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# KATs in Cancer: Functions and Therapies

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## Abstract

Post-translational acetylation of lysines is most extensively studied in histones, but this modification is also found in many other proteins and is implicated in a wide range of biological processes in both the cell nucleus and the cytoplasm. Like phosphorylation, acetylation patterns and levels are often altered in cancer, therefore small molecule inhibition of enzymes that regulate acetylation and deacetylation offers much potential for inhibiting cancer cell growth, as does disruption of interactions between acetylated residues and 'reader' proteins. For more than a decade now, histone deacetylase (HDAC) inhibitors have been investigated for their ability to increase acetylation and promote expression of tumor suppressor genes. However, emerging evidence suggests that acetylation can also promote cancer, in part by enhancing the functions of oncogenic transcription factors. In this review we focus on how acetylation of both histone and non-histone proteins may drive cancer, and we will discuss the implications of such changes on how patients are assigned to therapeutic agents. Finally, we will explore what the future holds in the design of small molecule inhibitors for modulation of levels or functions of acetylation states.

## Introduction

From transcriptional regulation to metabolic functions, protein acetylation is involved in several processes that keep a cell working properly. Acetylation is a dynamic process that involves the removal of a hydrogen atom on the episilon $NH3^+$ side chain of lysines followed by the transfer of an acetyl group from acetyl-CoA (AcCoA). This exchange neutralizes the positive charge on the lysine and also changes the structure of the R-group on this amino acid, leading to various effects on the protein modified. Lysine acetylation chemically blocks other modifications, such as methylation or ubiquitination, for example, which can in turn increased protein stability, alter subcellular localization, or change the spectrum of interacting proteins. As such, acetylation provides a rich regulatory 'switch'.



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**Conflict of Interest**

The authors declare no conflict of interest.

Acetylation levels are regulated by a balance in the activities of acetyltransferases and deacetylases. Although originally termed histone acetyltransferases (HATs), due to their actions towards abundant histone substrates, lysine acetyltransferases (KATs) are located both in the nucleus and in the cytoplasm, and they have many non-histone substrates as well. Deacetylases similarly have multiple substrates, but they are still primarily referred to as HDACs rather than KDACs. Several excellent reviews on HDAC families and their functions are available [1–3], so we will focus mostly on acetylation and KATs in this review.

## Histone Acetylation and Chromatin Regulation

In the nucleus, DNA is packaged into chromatin. The basic unit of chromatin is the nucleosome, which consists of 146 bp of DNA and histones, the proteins that provide the scaffold that DNA is wrapped around. Histones contain a globular domain that promotes histone-histone interactions within the nucleosome and also provides a binding surface for DNA. In addition, they contain tail domains that protrude out of the nucleosome, where they influence histone-histone interactions, interactions between histones and DNA, and between histones and other proteins. Although both the globular domains and the tail domains can be modified, the histone tails are particularly rich in modifications, including methylation, acetylation, phosphorylation, ubiquitination, and sumoylation. The many sites and types of modification provide a wealth of variable combinations, which in turn provides huge regulatory potential for remodeling chromatin states to either facilitate or inhibit gene transcription, DNA replication, repair, or recombination.

Acetylation has long been associated with chromatin opening and active gene transcription. Both individual nucleosomes and higher order chromatin folding can block access of RNA polymerase and other factors to gene promoters. Acetylation affects chromatin folding as the addition of the acetyl group neutralizes the positive charge of the lysine, weakening bonds between histones and the negatively charged DNA backbone, as well as the bonds between neighboring nucleosomes, allowing for more relaxed chromatin structures (Figure 1A). In addition, acetylation at specific lysine residues on particular histones can promote binding of regulatory factors involved in specific steps of the transcription process. For example, Histone H3 lysine 9 acetylation (H3K9ac), catalyzed largely by Gcn5/ PCAF, [4] is enriched at gene promoters, whereas H3K27ac, catalyzed largely by CBP/p300, is enriched at enhancer sequences. [5] These modifications promote binding of other factors through interactions with KAc reader domains, which are often located in other chromatin modifying proteins, including acetyltransferases, methyltransferases, and ATP-dependent chromatin remodelers such as Swi/Snf. [6–8]

## Readers of Acetyl-lysines: Bromodomains and YEATS domains

Bromodomains were the first, and until recently, the only, acetyl-lysine binding domains described. [9,10] These domains are highly conserved across evolution and many specifically bind acetylated lysines, while only poorly binding non-acetylated lysines, thus ‘reading’ the acetylation status of histones or other proteins. [10] As such, bromodomains provide bridges for histone-protein and protein-protein interactions (Figure 1C). The bromodomain family is split into many branches, each with different structural characteristics that provide specificity for different acetylation states or proteins. [11] Although these families have wide

variations in sequence, bromodomains contain a conserved binding site that is lined with a loop region linking 4 α-helices, which allows for binding to acetylated lysines. The sequence differences, variation in length of the loop region, as well as the post-translational modifications on the residues adjacent to the acetylated lysine provide specificity for substrate binding. [11,12] Intriguingly, many KATs themselves possess bromodomains, or are associated into stable complexes with bromodomain containing proteins, leading to the possibility of feed forward loops wherein they reinforce their own interactions with chromatin or with other proteins to facilitate even more acetylation. Such KATs include GCN5, PCAF, and CBP/p300.

Bromodomains have also been implicated in a wide range of diseases including cancer. [13,14,15,16] For example, Santillan *et al* found that the HAT and bromodomain of CBP were both important for maintenance of the cancer phenotype in leukemias caused by translocations of the *MLL* gene. [17] In this case, the bromodomain promoted increased proliferation of the leukemic cells. In another example, the *Brd4* and *Brd3* genes, members of the BET bromodomain family, are fused with the gene encoding nuclear protein in testis (NUT) in NUT midline carcinomas (NMC). [18] The resulting fusion protein, BRD-NUT, binds to acetylated histones through the bromodomain, leading to inappropriate gene expression [19], including expression of the oncoprotein c-Myc. [20] The translocation of IgH and Myc common in Burkitts lymphoma and multiple myeloma causes Myc expression to be amplified. This expression is maintained by binding of Brd4 to Igh enhancers that drives the expression of the Igh-Myc fusion protein in these cancers. [21,22] As we will see later, small molecule inhibitors of BET domains are showing clinical promise in a variety of Myc-driven cancers.

Interestingly, Lange et al found that the double PHD finger domain of DPF3, a member of the BAF chromatin remodeling complex, recognizes acetylated lysines on histones H3 and H4 as well as methylated lysines. [23,24] To date this is the only PHD domain family member identified that recognizes acetylated lysines.

New studies have identified the YEATS domain containing proteins as another possible family of acetyl-lysine readers. [25] In particular, the YEATS domain of the AF9 protein binds to H3K9ac, and these interactions promote recruitment of AF9 interacting proteins to genomic loci enriched with this modification. AF9 is part of a super elongation complex (SEC), and it also interacts strongly with the Dot1L histone methyltransferase. Thus, H3K9ac, which is largely mediated by Gcn5/PCAF, promotes both transcriptional elongation and methylation of H3 at K79 by Dot1L. Although only a few YEATS domain proteins have been analyzed for KAc binding so far, their conserved structure predicts that many if not all will bind this modification. Like bromodomains, though, different YEATS domains may display differential binding to specific sites of KAc. For example, the YEATS domain in the ENL protein binds to H3K27ac with greater affinity than H3K9ac, in contrast to the preferred binding of AF9 to H3K9ac. Interestingly, ENL is part of an alternative SEC and H3K27ac is enriched at enhancer regions. Taken together, these findings raise the possibility that differential sites of H3 acetylation direct different transcription related complexes to active enhancers, promoters, or gene bodies. The importance of such differential recruitment is highlighted by the fact that MLL-AF9 fusions lead to misdirection

of DOT1L activity and inappropriate gene expression patterns associated with leukemogenesis. [26]

Although they both bind acetyl-lysine, the structures of YEATS domains and bromodomains are quite different. Small molecule inhibitors of YEATS domains, then, could provide a new avenue for development of cancer therapies in the future.

## KATs and Cancer

KATs are divided into families based on their structure and sequence similarity. The best characterized include the GNAT family, which includes GCN5 and PCAF, the p300/CBP family, and the MYST family, which includes Tip60 and Moz/Morf (Figure 2). In addition to the histone acetyltransferase domain, KATs possess several domains that facilitate interactions with other proteins, including reader domains for acetylation and other modifications. Together these domains allow for specificity and diversity in KAT substrates. Substrates of these enzymes as well as their roles in biological functions are continuing to be defined. However, several, such as CBP/p300, have already been implicated in cancer development and progression. [27–30]

All KATs examined to date have important functions in cellular differentiation and embryo development. [31] Since many cancers represent failures in differentiation, it is not surprising that several KATs have also been associated with oncogenesis.

### GCN5

GCN5 (aka GCN5L2 and KAT2A; from here on referred to as GCN5) is the evolutionarily conserved KAT catalytic subunit of the SAGA and ATAC chromatin modifying complexes. [8] GCN5 was first identified in yeast as a transcriptional adaptor protein, and the Tetrahymena protein was later identified as the first HAT linked to transcriptional regulation. [8] In isolation, Gcn5 preferentially acetylates H3K9 and H3K14, both marks of active transcription. [4] As part of SAGA, it acetylates additional sites in H3 and also H2B. Like most HATs, GCN5 does not bind to DNA but is recruited to chromatin by sequence-specific DNA binding transcription factors. For example, GCN5 and another component of SAGA, TRRAP, have been linked to the Myc oncoprotein in mammalian cells. [32, 33] Myc is the most overexpressed gene in cancer, and it is involved in transcription of genes implicated in a wide range of cellular processes including growth, invasion, metastasis, and apoptosis. [34] The SAGA complex is recruited to chromatin by Myc, where GCN5 acts as a coactivator [35], creating an open chromatin conformation that allows for transcription of Myc target genes. [36, 37, 38] Myc is also a target of GCN5 acetyltransferase activity at K323 [39], and acetylation of this site increases the stability of the Myc protein. Myc often acts in concert with another transcription factor important in the regulation of cell growth, E2F1. Interestingly GCN5 also interacts with E2F1 and is important for its functions in gene regulation. For example, in small cell lung cancer, E2F1 recruits GCN5 to acetylate H3K9, facilitating transcription of the *E2F1, cyclin E,* and *cyclin D1* target genes [40], all of which promote cellular proliferation and tumor growth.

GCN5 may also contribute to oncogenesis through modification of non-histone proteins. For example, in many cases of acute lymphoblastic leukemia (ALL), a translocation event fuses E2A with the pre-B-cell leukemia transcription factor 1 (PBX1). The resulting oncoprotein, E2A-PBX1, aberrantly activates HOX contributing to the failure of differentiation of the leukemic cells. [41] Gcn5 acetylates and stabilizes this oncoprotein in ALL cells, further increasing target gene expression. [42] Gcn5 also interacts with tumor promoting proteins such as Pygopus homolog 2 (Pygo2), which is a component of the Wnt/beta-catenin pathway. Pygo2 directly interacts with GCN5 in the SAGA complex, bridging an interaction with beta-catenin. [43] Pygo2 enhances the growth of breast cancer stem-like cells and its HAT interacting domain is necessary for this function.

Gcn5 is also part of the ATAC KAT complex, which is distinct from SAGA. [44,45] Although ATAC has not yet been implicated in cancer, it contains a YEATS domain protein, YEATS2, which likely serves as a KAc reader. [25] ChIP-Seq data indicates that ATAC binds to both enhancer elements and promoters, whereas SAGA preferentially binds to promoters. [45] It will be interesting to determine if this differential distribution reflects the differential binding of bromodomains in Gcn5 and other SAGA components and the YEATS domain in YEATS2.

## PCAF

The acetyltransferase p300/CBP associated factor, PCAF, was first described by its competition with the oncoprotein E1A for binding to p300/CBP. [46] PCAF is a paralog of Gcn5 that resides in a SAGA-like complex [46] and an alternative ATAC complex [44,47] mutually exclusive of Gcn5. Both Gcn5 and PCAF also directly bind to p300/CBP. [48] Gcn5 and PCAF share some redundant functions, exhibited by the necessity to knockout both Gcn5 and PCAF in order to completely abolish H3K9 acetylation in MEFs [5]; however they also possess separate and distinct functions. [49] The phenotype of Gcn5 and PCAF knockout mice differ, as *PCAF* null mice show no obvious abnormal phenotypes, but *Gcn5* null embryos die early in gestation. [50,51] PCAF was one of the first KATs shown to acetylate non-histone proteins, namely p53. [52, 53] PCAF acetylation of p53 increases DNA binding of p53 to its target genes. The effects on p53 as well as the ability to displace E1A indicate PCAF might function as a tumor suppressor.

More recent data also indicates that PCAF may have an oncogenic function as well, through acetylation of additional non-histone substrates. PCAF influences metabolic processes by acetylating three lysines in ATP-citrate lyase (ACLY), which cleaves citrate in rapidly dividing cells to produce AcCoA, a building block for de novo lipid synthesis and an obligate cofactor for lysine acetylation. Cancer cells preferentially utilize this alternative method of lipid biosynthesis to build membranes and promote tumor growth. ACLY is overexpressed in lung cancer. [54] Lin et al showed that PCAF-mediated acetylation of ACLY stabilizes the protein by blocking lysine ubiquitination, leading to increased ACLY protein levels, increased cell proliferation, and increased lipid biosynthesis. [54]

PCAF is also involved in the Hedgehog (Hh) signaling pathway, which has been implicated in several cancers including medulloblastoma and glioblastoma. The Helin group found that PCAF is recruited by Gli, a downstream signaling molecule in the Hh pathway, to the

promoters of Hh target genes. PCAF acts as a coactivator of the expression of hedgehog target genes by acetylating H3K9. [55] Loss of PCAF also reduces the tumor promoting activity of neural stem cells in vivo. [55] PCAF may therefore be a therapeutic target for medulloblastoma and glioblastoma patients. PCAF was also shown to be necessary for Gli dependent transcriptional activation in the TGFbeta pathway. [56] Additionally, PCAF is up regulated in prostate cancer cells leading to AR transcriptional activity and cell growth. [57] PCAF has also been shown to acetylate and stabilize beta-catenin in colon cancer cells. [58] Taken together PCAF makes an attractive potential target for new cancer therapies.

## CBP/p300

CBP was first identified as the coactivator of the transcription factor CREB [59], while p300 was initially identified to interact with the adenovirus transforming protein E1A. [60] These two proteins were later found to be highly related, sharing 75% sequence similarity. [61] Deletion of CBP/p300 specifically reduces acetylation on H3K18ac and H3K27ac in MEFs. [5] CBP/p300 also acetylate transcription factors, such as p53 [62] and AR [63], thereby inhibiting their polyubiquitination and increasing their stability. CBP/p300 are large proteins with multiple functional domains, and they are involved in many different transcription programs. In fact, CBP/p300 have been reported to interact with more than 400 different cellular proteins to date [64], including factors important to cancer development and progression such as HIF-1, beta-catenin, c-Myc, c-Myb, CREB, E1, E6, p53, AR, and ER. Interactions between these transcription factors and CBP/p300 are crucial for efficient transcription of their downstream target genes, in keeping with the functions of CBP/p300 as transcriptional co-activators.

Like Gcn5 and PCAF, CBP and p300 have both shared and distinct functions. For example, CBP and p300 control the outcomes of Wnt/beta-catenin signaling in hematopoietic cells. CBP is essential for HSC self-renewal, while p300 is required for hematopoietic differentiation. [65] In addition, CBP activity is required for maximal HIF-2 signaling [66], while p300 positively regulates the transactivation of HIF-1. [67] Furthermore, p300, but not CBP, is the dominant co-regulator for androgen-regulated gene expression since 47% of androgen-regulated genes are p300-dependent, while only 0.3% are CBP-dependent. [68] Consistent with this finding, knockdown of p300, but not CBP, leads to an increase of caspase-dependent apoptosis in androgen-dependent and castration-resistant prostate cancer cells. [69]

Aberrations in both CBP and p300 show strong implications in cancer initiation and progression. Inactivation of one allele of CBP causes Rubinstein-Taybi syndrome (RTS), and RTS patients have an increased susceptibility for tumor development. [70] In addition, mice heterozygous for CBP invariably develop myelodysplastic/myeloproliferative neoplasm [71]. Genetic alterations and somatic mutations/deletions of CBP/p300 are correlated with transitional cell carcinoma of the bladder [72], follicular lymphoma (41%), diffuse large B-cell lymphoma (39%) [73], relapsed ALL [74], and microsatellite instability(MSI)-positive colon cancer cells. [75]

Although many studies indicate that CBP/p300 function as tumor suppressors, other studies indicate that CBP/p300 promote the tumor progression. Chromosomal translocations

involving MOZ or MLL fused with CBP or p300 are associated with AML through gain-of-function. [76] In addition, interaction of c-Myb with p300 is required for the induction of AML by AML oncogenes [77,78]. High CBP/p300 expression is associated with poor prognosis in small cell lung cancer. [79] High expression of p300 was also positively associated with higher grade, distant metastasis and later clinical stages of nasopharyngeal carcinoma. [80] Furthermore, the subcellular localization of p300 is also associated with cancer progression. Decreased expression of nuclear p300 and gain of cytoplasmic p300 expression are associated with disease progression and worse prognosis of melanoma patients. [81] Moreover, CBP/p300 is implicated in resistance in certain cancer types. P300 expression is reduced in doxorubicin-resistant bladder cancer cells and knockdown of p300 leads bladder cancer cells resistant to doxorubicin. [82] However, CBP/p300 are required in the IL-4 mediated castration resistance of prostate cancer cells. Downregulation of CBP/p300 abolished IL-4 mediated AR activation. [83] Overall, the changes in genetic alterations, expression level, and subcellular localization of CBP/p300 are associated with progression, prognosis, and resistance of many types of cancers.

Onco-viruses, such as HTLV-1, SV40, and HPV, induce cancer, mediated, at least in part, by manipulating CBP/p300 function. HTLV-1 is crucial for developing adult T-cell leukemia. [84] HTLV-1 Tax protein interacts with CBP/p300 to activate gene expression regulated by ATF/CREB and NF-kB pathways, but it inhibits p53-mediated gene expression. [85,86] In addition, transforming protein SV40 large T antigen (SVT) interacts with CBP/p300 [87], which is required by SVT-mediated transformation [88,89], and increases CBP/p300 protein levels through increasing the loading of CBP/p300-mRNA onto polysomes. [90] Furthermore, the high-risk HPV E6 protein interacts with CBP/p300 directly and blocks p300-mediated p53 acetylation and p53-dependent gene transcription. [91] Moreover, adenovirus E1A protein also interacts with CBP/p300 [92] and alters gene expression by reducing CBP/p300 recruitment on the promoters of differentiation-specific genes but increasing the CBP/p300 loading on the promoters of genes involved in cell proliferation. [93]

CBP/p300 can also promote tumorigenesis independently of its effects on gene transcription. p300 acetylates S-phase kinase-associated protein 2 (Skp2), which is a driving factor in tumorigenesis, leading to increased Skp2 stability and cytoplasmic retention. Cytoplasmic Skp2 enhances cellular migration through ubiquitination and destruction of E-cadherin. [94]

## Tip60

Tip60 is the acetyltransferase component of a multiprotein Tip60 complex that includes up to 16 subunits. The Tip60 complex also contains an ATPase, p400/TRAPP, and helicases, Tip49a and Tip49b. [95,96] The Tip60 complex preferentially acetylates H2AK5, H3K14, and H4K5/8/12/16. [97] Tip60 plays important roles not only in transcription but also in double-strand DNA break repair and apoptosis. DNA damage induces accumulation of Tip60 [98], which acetylates and activates ATM kinase activity at sites of DNA damage. [99–101] In addition, Tip60 also acetylates nucleosomal phosphor-H2Av, the Drosophila homolog of human H2A.X, which results in its exchange with unmodified H2Av at DNA DSB loci. [102] Furthermore, Tip60 complex induces transcription of DNA repair and apoptosis genes by

interacting with E2F1 and p53, respectively. [103,104,105] Tip60 also acetylates the Abelson murine leukemia viral oncogene homolog (Abl) and activates transcription-independent apoptotic activity of Abl [106] As to the transcription related function, Tip60 is identified as co-activator of AR, ER, PR, c-Myc, and more. [107,108,109,39,110] However, Tip60 is also reported to repress STAT3, c-Myb, and beta-catenin dependent transcription in part through recruiting HDACs. [111, 112,113]

The majority of studies investigating the relationship of Tip60 and cancer show that Tip60 functions as a tumor suppressor. Tip60 has a haplo-insufficient tumor suppressor activity in both mouse and human. [114] Tip60 heterozygosity impairs Myc-induced DNA damage repair in B cells and accelerates the onset of Myc-induced B-cell lymphomas when breeding the Tip60 heterozygous mice with Eu-myc transgenic mice, which develop spontaneous lymphoma and leukemia. [115] In human cancer samples, Tip60 mRNA or protein level was down regulated in colon, lung, mammary, head-and-neck carcinomas, metastatic prostate cancer, metastatic melanoma, lymphomas, and AML. [116117114118112119113] In addition, reduced Tip60 expression was associated with poor prognosis in primary and metastatic melanoma patients. [119] However, Tip60 was over expressed in cisplatin-resistant human lung cancer cells and knockdown of Tip60 expression rendered cells sensitive to cisplatin treatment. [120] Moreover, in hormore refractory or androgen independent prostate cancer, Tip60 predominantly accumulates in the nucleus rather than displays a more diffuse distribution pattern observed in benign prostate hyperplasia or primary prostate cancer. [116] Consistent with this finding, it is also reported that Tip60 is up regulated in castration-resistant LNCaP derivative CxR cells, which results in an increase of acetylated androgen receptor localizing in the nucleus and activation of androgen-dependent gene transcription even in the absence of androgen. [121]

## Other KATs

Many other KATs have been also linked to cancer. HBO1, a member of the MYST family is overexpressed in several breast cancer cell lines. HBO1 increases mammosphere formation when phosphorylated by cyclin E/CDK2 [122], suggesting that HBO1 overexpression may lead to a more cancer stem cell like phenotype. The most common translocation in AML fuses the KAT Moz, another MYST family member, with CBP. [123] This oncoprotein causes disruption of the association between the differentiation factor AML1 and MOZ, thereby inhibiting AML1 induced gene transcription. [124] Lack of AML1 target gene transcription leads to a more undifferentiated state characteristic of cancer cells.

## Acetylation of Non-histone Substrates

Over 6800 lysine acetylation sites have been identified in mammals [125] with 3600 sites on 1750 proteins identified in humans. [126] The acetylation of non-histone proteins initiates diverse outcomes (Figure 1B). For example, transcription factors such as E2F1 [127], c-Myc [39], and beta-catenin [58] are stabilized by acetylation, while acetylation of PTEN decreases its stability. [128] Acetylation may also affect the subcellular localization of a protein, as in the case of SRY, where acetylation triggers translocation to the nucleus. [129] The DNA binding activity [53] of p53, as well as its stability [130], increases upon acetylation. Acetylation of one of the residues of the chaperone protein Heat-shock protein 90 (Hsp90)

prevents association with both client proteins and its co-chaperones. [131,132] This modification not only affects the function of Hsp90 but also reduces the activity of its client proteins such as tyrosine kinase Chk1. [123]

Acetylation is being recognized as increasingly important in metabolism. In addition to mitochondria being the source of AcCoA, several mitochondrial proteins are subject to acetylation. Acetylation of the glycolytic enzyme Phosphoglycerate mutase-1 (PGAM1) stimulates its activity [133] whereas acetylation of the mitochondrial matrix protein AcCoA synthetase 2 (AceSC2) inactivates the enzyme. [134] Zhao *et al* found that almost every enzyme involved in the TCA cycle, glycolysis, gluconeogenesis, fatty acid metabolism, the urea cycle, and glycogen metabolism is acetylated in the liver. [135] Obviously acetylation has a profound impact on metabolism. As cancer cells have an altered metabolism that gives them a proliferative advantage, perhaps manipulation of these acetylation events might provide another avenue for therapy development.

The proteins mentioned here constitute only a subset of the many proteins that are regulated in some way by acetylation. In thinking about the functions of KATs in both normal cells and cancer, it is important to keep in mind that effects on the non-histone substrates may be as important, or even more important, as effects on histones. Clearly, additional work is needed to identify the full range of acetylated proteins in the cell and the consequences of changes in acetylation states in cancer and other diseases.

## Therapies targeting KATs

Given the wide-reaching importance of acetylation to cellular function, inhibitors of both KATs and HDACs have potential as anti-cancer therapies. HDAC inhibitors have been used in clinical trials for some time now, with varied results. [2, 3, 136] These drugs show some effect in leukemias and other blood borne cancers, especially in combination with other epigenetic inhibitors, such as decitabine. [137] However, they have largely failed in solid tumors. One intriguing possibility is that acetylation might augment the functions of Myc and other oncogenic proteins that drive tumor progression and growth. Use of an HDAC inhibitor in such cases might actually be detrimental rather than helpful. Genetic studies in mice indicate that deletion of HDACs enhance the severity of Myc driven lymphomas or solid tumors in mice [138], consistent with this idea. Clearly we need to know more about how acetylation contributes to cancer initiation and progression, so that more rationale therapies can be designed.

### Regulation of KAT Activity

Normal means of KAT regulation provide ideas for development of KAT inhibitors. Interestingly, KATs are regulated by multiple mechanisms. Many KATs are not fully active unless associated with their partner proteins in KAT complexes. [139,140] Association into the complex can affect not only the level of activity but also substrate specificity. [47] Gcn5, for example, has very limited activity and substrate range alone, but when part of the full SAGA complex, it efficiently acetylates multiple sites in histones H3 and H2B. [139] KATs themselves are also subject to posttranslational modifications that affect their activity, stability, and subcellular localization. Autoacetylation of p300 and MOF enhances their

enzymatic activity. [141,142] The nuclear localization signal in PCAF can be autoacetylated or acetylated by p300 in the cytoplasm, increasing PCAF activity and promoting its localization to the nucleus. [143] Some KATs, including GCN5 and PCAF, are also stabilized upon binding of their coenzyme, AcCoA. [144]

The many layers of regulation ensure that KAT activity is spatially and temporally restricted in the cell and in the organism, and they also provide specific vulnerabilities for development of small molecule inhibitors. For example, small molecules that interfere with AcCoA or substrate binding would directly impair KAT acetyltransferase activity. Such inhibition would affect acetylation of histones and associated transcription of oncogenes or downstream oncogene targets (Figure 3A). It would also affect acetylation of non-histone substrates, such as p53 and AR, thereby affecting the stability and activity of these transcription factors (Figure 3A). In practice, however, it can be difficult to develop inhibitors that specifically affect HATs and not other enzymes that utilize AcCoA.

Alternatively, small molecule inhibitors might be designed to block interactions between KATs and other proteins, such as beta-catenin and HIF, which would affect transcription of downstream genes. Although beta-catenin is not classified as a transcription factor, it directly interacts with the transcription factor TCF/LEF to regulate downstream target genes (Figure 3B). Similarly, KAT inhibitors might be designed to decrease KAT or transcription factor occupancy at target genes by interfering with interactions with histones or the transcriptional machinery.

We will summarize the current status of small molecule inhibitor development for the main three KATs families that have so far shown some inhibitory effect on cancer cell growth in vitro or on xenograft growth in vivo.

## GCN5-PCAF Inhibitors

So far, several small molecule inhibitors of GCN5 and PCAF have been developed and characterized in vitro. In most cases, these molecules are thought to act as substrate or AcCoA mimics. The first identified GCN5 inhibitor, α-methylene-γ-butyrolactone 3 (MB-3), which decreases GCN5 acetyltransferase activity potently, was reported to decrease acetylation and stabilization of the E2A-PBX1 oncoprotein in leukemia cells. [42] However, the effect of MB-3 on leukemia cell growth and proliferation is not clear. A series of thiazole derivatives, such as cyclopentylidene-[4-(4’-chlorophenyl)thiazol-2-yl)hydrazone (CPTH2) [145], CPTH6 [146], and BF1 [147], also decrease GCN5 activity in vitro. This inhibition is reversed upon increased concentration of H3, but not AcCoA [145], suggesting that thiazole derivatives inhibit acetylation by competing with substrate binding to GCN5. CPTH6 has been shown to impair viability and cell cycle progression, reflected by accumulation in G0/G1 phase, of leukemia cells. [146] This year, a novel thiazole-based HAT inhibitor BF1, was reported to inhibit the HAT activity of recombinant GCN5 and p300. BF1 treatment reduced overall levels of H3 acetylation in HeLa, neuroblastoma, and glioblastoma cells. However, BF1 administration had only modest effects on the viability of neuroblastoma cells, and had even less effect on the viability of HeLa or glioblastoma cells. [147]

The first selective PCAF inhibitor to be identified and synthesized was the bisubstrate compound, H3-CoA-20 (IC50, 0.3uM). [148] However, this bisubstrate inhibitor lacks cell-permeability, which limits its development as a therapeutic drug. Anacardic acid, a chemical compound from the cashew nut shell, is a potent inhibitor of PCAF and p300 (IC50, 5 and 8.5 μM, respectively). [149] Anacardic acid potentiated apoptosis induced by cytokine and chemotherapeutic agents, which correlated with the down regulation of various gene products that mediate proliferation, survival, invasion and angiogenesis regulated by NF-kB in a series of human cancer cell lines [150] (Table 1). One anacardic acid derivative, 6d, showed a twofold higher inhibitory effect than anacardic acid on PCAF HAT activity and histone acetylation in liver hepatocellular carcinoma HepG2 cells. [151] Garcinol, a potential anti-cancer agent [152] from Garcinia indica fruit rind, is a potent inhibitor of p300 and PCAF (IC50, 5uM and 7uM respectively). [153] Garcinol inhibits KATs by binding both the AcCoA binding site and the histone binding site, [154] and it suppresses proliferation or induces apoptosis of various cancer cells[153], including HeLa cells, breast cancer cells [155–157], lung cancer cells [158], pancreatic cancer cells [159], hepatocellular carcinoma(HCC) cells [160], and head and neck squamous carcinoma(HNSCC) cells [161] in vitro. Moreover, Garcinol has been reported to inhibit the growth of human HCC and HNSCC xenograft tumors in athymic nu/nu mice. [160,161] In addition, isothiazolones-based inhibitors for PCAF and p300, CCT077791 and CCT077792, inhibit the growth of a panel of human tumor cell lines. [162]

Unfortunately, the fact that these compounds are usually only effective in vitro when administered in micromolar concentrations, along with ambiguities regarding their specificity, greatly limits their utility as possible anticancer agents. Development of additional types of inhibitors, perhaps directed at bromodomains in Gcn5 and PCAF, might offer more promise in the future.

## CBP/p300 Inhibitors

Several studies have focused on potential therapies targeting CBP/p300, more so than any other type of KAT. Many kinds of CBP/p300 inhibitors have been identified or synthesized, and their effects have been tested on tumor cell growth in vitro or in vivo. The first identified selective p300 inhibitor was the bisubstrate inhibitor, Lys-CoA (IC50, 0.5uM). [148] However, Lys-CoA lacks cell-permeability, which can be somewhat improved by conjugation to a cell permeabilizing peptide. [163] Another well-studied CBP/p300 inhibitor is curcumin, which inhibits the KAT activity of purified p300 (IC50, 25uM) in vitro. [164] Curcumin inhibits p300-mediated acetylation of p53 and induces apoptosis in HeLa cells. [165] It can also affect cell proliferation of prostate cancer cells through modulation of aberrantly activated Wnt signaling. [166] In addition, curcumin suppresses CBP/p300 occupancy at AR target genes and inhibits xenograft tumor growth of androgen sensitive cells and CRPC cells. Co-treatment with curcumin and androgen deprivation reduces tumor growth and delays the onset of castration-resistant tumors. [167]

ICG-001 is a specific CBP/beta-catenin antagonist that blocks CBP/beta-catenin interactions (IC50, 3uM) but not p300/beta-catenin interactions. [168] Treatment with ICG-001 leads to the differentiation of pre-B ALL cells and eradication of drug-resistant primary leukemia when used in combination with conventional therapy in vitro (VDL (Vincristine, Dexamethasone

and L-Aparaginase) or Nilotinib for Philadelphia chromosome negative or positive ALL cells, respectively). ICG-001 also significantly improves the survival of NOD/SCID mice engrafted with primary ALL. [169]

Chetomin, a natural small molecule that disrupts the interaction of HIF-1 with CBP/p300, abolishes the differentiation inhibitory effect of HIF-1alpha. Combined administration of chetomin with forskolin, a differentiation inducer, significantly suppresses malignant glioma growth in vitro and in vivo in a xenograft model. [170] Another CBP/p300 inhibitor, C646, (IC50, 1.6uM) [171] induces cell cycle arrest and apoptosis selectively in AML1-ETO-positive AML cells. [172] C646 also promotes sensitivity to DNA damaging agents, leading to enhanced apoptosis of melanoma cells after combination treatment with cisplatin. [173] Furthermore, C646 treatment in $Foxp3^+$ T regulatory cells increased T cell receptor-induced apoptosis of T regulatory cells, limited tumor growth in immunocompetent but not in immunodeificient mice. [174]

Besides these well-established inhibitors for CBP/p300 HAT activity or CBP/p300 interaction with transcription factors, researchers continue to screen or synthesize novel compounds to inhibit CBP/p300 function. Plumbagin (RTK1), a natural compound isolated from Plumbago rosea root extract, inhibits specifically p300-mediated acetylation of p53. [175] NK13650A and NK13650B (IC50, 11 and 22 nM, respectively), a microbial metabolite, inhibits p300 HAT activity and inhibited hormone-dependent and-independent growth of prostate cancer cells. [176] Arylsulfonamide KCN1 interferes with the interaction between HIF-1alpha and CBP/p300 (IC50, ~590nM), and potently inhibits the growth of subcutaneous malignant glioma tumor xenografts. [177] L002 (IC50, 1.98uM), interacting with the active site of the p300 catalytic domain, potently suppressed tumor growth of MDA-MB-468 xenografts as well as proliferation of leukemia and lymphoma cell lines. [178] HBS, a protein domain mimic, targets the interaction of the HIF-1alpha with p300/CBP and suppresses tumor growth in a renal cell carcinoma murine xenograft model. [179] Windorphen, a selective small molecule targeting beta-catenin and inhibiting p300, robustly and selectively kills cancer cells that harbor Wnt activating mutations. [180] CH1iB, a novel small-molecule inhibitor of p300 targeting HPV16 E6-p300 interaction, reactivates p53 and enhances the anticancer effect of cis-platinum on HPV-positive head and neck squamous cell carcinoma cells. [181]

## Tip60 Inhibitors

Interestingly, Tip60 is down regulated in primary cancer cells but becomes up regulated in drug resistant cancer cells. [119,120] This discrepancy may be explained by the regulatory processes used by cells to decide between life and death. Since Tip60 is crucial for the DNA repair process, its down regulation causes cells to accumulate genomic instabilities induced by oncofactors, and can eventually lead to uncontrolled cellular growth. However, after treatment of cells with therapeutic DNA damage inducing agents, drug-resistant cells exhibit higher levels of DNA repair that requires Tip60. Thus, inhibition of Tip60 activity might provide a potential strategy to treat DNA damaging drug-resistant cancers. Other agents also affect Tip60 functions in DNA repair. Anacardic acid and its analogs, 6-alkylsalicylates, inhibit Tip60 [182] and sensitize HeLa cells to ionizing radiation. [183] In addition, pentamidine,

a bisbenzamidine derivative that inhibits Tip60 acetyltransferase activity, also increases the radio-sensitivity of HeLa cells. [184] Moreover, two newly identified Tip60 inhibitors, NU9056 (IC50, 2uM) and TH1834, are reported to inhibit cell proliferation and induce apoptosis in prostate cancer cells and breast cancer cells, respectively. [185,186]

### Limitations of KAT Inhibitors

Almost all of the studies on KAT inhibitors are currently still in a preclinical phase. Only curcumin has been moved forward into clinical trials as a potential anti-cancer therapy. According to data currently available in the ClinicalTrials.gov database, about 35 registered clinical trials are ongoing in cancer patients, including colorectal cancer, pancreatic cancer, lung cancer, and leukemia patients, with curcumin alone or combined with other chemotherapy agents. Better agents, with greater specificity and better pharmokinetic properties are sorely needed.

An alternative to inhibiting KATs directly is to inhibit readers of KAc. Bromodomain inhibitors are showing much promise in early trials as effective therapies for a variety of tumor types. Bromodomain inhibitors act as acetyl-lysine mimics that occupy the acetylated lysine binding site in bromodomain-containing proteins (Figure 3C), such as BRD4 and BRD2. [187] They affect the gene expression profile of leukemia or solid tumor cells, highlighted by downregulation of Myc expression, which results in suppression of tumor cell growth and proliferation. [188,189] A few bromodomain inhibitors, such as I-BET762, OTX015, CP-0610, and TEN-010, are in clinical phase I trials to test their efficacy on various hematological malignancies and solid tumors. [190] Combinational treatment using both a BRD4 inhibitor and an HDAC inhibitor has been reported to synergistically induce apoptosis of leukemia cells and improve the survival of mice engrafted with leukemia cells. [191] Such combination therapies may also prove greatly beneficial. Since most KATs contain bromodomains, combinational treatment of inhibitors targeting these domains together with BET bromodomain inhibitors might also have synergic effects on inhibiting tumor growth, by limiting both the expression and the function of oncoproteins such as c-Myc. Combination therapies are attractive as they may allow use of the two agents in low dose, thereby increasing effectiveness while also reducing side effects or toxicities associated with use of single inhibitors in high dose.

## Conclusion and Perspectives

Although aberrations of KATs have been reported widely in human cancers, our understanding of the functions of KATs in tumor development and progression is still limited. While some studies show that KATs act as tumor suppressors, other studies indicate that KATs promote tumor progression by promoting oncogene expression or function, providing a strong, rationale for the development of KAT inhibitors as anti-cancer agents. The paradox that both KAT and HDAC inhibitors may be beneficial as anti-cancer agents illustrates the necessity of defining the full range of functions of these enzymes in specific cancer settings. Alterations in the balance of these enzyme activities might lead to hallmark changes in histone modification status that could provide cancer biomarkers for predicting prognosis and for determining best treatment options for cancer patients. [192] A greater

understanding of the functions of KATs and HDACs in both normal cells and in cancer will also allow better design of combination therapies using inhibitors for these enzymes together with other epigenetic agents, such as bromodomain inhibitors.

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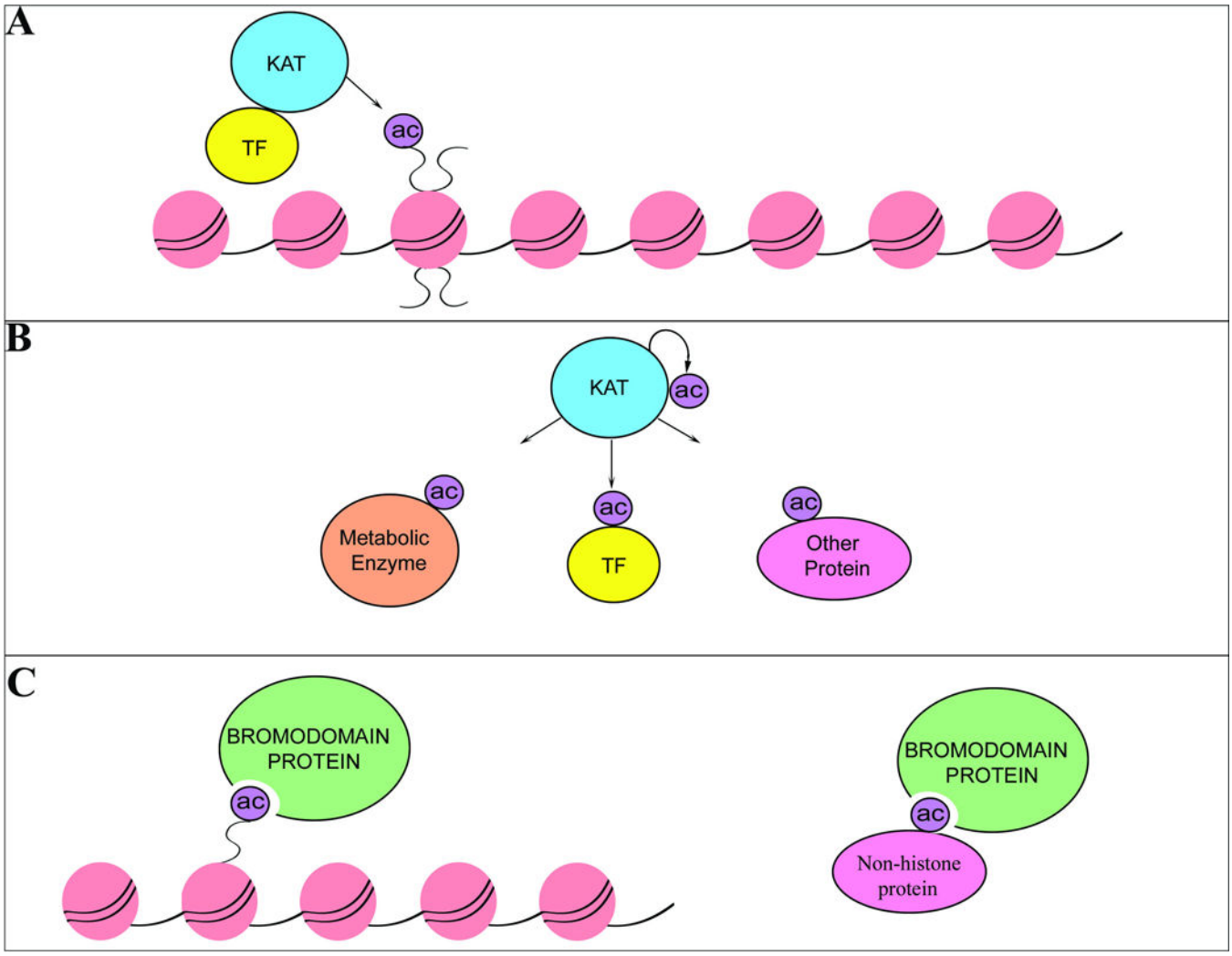


**Figure 1. Mechanisms of action of acetylation**

A. KATs target both tails and globular domains of all 4 histone proteins. B. KATs acetylate non-histone proteins including transcription factors (TF) as well as metabolic enzymes and other nuclear and cytoplasmic proteins. C. Bromodomain-containing proteins bind to acetyl-lysines on histone tails and on non-histone proteins.

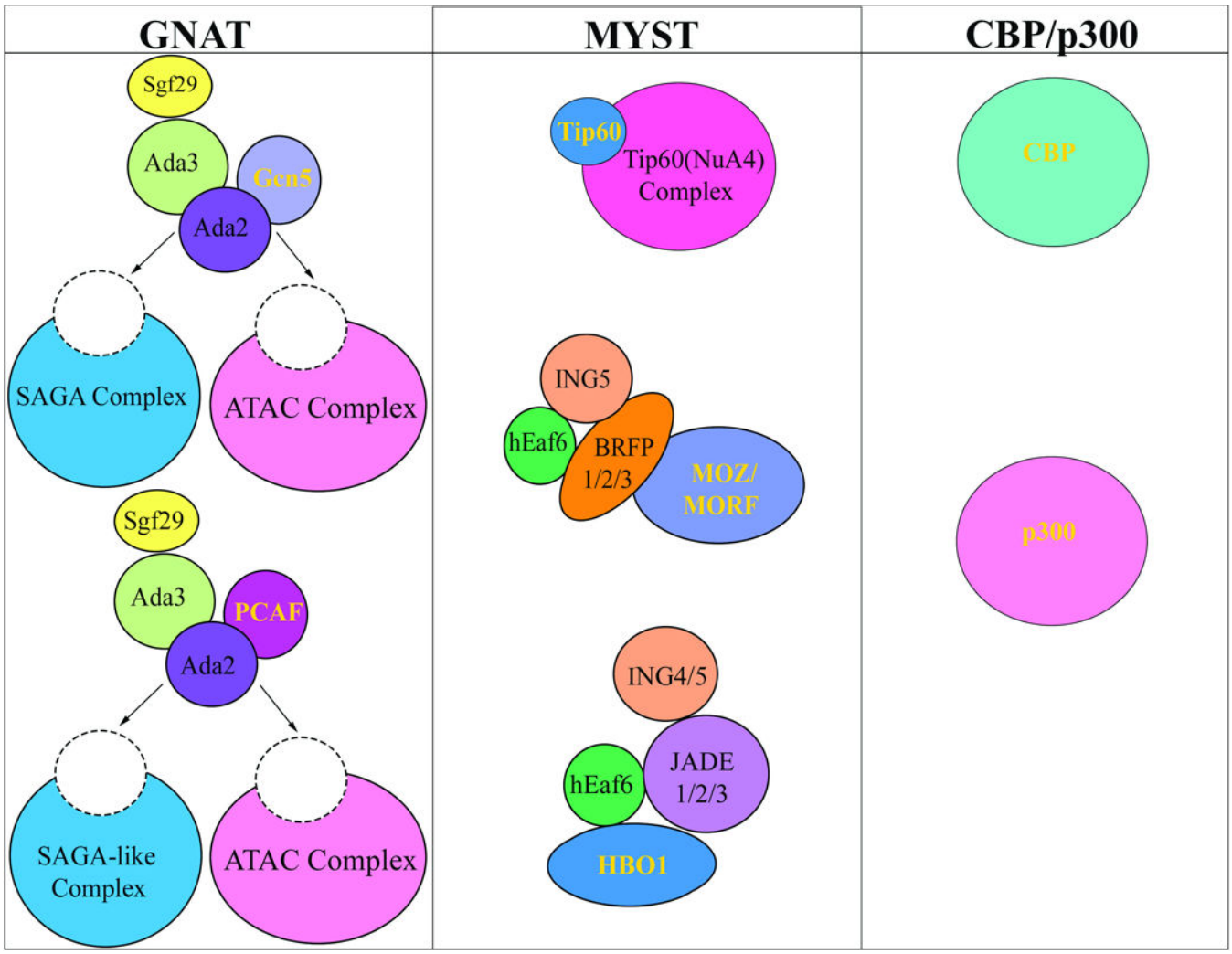


**Figure 2. Selected KAT families**

Lysine acetyltransferases are classified into different families dependent on their structure. The major families are GNAT, MYST, and CBP/p300. Not all subunits in complexes are represented.

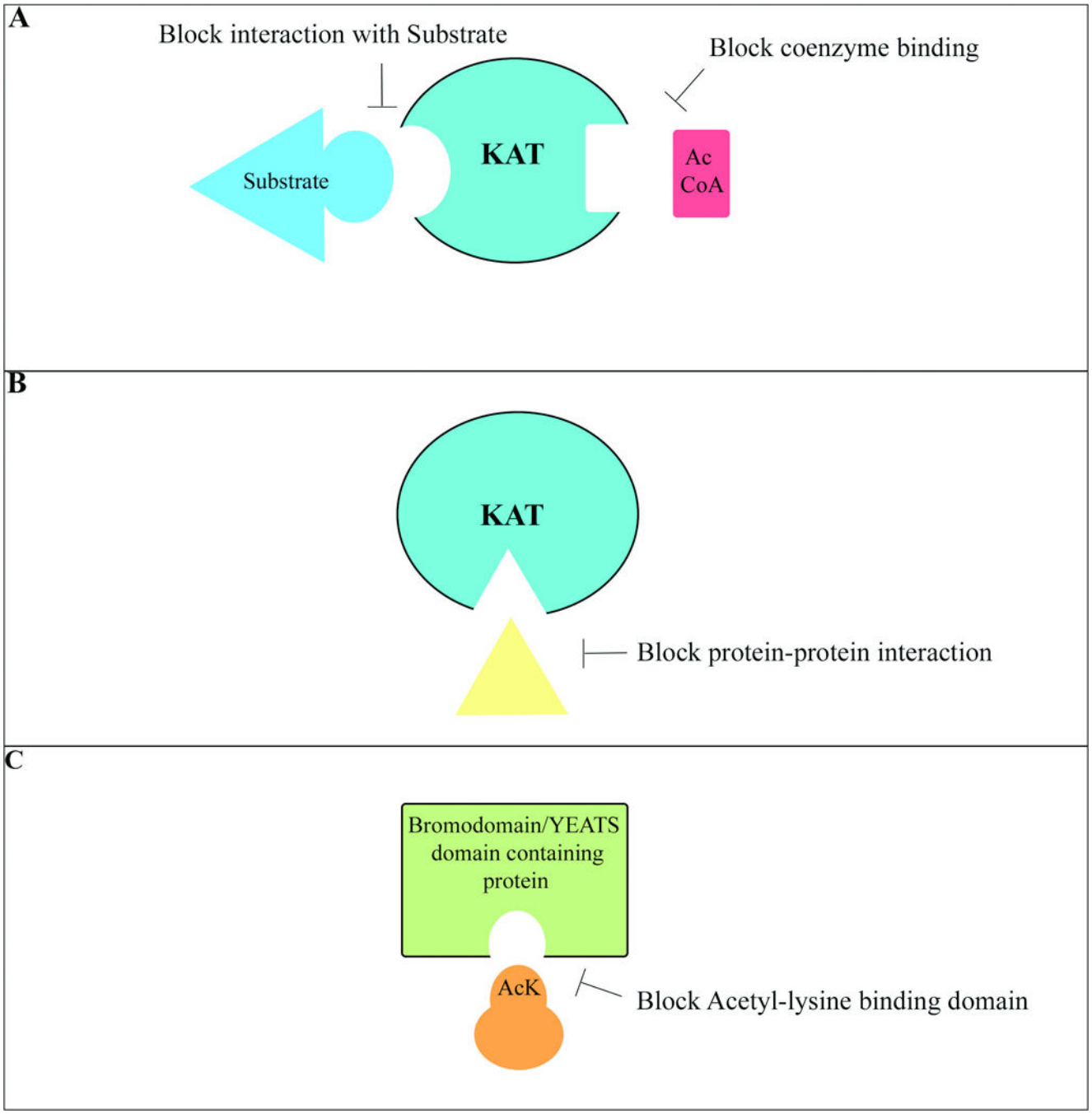


**Figure 3. The mechanisms of small molecule inhibitors targeting lysine acetylation**

A. Small molecule KAT inhibitors can impair KAT acetyltransferase activity by interfering with AcCoA or substrate binding. The substrates include histone and non-histone proteins, such as p53 and AR. B. Small molecule KAT inhibitors can block interactions between KATs and other proteins, such as beta-catenin and HIF, which would affect transcription of downstream genes. C. Bromodomain inhibitors act as acetyl-lysine mimics that occupy the acetylated lysine binding site in bromodomain-containing proteins.

## Table 1

KATs inhibitors.

| Targeted KAT | Molecule | Mechanism | Category | Affected cells or tumors |
|---|---|---|---|---|
| GCN5 | MB-3 | NA | Synthetic compound | leukemia cells [42] |
| GCN5/p300 | CPTH2, CPTH6, BF1 | competes with substrate | thiazole derivatives | leukemia cells, neuroblastoma cells [145–147] |
| PCAF/p300 | anacardic acid | NA | Natural compound, phenolic lipid | myeloid KBM-5 cells, T-cell lymphoma Jurkat cells, lung adenocarcinoma H1299 cells, embryonic kidney A293 cells, prostate cancer Du145 cells, squamous cell carcinoma SCC4 cells [150] |
| | Garcinol | inhibits AcCoA and histone binding | Natural compound, polyisoprenylated benzophenone | HeLa cells, breast cancer cells, lung cancer cells, pancreatic cancer cells, HCC cells, and HNSCC cells, HCC and HNSCC xenografts [153,155–157,158,159,160,161] |
| | CCT077791 and CCT077792 | NA | isothiazolones derivative | colon tumor HCT116 and HT29 cells [162] |
| PCAF | H3-CoA-20 | inhibits AcCoA and substrate binding | bisubstrate inhibitor | NA |
| | 6d | NA | anacardic acid derivative | HCC HepG2 cells [151] |
| CBP/p300 | curcumin | promotes CBP/p300 degradation, inhibits KAT activity | Natural compound, diarylheptanoid | HeLa cells [165] |
| | | | | prostate cancer cells, prostate tumor xenograft [167] |
| | chetomin | blocks interaction of HIF-1 and CBP/p300 | Natural compound, antibiotic metabolite | glioma xenograft [170] |
| | C646 | inhibits AcCoA and substrate binding | Synthetic compound based on benzoic acid | AML1-ETO(+) AML cells, melanoma cells, TC1 or AE17 xenograft tumors [172,173,174] |
| | KCN1 | blocks interaction of HIF-1 and CBP/p300 | Arylsufonamide | subcutaneous malignant glioma tumor xenograft [177] |
| | HBS | blocks interaction of HIF-1 and CBP/p300 | protein domain mimetic | renal cell carcinoma xenograft [179] |
| CBP | ICG-001 | blocks CBP/beta-catenin interaction | Synthetic compound | Colon cancer cells and xenograft, pre-B ALL cells, primary ALL xenograft [168,169] |
| p300 | Lys-CoA | inhibits AcCoA and substrate binding | bisubstrate inhibitor | NA |
| | Plumbagin(RTK1) | inhibits AcCoA and histone binding | Natural compound | NA |
| | NK13650 | NA | microbial metabolite | prostate cancer cells [176] |
| | L002 | interacts with p300 catalytic domain | NA | leukemia and lymphoma cell, MDA-MB-468 xenograft [178] |
| | Windorphen | blocks CBP/beta-catenin interaction | Acrylaldehyde derivative | colon adenocarcinoma SW480 cells, prostate cancer DU145 and PC3 cells [180] |
| | CH1iB | mimics C-terminal domain of HIF-1, blocks interaction of HIF-1 and CBP/p300 | Synthetic compound | HPV(+) HNSCC cells [181] |

| Targeted KAT | Molecule | Mechanism | Category | Affected cells or tumors |
|---|---|---|---|---|
| Tip60 | anacardic acid | NA | phenolic lipid | HeLa cells, squamous cell carcinoma SQ20B and SCC35 cells [182,183] |
| | 6-alkylsalicylates | | anacardic acid analog | |
| | pentamidine | NA | bisbenzamidine derivative | HeLa cells [184] |
| | NU9056 | NA | isothiazolones derivative | prostate cancer cells [185] |
| | TH1834 | inhibits AcCoA binding | Synthetic compound | breast cancer cells [186] |

NA: Non Applicable; HCC: hepatocellular carcinoma; HNSCC: head and neck squamous carcinoma.