transcriptional regulatory protein modules [20]. What is less clear is how the amino-terminal histone tail modifications and the activity of the conserved transcriptional regulatory modules are coordinated. Thus, interest focused on the mechanisms by which histone modifications exert their effects.

Among these modifications, acetylation is the one so far more thoroughly analysed [21]. The histones amino termini lysines undergo acetylation-deacetylation switches depending on the different physiological conditions [22]. The balance between these modifications is achieved through the action of enzymes dubbed histone acetyltransferases (HATs) and histone deacetyltransferases (HDACs). These specific enzymes catalyse the transfer of an acetyl group from acetyl-CoA molecules to the lysine ε-amino groups on the N-terminal tails of histones [23].

Acetylation of lysines neutralizes the charge on histones, therefore, increasing chromatin accessibility. On the other hand, acetylation, like the remaining covalent modifications, is also important as a signal for the binding of trans-acting factors. Numerous activating factors possess a region dubbed bromodomain specifically interacting with acetylated lysines [24–27]. Following the discovery of histone acetylation [19], numerous studies have shown that this type of modification occurs throughout the whole eukaryotic genome [28–31]. These studies provided important support to the argument that both mechanisms, charge neutralization and recruitment of transacting factors, are likely to be important [32]. The interplay between different patterns of modifications was reviewed [33, 34].

HISTONE ACETYLTRANSFERASES

Two main superfamilies of HATs have been well characterized: the GNAT (Gcn5-related N-AcetylTtransferase) and the MYST (MOZ, Ybf2-Sas3, Sas2 and Tip60) families.

Homologues of Gcn5 have been found in different organisms such as human [35], mouse [36], *Saccharomyces cerevisiae* [37, 38], *Drosophila melanogaster* [39], *Arabidopsis thaliana* and *Toxoplasma gondii* [40]. In mammals, two related Gcn5 acetyltransferase subclasses were described: GCN5 and p300/CREB-binding protein-associated factor (PCAF). *In vitro* and *in vivo* studies were performed to investigate the human GCN5 function, which was found to be involved in the acetylation of histone H3 and, to a lesser extent, of histone H4, acting as a transcriptional adaptor [35]. PCAF acts as a HAT and as a co-activator in several processes: myogenesis [41], nuclear-receptor-mediated activation [42, 43], and growth-factor-signalled activation [44]. PCAF is also able to acetylate transcription-related non-histone proteins like TFIIE, TFIIF, MyoD, p53, HIV tat, HMGN2 and HMGA1.

p300/CBP is yet another family of HATs. Recombinant p300 and CBP acetylate the amino-terminal tails of all four histones [45, 46]. Like PCAF, p300/CBP is known to acetylate and regulate transcription-related proteins other than histones [47]. They are considered as global transcription co-activators playing critical roles in different cellular processes: cell-cycle, differentiation, apoptosis [48].

Other acetyltransferases, whose function is conserved from yeast to human are: Hat1, Hat2 (histone acetyltransferases B) and Elp3. Yeast Hat1 and Hat2, acting on free non-nucleosomal histones, are potentially involved in the chromatin assembly process, perhaps at the replication forks or at silenced telomeres [49, 50]. Hat1 was recently shown to be also involved in DNA double-strand break (DSB) repair, being directly recruited to sites of DNA damage [51].

Elp3 is able to acetylate all four histones and, even though its gene is not essential, the importance

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of its activity is shown by the fact that this protein is evolutionarily conserved in numerous eukaryotes [52]. Its function seems to be redundant with that of Gcn5, at least in *S. cerevisiae* [53]. Elp3 is also involved in transcriptional elongation as part of the RNA polymerase II holoenzyme [54].

The MYST family contains a large number of members: yeast Esa1, *Drosophila* MOF, human MOZ, Ybf2/Sas3, Sas2, Tip60, HBO1 and MORF [55].

MOZ is a monocytic leukaemia zinc finger protein involved in the oncogenic transformation leading to leukaemia. In the case of myeloid leukaemia, MOZ is found fused with CBP [55]. In most cases of leukaemia, MOZ is fused to different transcription-related factors [56–58] presumably leading to perturbed acetyltransferase function.

Tip60 is involved in the regulation of gene transcription, although it functions as co-activator or co-repressor in a context-dependent way [59, 60]. Tip60 has several putative functional domains: a chromatin organization modifier domain (chromodomain), a zinc finger-like domain and a HAT domain. It was shown that the HAT domain acetylates nucleosomal histones during DNA repair although it is not clear whether its acetylation activity is required during transcription [61].

MOnocytic leukaemia zinc finger protein-Related Factor (MORF), another member of the MYST family, is able to acetylate both free histones, particularly H3 and H4, and nucleosomal histones with a preference for H4. MORF was found to be rearranged in some types of acute myeloid leukaemia [62].

HBO1-associated Hat activity seems to play a direct role in the DNA replication process [63]; in fact, HBO1 is one of the proteins interacting with the human origin recognition complex (ORC) [64].

The yeast Gcn5 is the best studied HAT. Originally identified as a transcriptional adaptor or co-activator [37, 65], microarray analyses showed that numerous genes require Gcn5 for their appropriate expression [66]. This HAT primarily acetylates histones H3 and H2B [67, 68]. Gcn5 is the catalytic subunit of large complexes such as SAGA and ADA [69]. The first one contains Ada1–5, Spt3, Spt7, Spt8 and several TBP-associating factors (TAFs) and Tra1 [70]. Among the factors identified as unique components of these complexes, Ahc1 is found only in the ADA complex [71]. Some transcriptional adaptor proteins, like Ada2 and Ada3, are common to both complexes [69, 72]. The HAT complexes could participate in the transcription process as co-activators being specifically recruited by activators to the promoter [73]. In addition to its targeted co-activator function, Gcn5 could also acetylate histones genome-wide [28, 74]. Global Gcn5 HAT activity has a role in modulating transcription independently of its known co-activator function [75]. Global acetylation affects the activation process by facilitating the pre-initiation-complex (PIC) formation, either by increasing the affinity of one or more general transcription factors for the core promoter or by creating a more accessible chromatin environment [75]. The fact that global acetylation can regulate gene expression explains why at many promoters, transcription activation is not associated with increased histone acetylation [76].

Esa1 protein, like Gcn5, is a HAT A enzyme, involved in transcriptional regulation. Esa1 is a catalytic subunit of the nucleosome acetyltransferase of histone H4 (NuA4) complex [69, 77]. Besides its activity on H2A [68, 77], Esa1 is responsible for the vast majority of genome-wide H4 acetylation *in vivo* [78].

Gcn5 and Esa1 are the major HATs, substantially contributing to the regulation of genome-wide gene expression, whereas Hat1, Elp3, Hpa2 and Sas3 do not affect global acetylation levels [79].

Transcription factor IID (TFIID) also plays a central role in regulating the expression of most eukaryotic genes. TAF1 is the largest subunit of the TFIID complex: it was first identified as HAT through *in vitro* acetyltransferase assays and was shown to possess substrate specificity similar to that of Gcn5 [80]. The HAT activity of TAF1 has histone residues specificity similar to Gcn5 [81], although recent data show that the two proteins are not functionally equivalent [79]. TAF1 HAT activity in yeast is weaker compared with that of other HATs, while in higher eukaryotes its physiological role is more important [82]. The histone H4 tails are also the target of Bdf1 (Bromodomain factor 1), another component of TFIID [83]. A recent model suggests that H4 acetylation at promoters is more linked to Bdf1 than to TAF1, suggesting that the promoter regions that are acetylated at H4 and occupied by Bdf1 are not necessarily committed to TFIID recruitment [79].

Most HATs exist as multisubunit complexes *in vivo*, as reviewed [84]. The complexes are typically more active than their respective catalytic subunits,

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the specificity of action being ensured by their non-catalytic subunits [60].

HISTONE DEACETYLASES

Yeast cells contain a group of related HDACs that include Rpd3, Hda1, Hos1, Hos2 and Hos3 [85]. In higher eukaryotes, two families of HDAC can be generally identified and the histone deacetylases HDACs and the sirtuins.

The HDAC enzymes have a highly conserved domain, approximately 390 aminoacids, and can be divided into two classes, I and II, based on their homology to yeast HDACs. It was observed that these enzymes diverged early in evolution and were conserved in a large variety of eukaryotes [86]. Mechanistically, they behave similarly and require an active zinc to mediate deacetylation catalysis [87]. HDAC1, 2, 3 and 8 belonging to class I are similar to Rpd3 and are localized in the nucleus. The human enzymes are ubiquitously expressed in many cell lines and tissues. The class II has homology with yeast Hda1. According to sequence homology and domain organization, this class is further divided into class IIa, encompassing HDAC4, 5, 6, 7 and 9, and IIb to which HDAC6 and 10 belong [88]. These latter proteins are unique since they harbour two catalytic domains. Class II HDACs shuttle between nucleus and cytoplasm upon certain cellular signals and are expressed in a limited number of human tissues.

Sirtuins, generally indicated as class III HDACs, are both structurally and mechanistically very different from the other classes. They are homologous to the yeast Sir2/Hst family and, accordingly, their primary substrates do not seem to be the histone proteins [89, 90]. As for the mechanism regulating their activity, these enzymes have an absolute requirement for cofactor NAD^+ [91].

Since the HDACs are not able to bind directly to DNA, the classes I and II are mainly associated with stable multiprotein complexes such as Sin3, NuRD and CoREST. Sin3 and NuRD complexes are made of several associated proteins (SAP18–SAP30 and MTA2, respectively), a 'core complex' consisting HDAC1/2 and the histone binding protein RbAp46/48. The CoREST complex contains, instead of RbAp46/48, a protein homologous to MTA1- and MTA2-dubbed CoREST which is characterized by the SANT domain, critical for protein–protein interaction [86].

ROLE OF HISTONE ACETYLATION

The acetylation state of different promoters is maintained by specific combinations of HATs and HDACs; analyses performed over large chromosomal domains indicate that the state of acetylation is in a continuous genome-wide flux [92, 93].

In terms of charge neutralization, histone acetylation and deacetylation regulate transcription by manipulating the higher-order folding properties of the chromatin fiber. Acetylation of lysine residues might not merely alter chromatin structure but might also provide unique binding surfaces for repressors and activators of transcription [21]. Yeast and multicellular eukaryotes utilize similar molecular mechanisms to connect histone acetylation and transcriptional regulation but they show a different ratio between permissive and restrictive chromatin [76].

Histone acetylation has been extensively analysed looking for a possible definition of its role in gene expression. One of the best characterized genes in terms of histone acetylation and promoter accessibility is *S. cerevisiae ADH2*. This gene, coding for the enzyme alcohol dehydrogenase II, is tightly regulated by glucose and becomes active when the glucose concentration of the medium is lowered or in the presence of non-fermentable carbon sources [94]. It was shown that, in the absence of Rpd3 and Hda1 histone deacetylases, the structure of the TATA box-containing nucleosome is destabilized. This acetylation-dependent chromatin remodelling is not sufficient to allow the binding of the TATA box-binding protein, but facilitates the recruitment of both the transcriptional activator Adr1 and faster kinetics of *ADH2* mRNA accumulation [95]. On the contrary, in the absence of Gcn5, chromatin remodelling and mRNA accumulation occurring after derepression are less efficient. In the presence of an Esa1 temperature-sensitive mutation, the mRNA amount is lower even in permissive conditions.

This study provided the first *in vivo* evidence for the involvement of deacetylation/acetylation in modulating the accessibility of chromatin. The requirement of Gcn5 and Esa1 acetyltransferases in transcriptional activation was recently described for a set of glucose-repressed Adr1-dependent genes in *S. cerevisiae* [96]. This group of co-regulated genes offers the opportunity to deeply investigate the mechanisms by which acetylation exerts its role in transcription. Up to now, it is not completely clear if the contribution of histone acetylation

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to transcription is based on the charge effects, or if it is due to the fact that the acetyl groups (as well as other epigenetic modifications) create signals for the binding of proteins involved in chromatin remodelling and/or transcription initiation. Even if both mechanisms were actually relevant, it would be important to know whether the acetylation of the H3 and H4 N-terminal tails have redundant functions in chromatin remodelling and gene activation. In derepressing conditions, for the group of Adr1-dependent co-regulated genes, H4 acetylation is kept constant while the level of acetylation on H3 increases in an Adr1- and Gcn5-dependent manner. Surprisingly, in the absence of Gcn5 activity, there was no change in H3 acetylation levels but an increase in H4 levels was observed, suggesting that H3 and H4 play different roles (Figure 1), and is not simply explained by charge neutralization (Agricola *et al.*, unpublished observations).

CANCER AS EPIGENETIC DISEASE

Cancer is considered as an ensemble of diseases in part arising from chromosomal abnormalities and mutations in tumour-suppressor genes and oncogenes. Molecular and cellular mechanisms in malignant cell transformation increasingly indicate that cancer is also, in part, an epigenetic disease. The loss of DNA methylation at CpG dinucleotides in cancer cells was reported [97], and since this observation, the relations between cancer and DNA methylation were thoroughly studied [98–101].

Epigenetics not only consists of DNA methylation, but also includes the other modifications of histones with a role in gene expression. Among histone modifications, methylation and deacetylation are the epigenetic processes more mechanistically linked to pathogenesis [102]. Recent evidence indicates that their deregulation and mis-targeting contributes to the development of malignancies. Unfortunately, our knowledge of the behaviour of histone modifications in cancer cells is limited, at least when compared with that of DNA methylation. It was shown that both acetylation and methylation participate in tumour-suppressor genes silencing [103, 104].

A deeper understanding of the epigenetic states in cancer cells is prompting investigators to integrate the different analyses aiming to identify the genetic determinants of epigenetic states [91, 105].

Recently, novel studies on post-translational modifications of histones were reported characterizing the kind of modification occurring in normal tissues, cancer cell lines and in primary tumours. The final goal of this approach is the identification of common hallmarks of human tumour cells in order to define unambiguous tools for cancer diagnostics and efficient drug therapies [106, 107]. Histone modification patterns are obviously not identical among different types of cancers and even subsequent stages of cancer display differently modified histone tails. Thus, classifying tumour types into specific epigenetic patterns could help in distinguishing them [108].

The next and important task in tumour science is to understand how histone modifying complexes are involved in epigenetic modifications and how chromatin remodelling complexes are affected [109, 110].

HISTONE ACETYLATION AND CANCER

Epigenetics-based mechanisms leading to carcinogenesis can be divided into three different categories: the first is the repression of normally active genes; the second is the activation of normally repressed genes; the last is the replacement of core histones by specifically modified histone variants [111].

In the first two categories, abnormal activity of HATs and HDACs is involved, which seems to be either due to mutations of genes encoding for these enzymes or due to their binding and recruiting patterns. It was observed in tumours that a significant imbalance of acetylation and deacetylation levels takes place. Interestingly, the results are cell cycle arrest, re-differentiation or apoptosis [112].

Histone acetylation plays many fundamental roles in cellular processes, one of them being crucial to cell proliferation. It is not surprising that mutations or chromosomal modifications involving HATs result in the development of malignancies [91].

A characteristic feature of human leukaemia is the presence of chromosomal translocations leading to the expression of fusion proteins, whose effects can be dual. Several translocations can inactivate the wild-type function of HATs causing the silencing of genes regulated by these enzymes. On the other hand, fusion proteins can derive from a HAT and a DNA-binding protein which can activate genes usually not expressed. This is the case of the acute

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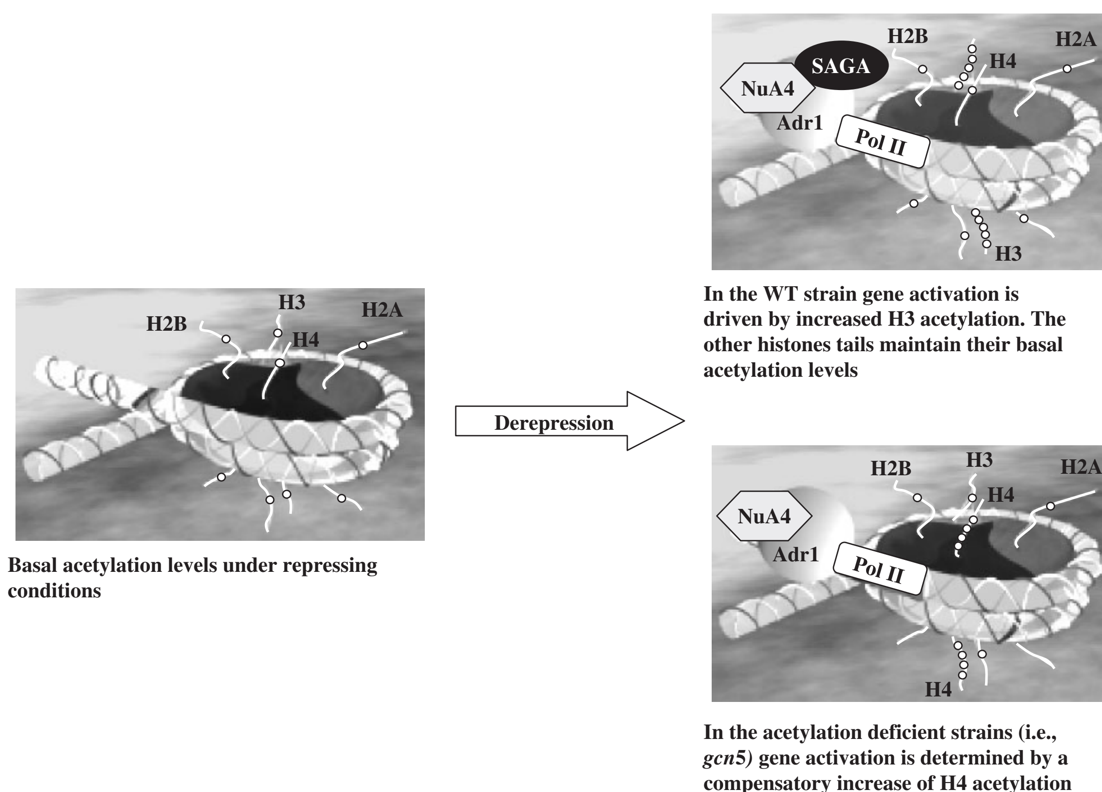

Figure 1: Model describing different roles for H3 and H4 histones in transcription activation.

myeloid leukaemia (AML) in which a fusion between CBP and alternatively MOZ or mixed lineage leukaemia (MLL) has occurred [113–115]. The resulting protein also acquires a new function since it can add acetyl groups to different substrates.

In a recent comparative analysis of normal cells, primary tumours and cancer cell lines, an altered recruitment of the acetyltransferases MOZ, MOF and MORF was found in cancer cell lines and this correlates with a global loss of the otherwise normally acetylated H4-K16. This last feature was shown to be a common hallmark of human cancer and is usually accompanied by trimethylation at H4-K20 [106].

In addition, mutations of certain HATs also cause cancer, as observed in mice [116, 117] and in several cases of human leukaemia [118]. A biallelic mutation of the p300 locus was identified in human epithelial cancer [119].

Another important disease in which HATs are not normal is the congenital Rubistein–Taybi syndrome where monoallelic mutations of both p300 and CBP increase susceptibility to cancer [121–123].

Cancer may also develop if certain viral proteins inhibit the HAT activity. Oncogenic viral proteins can actually bind p300, CBP and PCAF, thus inhibiting their activity or blocking the interaction between co-activators and DNA-binding proteins or basal transcription factors [124]. The adenovirus E1A protein is responsible for malignant cellular transformation when acetylated by CBP/p300 and PCAF, since it loses its association with transcription repressor complexes thus promoting aberrant gene activation [125].

HATs can also acetylate non-histone proteins such as p53, p21 and myc, each of them implicated in cancer development when altered [126, 127].

HISTONE DEACETYLATION AND CANCER

Specific alterations in genes coding for HDACs have not been reported. These complexes apparently act in cancer development with more than one single mechanism. On one hand, abnormal hyperacetylation of histones results in transcriptional activation of tumour-suppressor genes whereas, on the other hand, HDACs substrates are also non-histone proteins involved in important physiological processes [128, 129].

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The most informative evidence on HDACs role in cancer comes from studies on leukaemia. Acute promyelocytic leukaemia (APL) is caused by fusion of retinoic acid receptor-α (RARα) with promyelocytic leukaemia (PML) and promyelocytic leukaemia zinc finger (PLZF). These aberrant proteins bind to retinoic-acid response elements (RAREs) and recruit HDACs. This binding has high affinity and prevents the response to physiological concentrations of retinoids which induce the normal differentiation and development of myeloid cells [102, 130–133].

Another type of leukaemia is also due to the activity of histone deacetylases resulting in silencing of AML1, a gene that in normal cells acts as both transcriptional activator and repressor and is required for the differentiation of haematopoietic cells. Its correct function requires the binding to defined co-repressors and HATs, but an oncogenic translocation may cause a fusion between AML1 and ETO, a nuclear phosphoprotein. AML1-ETO strongly interacts with HDACs preventing transcription of AML1 target genes and leading to leukaemic transformation [111, 134–136].

Overexpression of HDAC-associated factors has been so far observed in solid tumours. Metastasis tumour antigen (MTA1) is associated with HDACs in the Mi-2/NuRD complex [137] and its expression correlates well with metastatic progression in oesophageal squamous cell carcinoma and in breast cancers [138–140]. The mechanistic consequences are not well established, but hyperexpression of MTA1 seems to correlate with lower levels of acetylated histone H4 [138]. In addition, it was recently shown that the transcriptional activity and stability of HIF1-α protein, a key regulator of angiogenesis factors, are enhanced because MTA1, when overexpressed, recruits HDAC1 thus deacetylating the protein [140].

A functional interaction between the HDAC2 complex, c-Myc and Wnt pathway was also reported. Colon cancer is frequently associated with a loss of the tumour-suppressor Adenomatosis Polyposis Coli (APC) whose effect is an increase of HDAC2 expression through a Myc- and Wnt-dependent mechanism. This results in the protection of cancer cells against apoptosis [141].

As for non-histone proteins, one of the most important is the tumour-suppressor, p53. Acetylation regulates its stability as oncosuppressor, its interaction with DNA and, eventually, its transcriptional activity [142]. In many cancers p53 is not functional and its HDACs-caused deacetylation has been linked with tumorigenesis [143].

HISTONE ACETYLASES AND HISTONE DEACETYLASES INHIBITORS

The better understanding of epigenetics in tumorigenesis has allowed development of epigenetic drugs, currently being tested in clinical trials. The first drugs tested were DNA-demethylating agents, but the possibility of their use is controversial [108]. Other epigenetic drugs are HAT inhibitors (HATi) and HDAC inhibitors (HDACi) [144].

HDAC inhibitors were developed more than HAT inhibitors because of the greater relevance of histone deacetylases in cancer. The observation that the loss of lysine acetylation occurs prior to the histone methylation in gene silencing has further encouraged this approach [145]. Several inhibitors with different chemical features have been reported to be efficient both *in vitro* and *in vivo* in arresting cancer cell growth and/or apoptosis, with little toxicity. An important attribute of HDACi is that they induce cancer cell death at concentrations to which normal cells are relatively resistant [146].

These compounds can be classified into four categories according to their chemical properties: hydroxamic acids such as trichostatin A (TSA) and suberoylanilide hydroxamic acid (SAHA), carboxyl acids such as butyrate and sodium valproate, benzamides and aliphatic acids [110].

Generally, HDACi have minimal toxicity and a wider therapeutic range, but the mechanism by which they act has not been determined. They could either activate tumour-suppressor genes or repress oncogenes through histone lysine modification. Alternatively, it has been proposed that these compounds could modify non-histone proteins [102].

Several effects of HDACi were described on many different cellular processes that are deregulated in neoplastic cells. *CDK-N1A* is one of the genes whose expression is modified by HDAC inhibitors in cancer cells. It encodes for $p21^{waf}$, a cell-cycle kinase inhibitor responsible for the cell-cycle arrest in G1 and G2 phases and subsequent cell differentiation. The $p21^{waf}$ promoter is bound by a large protein complex that contains, among the others, two histone acetylases Gcn5 and p300; it was shown that SAHA decreases HDAC1 activity and recruits

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RNA polymerase II causing transcriptional activation of the gene [147, 148].

p53, Ku70 and Hsp90 are among the non-histone proteins involved in cancer which are modified by the HDACi. In prostate cancer cells, these chemical compounds do stabilize the p53 acetylation which induces cell arrest by decreasing Mdm2-mediated ubiquitination and subsequent proteasome degradation [149, 150].

Treatment of neuroblastoma cells with TSA induces acetylation of Ku70 which dissociates from Bax, a protein that activates the caspase-dependent apoptosis in mitochondria [151].

Hsp90 is a chaperone required for protein degradation including oncoproteins. Thus, its HDACi-induced hyperacetylation leads to the inactivation of the proteins which are responsible for malignancies [152].

Exposure of primary AML cells to therapeutic doses of valproic acid (VPA) unexpectedly increased not only acetylation of lysines, but also di- and tri-methylation of H3-K4. This pattern of histone modifications associates with increasing transcription at the loci which are impaired in AML leukaemia and this treatment is also modulating the expression of the deacetylases themselves. The results of this study are of relevance to the development of HDACi-based therapeutic strategies [153]. The effects of few HDAC inhibitors, such as butyrate derivates, valproic acid and depsipeptide, were also investigated in AML clinical studies with satisfactory results, showing their ability to mediate antileukaemic effects in AML. The potential anticancer activity of HDAC inhibitors was tested in several other clinical trials [154–157].

Combination of HDACi with other epigenetic drugs, such as DNA-demethylating agents, has afforded promising results *in vitro* [158].

HATs inhibitors are less studied. The most important is a natural inhibitor, curcumin (diferuloymethane), a major curcuminoid derived from the plant *Curcuma longa*. It specifically inhibits the p300/CREB-binding protein through the involvement of Reactive Oxygen Species (ROS) [112]. Recently, curcumin was shown to repress both HAT-dependent transcription and the acetylation of non-histone proteins [159]. It also suppresses cellular transformation, proliferation, and metastasis by inhibition of IKK (IKappaB Kinase complex) and activation of Akt leading to the subsequent inactivation of NF-kB [160].

PERSPECTIVES

Technologies designed to examine epigenetic phenomena at the genomic level have shown remarkable progress over the last few years. The possibility to obtain a global view of epigenetic marks in different cell types will advance our understanding of the epigenetic code and its function in normal and disease states as well as the role of the environment in human health. This represents the principal aims of the 'Human Epigenome Project' (HEP), as suggested by the AACR (American Association for Cancer) [161].

Key Points

- Nucleosomes are the fundamental units of chromatin. They are composed by 146 bp of DNA and by an octamer core of histone proteins. Covalent modifications of histone proteins regulate the structure and function of nucleosomes. All the changes in chromatin that do not involve a change in DNA sequence are defined as epigenetics.
- Acetylation is one of the most studied epigenetic modifications. It consists of the covalent addition of acetyl groups to the lysines of histone N-terminal tails. This modification not only alters chromatin structure by charge neutralization but may also provide unique binding surfaces for repressors and activators of transcription.
- Molecular mechanisms in cell transformation processes increasingly indicate that cancer is also an epigenetic disease. Imbalance of acetylation and deacetylation levels results in development of malignancies. HAT and HDAC inhibitors are used as drugs in treatment of different types of cancers.

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