Histone Acetyltransferases in Cancer: Guardians or Hazards?

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ABSTRACT: Histone acetyltransferases (HATs) catalyzing N-epsilon-lysine or N-alpha-terminal acetylation on histone and non-histone substrates are important epigenetic regulators controlling gene expression and chromatin structure. Deregulation of these enzymes by genetic or epigenetic alterations accompanied by defects in gene transcription have been implicated in oncogenesis. Therefore, these enzymes are considered promising therapeutic targets, offering new horizons for epigenetic cancer therapy. However, recent observations suggest that these enzymes function as both oncogenes and tumor suppressors. In this review, we present the current evidence demonstrating that individual HATs can either prevent cancer cell proliferation or drive malignant transformation depending on the molecular context and cancer type. We therefore advocate that future therapeutic interventions targeted toward these enzymes should carefully consider the fact that HATs commonly have a two-sided role in carcinogenesis.

KEY WORDS: histone acetyltransferases, acetylation, histone modifications, cancer, epigenetics

ABBREVIATIONS: 5-FU, 5-fluorouracil; **AML**, acute myeloid leukemia; **AR**, androgen receptor; **CaP**, prostate cancer; **CBP**, CREB-binding protein; **CRC**, colorectal cancer; **DLBCL**, diffuse large B-cell lymphoma; **GC**, gastric cancer; **GCN**, general control non-depressible 5; **HAT**, histone acetyltransferase; **HATa**, HAT activator; **HATi**, HAT inhibitor; **Hbo1**, histone acetyltransferase bound to ORC1; **HCC**, hepatocellular carcinoma; **IL**, interleukin; **MOF**, males absent on the first; **MORF**, MOZ-related factor; **MOZ**, monocytic leukemia zinc-finger; **Naa40**, N-alpha acetyltransferase 40; **NF-κB**, nuclear factor-kappa beta; **NSCLC**, non-small cell lung cancer; **PCAF**, p300/CBP associated factor; **Tip60**, Tat interactive protein of 60 kDa**; TSG**, tumor-suppressor gene

I. INTRODUCTION

Cancer is a complex disease that develops through a multistage process that includes, among many other hallmarks, excessive proliferative signaling and resistance to cell death, which are promoted by the activation of oncogenes and silencing of tumor-suppressor genes (TSGs).[1] In healthy cells, certain wild-type genes called proto-oncogenes are essential to preserve cellular homeostasis by governing cell growth and survival. However, during neoplastic transformation, deregulated proto-oncogenes such as rat sarcoma are turned into cancer-promoting oncogenes that harbor the ability to transform a normal cell into a malignant state through the induction of growth-stimulating signals.[2–7] As a result, malignant cells acquire the hallmark capabilities of uncontrolled cell proliferation and resistance to cell death or differentiation.[1] Conversely, under physiological conditions, TSGs or anti-oncogenes inhibit cell proliferation and thus operate as tumor "breaks" through negative regulation of cell growth or invasion and stimulation of differentiation or cell death.[8] Normally, deactivation of TSGs requires the loss of both alleles of the gene in order for a malignant phenotype to emerge, as originally proposed in Knudson's "2-hit" hypothesis. Before cancer initiation, the first "hit" in a TSG occurs in the germline or in somatic cells and is followed by a second somatic hit, thereby leading to carcinogenesis.[9] Although a typical TSG is recessive by definition, exceptions have been observed, such as haploinsufficiency, in which a single hit event in one allele is sufficient to promote cancer initiation.[10]

For many years, cancer initiation, promotion, and progression have been solely attributed

to genetic alterations. Typically, gain-of-function mutations affecting proto-oncogenes, such as point mutations, gene amplifications, and chromosomal translocations, as well as loss-of-function mutations in TSGs, including deletions, insertions, missense point mutations, and frame-shift mutations, comprise fundamental genetic mechanisms of the tumorigenic process. However, for more than a decade now, epigenetic modulations of oncogenes and TSGs have emerged from the shadows and enlightened our understanding regarding the highly complex procedure of malignant transformation.[11]
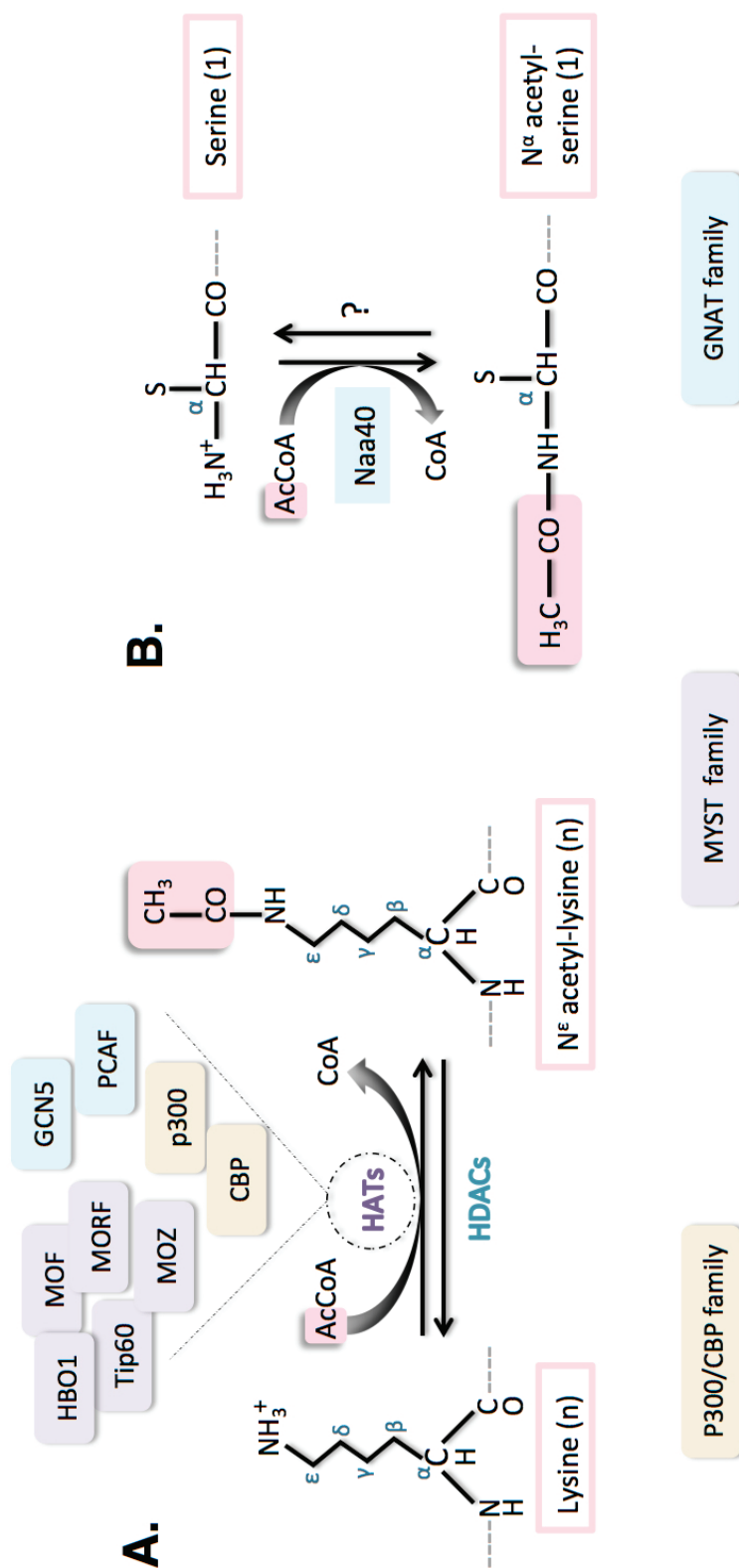
Eukaryotic cells package their genomes in a highly regulated structure within their nucleus known as chromatin. Two copies of each of the four core histone proteins, H2A, H2B, H3, and H4, form an octamer around which 147 base pairs of DNA are wrapped, constructing the nucleosome, which is the fundamental repeating unit of chromatin. The globular domain of histones and their tails protruding outward from the nucleosome core are decorated with a plethora of chemical groups broadly known as histone modifications.[12] One of the most extensively studied histone modification is acetylation, which typically exists in two distinct types. The most common type is N^ε lysine acetylation, which comprises the covalent attachment of an acetyl moiety from acetyl-coenzyme A (Ac-CoA) to the ε-amino group of an internal lysine residue (Fig. 1A). The occurrence of N^ε lysine acetylation, like most histone modifications, is orchestrated by two specialized groups of modifying enzymes: the "writers" (histone acetyltransferases or HATs), which catalyze the addition of the acetyl group, and the "erasers" (histone deacetylases or HDACs), which remove those acetyl groups from lysine residues.[13] A less investigated form of histone acetylation is the N^α-terminal acetylation (N^αt-ac), which is deposited at the N-terminal tip of histone proteins instead of the side chain of lysine residues (Fig. 1B).[14] Although writers for N^α-terminal acetylation have been identified, it still remains unknown whether erasers for this modification exist. Generally, the highly dynamic histone acetylation is a transcriptionally active signature having direct and indirect impacts on chromatin structure. The addition of

an acetyl group on lysine side chains neutralizes the positive charge of histone proteins and thereby weakens the association with the negatively charged phosphate backbone of DNA, unlocking chromatin for transcription. Alternatively, acetyl lysine marks can function as docking sites for bromodomain-containing proteins, which act as readers of these acetyl tags in order to recruit additional effector proteins, such as chromatin remodelers, to alter chromatin architecture, ultimately enabling access to the transcriptional machinery (Fig. 2A).[15]

Lysine acetylation and histone modifications, in general, comprise one of the main epigenetic mechanisms through which chromatin structure and gene expression are tightly regulated.[16] Beyond histone proteins, HATs govern gene expression by operating as coregulators that acetylate and control the activity of important transcription factors (Fig. 2B).[17] Proper transcriptional regulation mediated by acetylation mainly relies on the balance between the opposing functions of the writers (HATs) and the erasers (HDACs).[18] Importantly, gene mutations and functional misregulation affecting the expression or activity of HATs and/or HDACs disrupts this balance, leading to abnormal gene expression that ultimately gives rise to malignant transformation (Fig. 3).[10] Accordingly, there is accumulating evidence that restoring the normal expression or function of histone-modifying enzymes provides new therapeutic avenues for cancer treatment.[19]

II. THE DOUBLE FACES OF HATS IN TUMORIGENESIS: ONCOGENES AND TUMOR SUPPRESSORS

In the early 1960s, revolutionary work from Vincent Allfrey and colleagues identified histone lysine acetylation and proposed a role for this modification in transcriptional regulation.[20] Since then, remarkable work carried out by several groups established the importance of histone acetylation in gene activation and discovered the enzymes that control its occurrence.[21] As stated above, histone acetylation is catalyzed by HATs, which are evolutionarily conserved enzymes classified into three major families based on their structure and sequence homology: MYST
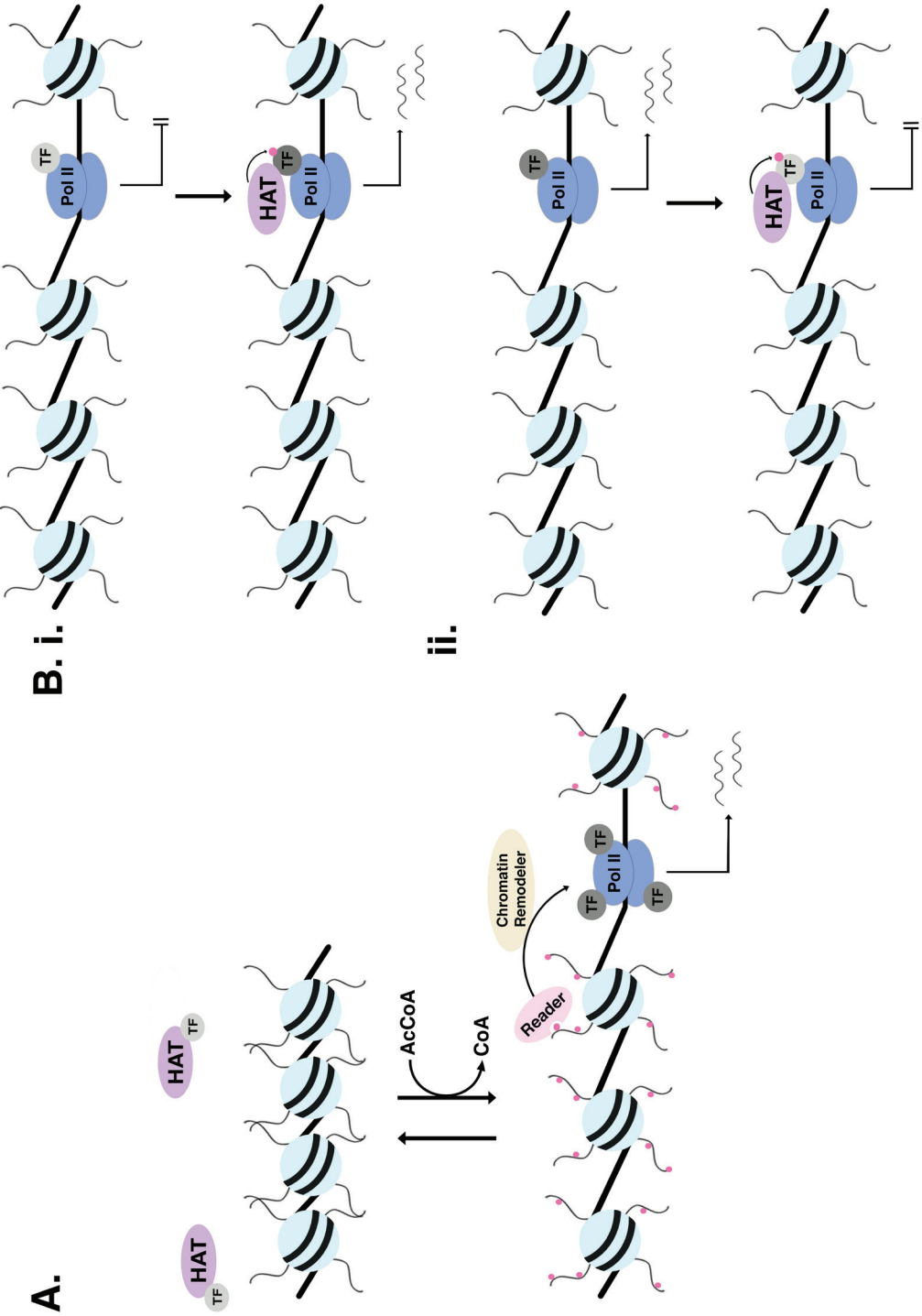
FIG. 1: HAT families and types of acetylation. (A) MYST (Tip60, HBO1, MOF, MOZ, MORF), GNAT (GCN5, PCAF), and p300/CBP (p300, CBP) lysine acetyltransferases catalyze the reversible transfer of an acetyl group from AcCoA to the ε-amino group on the side chain of internal lysine residues. (B) The Nα-terminal acetyltransferase Naa40 of the GNAT family transfers an acetyl moiety from Ac-CoA to the α-amino group of the first amino acid residue on histones H4 and H2A. It remains unclear whether N-terminal acetylation is reversible because no eraser enzymes have yet been identified for this modification.

FIG. 2: Regulatory mechanisms used by HATs. (A) HATs are recruited to chromatin by transcription factors to catalyze the addition of acetyl groups on histone proteins, resulting in an "open" chromatin structure that enables access to the transcriptional machinery. The HAT-mediated acetyl marks are read by reader proteins that recruit additional effector molecules (e.g., chromatin remodelers) to further decondense chromatin, facilitating the expression of target genes. (B) Apart from histones, HATs also bind and acetylate non-histone proteins such as transcription factors, influencing their transcriptional activity. (Bi) HATs interact and acetylate transcription factors, which are then activated to stimulate the transcription of target genes. (Bii) Alternatively, HATs bind and acetylate previously activated transcription factors, preventing their function, which leads to transcriptional silencing of target genes.

(MOZ, Ybf2/Sas3, Sas2 and TIP60), GNAT (Gcn5-related N-acetyltransferase) and p300/CBP (p300 and CREB-binding protein) (Table 1).[22] Given the important role of histone acetylation in transcriptional regulation, it is not surprising that aberrant patterns of this epigenetic mark triggered by impaired HAT activity have been reported and linked to cancer initiation and progression (Fig. 3).[18,23] Specifically, reduced HAT activity on conventional TSGs and increased HAT activity on typical oncogenes facilitates the establishment of cancer hallmarks such as evasion of cell cycle arrest, reduced apoptosis, and uncontrolled cell proliferation (Fig. 3). Interestingly, beyond transcriptional misregulation of cancer-associated genes, the genes that express HATs are themselves subjected to gain-of-function or loss-of-function mutations.[24] Therefore, it is conceivable that HATs possess a paradoxical dual function nature in carcinogenesis that can be either oncogenic or tumor suppressive depending on the molecular or cellular context (Table 1).[24]

A. MYST Family of HATs

The MYST family of HATs initially acquired the name from its founding members, MOZ (Monocytic leukemia zinc-finger), Ybf2/Sas3, Sas2, and TIP60.[25] Currently, five human HATs, Tip60, HBO1, MOF, MOZ, and MORF (MOZ-Related Factor), belong to the MYST family, all sharing the highly conserved MYST domain, which harbors a C2HC nucleosome-binding region followed by an Ac-CoA-binding motif.[17,26] Emerging data suggest that MYST family members have profound roles in a vast variety of cellular processes such as transcription, DNA damage repair, cell growth, and apoptosis. Therefore, it is reasonably expected that, when HATs are deregulated, this may lead to a diverse range of diseases including cancer.

1. Tip60/KAT5

Tip60 (Tat interactive protein of 60 kDa) is the most studied MYST acetyltransferase that catalyzes the transfer of acetyl groups at lysines 5 (K5), 8 (K8), 12 (K12) and 16 (K16) on histone H4 and K5 on histones H2A, H2A.X, and H2A.Z.[27] Tip60 influences multiple biological processes through a dual mode of action. It functions either as a bona fide transcriptional activator through its intrinsic HAT activity or as a coregulator of several transcription factors that promote or suppress cancer.[28–30]

Several studies depict Tip60 as an oncogene. For instance, Tip60 is significantly increased in malignant pleural mesothelioma compared with normal pleura in both primary tissues and established cell lines, whereas Tip60 inhibition perturbs cell proliferation and triggers apoptosis.[31] Another study has shown that, in response to growth-stimulating signals, Tip60 is recruited to chromatin via the MYC transcription factor and through histone acetylation activates MYC target genes, promoting cell proliferation.[32] In addition, Tip60 has been linked to the DNA damage response pathway because it was reported that cells lacking a catalytically active Tip60 are impotent to repair DNA double-strand breaks.[33] Specifically, upon DNA damage, Tip60 is activated, leading to histone acetylation as well as acetylation and activation of the ataxia telangiectasia mutant (ATM) protein, which are crucial events for subsequent induction of proteins necessary for DNA repair.[34] Therefore, the above evidence implies that Tip60 could facilitate resistance of cancer cells to DNA damage, inducing chemotherapeutic agents. Indeed, it was shown that overexpression of Tip60 and upregulation of its corresponding H4K16ac mark were correlated with resistance of epidermoid and prostate cancer (CaP) cells to cisplatin due to transcriptional activation of key DNA repair genes.[35] Similarly, an additional study illustrated that Tip60 binds to and acetylates E2F1 protein, stimulating the accumulation of the excision repair cross-complementation group 1 (ERCC1) enzyme and promoting resistance of lung adenocarcinoma cells treated with cisplatin. Consistent with this, Tip60 knockdown enhances the sensitivity of these cancer cells to cisplatin.[36] Moreover, Tip60 functions as coactivator of the androgen receptor (AR) by directly interacting with AR and enhancing its transcriptional activity. Halkidou et al. also implicated TIP60 in CaP development by demonstrating that androgen withdrawal correlates with upregula-
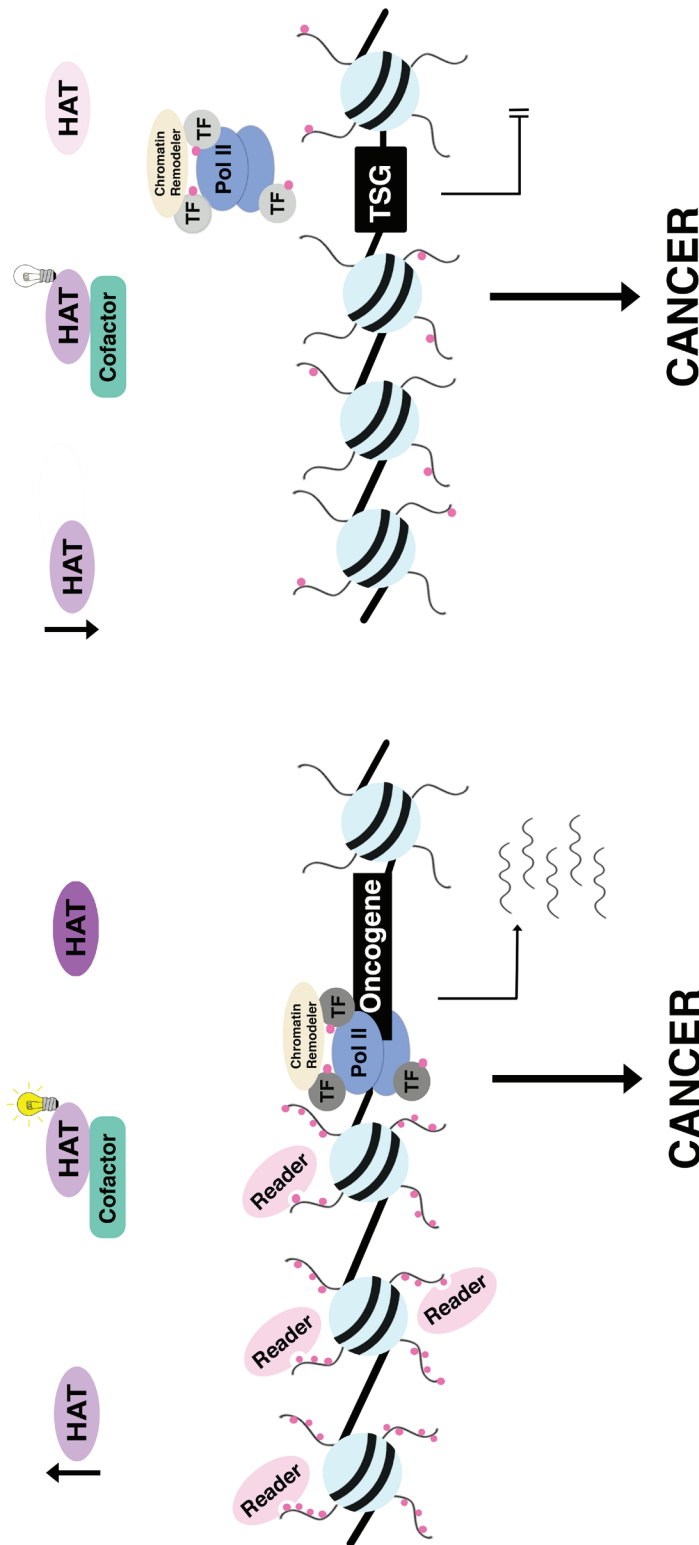
FIG. 3: HATs can act as oncogenes and tumor suppressors. Misregulation of HATs during oncogenesis is attributed to malfunction in their expression levels, recruitment, or enzymatic activity. (A) HATs are considered to be oncogenic due to overexpression, increased recruitment to chromatin by several oncoproteins such as fusion chimeras and viral proteins, and/or increased catalytic activity. Either scenario increases histone acetylation marks and transcription factor activity, leading to elevated expression of key oncogenes and ultimately cancer. (B) HATs can function as TSGs because their downregulation, inhibition of their recruitment to chromatin by direct association with cofactors, or reduced enzymatic activity leads to silencing of targeted TSGs and malignant transformation.

TABLE 1: The double faces of HATs in carcinogenesis

HATs	Histone substrate	Coregulator	Role as Oncogene or TSG	Tumor type	Reference(s)
MYST family					
Tip60/KAT5	H4 (K5, K8, K12, K16), H2A (K5)	c-Myb, STAT3, MYC, ATM, E2F1, p53, AR	Oncogene	Malignant pleural mesothelioma, cervical, epidermoid, CaP, lung	31–38
			TSG	Breast, lymphomas, head-and-neck, GC, melanoma, CRC, breast, lung, AML, CaP	39–48
Hbo1/KAT7/MYST2	H4 (K5, K12, K16), H3 (K14)	ORC1, PML-RARα	Oncogene	Breast, ovarian, testis, bladder, stomach/ esophagus	49,56–62
			TSG	Acute promyelocytic leukemia, AML	63,64
MOF/KAT8/MYST1	H4K16, H4 (K8, K9)	Nrf2, p53	Oncogene	NSCLC, OTSCC, CaP	67–71
			TSG	Ovarian, HCC, RCC, medulloblastoma, breast	72–79
MOZ/KAT6A/MYST3	H3 (K9, K14, K16, K27)	p53, AML1	Oncogene	AML, breast	81–92
			TSG	AML	83,89,96
MORF/KAT6B/MYST4	H3 (K23)	ING5	Oncogene	AML, uterine leiomyomata, retroperitoneal leiomyoma, CaP	93–95
			TSG	SCLC, adrenal, cervical	97–99
GNAT family					
PCAF/KAT2B	H3 (K9, K14)	E2F1, GLI1, SMAD4, PAX3-FOXO1, p53, AE1	Oncogene	Medulloblastoma, glioblastoma, ARMS	101–104
			TSG	HCC, osteosarcoma, NSCLC, GC, CRC	105–111
GCN5/KAT2A	H3 (K9, K14, K56), H4, H2A	E2F1, c-MYC	Oncogene	HCC, NSCLC, CRC, glioma, UC, CaP, esophageal squamous cell carcinoma, AML	112–120
			TSG	Lymphoma	121
Naa40/NatD/Patt1	N-acH4, N-acH2A		Oncogene	CRC	133
			TSG	HCC	130
P300/CBP family					
P300	H2A, H2B, H3 (K18, K27, K56, K122), H4	β-catenin, AR, c-Myb, p53	Oncogene	Breast, nasopharyngeal, HCC, CaP, AML	136–145,158–160
			TSG	MDS-associated AML, CRC, breast, pancreatic, ovarian, lung, DLBCL, bladder, melanoma	146–153,167–169
CBP	H2A, H2B, H3 (K18 K27, K56, K122), H4	cAMP, MOZ-TIF2, AR, BRCA1	Oncogene	AML, SCLC, CaP	157–160
			TSG	AML, lung, lymphoma, ALL, osteosarcoma cervical, CRC	161–169

tion, nuclear localization, and recruitment of Tip60 onto the *PSA* gene promoter in CaP cells both *in vitro* and *in vivo*.[37] Furthermore, Tip60 plays an important role within the nuclear factor-kappa beta (NF-κB) pathway. Specifically, upon inflammatory signals, Tip60 is recruited to the promoters of the NF-κB target genes interleukin-6 (*IL-6*), *IL-8*, *C-IAP1*, and *XIAP* and mediates histone acetylation, resulting in a more accessible chromatin state and transcriptional activation.[38]

Conversely, a significant body of work supports the function of Tip60 as a TSG. Importantly, the Tip60 gene (*HTATIP*) has been characterized as a haploinsufficient TSG in breast cancer, head and neck cancer, and lymphomas that is necessary for the oncogene-driven DNA damage response.[39] Downregulation of Tip60 was significantly correlated with age, tumor invasion, metastasis, and other clinicopathological features in patients with gastric cancer (GC) and colorectal cancer (CRC).[40,41] Interestingly, Tip60 downregulation in CRC is frequently accompanied by changes in the mRNA levels of its upstream regulator, p400, thus altering the p400/Tip60 ratio, which negatively affects Tip60 functional activity. Restoring p400/Tip60 balance promotes apoptosis, cell cycle arrest, and increased sensitivity of CRC cells to the chemotherapeutic drug 5-fluorouracil (5-FU).[42] In addition, low Tip60 expression is an independent prognostic factor for inferior 5-year melanoma patient survival and is associated with tumor metastasis, whereas increased Tip60 expression inhibits cell migration and increases drug-induced apoptosis in melanoma cells.[43] Moreover, Tip60 LOH disrupts genomic integrity in mammary tumors due to a negative correlation with defective homologous recombination gene expression signature and thus loss of DNA damage repair ability.[44] Reduced Tip60 expression levels were also identified in lung cancer patient samples compared with normal tissue.[45] A possible explanation for this downregulation was provided by Eymin et al., who showed that lack of Tip60 activity inactivates a p14[ARF]-mediated tumor suppressive pathway in lung cancer cells.[46] Furthermore, acute myeloid leukemia (AML) patient samples express low levels of Tip60 compared with normal samples. Normally, high lev-

els of Tip60 reduce the transcriptional activity of the c-Myb proto-oncogene by recruiting HDACs, and thus loss of Tip60 drives c-Myb-mediated AML.[28] Finally, another study supporting the role of Tip60 as a TSG reports that Tip60 is downregulated in metastatic CaP cells and, as a result, it is not recruited to the promoter of the metastasis suppressor gene *KAI1*, which remains hypoacetylated and inactive. Consistent with this, Tip60 overexpression in CaP cells leads to recruitment of Tip60 onto the *KAI1* promoter, resulting in restoration of *KAI1* expression through histone acetylation.[47,48]

2. Hbo1/KAT7/ MYST2

Hbo1 (Histone acetyltransferase bound to ORC1) is the least studied HAT within the MYST family. Hbo1 catalyzes acetylation on histone H4 preferentially at K5 and K12.[49] Nevertheless, it appears that Hbo1 also mediates H3K14 acetylation to control transcriptional activation of key regulatory genes that orchestrate embryonic development and fetal liver erythropoiesis.[50,51] Although little is known about its link to carcinogenesis, it has already been ascribed as an oncogene and TSG. Initially, it was reported that Hbo1 plays a crucial role in DNA replication through its binding to origin recognition complex 1 (ORC1).[49,52–55] The ability of Hbo1 to coordinate transcription with replication licensing raises the question as to whether its deregulation can contribute to cellular proliferation defects and tumorigenesis.

Indeed, Iizuka et al. showed that Hbo1 protein levels are significantly increased in breast, ovarian, testis, bladder, and stomach/esophagus cancers.[49] Other groups revealed that Hbo1 overexpression enhances the oncogenic potential of breast cancer cells and promotes cancer stem-like cell properties in human mammary epithelial cells.[56,57] Moreover, Hbo1 stimulates transcription of nuclear hormone receptor target genes.[58–60] For example, Hbo1 supports cell growth and survival of tamoxifen-treated breast cancer cells by activating ERα-regulated oncogenes such as *E2F1*, *RRM2*, and *CTSD* and silencing of ERα-controlled TSG such as *IL-24*. Accordingly, depletion of Hbo1 in these cells leads

to efficient reduction of cell proliferation.[61] A very recent study by Chen et al. demonstrates that high Hbo1 expression levels in bladder cancer patients correlates with poor overall survival. In addition, they showed that Hbo1 ectopic expression enhanced tumor growth, whereas Hbo1 downregulation suppressed cell proliferation *in vitro* and *in vivo* through the Wnt/β-catenin signaling pathway, supporting its role as an oncogene.[62]

In contrast to its oncogenic properties, Hbo1 can function as a TSG in hematological malignancies. Specifically, it was shown that the PML-RARα fusion oncoprotein binds directly to the Hbo1 promoter and suppresses its expression at the transcriptional level in acute promyelocytic leukemia, implying that Hbo1 functions as a TSG in this cancer.[63] Later work from the same group showed that Hbo1 and its associated H4K5ac were downregulated in blast cells derived from AML patients and this was associated with poor prognosis.[64]

3. MOF/KAT8/MYST1

MOF (Males absent on the first) is another member of the MYST family that primarily transfers an acetyl group from Ac-CoA to the side chain of K16 on histone H4, but can also target K5 and K8 on the same histone.[65,66] MOF has been shown to modulate pivotal biological processes with an inevitable link to oncogenic transformation, including gene regulation, DNA damage repair, and cell cycle. Mutated or deregulated MOF perturbs the levels of H4K16ac, causing abnormal expression of oncogenes or TSGs and thereby leading to defective DNA damage repair, genomic instability, cell cycle abnormalities, and eventually carcinogenesis.

The expression pattern of hMOF varies dramatically among different tumor types. Several studies illustrated the potential of human MOF (hMOF) and H4K16ac as a clinical marker in non-small cell lung cancer (NSCLC), in which they were found to be significantly overexpressed compared with adjacent nonmalignant lung cells. Furthermore, hMOF depletion through RNAi in the Calu-6 lung cancer cell line has been shown to inhibit cell proliferation.[67] Similarly, upregulated hMOF in H1299 and

A549 NSCLC cancer cell lines catalyzes H4K16ac at the promoter of the *Skp2* oncogene, increasing its expression levels and thereby leading to transition toward the G_1/S phase of the cell cycle, which favors cell growth, migration, and adhesion.[68] In another study, it was shown that, in NSCL cancer cells, hMOF interacts with and acetylates the Nrf2 transcription factor to increase its nuclear localization and thus facilitate Nrf2-mediated transcriptional activation of target genes such as drug-metabolizing enzymes, efflux transports, and antioxidant enzymes, which control cell growth and drug resistance.[69] In addition, hMOF is frequently upregulated in 62.5% of patients with oral tongue squamous cell carcinoma (OTSCC) and its high expression is correlated with shortened patient survival. This oncogenic effect was further supported in the established OTSCC cell line SCC9, in which hMOF knockdown using short hairpin RNAs reduced both *in vitro* cell proliferation and *in vivo* tumor growth. Functionally, loss of hMOF blocked *EZH2* expression by interfering with its promoter activity and EZH2 expression is required for hMOF to mediate its effects on SCC9 cell growth.[70] Moreover, upon androgen stimulation of CaP cells, hMOF is recruited to chromatin by PKN1 and WDR5 and catalyzes H4K16ac at AR target genes (e.g., *IGF1R*, *KLK3*) to activate their transcription, accelerating CaP cell growth and colony formation.[71]

Conversely, hMOF expression and its corresponding H4K16ac are significantly reduced in 81% of patients with ovarian cancer and this is accompanied with a concomitant downregulation of the hMOF-regulated gene *HCP5*.[72] A second study supported this work by demonstrating that hMOF is markedly decreased in ovarian cancer patient samples compared with normal tissue and hMOF overexpression correlates with enhanced overall patient survival.[73] In addition, hMOF downregulation was reported in hepatocellular carcinoma (HCC) patient specimens and HCC cancer cell lines and was correlated with worse patient outcome. Depletion of hMOF in HCC cells stimulates cell growth and colony formation, whereas enhancement of hMOF expression inhibits cell proliferation and *in vivo* tumor volume. Mechanistically, hMOF binds

directly and induces promoter activity and expression of *SIRT6*, thus blocking the transcription of the SIRT6-regulated genes *survivin*, *Afp*, *IGF2*, *H19*, and *GPC3*.[74] Reduced hMOF expression in both mRNA and protein levels was also observed in primary renal cell carcinoma (RCC) samples and established RCC cell lines and was tightly associated with decreased H4K16ac levels. Because loss of hMOF and H4K16ac do not influence the expression of the known CA9 diagnostic marker, hMOF was proposed to be a novel CA9-independent biomarker for RCC.[75] Moreover, patients with primary breast cancer and medulloblastoma exhibited significantly reduced hMOF mRNA and protein levels with parallel loss of H4K16ac. Medulloblastoma patients with downregulated hMOF exhibit worse prognosis, indicating that hMOF serves as a new prognostic marker for medulloblastoma outcome.[76] Mechanistic evidence in breast cancer cells shows that hMOF-mediated deposition of H4K16ac at the promoter of the *TMS1* pro-apoptotic gene leads to proper nucleosome positioning and active gene expression. In contrast, abrogated hMOF expression and loss of H4K16ac at the *TMS1* locus result in aberrant nucleosome positioning, gene silencing, and eventually carcinogenesis.[77] More recently, work from the same group provided further evidence of how hMOF catalytic activity modulates TSG activation in human cancers. Specifically, the investigators have shown that H4K16ac catalyzed by hMOF recruits the BRD4/pTEFb compex at specific TSGs to overcome Pol II pausing and promote the transition from initiation to transcriptional elongation.[78] Beyond histone acetylation, hMOF functions as a coregulator of transcription factors that have tumor-suppressive roles. For instance, upon DNA damage, hMOF interacts and acetylates p53 on lysine 120, an event that is critical for the p53-dependent expression of pro-apoptotic genes.[79]

4. MOZ/KAT6A/MYST3 and MORF/KAT6B/MYST4

MOZ and MORF are two closely related MYST-type HATs that together catalyze the majority of detected histone H3 acetylation.[80] Both of these HATs have been implicated in carcinogenesis, functioning either as oncogenes or tumor suppressors.

MOZ plays a crucial role in normal hematopoiesis and is necessary for the maintenance of hematopoietic stem cells. Therefore, MOZ misregulation is a frequent event in leukemogenesis. In particular, the locus of MOZ on chromosome 8p11 is often involved in chromosomal translocations, resulting in the expression of various oncogenic fusion gene products, which aberrantly reorganize cofactor recruitment and histone acetylation at target genes. A very well-known cytogenetic abnormality is the t(8;16)(p11;p13) translocation, which fuses *MOZ* with the *CBP* gene located at 16p13, leading to the rare and aggressive FAB M4/M5 subtypes of AML characterized with poor prognosis.[81,82] At the molecular level, Kitabayashi et al. proposed that the MOZ-CBP fusion protein induces leukemia by diminishing AML1-dependent transcription.[83] Another rearrangement observed in therapy-related AML is t(8;19)(p11;q13), which fuses *MOZ* to the leucine twenty homeobox (*LEUTX*) gene on 19q13.[84] In addition, the chromosomal translocation t(8;22)(p11;q13) results in the MOZ-p300 chimeric oncoprotein, which is involved in AML through aberrant histone acetylation.[85,86] Moreover, the t(8;20)(p11;q13) translocation, which fuses *MOZ* with the nuclear receptor coactivator 3 (*NCOA3*), has been detected in M5 AML.[87] Importantly, inv(8)(p11;q13) generates the MOZ-TIF2 fusion oncoprotein, which binds bromodomain-PHD finger protein 1 (BRPF1) directly and together they interact with and activate the expression of the HOX genes (*Hoxa9* and *Hoxa10*) through MOZ-dependent H3 acetylation, favoring leukemic transformation.[88] It was also reported that the MOZ-TIF2 fusion product binds within the *RARβ2* promoter region and alters ATRA-induced H3K9ac and H3K14ac, as well as the recruitment of coactivators, leading to transcriptional silencing of the *RARβ2* TSG.[89] The HAT activity of the MOZ-TIF2 chimera has also been involved in leukemogenesis by preventing senescence through inhibition of *p16^{INK4α}* and *p19^{ARF}* transcription.[90] In addition the MOZ-TIF2 fusion protein, MOZ itself blocks senescence by catalyzing H3K9ac and H3K27ac within the promoter region

of *Cdc6*, *E2f2*, and *Ezh2* to maintain their transcriptional activation and thus inhibit the senescence-inducing INK4A-ARF pathway.[91] Beyond hematological malignancies, MOZ upregulation has also been reported in solid tumors. Specifically, it was shown that MOZ knockdown reduces cell proliferation, cologenic ability, and mammosphere-forming capacity of breast cancer cells harboring the 8p11-p12 amplicon.[92]

Although MORF is structurally and functionally similar to MOZ, its role as an oncogene is not reported as extensively. Interestingly, in the M5a subtype of childhood AML, a t(10;16)(q22;p13) chromosome translocation that fuses the *MORF* gene on 10q22 to the *CBP* gene located at 16p23 has been detected.[93] Apart from the observations in hematological malignancies, MORF fusions have also been detected in uterine leiomyomata such as at the t(10;17)(q22;q21) translocation, which fuses *MORF* with various candidate genes (e.g., *GCN5L2*) found near the 17q21 breakpoint.[94] Moreover, the MORF-KANSL1 fusion protein generated by the t(10;17)(q22;q21) chromosome translocation was detected in retroperitoneal leiomyoma.[93] Furthermore, MORF has been implicated in CaP cell growth through the regulation of PI3K/AKT signaling pathway.[95]

MOZ and MORF have also been assigned tumor-suppressive roles despite the lack of compelling evidence. For instance, in contrast to the above indications, MOZ and MOZ-TIF2 chimera have been implicated in the transcriptional activity of the AML1 transcription factor, thereby favoring cellular differentiation and suppression of leukemia.[83,89] Another report demonstrated that, upon DNA damage, MOZ interacts with p53, resulting in increased p53-dependent transcription of *p21*, which directs G1 cell cycle arrest.[96] Furthermore, inactivation of the MORF gene due to homozygous deletion indicates its tumor-suppressive character in SCLC primary tumors and cell lines. MORF knockdown and consequent loss of MORF-mediated H3K23ac stimulates cell proliferation *in vitro* and *in vivo,* whereas rescue experiments that recover MORF expression reduce tumor volume.[97] A recent report also shows that MORF enhances the transcription of the Brahma (*BRM*) gene, the product of which is a potent TSG.[98]

Last, it was reported that MORF associates directly with the ING5 tumor-suppressor protein.[99]

B. GNAT family of HATs

The GNAT (GCN5-related N-AcetylTransferase) superfamily of HATs consists of several members, all sharing conserved sequence motifs, including the Q/RxxGxG/A Ac-CoA-binding region.[100] Generally, GNATs are involved in the control of cellular proliferation, mainly through their effects on the cell cycle, and, importantly, defects in their activity lead to altered epigenetic regulation and cancer. The best characterized GNAT histone acetyltransefrases, which have pivotal roles as oncogenes and TSGs, are the closely related PCAF and GCN5, as well as the unique N^α-acetyltransferase Naa40.

1. PCAF/KAT2B

Early evidence linked PCAF (p300/CBP Associated Factor) to the regulation of cell cycle progression by acting as a coactivator of transcription factors such as E2F1.[101] In addition to E2F1 control, PCAF is a positive regulator of the Hedgehog (Hh)-Gli signaling pathway that is activated in medulloblastoma and glioblastoma cells. PCAF interacts directly with GLI1 and colocalizes at Hh target gene promoters, where it mediates H3K9ac to activate their expression and thereby enhance cell proliferation. Conversely, PCAF deficiency diminishes Hh activity, triggering apoptosis in medulloblastoma and glioblastoma cell lines, and reduces the tumor-forming ability of neural stem cells *in vivo*.[102] The oncogenic role of PCAF was supported by another study demonstrating that, in cancer cells, GLI1 and SMAD4 require the PCAF-mediated histone acetylation activity in order to promote the expression of TGFβ downstream genes, including *BCL-2*, *IL-7*, and *Cycline D1*.[103] Furthermore, it was shown that PCAF is highly expressed in alveolar rhabdomyosarcoma (ARMS) primary tumors compared with normal muscle cells. PCAF expression in ARMS cells promotes oncogensis by mediating acetylation and stabilization of PAX3-FOXO1, whereas PCAF knockdown in these cells reduces PAX3-FOXO1 levels,

restraining tumor progression *in vitro* and *in vivo*.[104]

Although the above studies confer the oncogenic potential of PCAF, there is now substantial evidence supporting its tumor-suppressive role. The function of PCAF within the Hh signaling pathway appears to be highly contradictory. In contrast to the data described above, a recent study showed that aberrant loss of PCAF in HCC cell lines results in enhanced targeting of GLI1, thereby inducing epithelial-mesechymal transition (EMT), which leads to cell migration and invasion. This tumor-suppressive role of PCAF in HCC was supported by the fact that it is downregulated in HCC primary tissues and its reduction correlates with increased tumor invasion and poor clinical outcome.[105] A second study supporting the negative impact of PCAF on the Hh pathway reported that GLI1 is acetylated directly by PCAF when expressed in HCC cells, preventing GLI1 nuclear localization and loading on target gene promoters. Therefore, *BCL-2* expression is reduced, whereas *BAX* is actively transcribed, leading to 5-FU increased sensitivity and apoptosis of HCC cells *in vitro* and in xenograft mouse models.[106] This is consistent with previous work from the same group showing that PCAF overexpression in HCC cells induces direct histone H4 acetylation and inactivates AKT signaling, leading to apoptosis and cell cycle arrest *in vitro* and reduced tumor growth *in vivo*.[107] Furthermore, upon exposure of various cancer types in different p53-activating stress signals, PCAF stimulates p53-dependent transcription of *p21* through deposition of H3K9ac and H3K14ac at its promoter, resulting in G1 cell cycle arrest.[108] In addition, Ying et al. showed that the expression levels of PCAF are reduced in GC primary tissues and cell lines and that this downregulation is significantly associated with clinicopathological features and poor GC patient survival. Conversely, forced PCAF expression in GC cells and xenograft mouse models decreased colony and tumor formation, respectively.[109] A recent study provided mechanistic evidence on the tumor-suppressive role of PCAF in GC. Specifically, PCAF interacts with AE1, promoting its proteasomal degradation, which in turn leaves the AE1-interacting partner p16 to move freely into the nucleus. Inside the nucleus, p16 associates with

CDK4, interrupting its binding toward Cyclin D1 and thus inducing G1 cell cycle arrest.[110] Finally, PCAF has been implicated as a tumor suppressor in CRC cells, in which it is downregulated, resulting in histone hypoacetylation and decreased expression of the *CXCL12* metastasis-associated gene.[111]

2. GCN5/KAT2A

GCN5 (General Contol Non-depressible 5), the founding member of the GNAT family of HATs, is implicated in the modulation of fundamental cellular functions, including cell cycle and DNA damage repair. Based on the existing literature, the role of GCN5 in carcinogenesis appears to be primarily oncogenic rather than tumor suppressive.

GCN5 expression levels are upregulated in HCC primary samples and cell lines and promote cancer cell survival by increasing the transcription of *AIB1* oncogene through the addition of H3K9ac marks on the *AIB1* promoter.[112] Upregulation of GCN5 was also frequently detected in NSCLC and positively associated with larger tumors. In NSCLC cells, GCN5 is recruited by E2F1 to the *E2F1* promoter itself and the promoter of E2F1-regulated genes *cyclin E1* and *cyclin D1*, where it catalyzes histone H3 and H4 acetylation to activate their transcription, thereby potentiating the transition of cells from the G_1 to the S phase of the cell cycle.[113] In addition, expression of GCN5 is induced by c-MYC and E2F1 transcription factors to accelerate tumor growth and inhibit apoptosis in colon cancer cells.[114] In a reciprocal manner, GCN5 regulates the function of c-MYC oncoprotein by increasing its protein stability through acetylation.[115] GCN5 is also upregulated in glioma patient samples and cell lines, where it stimulates STAT3 and AKT signaling pathways to facilitate cell growth and invasion.[116] Moreover, high expression levels of GCN5 were observed in urothelial carcinoma (UC) patient samples, whereas GCN5 depletion induced G_1 cell cycle arrest and apoptosis in UC cell lines.[117] Recently, a genome-wide study identified GCN5 as an important regulator of abnormal gene transcription in prostate adenocarcinoma samples[118] and whole-exome sequencing identified point mutations in the

GCN5 gene, which are highly correlated with lymph node metastasis of esophageal squamous cell carcinoma.[119] In addition, a study using CRISPR screening revealed a leukemogenic function for GCN5 because its inhibition induces myeloid differentiation and apoptosis in AML cell lines and suppresses the growth of primary human AML cells. The effects mediated by GCN5 inhibition have been attributed to upregulation of genes implicated in the MLL-AF9 leukemogenic program and downregulation of myeloid differentiation genes.[120] The only indication of GNC5 acting as a TSG comes from a study showing that GCN5 deficiency in chicken lymphoma cells confers resistance against pharmacological ER-stress-induced apoptosis through enhanced transcription of *Bcl-2*.[121] However, additional evidence is required to support a potential tumor-suppressive role for GCN5 in carcinogenesis.

3. Naa40/NatD/Patt1

Naa40 (N-alpha-acetyltransferase 40) belongs to the N-terminal acetyltransferase (NAT) family of enzymes and is a unique HAT within the GNAT superfamily.[100,122] In contrast to all of the other HATs mentioned in this review, which catalyze the ε-amino acetylation of internal lysine residues, Naa40 specifically deposits an acetyl-group to the α-amino group of the first amino acid residue, serine (S1), on histones H4 and H2A (Fig. 1B).[123–125] Similarly to N^{ε}-lysine acetylation, the addition of the acetyl moiety neutralizes the positively charged free α-amino group, thus inhibiting ionization and other modifications from occurring at the N-terminus and forming a larger more hydrophobic N^{α} terminal amino acid.[126–128] Despite the fact that the evolutionarily conserved histone N^{α}t-ac is a very abundant modification, its biological significance and functional effects on chromatin remained in the shadows for decades. Only recently have new findings shed light on the regulatory role of Naa40 and its associated histone acetylation in cellular aging and carcinogenesiss.[129–133] Pavlou et al. proposed an oncogenic function for Naa40 in tumor development when they demonstrated that loss of Naa40 triggers p53-independent apoptosis in CRC cell lines

whereas depletion of Naa40 in noncancerous cells does not affect their viability.[133] Conversely, Naa40 is downregulated in HCC tissues compared with adjacent normal liver cells and Naa40 overexpression in HCC cell lines increased chemotherapy-induced apoptosis, suggesting that Naa40 acts as a TSG in HCC.[130] Nevertheless, the precise role of Naa40 in cancer remains unclear and further investigations are required to determine whether it functions as an oncogene or TSG.

C. p300/CBP family of HATs

p300, together with the highly related protein CBP, comprise the p300/CBP family of acetyltransferases. These two HATs are very similar both at the amino acid (63%) and DNA (86%) sequence levels, which also translates into significant structural resemblance.[80] Both of these HATs have been implicated with complementary roles in different cellular processes, including proliferation, apoptosis, and DNA damage repair.[134]

1. p300/EP300/KAT3B

p300 (also called EP300 for E1A binding protein p300) was first discovered via its interaction with E1A adenoviral protein.[135] During carcinogenesis, aberrant p300 activity affects transcription through either direct histone acetylation or by acting as a cofactor of several transcription factors that are oncogenes or tumor suppressors. Overexpression of p300 was observed in primary breast cancer samples and it was tightly correlated with tumor recurrence and poor clinical outcome.[136] High expression of p300 was also detected in patients with nasopharyngeal carcinoma and was associated with clinicopathological features of an aggressive phenotype and decreased overall survival.[137] Similarly, p300 overexpression was detected in patients with aggressive HCC carcinomas.[138] *In vitro* studies showed that p300 depletion blocks EMT-related progression of HCC cells and inhibits hepatoma cell survival and proliferation by blocking β-catenin nuclear translocation and *cyclin D1* transcription.[139] Moreover, it was demonstrated clearly that p300 plays a signifi-

cant oncogenic role in CaP. p300 binds and acetylates AR, affecting coactivator/corepressor complex association and the expression of AR-target genes leading to abnormal CaP cell growth.[140] In addition, p300 is recruited to the promoter of *FASN* oncogene where it catalyzes H3K27ac in order to activate its expression leading to lipid accumulation and increased growth of CaP cells *in vitro* and in xenografts.[141] Furthermore, p300 depletion in hormone-dependent and castration resistant CaP cells induces caspase-dependent apoptosis through AR inhibition and p65 degradation. At the same time, it attenuates CaP cell invasion via reduced *MMP-2* and *MMP-9* expression.[142] p300 also plays a role in anti-tumor immunity because its absence triggers apoptosis in regulatory T cells, with a subsequent inhibition of tumor growth.[143] In AML cells, p300 acts as a co-regulator of the c-Myb oncogene, an interaction that is required for AML1-ETO and MLL chimeras to block differentiation and promote expansion of myeloid progenitor cells.[144] Another study also found that, in AML patient samples and mouse models, the self-renewal capacity of cord blood CD34^{+} cells during leukemogenesis is dependent on p300-mediated AML1-ETO acetylation.[145]

Remarkably, 6 years after the aforementioned study, the same group published new work proposing a role for p300 as a TSG. They showed that loss of p300 increases the capacity of hematopoietic stem and progenitor cells to self-renew in the NHD13 transgenic mouse model that phenotypically copies human myelodysplastic syndrome (MDS). Furthermore, lack of p300 inhibits apoptosis of NHD13-expressing bone marrow cells through elevated activation of the MAPK and JAK/STAT signaling pathways, thereby leading to enhanced MDS-associated leukemogenesis.[146] Consistent with a role of p300 as a TSG, its gene is frequently mutated in various epithelial cancers, including colorectal, breast, pancreatic, ovarian, and lung carcinomas, with the majority of mutations predicting a truncated product.[147] In addition, *p300* mutations decreasing or abolishing its enzymatic activity are partly accountable for the survival of diffuse large B-cell lymphoma (DLBCL) cells due to aberrant histone acetylation and altered gene expression pro-

files.[148] p300 has also been implicated in the chemosensitivity of cancer cells to drugs because its suppression in bladder cancer cells confers resistance to doxorubicin.[149] Moreover, low levels of nuclear p300 in melanoma tissues is a prognostic marker for disease progression and poor patient survival.[150] It is also worth noting that p300 interacts with and acetylates p53 *in vitro* and *in vivo*, thereby influencing its tumor-suppressive function and, interestingly, *p53* mutations disrupting this interaction may lead to cancer.[151–153]

2. CBP/CREBBP/KAT3A

CBP (CREB-Binding Protein) was named after its discovery as a transcriptional coactivator of cAMP response element-binding (CREB) protein.[154] Shortly after its identification, a breakthrough discovery revealed the HAT activity of CBP coactivator, which is able to stimulate transcription.[155,156] Not surprisingly, both the HAT- and coregulator-dependent functions of CBP are implicated in cancer. During leukemogenesis, CBP is bound and recruited to chromatin by MOZ-TIF2 fusion oncoprotein, where it catalyzes histone acetylation and aberrant gene transcription, which is crucial for the induction of myeloid transformation by MOZ-TIF2.[157] Furthermore, the *CBP* gene is involved in chromosomal translocations generating fusion oncoproteins such as CBP-MOZ, CBP-MORF, and MLL-CBP.[24] As mentioned previously, CBP shares high sequence and structural similarity with p300. Therefore, their cooperative function in tumorigenesis is inevitable. Surgically resected SCLC patients with CBP-positive tumors exhibit medium overall survival, whereas p300 and CBP double-positive tumors are characterized by significantly poorer outcome.[158] In addition, *in vitro* and *in vivo* studies have shown that CBP is critical for the induction of AML and the maintenance of the self-renewal properties of myeloid cells that were transformed by AML1-MT2 and AML1-NHA9 fusion proteins. As expected, myeloid transformation is regulated by the cooperative function of CBP, with p300 illuminating their functional redundancy. As a result, concomitant inhibition of CBP and p300 catalytic activity using a selective small-molecule inhibi-

tor alters the transcription of genes associated with cell cycle progression, DNA replication, and DNA repair, affecting genomic integrity.[159] Furthermore, stimulation of CaP cell growth mediated by IL-4 induction requires enhanced expression of CBP/p300 in order to interact with AR and activate androgen-responsive genes through histone acetylation.[160]

Although all of the above studies indicate that CBP promotes carcinogenesis, several other reports strongly support its anti-cancer potential. For instance, it has been observed that inactivation of one copy of the *CBP* gene generates Rubinstein–Taybi syndrome, with patients exhibiting a predisposition to tumor development.[161] Kung et al. presented the first experimental evidence for a direct anti-oncogenic role of CBP in carcinogenesis by demonstrating that haploinsufficiency of *CBP* deregulates normal hematopoiesis through the inhibition of differentiation.[162] Moreover, missense, nonsense and frame-shift mutations at the *CBP* locus, as well as LOH were detected in lung cancer tissues and cell lines.[163] Moreover, sequence or deletion mutations within the *CBP* HAT catalytic domain resulting in LOH are frequently observed in follicular lymphoma (FL) and DLBCL types of B-cell non-Hodgkin's lymphoma and are associated with *BCL6* silencing and *p53* overexpression.[164] A similar study showed that *CBP* mutations in FL and DLBCL impair histone acetylation and MEF2-directed transcription of target genes.[165] In addition, genomic deletion or inactivating mutations in the HAT domain of *CBP* were observed in 18.3% of patients with relapsed acute lymphoblastic leukemia and resulted in the inhibition of histone acetylation and expression of CBP downstream genes such as glucorticoid-responsive genes.[166] Similar to its oncogenic activity described above, CBP acts as a tumor suppressor while cooperating with p300 to block tumorigenesis. Specifically, CBP/p300 are recruited to the promoters of the NKG2 ligand (NKG2-L) genes *hMICA/B*, *hULBP2*, and *mRAE-1* to increase histone acetyl marks, thereby upregulating their expression on the surface of cancer cells and facilitating immunosurveillance of tumors.[167] An additional study reported that CBP/p300 physically and functionally cooperate with the BRCA1 tumor-suppressor protein and this interaction is disrupted by the E1A adenoviral oncoprotein.[168] Finally, a high percentage of CRC cells with microsatellite instability bear CBP/p300-inactivating mutations, implying that CBP/p300 expression is critical for the survival of these cancer cells.[169]

III. HATs AS AN EPI-WEAPON IN CANCER THERAPY

In contrast to the stable genetic mutations, epigenetic alterations are highly dynamic and thus have the potential to be restored when deregulated. Given the explosion of research reports manifesting the crucial role of HATs during malignant transformation, they are appropriately considered promising therapeutic targets within a new era in cancer treatment.[170] However, the existing paradox of the dual function of HATs as oncogenes and TSGs in carcinogenesis demands that decisions on how these enzymes are targeted within therapeutic approaches are taken after thorough consideration.

Nevertheless, an outstanding progress has been made in the development of HAT inhibitors (HATi's) to block the oncogenic functions of these enzymes. Generally, HATi's block the interaction of the acetyltransferases with either Ac-CoA or their substrates, thereby obstructing histone acetylation and oncoprotein transcription, as well as acetylation-mediated activation of several oncogenic transcription factors.[171] Lys-CoA and H3-CoA-20 were the first identified HAT inhibitors specific for p300 and PCAF, respectively.[172] α-methylene-γ-butyrolactone (MB-3) is a small-molecule inhibitor against GCN5 that specifically impedes acetylation and stabilization of E2A-PBX1 in AML cells.[173] The newly identified Tip60-specific inhibitor NU9056 inhibits cell growth and triggers apoptosis in CaP cells.[174] In addition, the function of ICG-001 and its specificity toward CBP stems from its potential to inhibit the physical interaction between CBP and β-catenin oncoprotein.[175] Most recently, a novel p300/CBP-selective inhibitor, A-485, has been shown to prevent cell growth effectively in lineage-specific tumors, including hematological malignancies and CaP.[176] Moreover, the pan-HATi PU139 stimulates

apoptosis *in vitro* accompanied by a reduction in histone acetylation levels and attenuates tumor volume in neuroblastoma xenografts alone or in combination with doxorubicin.[177] Beyond small-molecule inhibitors, natural compounds including curcumin, anacardic acid, oridonin, EGCG, quercetin, and resveratrol alone or in combination with chemotherapeutic agents were identified as important inhibitors against several HATs.[178–183] Although HATi's exhibit potent anti-cancer effects *in vitro*, *in vivo* studies have been discouraging due to their decreased solubility and cell impermeability. The only HATi that proceeded into clinical trials is the p300/CBP-specific inhibitor curcumin (https://clinicaltrials.gov/ct2/show/NCT02724202?term=curcumin&draw=3&rank=25).

Despite the increased attention on the therapeutic potential of HATi's, they can only be used in cancers in which HATs have a clear oncogenic effect. But how should hypoacetylated cancers harboring HATs with tumor-suppressive roles be targeted? One possibility is the use of HAT activators (HATa's), which are currently underexplored. The CTBP anacardic acid derivative represents the most studied HATa that targets p300 specifically.[184] A second possibility involves an innovative approach that relies on CRISPR-mediated epigenome engineering in order to restore HAT activity and thus TSG transcriptional activation. Specifically, a catalytic inactivated Cas9 enzyme (dCas9) is combined to the HAT catalytic domain of p300 and this fusion protein is recruited by a single guide RNA to the promoters and distal enhancers of TSGs of interest to reactivate their expression through the deposition of H3K27ac marks.[185–187] However, further research is needed in order to overcome the existing limitations and refine this approach before bringing this powerful weapon into the clinical setting**.**

IV. CONCLUDING REMARKS

Ever since HATs were identified, an extensive body of work has generated remarkable evidence on their role in a variety of fundamental cellular processes such as gene transcription and DNA repair and replication. Therefore, it is not surprising that aberrant HAT ac-

tivities contribute to the origin of cancer. Although several published studies and ongoing research implicate HAT deregulation within the development of various cancer types, we still lack complete knowledge of the underlying molecular mechanisms and this constitutes a major hurdle in exploiting the full potential of HATs as druggable targets. Therefore, additional studies are needed to enhance our understanding of the molecular mechanisms used by HATs to decipher precisely their role as either oncogenes or TSGs in specific neoplasms, which will improve the design of therapeutic interventions.

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