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Review Article

Histone Acetylation Modifiers in the Pathogenesis of Malignant Disease

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Abstract

Chromatin structure is gaining increasing attention as a potential target in the treatment of cancer. Relaxation of the chromatin fiber facilitates transcription and is regulated by two competing enzymatic activities, histone acetyltransferases (HATs) and histone deacetylases (HDACs), which modify the acetylation state of histone proteins and other promoter-bound transcription factors. While HATs, which are frequently part of multisubunit coactivator complexes, lead to the relaxation of chromatin structure and transcriptional activation, HDACs tend to associate with multisubunit corepressor complexes, which result in chromatin condensation and transcriptional repression of specific target genes. HATs and HDACs are known to be involved both in the pathogenesis as well as in the suppression of cancer. Some of the genes encoding these enzymes have been shown to be rearranged in the context of chromosomal translocations in human acute leukemias and solid tumors, where fusions of regulatory and coding regions of a variety of transcription factor genes result in completely new gene products that may interfere with regulatory cascades controlling cell growth and differentiation. On the other hand, some histone acetylation–modifying enzymes have been located within chromosomal regions that are particularly prone to chromosomal breaks. In these cases gains and losses of chromosomal material may affect the availability of functionally active HATs and HDACs, which in turn disturbs the tightly controlled equilibrium of histone acetylation. We review herein the recent achievements, which further help to elucidate the biological role of histone acetylation modifying enzymes and their potential impact on our current understanding of the molecular changes involved in the development of solid tumors and leukemias.

DNA in chromatin is organized in arrays of nucleosomes, where two copies of each histone protein—H2A, H2B, H3, and H4—are assembled into an octamer that has approximately 146 base pairs of DNA wrapped around it in 1.8 turns to form a nucleosome. The nucleosome is an invariant component of euchromatin and heterochromatin in the interphase nucleus, and of mitotic chromosomes. This highly conserved nucleoprotein complex occurs fundamentally every 200 ± 40 bp throughout all eukaryotic genomes (1). During mitosis, the tightly packed metaphase chromosomes need to be accurately distributed between two daughter cells, while the DNA has to be accessible to various enzymatic machineries during interphase, when DNA is replicated, specific parts are transcribed, and mutated DNA segments are repaired. Under these circumstances, the nucleosomal architecture represents a major structural obstacle that

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limits the access of factors to nucleosome-bound DNA (2). The interaction of DNA with histone proteins is highly complex and may—at least in part—be explained by electrostatic interactions between negatively charged phosphate groups in the DNA backbone and positively charged amino acids in the histone proteins (3–5). A number of post-translational modifications of the histone components of chromatin, including acetylation, phosphorylation, ubiquitination, methylation, and ADP-ribosylation, which altogether affect transcriptional regulation, have been described (6–8). However, our focus in this review is on the role of histone modification through acetylation in the pathogenesis of cancer.

First observations linking transcriptional activity with histone acetylation and deacetylation of the ε-amino groups of conserved lysine residues, which are present in the amino terminal tails of all four core histones (H2A, H2B, H3, and H4), were made more than three decades ago (9). These observations have been reinforced by studies that demonstrated transcriptionally active euchromatin domains to be highly acetylated and/or hypomethylated (9–12), while densely methylated inactive DNA has been associated with hypoacetylated histone proteins (9,13,14). Notably, most DNA in mammals is methylated at CpG dinucleotides, with the exception of promoter elements, which contain undermethylated CpG islands (15). Methyl-CpG binding protein 2 (MeCP2) is a protein that recognizes methylated DNA and interacts with histone deacetylases, which are part of the mSIN3A/histone deacetylases (HDAC) multisubunit repressor complex. This suggests that MeCP2 mediates silencing of methylated DNA through deacetylation (16–18) (Fig. 1).

It took more than three decades to test the validity of the hypothesis that linked transcriptional activity with the post-translational modification of histone proteins, following the identification of the regulators of histone acetylation, histone acetyltransferases, and histone deacetylases (19). These enzymes allow reversible modification of histone proteins through the addition or removal of acetyl groups, which alter the strength of the bonding between histones and DNA, thereby modifying the regulation of biological processes such as DNA replication and repair, gene expression, chromatin assembly, condensation, and cell division (see also 20,21 for reviews). In addition to the effect of histone acetyltransferases (HATs) and HDACs on the charge of the histone octamer, these enzymes may also directly alter the activity of basal and sequence-specific transcription factors as well as other cellular regulators (cell-cycle regulators, signaling cascades, etc.) (Fig. 2) (5,22,23).

Histone Modification and Transcriptional Control

The work of many investigators during the last few years has contributed to almost explosive advances in our understanding of the molecular details of transcriptional regulation and chromatin modification within the context of the highly complex interplay of protein–DNA binding factors and protein–protein interactions. It is now becoming increasingly obvious that most enzymes that regulate the acetylation state of histone proteins and other promoter-bound transcription factors (i.e., HATs and HDACs) exert their enzymatic activities as members of large multisubunit protein complexes. A deregulation of the tightly controlled equilibrium of acetylation and deacetylation plays a causative role in the generation as well as in the suppression of several types of cancer (20,24–27). Depending on the specific target promotors, hyperacetylation and deacetylation may exert contradictive effects on gene expression (28) and suppress tumorigenesis in some cases, while they facilitate cancer development in others. This could be either (1) a consequence of chromosomal translocations, where histone acetylation modifiers may be fused to or recruited by a newly generated transcription factor hybrid protein, which alters the expression of specific target genes, or (2) an effect of overall changes in the concentrations of functionally available histone acetylation modifiers.

Histone Acetyltransferases

The first HAT gene to be cloned was *HAT1,* a yeast histone acetyltransferase, initially identified as a temperature-sensitive mutant lacking the capability to acetylate specific lysine residues of the Histone H4 peptide (29–31). This was followed by the discovery of a homolog of the yeast HAT GCN5 (general control of amino acid synthesis) in Tetrahymena, which was identified by virtue of its HAT enzymatic activity (19). GCN5 is known to be the

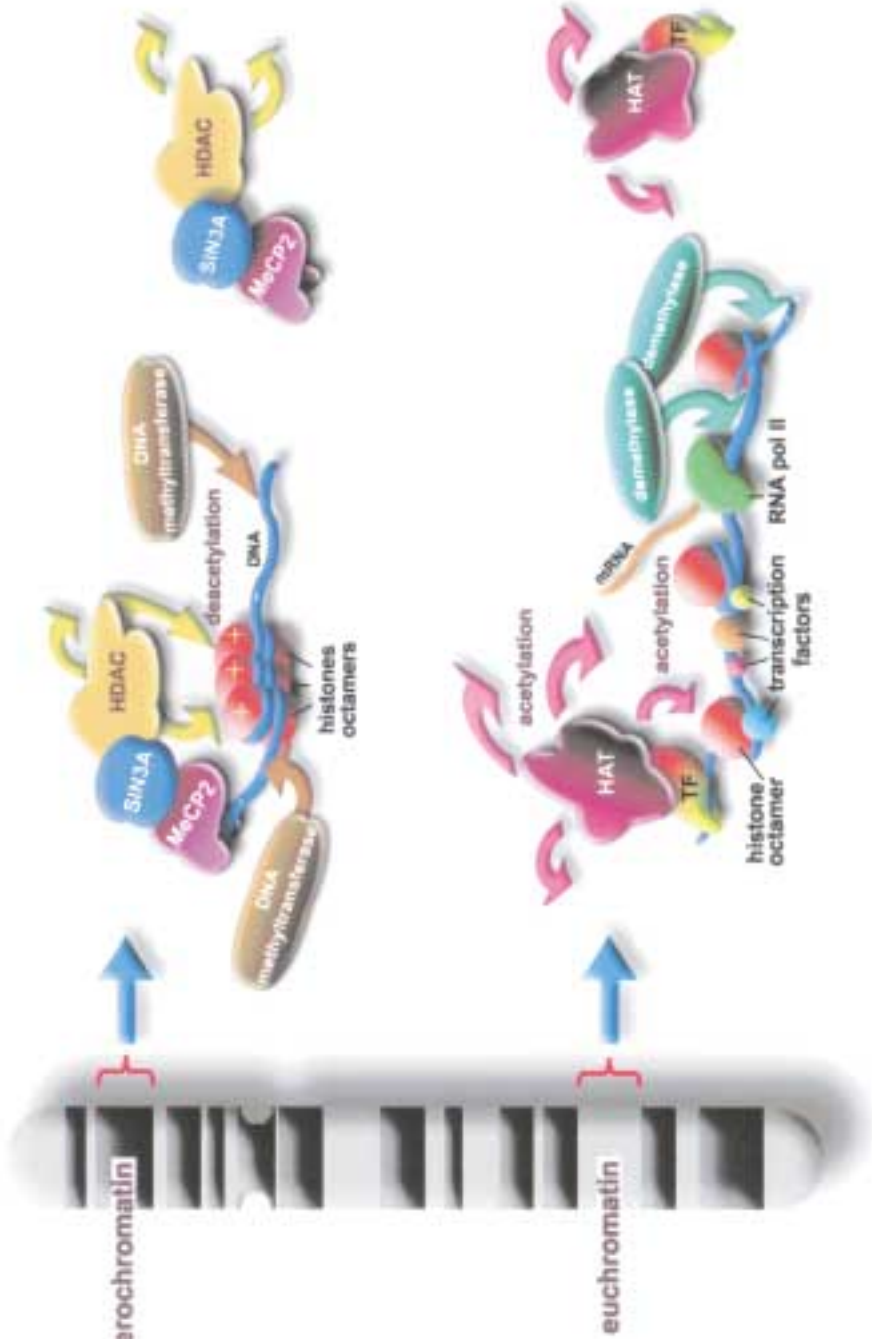

Fig. 1. In a Giemsa-stained chromosome (left) the unstained regions (white) represent regions, which are thought to be less compact and transcriptionally active (euchromatin), and heavily stained regions (black) are considered transcriptionally inactive and highly condensed (heterochromatin). These observations have been reinforced by studies that demonstrated transcriptionally active euchromatin domains to be highly acetylated when compared to transcriptionally silenced chromosomal regions, which are hypoacetylated (9–12, 228–230). Electrostatic interactions between DNA (negatively charged) and N-terminal histone protein tails (which positively charged when deacetylated and loose their positive charge through acetylation) may at least in part serve as an explanation for the highly complex mechanisms that are involved in chromatin compaction. MeCP2, which recognizes methylated DNA, recruits HDACs, which are part of multisubunit repressor complexes (e.g., SIN3a or N-COR/SMRT-SIN3a) and mediates silencing of methylated DNA through deacetylation (15–17). Under such conditions chromosomal DNA is inaccessible to DNA-binding factors, which are necessary for transcription, repair, replication, etc. Conversely, demethylation and/or hyperacetylation are associated with transcriptional activation and the unfolding of chromatin, thereby allowing access to transcription factors and other regulators (231–233).

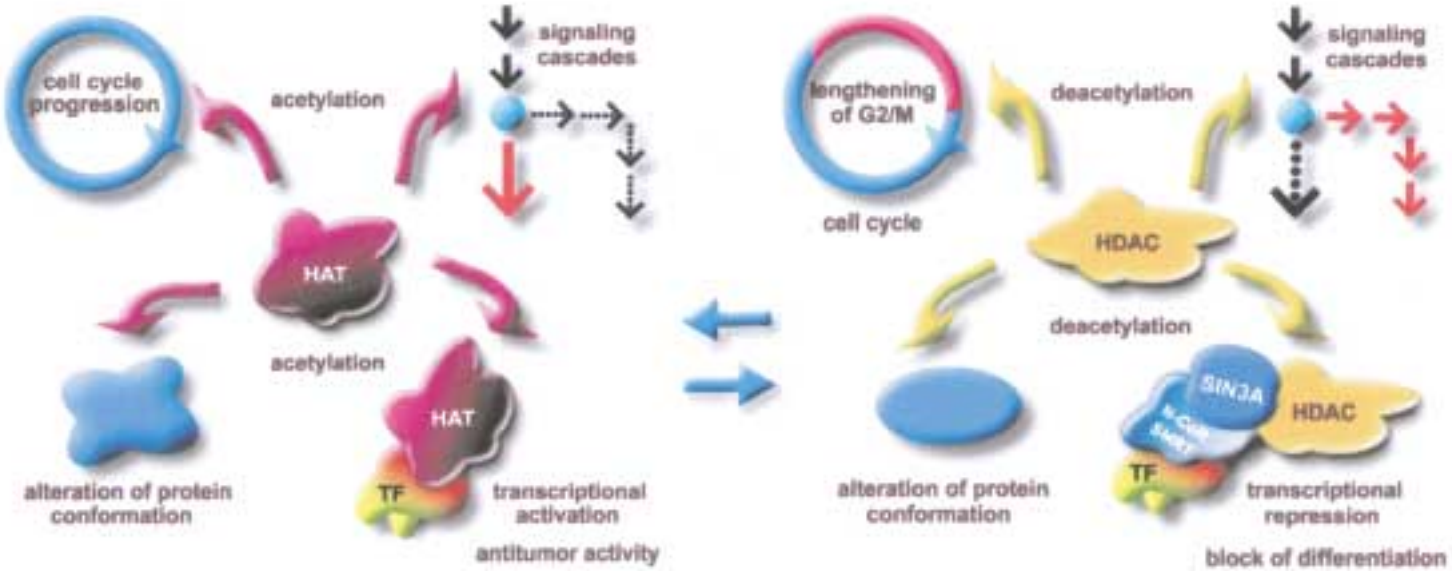

Fig. 2. Histone acetylation levels in cells result from a dynamic equilibrium between the competing enzymatic activities of HATs and HDACs. Changes in histone acetylation levels have been reported to affect transcriptional regulation, signal transduction cascades, cell survival, differentiation, and the activities of target proteins (e.g., transcription factors, cell-cycle regulators, etc.). While HDACs, which may be recruited to specific promotors by transcription factor-bound multisubunit repressor complexes (e.g., N-COR/SMRT-SIN3A) have mainly been associated with transcriptional repression (16,74,75,80–83,158,193,194,234), HATs may be part of enhancer complexes and have predominantly been associated with transcriptional activation (19,41,151,235,236). In addition, HAT modifiers have been implicated in the regulation of diverse signaling cascades (122,237,238), in the alteration of protein conformation and protein activities (e.g., hormone receptors, transcription factors, DNA-associated regulators) (20,239–241), and in the regulation of cell-cycle events, whereas HDAC has been observed to result in a lengthening of G2 and M phases (20,242). Inhibition of HDAC arrested the cell cycle in G1 and G2 (20,212). HATs, on the other hand, have been connected mainly with cell-cycle progression (235,243–246).

catalytic unit of both the yeast ADA (Ada2-Ada3-Gcn5) and SAGA (SPT-ADA-GCN5-acetyltransferase) coactivator complexes, which exert HAT activity (32–34) and of the human SAGA-homolog STAGA (SPT3-TAF_{II}31-GCN5 acetyltransferase) (35). Since then, a number of enzymes with HAT activity have been identified in humans, including CREB binding protein (CBP)/p300 (36–38); p300/CBP associated factor (p/CAF) (36,38,39); the p160 family of proteins (NCOA1-3) (40–43); the MYST family, which includes the human proteins monocytic leukemia zinc finger (MOZ), monocytic leukemia zinc finger protein-related factor (MORF), Tat interacting protein 60 (Tip60), and histone acetyltransferase binding to ORC (HBO1) (44–51); $hTF_{III}C90$ (52,53); and $TAF_{II}250$ (54). For the HAT proteins MOF (45), HAT-A4 (55), Esa1 (45), NuA3/NuA4 (56), and Elp3 (57), a human homolog has not been identified to date.

So far, only one report for a *HAT* knock-out is available, where *p300* nullizygous mice were found to die early after gestation, exhibiting defects in neurulation, cell proliferation, and heart development and where heterozygous mice also revealed considerable embryonic lethality. In the same study, cells derived from *p300*-deficient embryos displayed specific transcriptional defects and proliferated poorly. Mice that were double heterozygous for *p300* and *CBP* were consistently associated with embryonic death (58). Taken together, HATs can be subdivided into two broad categories, type A and type B, by virtue of their subcellular localization. While type A HATs, which are located in the nucleus, essentially are believed to acetylate chromosomal histones, thereby playing important roles in the regulation of gene expression, type B HATs are found in the cytoplasm, where they acetylate cytoplasmic histones prior to chromatin assembly (for review see 20,21,27,59,60) (Table 1).

Histone Deacetylases

First links between the modification of histone acetylation in conjunction with transcriptional activity were observed in the early 1960s (9). In the 1970s, an inhibition of histone deacetylase activity was shown to result in the accumulation of acetylated histones in vivo (61). Finally, the biochemical fractionation of yeast extracts led to the discovery of two distinct yeast histone deacetylating activities, HDA, the catalytic subunit of a 350-kDa histone deacetylase complex, which contains the histone deacetylase 1 (HDA1) protein and HDB, the catalytic subunit of a 600-kDa histone deacetylase complex, which contains reduced potassium dependency 3 (RPD3). HDA1 and RPD3 share a significant degree of sequence homology at the protein level. Both proteins act mainly as negative regulators of transcription. They may however, counteract repression at telomeric loci, where the general hyperacetylation of histones is associated with gene activation. Whether this observation, that HDAC enzymes repress genes in some parts of the genome while they activate transcription in other parts, reflects indirect mechanisms (e.g., reduction of the expression of genes, which encode other repressor proteins) or direct, gene-specific effects, remains still to be elucidated (28,62,63). Functionally, HDA1 and RPD3 have nonoverlapping effects on the modulation of lifespan: while the deletion of *RPD3* was observed to extend life in yeast, this was not the case for *HDA1,* unless it was combined with the deletion of additional genes (e.g., *SIR3*). The simultaneous deletion of both *HDA1* and *RPD3* has been shown to decrease lifespan and because the expression of both enzymes declines with age, this could provide a possible explanation for the increase in mortality during senescence (64). While HDA activity in yeast is strongly inhibited by Zn^{2+}, spermine, and spermidine (65), RPD3 mutants are highly sensitive to cycloheximide (63). Null mutants of both *HDA1* and *RPD3* are viable and result in a general increase of histone acetylation and gene expression, except for genes located in telomeric regions, where histone acetylation has been associated with silencing (28).

Using trapoxin, a potent histone deacetylase inhibitor, as a bait in an affinity matrix, HDAC1, the first human RPD3 ortholog, was purified (66). HDAC2, a closely related protein, was found when screening studies for corepressors that interact with YY1, a transcription repressor/activator, were performed (67). Moreover, HOS1, HOS2, and HOS3, three yeast histone deacetylases, which are homologous to both HDA1 and RPD3, were identified (28). In most cases, RPD3 is physically associated with SIN3 (also referred to as RPD1) and exerts its transcriptional repression function within a 2-MDa corepressor complex, which is distinct from the 600-kDa HDB complex described above (63,68–71). This corepressor complex is recruited to promoters by sequence-specific

Table 1. Human histone acetyltransferases

Family	Members	Alternate Symbols	Cytogenetic Position	Histone Preference (K: lysine specificity)				HAT type (A: nuclear, B: cytoplasmic)		References
				H2A	H2B	H3	H4	A	B	
HAT	*HAT1*	—	2q31.2-q33.1	(++)			++	(+)	+	(29–31,55)
	HAT2	—	n.a.	K_5			$K_{5,12}$			
GCN5	*GCN5L1*	—	12q13-q14			+++	+	+		(19,32–35)
	GCN5L2	—	17q21			K_{14}	$K_{8,16}$			
P/CAF	*P/CAF*	—	3p24			++	++	+		(36–38,102)
						K_{14}	K_8			
p300/CBP	*p300*	—	22q13.2	++	++	++	++	+		(36–38)
	CBP	—	16p13.3	K_5	$K_{5,12}$ $_{15,20}$	K_{14} $_{18,23}$	$K_{5,8>}$ $_{12,16}$			
p160	*NCOA1*	*SRC-1*	2p23							
	NCOA2	*GRIP-1* *TIF2*	8q13							
	NCOA3	*AIB1* *RAC3* *ACTR* *P/CIP* *TRAM-1*	20q12	(+)	(+)	+	+	+		(40–43,104)
MYST	*MOZ*	—	8p11							
	MORF	—	10q22.2	++		++	++	+		(44–51)
	HBO1	—	Xq21				K_{16}			
	Tip60	—	11							
$TF_{II}D$ complex	$TAF_{II}250$	*TAF2A* *CCG1* *BA2R*	Xq13			+++	+	+		(54)
$hTF_{III}C90$	$hTF_{III}C90$	—	NA			++		+		(52,53)

repressor proteins, including the mammalian heterodimeric repressors Mad/Max and Mxi/Max, which are repressors in large part because of their ability to recruit the RPD3/SIN3 complex to DNA-bound regulators of transcription (66,72–79), while other repressors (e.g., unliganded nuclear receptors) recruit the RPD3/SIN3 complex via SMRT (silencing mediator of retinoic acid and thyroid hormone receptors) or nuclear corepressor (N-COR) (78–82) and regulators like UME6 recognize URS1 and bind SIN3, which in turn interacts with RPD3 (75,83). RPD3, which contains the catalytic deacetylase subunit of the SIN3/RPD3 complex, is clearly required for repression by SIN3 (83). However, although it is likely that the SIN3/RPD3 complex performs multiple functions, some of which may play a more prominent role in the repression of transcription, it remains to be elucidated whether histone deacetylation per se is the primary mechanism of transcriptional repression (Table 2).

So far, seven human histone deacetylase proteins, all of which share a highly conserved catalytic domain, have been identified, of which HDAC1, HDAC2, and HDAC3 are orthologs of yeast RPD3 (66,67,84–86), while HDAC4, HDAC5, HDAC6, and HDAC7 are yeast HDA1 orthologs (87,88). All human RPD3 orthologs that have been reported so far repress transcription when targeted to DNA via a DNA-binding domain. They all bind transcription factor YY1, which can act both as an activator and a repressor of transcription (89). Accordingly, the inhibition of HDACs by trichostatin or trapoxin is associated with the activation or repression of specific gene products (90). While mammalian HDAC1 and HDAC2 have been shown to interact with mSIN3 and the N-COR or SMRT corepressor complexes, which may associate additional proteins (e.g., SAP18, SAP30, RbAp48, or RbAp46), HDAC3 does not appear to be part of such multiprotein complexes (74,75,80–82,91). Unlike the other deacetylases, HDAC4, which

Table 2. Human histone deacetylases

Family	Members	Alternate Symbols	Cytogenetic Position	Histone Preference (K: lysine specificity) H2A	H2B	H3	H4	HD type HDA	HDB	References
RPD3 orthologs (class I HDACs)	*HDAC1*	—	1p34.1							(28,63,66, 70,74,75,
	HDAC2	—	6q21	+	+	+	+		+	80–83,85,
	HDAC3	—	5q31.1			$K_{5,12\ 16(\cdots)}$	$K_{9,14,\ (\cdots)}$			88,195,234, 242,247)
HDA1 orthologs (class II HDACs)	*HDAC4*	*HDAC-A*	2q37.2							
	HDAC5	*NY-CO-9*	17							
	HDAC6	—	×	+	+	+	+	+		(28,87,88, 92,248)
	HDAC7	*MITR*	7p15-p21							

belongs to the HDA1 family of HDACs, has been reported to shuttle between the nucleus and the cytoplasm in a process involving active nuclear export (87,92). Unfortunately, human orthologs of the yeast histone deacetylases HOS1 (28), HOS2 (28,93) and HOS3 (28,94) have not been reported so far.

Histone Acetylation, Solid Tumors, and Leukemias: When HATs Are the Key Players

More recently, an increasing number of disease processes have been observed to involve abnormalities of the tightly regulated interplay of acetylating and deacetylating cellular events, which are maintained by the enzymatic activities of HATs and HDACs (95–100). A decrease in the amount of functionally available HDACs (e.g., if *HDAC* loci are part of chromosomal deletions) or an increase of functionally active HAT enzymatic activities (e.g., if chromosomal segments, which encode HAT proteins, are amplified) may shift the equilibrium of histone acetylation toward acetylation, which in turn has an effect on conformation and activity of associated transcription factors (e.g., GATA-1, $TF_{II}E\beta$, $TF_{II}F$, EKLF, and p53) (23) and subsequently on gene expression, interaction targets, and activities of downstream signaling pathways (28,101–104). If, by contrast, HATs are fused to a transcription factor in the context of a chromosomal translocation (46–48, 105–110), which creates a novel chimeric protein, hyperacetylation may be confined to the target promoters of that specific transcription factor and, because transcription factors have many domains of protein–protein interaction, the transcription factor/HAT-fusion may allow acetylation of associated regulators and result in the transcriptional activation of a restricted number of genes. As a consequence, chromosomal regions that were silenced under normal conditions may now be derepressed and change the entire pattern of gene expression within affected cells: genes that were previously silenced may now be activated or even overexpressed, whereas other genes, which were previously expressed, may now secondarily be repressed (5,28,111). HAT enzymes have been found amplified, translocated, overexpressed, deleted, or point mutated in several types of cancers:

- An overexpression of HAT enzymatic activities has, for example, been described for the steroid receptor coactivator-1 (SRC1) homolog AIB1, which is involved in the pathogenesis of both breast and ovarian cancers. The associated *HAT* defect that has been described for this particular type of cancer is a more than 20-fold amplification of the chromosomal region, which contains the AIB1 gene, and has been determined by fluorescence in situ hybridization (FISH) (104,112).

- Changes in the availability of functionally available HATs may also directly affect functions and activities of nonhistone proteins, in view of the fact that some histone acetyltransferases (p300, P/CAF, and TAF-250) have been described to directly acetylate general transcription factors ($TF_{II}F$ and $TF_{II}E\beta$) (113), sequence-specific transcription factors (e.g., GATA-1 or EKLF) (114, 115), tumor suppressors (e.g., p53 or NFκB) (116–118), architectural chromatin proteins (e.g., HMGI(Y)) (119), and DNA repair complexes, where it seems to increase the DNA-binding capacity of the protein (115,116).
- Both p300 and CBP possess HAT activity, which is partly intrinsic and partly the result of association with other proteins (e.g., p/CAF) (36–38). The CBP/p300 HAT-protein complex integrates many signaling pathways (e.g., the TGF-β signaling pathway) (120–122) and is able to interact with a series of transcription factors (e.g., CREB, c-Jun, JunB, c-Fos, Myb, MyoD, YY1, nuclear receptors and basal components of the transcriptional apparatus, etc.) (123) and to participate in the direct or indirect stimulation of transcription through scaffolding different classes of transcriptional regulators onto specific chromatin domains (124,125). p300 and CBP have been envisioned as negative regulators of cell growth; mutations or translocations of the *p300* or of the *CBP* genes have been found to be associated with several solid tumors (e.g., point mutations of *p300,* which may be found in colorectal and gastric carcinomas, are usually located within the cysteine histidine-rich regions of the protein, known to play important roles in the biological activities of p300 (121,126,127); loss of heterozygosity for *p300* in 80% of glioblastomas (128) and acute leukemias (e.g., in the M4/M5 subtype of acute myeloid leukemia [AML] where *CBP* is found translocated and fused to the putative acetyltransferase *MOZ* [t(8;16)(p11;p13)], which is a human homolog of the yeast *SAS* genes [SAS: something about silencing]) (48,109,129). Remarkably, p300 mutations are located within the cysteine histidine-rich regions, which have been observed to play an important role in the biological activities of p300 (130). In addition, it has been reported that the oncogenic viral proteins E1A and SV40 are able to antagonize CBP-dependent transcription, thereby promoting cellular proliferation (38,131–133).

Leukemia-associated chromosome 8 inversions of the genotype inv(8)(p11;q13) characteristically fuse *MOZ* to *TIF2/NCOA2/GRIP1* (transcriptional mediator/intermediary factor 2) (134,135), a NR (nuclear hormone receptor) coactivator that itself binds CBP/p300 (136,137). The phenotype of the resulting MOZ-TIF2 fusion is therefore highly similar to the MOZ-CBP fusion.

In other leukemias, particularly therapy-related AML, myelodysplastic syndrome, and chronic myelomonocytic leukemia, *CBP* may be fused to *MLL* (mixed lineage leukemia), a gene that has been associated with the myelodysplastic syndrome [t(11;16)(q23;p13)](48,105–108). In both translocations (*MLL–CBP* and *MOZ-CBP*) the HAT domain of CBP remains intact within the fusion protein and because both MOZ and MLL have been implicated in the modification of chromatin structure, it is likely that the molecular mechanism through which the fusion proteins perturb growth is by dysregulating gene expression patterns (130).

In a separate subset of AMLs, which has been reported to be associated with therapy-induced leukemia, the *p300* gene was found rearranged and fused in frame with the *MLL* gene [t(11;22)(q23;q13)] (106,138). This suggests that alterations of CBP function may occur in the later stages of leukemogenesis, possibly as a way to eliminate cell-cycle checkpoints and apoptotic responses (130). Notably, the MLL fusion proteins described herein lack the carboxy terminal SET (suppressor of variegation) domain, which is a hall-mark of many chromatin-associated proteins (139,140). The MLL SET domain interacts with the human SWI/SNF (switch defective/sucrose nonfermenting) chromatin-remodeling complex, a powerful transcriptional activator that belongs to a family of DNA-stimulated ATPases that can either disrupt the structure of nucleosome core particles or influence the mobility and spacing of nucleosome arrays (141,142). Therefore, a fusion of MLL and CBP results in the dysregulation of transcription by failing to recruit SWI/SNF. Conversely, the leukemia-associated *MLL–AF9* and *MLL-ENL* translocations fuse *MLL* to genes, which encode transcriptional activators expressing carboxy terminal domains, which are highly homologous to SET and may function as distinct targets for the SWI/SNF complex

(143–146). Somatic mutations within the *SWI/SNF* complex have been identified in several aggressive pediatric malignant rhabdoid tumors (147).

Humans lacking one functional allele of the *CBP* gene, having point mutations or microdeletions within the 16p13.3 chromosomal region that contains *CBP,* develop a condition, which has been described as "Rubinstein-Taybi syndrome" (autosomal dominant). Individuals exhibiting this condition have a particular propensity for malignancy, skeletal abnormalities, and growth retardation (128,148). Concordantly, *CBP*-heterozygous mice reveal skeletal abnormalities corresponding to the changes that are seen in Rubinstein-Taybi syndrome (149). Interestingly, in spite of apparently overlapping functions between CBP and p300, patients with Rubinstein-Taybi syndrome have an intact *p300* allele, which is potentially unable to sufficiently substitute for CBP (130,150).

Unfortunately, it is not presently clear exactly how p300 and CBP are involved in the development of cancer. What is known, however, is that p300 and CBP, which have well-documented activity as transcriptional activators, are important key players in cell-cycle control, within apoptotic pathways, in the promotion of differentiation, and in p53 signaling and activation (116,124,151,152). In a simplified scenario the anti-oncogenic properties of p300 and CBP seem to go hand in hand with the anti-oncogenic activities that have been proposed for p53; since p300 forms a complex with p53 that exerts its anticancerogenic activity by negatively regulating cell growth. Several promoter/enhancer elements, such as the AP1 and c-Fos elements, function in a p300-dependent manner (153), which has been correlated with a promotion of G1-S transition, resulting thereby in cellular proliferation and potentially transformation (154). Although the formation of p53–p300 may in part be responsible for the recruitment of p300 onto some promoters, it may inhibit the transactivating effects of p300 on others (e.g., on promoters containing the DNA binding sites for the transcription factor AP1, where increased levels of p300 are able to overcome p53-mediated inhibition of AP1). Most interestingly, p53 binds to p300 in a region that is required for its intrinsic HAT activity (37). However, this region is distinct form the domains that bind to c-Jun (155), P/CAF (38), and TBP (156), all of which are important modulators of transcription. It has therefore been suggested that p53 might function through direct protein–protein interactions via p300 and possibly also through other p300-associated factors (124).

It has been observed that factors like the nuclear hormone receptors (e.g., RAR/RXR) mediate transcriptional repression by recruiting HDAC complexes in their unliganded form (80–82), while they exhibit ligand-inducible transcriptional activator functions through the recruitment of HAT-coactivator complexes (p300/CAF) when hormone is bound (Fig. 3) (4,5,40,150,157). Similarly, E2F and Rb, for example, form a repressor complex, which recruits HDAC1 and HDAC2 (158,159) and subsequently represses the cyclin E promoter. Frequently, phosphorylation is a key event that induces a conformational change within a transcription factor or other regulatory elements (e.g., NFκB, the IFNβ enhancer complex or Rb), which then readily recruits a HAT-coactivator complex and stimulates transcription (160–162).

Histone Acetylation, Solid Tumors, and Leukemias: When HDACs Are the Key Players

Leukemias are generally associated with characteristic chromosomal translocations, which may result either in the generation of a chimeric protein with novel functional properties or in the aberrant expression of a regulatory element. Usually, chromosomal translocations affect only one allele of a gene. Therefore, to cause a phenotypic effect, the activity of the newly generated fusion protein needs to be dominant over that of the wild-type protein. Frequently, the translocations found in leukemias target regulatory transcription factors that control cellular proliferation, survival, and differentiation and may obviate the need for multistep mutation pathways because they are observed for proto-oncogenes and tumor suppressor genes in solid tumors (163,164). In accordance with the disease-linked *HAT* defects that have been described above, *HDAC* defects may very similarly be associated with a tumorigenic phenotype of affected cells. When HDACs are excessively available or if the amount of functionally available HATs is decreased, the balance of histone acetylation will be shifted toward deacetylation, resulting subsequently in a dysregulation

of gene expression. Several transcriptional repressors (e.g., Mad and members of the nuclear receptor superfamily), trans-cription factors, and cellular regulators have been described to associate with HDAC activities (5).

- The analysis of the transforming chimeric proteins PML-RARα [t(15;17)(q22;q21)] (163,165–167) and PLZF-RARα [t(11;17)(q23;q21)] (167–170), which are found in different acute promyelocytic leukemias (APL), has shown a clear connection between the action of histone deacetylases and the development of cancer. In these instances the promyelocytic leukemia gene (*PML*) [t(15;17)(q22;q21)] or the promyelocytic leukemia zinc finger gene (*PLZF*) [t(11;17)(q23;q21)] are fused to the retinoic acid receptor-alpha (*RARα*) and are no longer responsive to physiological levels of retinoic acid (167,171,172). These chromosomal changes result in a block of cellular differentiation (i.e., in the clonal expansion of cells arrested in the promyelocyte stage of development) yielding the clinical picture of an acute leukemia (78,171,172). While patients featuring the *PML-RARα* [t(15;17)(q22;q21)] translocation, readily differentiate upon treatment with all-trans-retinoic acid (ATRA) (78,171), patients having the *PLZF-RARα* [t(11;17)(q23;q21)] type of translocation do not respond adequately to treatment with ATRA (78,171). On the molecular level, RARα represses target genes by tethering corepressors such as N-COR and SMRT to promoter DNA (78,173). These corepressors are part of one or more large complexes that also contain mSIN3A and HDAC proteins (5). In cells that express PML-RARα, retinoic acids lead to the dissociation of the SMRT-mSIN3A-HDAC1 and N-COR-mSIN3A-HDAC1,2 complexes from RARα (97,98,172). By contrast, cells that express PLZF-RARα have two N-COR binding sites, one in the RARα region (which is responsive to retinoic acids) and one in the PLZF amino terminal region (which is nonresponsive to retinoic acids) of the fusion protein (97). Because PLZF binds N-COR and SMRT independently from RARα, the HDAC corepressor complex is readily released from RARα upon treatment with retinoic acids, but not from PLZF (97). As a consequence, transcriptional repression is preserved. However, the sensitivity of PLZF to ATRA may be restored by the treatment with an HDAC inhibitor (e.g., trichostatin A, an antibiotic). The PLZF-bound HDAC corepressor complex is then readily released, allowing these leukemic cells to differentiate (97,98,172,174, 175).
- An additional example of a translocation found in AML and that has been shown to involve HDACs is the translocation t(8;21)(q22;q22), which results in a fusion of *AML-1* and *ETO* (176–178) and accounts for approximately 10–12% of AMLs (164). Similarly, *AML-1* may be fused to *MTG16* (myeloid tumor gene 16) in the context of a translocation t(16;21)(q24;q22) (179–181), or to *EVI1,* a transcriptional repressor, in association with a translocation t(3;21)(q26;q22) (177,182, 183). In all these translocations of *AML-1,* the Runt homology domain, which is the region of AML-1 that interacts with both DNA and the core binding factor CBFβ, is preserved (178,184,185). Other translocations that are frequently seen are an inversion of chromosome 16 [inv(16)] in AML, where the *CBFβ* gene, which forms a transcription factor complex with *AML-1,* is fused to the smooth muscle myosin heavy chain gene *MYH11* (164) and the translocation t(12;21)(p12;q22), which is found in 15–35% of pediatric B-lineage ALLs and where a *TEL-AML1* gene fusion yields a novel chimeric protein (186,187). The ability of CBFβ to associate with AML-1, hereby increasing the affinity of AML-1 for its DNA-binding site, is retained even when chromosome 16 is inverted (184,185). Because all the translocations mentioned in this paragraph [t(8;21)(q22;q22), t(3;21) (q26;q22), t(12;21)(p12;q22) and inv(16)] interfere with the transcriptional regulation of AML-1 responsive genes (177,178,188–191), evidence emerges that transcriptional repression of AML-1 target genes is critical in the pathogenesis of AMLs. In the case of AML-1/ETO, overexpression of *AML-1* and anti *AML-1/ETO* antisense oligonucleotides can induce differentiation in cells containing this fusion protein (185,191). In analogy to the observations that have been made for PML-RARα and PLZF-RARα, ETO has been found to interact with N-COR and mSIN3A, thereby recruiting histone deacetylases to repress transcription. This effect can be inhibited by histone deacetylase inhibitors (95,192). Additionally, it has been found that critical domains that mediate the interaction

of ETO with N-COR both when *AML-1* is fused to *ETO* [t(8;21)(q22;q22)] and when it is fused to *MTG16* [t(16;21)(q24;q22)] are highly conserved, suggesting that t(16; 21)(q24;q22) equally represses transcription through the recruitment of HDACs. Besides CBFβ, AML-1 associates with other transcription factors and regulators and activates transcription if bound to HATs (e.g., CBP and p300) (191) or represses transcription when it interacts with mSIN3 (192) (Fig. 3).

- Other than the indirect recruitment of HDAC with the assistance of protein complexes, which include mSIN3A, N-COR, and SMRT or Rb, several transcription factors (e.g., YY1) and regulators are able to recruit HDAC enzymes directly (reviewed in 21), thereby interfering with the generation of a functional initiation complex. These HDAC-associated effects on transcriptional regulation may be abrogated by HDAC-inhibitors (trapoxin, trichostatin A, etc.). The retinoblastoma protein (RB), which is important in the induction of cell-cycle arrest under unfavorable growth conditions, mediates E2F-bound promoter repression through its interaction with HDAC1. This binding of HDAC to RB has been highlighted by the observations that tumor-specific mutations found in RB disrupt its association with HDAC (159,193,194) and that viral oncoproteins (e.g., HPV16 E7 or the SV40 T-antigen) are able to displace HDAC from RB (193,194). These findings suggest a fundamental role for histone modification in the suppression of cancer.
- So far, the chromosomal localizations of the human *RPD3* orthologs *HDAC1-3* (102,195) and the *HDA1* orthologs *HDAC4-7* have been identified more or less precisely (87) (Table 2) and, interestingly, *HDAC1-3* and *HDAC7* localize to chromosomal sites, which are particularly fragile and frequently altered through mutations, translocations, and deletions, particularly in myeloproliferative disorders and solid tumors (101–103, 196). This may potentially result in a shift of the acetylation equilibrium toward acetylation.

It had long been epidemiologically postulated that a diet high in fiber was associated with a low incidence of colon cancer (197–200) until the Nurses' Health Study at Harvard, which was conducted on 88,757 middle-aged women, proved that the "protective effect" of dietary fiber against colorectal cancer or adenoma was not significant (198). Even though there is considerable and to some extent inconclusive literature on dietary fiber in connection with colon cancer, it appears that butyrate, a fiber fermentation product, could in fact have a protective effect against colon cancer (201–204). More recently, several investigators demonstrated that butyrate administration effectively reduced incidence and size of colonic tumors (205,206), their likelihood to metastasize (207), and that it shifted their histological phenotype to one that appeared less aggressive (206). Even though the molecular mechanisms by which butyrate mediates its protective effects are still very unclear, butyrate has been shown to induce both histone and nonhistone hyperacetylation through a noncompetitive and nonspecific inhibition of HDACs via a serine-threonine protein phosphatase of the PP1 type (208–210). In addition to its capability to induce differentiation, butyrate has been found to cause a G1 cell-cycle arrest (211,212), which is mediated through induction of the G1 cell-cycle inhibitor *p21* gene (213), thereby requiring an inhibition of HDAC1. The fact that *p21* is deleted in the human colon carcinoma cell line HCT1116 further supports that p21 is essentially involved in butyrate-mediated cellular growth arrest (214). Because butyrate is rapidly metabolized and it has not been possible to maintain adequate butyrate concentrations in patients, butyrate homologs and alternative substrates [e.g., trichostatins and trapoxins (215,216), depudecin (217), oxamflatin (218), benzamide derivatives (219)], which appear more promising than butyrate itself (e.g., phenylbutyrate and tributyrin) are currently under study (220–224).

Conclusion and Future Directions

The equilibrium of reversible histone acetylation is maintained by the activity of two families of enzymes, HATs and HDACs, which have been found to participate in the regulation of cellular proliferation and differentiation as cofactors of several mammalian transcriptional complexes. More recently, increasing evidence suggests a close connection between imbalanced histone acetylation and carcinogenesis. This goes hand in hand with the widely

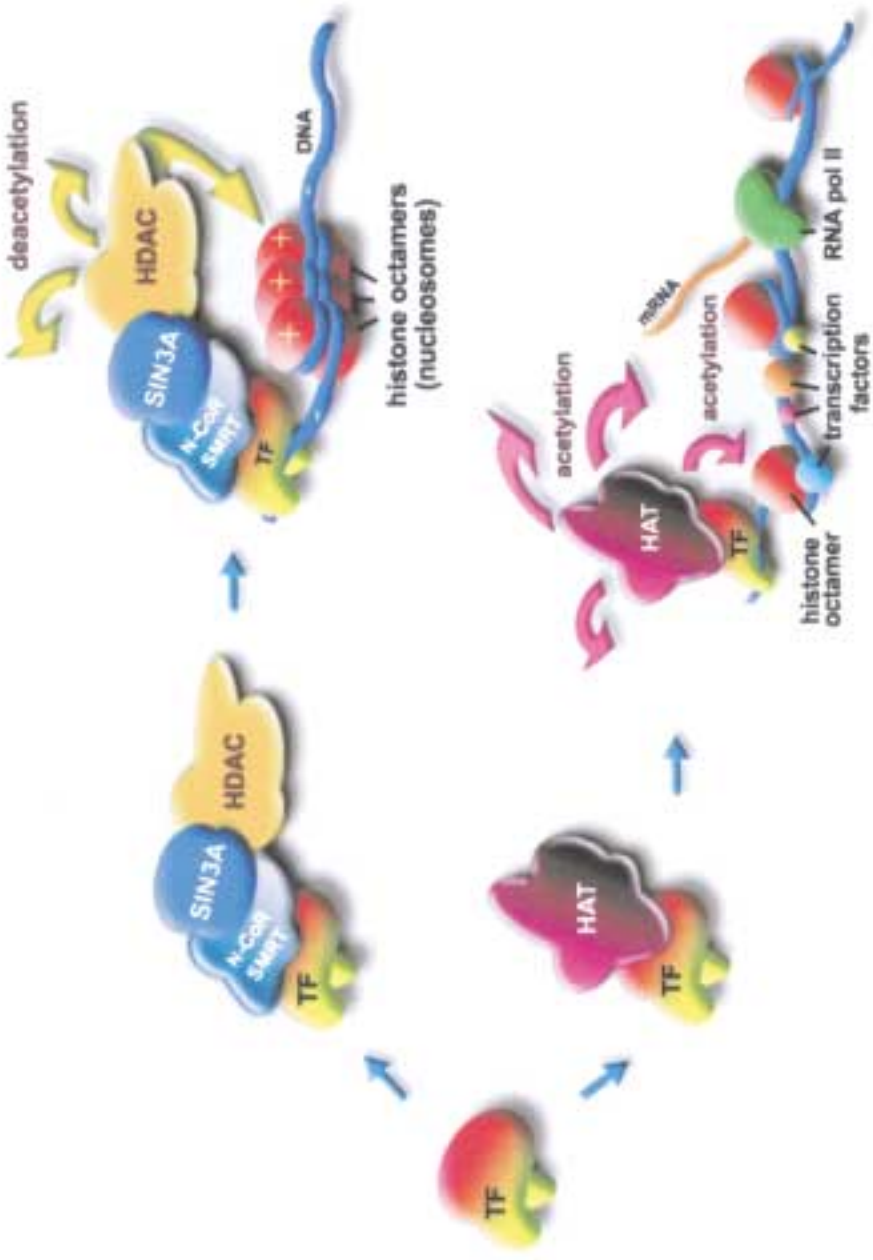

Fig. 3. Some factors that associate with histone modifying-enzymes (nuclear hormone receptors, transcription factors, and other regulators) have the capacity to mediate both transcriptional activation and repression, depending on whether they associate with HATs or HDACs.

accepted concepts that reversible modification of chromatin influences its transcriptional competence and that promoters may be targeted specifically by either activating or repressing complexes. Histone acetylation modifiers have been found to be engaged and mutated in several types of cancer. Although genes encoding *HAT* enzymes have been found to be preferentially translocated, amplified, overexpressed, or point mutated, *HDACs* have repeatedly been identified to mediate the function of oncogenic translocation products, thereby accounting for at least 30% of AMLs, 25% of childhood B-ALLs, and more than 99% of APLs (26). They have also been found to associate with tumor suppressor proteins, which themselves are frequently mutated (e.g., RB). Many questions persist regarding the molecular mechanisms that involve histone-modifying enzymes. The further characterization of HATs and HDACs will therefore not only continue to unravel the role that these enzymes play in transcription, it will also help to identify the molecular mechanisms that promote leukemogenesis. Additionally, it looks like acetylation is not just limited to histones. It could therefore, in analogy to phosphorylation, be a process that influences the function of many proteins and cellular processes. The identification of proteins that interact with histone-modifying enzymes and target genes, which are misregulated as a consequence of mistargeted, or defective histone-modifying enzymes may help to hasten the development of less toxic, more refined and specific forms of pharmacological interventions for some forms of cancer and leukemias. First experiences with histone deacetylase inhibitors as "differentiation therapy" reagents have shown promising results for several types of leukemias (96,172,221–224) and solid tumors (220,225–227) with few, if any, significant side effects, indicating that such treatment could have great therapeutic advantages when compared to conventional chemotherapeutic agents. Even though almost explosive advances in the understanding of the molecular details of transcriptional regulation and chromatin modification through acetylation have been reported in the last few years, many questions remain. The identification of novel HAT/HDAC interaction targets, the analysis of HAT/HDAC levels in primary cells, and the response and tolerability of histone deacetylase inhibitors in patients may help to answer and generate new questions, such as how far a therapeutic modulation of intracellular acetylation levels could complement or replace existing chemotherapeutic strategies in the treatment of cancer.

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