Regulation of KAT6 Acetyltransferases and Their Roles in Cell Cycle Progression, Stem Cell Maintenance, and Human Disease

Fu Huang,^a Susan M. Abmayr,^{b,c} Jerry L. Workman^b

Institute of Biological Chemistry, Academia Sinica, Nankang, Taipei, Taiwan^a; Stowers Institute for Medical Research, Kansas City, Missouri, USA^b; Department of Anatomy and Cell Biology, University of Kansas Medical Center, Kansas City, Kansas, USA^c

The lysine acetyltransferase 6 (KAT6) histone acetyltransferase (HAT) complexes are highly conserved from yeast to higher organisms. They acetylate histone H3 and other nonhistone substrates and are involved in cell cycle regulation and stem cell maintenance. In addition, the human KAT6 HATs are recurrently mutated in leukemia and solid tumors. Therefore, it is important to understand the mechanisms underlying the regulation of KAT6 HATs and their roles in cell cycle progression. In this minireview, we summarize the identification and analysis of the KAT6 complexes and discuss the regulatory mechanisms governing their enzymatic activities and substrate specificities. We further focus on the roles of KAT6 HATs in regulating cell proliferation and stem cell maintenance and review recent insights that aid in understanding their involvement in human diseases.

Histone acetyltransferases (HATs) play important regulatory roles in many DNA-dependent processes by acetylating lysine residues in histones. To date, more than 20 HATs have been identified. Most HATs belong to one of 4 families based on their homologies, as follows: the Gcn5-related acetyltransferase (GNAT) family, the p300/CBP family, the SRC/p160 family, and the MYST family (named after its founding members, MOZ, Ybf2/Sas3, Sas2, and Tip60) (1). Lysine acetyltransferase 6 (KAT6) belongs to the MYST family and has been linked to cell cycle regulation and leukemia (2–4). In addition, mutations and misregulation of the human KAT6 genes, *MOZ/MORF*, have been identified in solid tumors and patients with developmental disorders (5–14). To gain better understanding of the roles of KAT6 HATs in human diseases, it is critical to know how their functions are regulated. Recently, several studies have revealed mechanisms of regulation of KAT6 HATs, and increasing evidence has provided insights into their roles in cell cycle progression and stem cell maintenance in a wide range of species. These findings are summarized in this perspective.

THE COMPOSITION AND HOMOLOGY OF THE KAT6 HAT COMPLEXES

The yeast KAT6 *SAS3* gene was first identified in 1996 in a screen for enhancers of silencing defects in a *sir1Δ* mutant (15). Between 1997 and 2000, the NuA3 (nucleosomal acetyltransferase of histone H3) complex was discovered and found to predominantly acetylate histone H3 in nucleosomes. Sas3 was identified as its catalytic subunit (16–18). Subsequent studies further determined the 5 subunits in the complex, Sas3, Nto1, Yng1, Eaf6, and Taf14 (Fig. 1) (18–20). A sixth subunit, the proline-tryptophan-tryptophan-proline (PWWP) domain-containing protein Pdp3, was recently found to be stably associated with the NuA3 complex, and two alternative NuA3 complexes were proposed, NuA3a (conventional NuA3) and NuA3b (NuA3a + Pdp3) (21, 22).

The mammalian KAT6A MOZ was identified in 1996 as a fusion partner of CBP in acute myeloid leukemia (AML) patients (2), and in 1999, KAT6B MORF was identified as its paralog (23). However, characterization of the MOZ/MORF complexes was lacking until 2006, when MOZ/MORF were reported to copurify with ING5, EAF6, and BRPF1, -2, and -3 (BRPF1/2/3) (24). Using

coimmunoprecipitation and *in vitro* reconstitution assays, the quartet composition of the MOZ/MORF complexes was further verified, and BRPF1 was demonstrated to serve as the scaffold subunit that interacts directly with ING5, EAF6, and MOZ/MORF (Fig. 1) (25).

In 2001, the *Drosophila* KAT6, Enok, was identified in an ethyl methane sulfonate mutagenesis screen as a critical factor for neuroblast proliferation (4). We have recently purified the Enok complex and found that Enok also forms a quartet complex with Br140, Ing5 (CG9293), and Eaf6 (Fig. 1) (26). As Br140, Ing5, and Eaf6 are the fly orthologs of BRPF1/2/3, ING4/5, and EAF6, respectively (27), the KAT6 complexes are highly conserved between flies and mammals. The areas of greatest divergence in KAT6 complex composition between yeast and higher organisms include the following: (i) Taf14 is absent in the Enok and MOZ complexes, (ii) Yng1 is the ortholog of ING1/2 instead of ING5 (28), and (iii) Pdp3 does not share significant sequence similarity with the PWWP domain in Br140 or BRPF1/2/3. However, although Yng1 is not the authentic ortholog of ING5, both Yng1 and ING5 contain a plant homeodomain (PHD) finger that recognizes trimethylated histone H3 lysine 4 (H3K4me3). In addition, while the yeast homolog of BRPF1/2/3, Nto1, lacks the PWWP domain found in BRPF1/2/3, Pdp3 carries a PWWP domain to compensate for this difference (21). Therefore, the structural modules in the KAT6 complexes are evolutionarily conserved from yeast to mammals, strongly suggesting that KAT6 HATs play crucial and conserved roles in a wide range of species.

READER DOMAINS IN THE KAT6 COMPLEXES

As shown in Fig. 1, each KAT6 complex in different species contains 4 to 7 “reader” domains that can recognize unmodified

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Address correspondence to Susan M. Abmayr, SMA@stowers.org, or Jerry L. Workman, JLW@stowers.org.

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FIG 1 The KAT6 HAT complexes are evolutionarily conserved. Top, composition of the KAT6 complexes in budding yeast, flies, and mammals, respectively. Homologs in different organisms are marked with the same color. For simplicity, only the NuA3b (NuA3a + Pdp3) complex is shown for budding yeast. Bottom, tables list the domains in complex subunits that recognize histone modifications, with the numbers of domains shown in parentheses. PHD, plant homeodomain; Bromo, bromodomain; PWWP, proline-tryptophan-tryptophan-proline domain.

and/or modified histones, and many of these domains have been shown to play a role in modulating the function of KAT6 HATs. The PHD finger in Yng1 binds to H3K4me3 and recruits the NuA3 complex to the 5' region of genes to acetylate H3K14, and recognition of H3K4me3 by the ING5 PHD finger can stimulate the *in vitro* HAT activity of MORF (Fig. 2) (19, 20, 29). Interestingly, the tandem PHD finger (PHD12) in MOZ has been shown to recognize unmodified histone H3 arginine 2 (H3R2) and acetylated H3K14 (H3K14ac) and contribute to the recruitment of MOZ to the promoter of *HOXA9* (30–32). As MOZ can acetylate H3K14, the recruitment of MOZ to H3K14ac-enriched regions by its PHD12 finger suggests a mechanism that facilitates the propagation of MOZ-mediated acetylation of H3K14. In addition, the first and second PHD fingers (PZP [PHD-Zn knuckle-PHD] domain) in BRPF1/2 preferentially bind to unmodified H3K4 and DNA, respectively (33–36). Binding of the BRPF1 PZP domain to nucleosomes facilitates DNA unwrapping and increases DNA accessibility. Moreover, this domain is critical for the HAT function of the MOZ complex toward nucleosomal substrates but is dispensable for that toward free histones (36). Intriguingly, while the ING5 PHD finger binds to H3K4me3, this histone mark was shown to inhibit H3 tail binding by both the MOZ PHD12 finger and the BRPF1/2 PZP domain (30–33, 35). Therefore, all PHD modules in the KAT6 complexes may dynamically coordinate with each other and with different histone modifications to regulate the function of KAT6 HATs.

In addition to the PZP domain, BRPF1/2/3 contains a bromodomain and a PWWP domain. The BRPF1 bromodomain has recently been shown to recognize acetylated histones, including the active marks acetylated histone H2A lysine 5 (H2AK5ac), H4K12ac, and H3K14ac (37, 38), and its PWWP domain was demonstrated to be an H3K36me3 reader (39). Similarly, the PWWP domain in yeast Pdp3 also recognizes the H3K36me3 mark, and Pdp3 has been shown to contribute to the transcription of NuA3 target genes (21, 22). In flies, a *Br140* mutant allele with a

point mutation in its PWWP domain (changing the highly conserved proline residue to leucine) exhibited axon-targeting defects similar to those of an *enok* mutant allele that is truncated in the middle of its HAT domain (40). These data suggest that the Br140 PWWP domain and its recognition of H3K36me3 are required for the HAT function of Enok.

ENZYMATIC SPECIFICITIES AND ACTIVITIES OF KAT6 HATS

The histone substrates of KAT6 HATs identified to date include H3K9, -K14, and -K23 (Fig. 2) (41–44). While MOZ acetylates H3K14 *in vitro* and is important for the H3K9ac levels at several target genes, the global levels of H3K9ac and H3K14ac are not affected in the absence of MOZ, indicating that other HATs can compensate for the loss of MOZ-mediated histone acetylation (25, 42, 45). Similarly, the loss of Sas3 does not affect global H3K9ac and -K14ac levels, but disrupting the HAT activity of Sas3 led to decreased levels of H3K9ac and -K14ac in the absence of a HAT in the GNAT family, Gcn5 (3). In striking contrast to the subtle effects of the loss of MOZ or Sas3 alone on the bulk levels of H3K9ac and -K14ac, the global H3K23ac levels are highly dependent on the HAT activity of Enok in flies (43, 46). In addition, since H3K23ac is abundant in fly cells (47% of H3), the depletion of Enok resulted in an ~35% reduction in global histone H3 and H4 (H3+H4) acetylation levels (46). This significant effect of Enok depletion on global H3+H4 acetylation levels is unique, as individually depleting any of the other 22 lysine acetyltransferases (including Gcn5/KAT2, Nej/KAT3, Tip60/KAT5, and Chm/KAT7) has much weaker effects that are all less than 10% (46). Therefore, Enok may have a role in regulating the bulk charges of histones in specific chromatin regions. Consistent with the studies in flies, global H3K23ac levels in human cells depend on the KAT6B MORF, confirming that KAT6 is the major HAT for establishing the H3K23ac mark in higher organisms (44).

In flies, all components in the Enok complex were shown to

FIG 2 Functions of KAT6 HATs are regulated by subunits in the complex. Recognition of histone marks by domains in each complex subunit is shown by gray solid lines. Recognition of histone marks predicted according to the structural homology is shown by gray dashed lines. Red lightning marks represent stimulation of enzymatic activity of Enok and MOZ by Br140 and BRPF1, respectively. Red arrows point to acetylation marks added by the KAT6 HATs.

contribute to the Enok-mediated acetylation of H3K23 *in vivo* (26). Interestingly, in addition to stimulating the HAT activity of Enok, Br140 expands its substrate specificity *in vitro* and is required for maintaining its protein levels *in vivo*. This regulation of Enok specificity by Br140 is consistent with the previous report that BRPF1 can associate with mammalian KAT7 HBO1 and switch its substrate specificity. HBO1 can form different complexes by interacting with either BRPF1 or another scaffold protein, JADE1/2/3. While the HBO1-JADE1/2/3 complex preferentially acetylates histone H4 in nucleosomes, the HBO1-BRPF1 complex targets histone H3 (33). Taken together, the scaffold subunit Nto1/Br140/BRPF1 may play essential roles in regulating the integrity, enzymatic activity, and substrate specificity of KAT6 HAT complexes.

ROLES OF KAT6 HATS IN CELL CYCLE REGULATION AND STEM CELL MAINTENANCE

KAT6 HATs have long been linked to the regulation of cell proliferation (2–4). Inactivating the HAT activity of Sas3 in the absence of Gcn5 resulted in the accumulation of cells at the G₂/M phase, indicating that Sas3 has a role in cell cycle progression (3). Recently, the largest subunit of the PCNA loader replication factor C (RFC) complex, Rfc1, has been reported to copurify with the Sas3-containing NuA3b complex (22). Since the RFC complex is critical for DNA replication, the interaction between Sas3 and Rfc1 may contribute to proper progression through the cell cycle (Fig. 3, top). Intriguingly, Sas3 was reported to interact genetically with Gas1, a β -1,3-glucanotransferase recently shown to regulate gene silencing, in the DNA damage response pathway (47). Dele-

FIG 3 KAT6 HATs are generally involved in cell cycle regulation and stem cell maintenance. Reported interactions and functions are shown by thick solid arrows. Blue double-headed arrows represent genetic interactions between two proteins, red ones represent physical interactions between two proteins, and green ones represent fusions of two proteins. Functional links that are speculated based on published evidence are shown by dotted arrows with question marks. Thin black arrows indicate upregulation ($\uparrow$) or downregulation ($\downarrow$) of the indicated process/pathway/protein level. The two subunits of RFC/RFC-like complexes, Rfc1 and Elg1, are shown in yellow. The polycomb complex/protein, PRC1 complex and BMI1, are shown in purple.

tion of *GAS1* resulted in defects in checkpoint activation upon DNA damage. However, deleting *SAS3* rescued the defective checkpoint activation and sensitivity to DNA damage of the *gas1Δ* mutant. Therefore, Sas3 may play roles in three closely related processes: DNA replication, the DNA damage response, and cell cycle progression.

Enok is essential for neuroblast proliferation in flies (4). As a consequence, disrupting the HAT activity of Enok in neuroblasts resulted in defective development of the fly memory center mushroom body. However, the mechanisms underlying its roles in cell proliferation have long been unclear. We have recently discovered that the Enok complex promotes the G_1/S transition by interacting with the PCNA unloader Elg1 complex and inhibiting its PCNA-unloading function (Fig. 3, middle) (26). In addition, Enok has an Elg1-independent role in reducing the rate of G_2/M progression, suggesting that Enok functions at multiple stages in

the cell cycle. Enok is also important for germ line stem cell (GSC) maintenance (48). Loss of functional Enok in the germ line led to rapid loss of GSCs and elevated levels of the RNA-binding protein Bruno in GSCs. Since overexpression of *bruno* in the germ line resulted in reduced numbers of GSCs, Enok may contribute to GSC maintenance by downregulating Bruno levels in the GSC. Furthermore, Enok has a nonautonomous role in maintaining GSCs by regulating the niche size and the BMP signaling pathway in the niche. Intriguingly, three subunits in the Enok complex (Enok, Br140, and Eaf6) copurified with the polycomb repressive complex 1 (PRC1) (49). As polycomb group proteins are also involved in GSC maintenance (50–52), it is conceivable that the Enok-PRC1 interaction may also contribute to this essential process (Fig. 3, middle).

In mammals, MOZ has both positive and negative roles in regulating senescence by acetylating nonhistone and histone sub-

strates (Fig. 3, bottom). MOZ, PML, and p53 interact with each other. Their interaction increases the MOZ-mediated acetylation of p53, which enhances the activity of p53 to drive p21 expression and subsequent senescence (53, 54). On the other hand, MOZ is important for the expression of several repressors of the *INK4A/ARF* locus by maintaining the H3K9ac levels at those genes. Therefore, it plays a role in suppressing INKA/ARF-dependent senescence (45, 55). As ARF activates the function of p53, MOZ may act as a fine-tuning regulator of the ARF-p53 pathway in senescence through acetylating p53 or H3K9. MOZ is also a key regulator of hematopoiesis (reviewed in reference 56) and is important for the maintenance of hematopoietic stem cells (57). MOZ can interact with AML1 and PU.1, two essential transcriptional factors for hematopoiesis, and enhance AML1- and PU.1-dependent transcription (57, 58). Furthermore, several studies have shown that MOZ activates the expression of *HOX* genes in embryos and blood cells by acetylating H3K9 (30, 42, 59, 60), suggesting another mechanism underlying the roles of MOZ in hematopoiesis, since *HOX* genes are critical for the development of the hematopoietic system (reviewed in reference 61). Similar to the importance of MOZ in hematopoietic stem cell renewal, both MOZ and BRPF1 are involved in the maintenance of neural stem cells (55, 62), raising the possibility that the MOZ complex has a general role in maintaining stem cells.

As described above, the KAT6 HATs function in cell cycle regulation and/or stem cell maintenance in many species. Additional mechanistic clues further suggest possible similarities between the yeast/fly/mammalian KAT6 HATs in their roles in cell cycle progression and development. First, Rfc1 and Elg1 form two related RFC/RFC-like complexes that consist of 4 common small subunits (Rfc2 to -5) and 1 large subunit (Rfc1 or Elg1). Therefore, the Sas3-Rfc1 and Enok-Elg1 interactions suggest an evolutionarily conserved link between the KAT6 complexes and the RFC-like complexes. Second, MOZ has been shown to genetically interact with the polycomb protein BMI1 in regulating *HOX* gene activation (60). Together with the finding that Enok copurified with the repressive PRC1 complex (49), these observations suggest that the activator KAT6 complex may associate with PRC1 at specific gene loci to dynamically regulate gene expression during development.

INVOLVEMENT OF KAT6 HATS IN HUMAN DISEASE

Human KAT6A MOZ and KAT6B MORF are involved in tumorigenesis. The *MOZ* and *MORF* genes are recurrently rearranged in AML, resulting in fusions of MOZ and MORF to other proteins. The MOZ- and MORF-linked fusion proteins that have been identified in AML include MOZ-CBP, MOZ-p300, MOZ-TIF2, MOZ-NcoA3, MOZ-LEUTX, and MORF-CBP (2, 63–69). Among these fusion proteins, MOZ-TIF2 has been demonstrated to have transforming activity in cultured cells and to induce AML in mice (70). It therefore has been used as an AML model in several studies (71, 72). The HAT domain of MOZ contains a C₂HC zinc finger and an acetyl coenzyme A (acetyl-CoA) binding site, and both of them are important for *in vitro* HAT activity (70). Notably, while the C₂HC zinc finger in MOZ and the CBP-binding domain in TIF2 are strictly required for the ability of MOZ-TIF2 to induce AML in mice, compromising the HAT activity of MOZ by mutating its acetyl-CoA binding site only reduced the penetrance of AML from 88% to 50% (70). The C₂HC zinc finger is conserved between MOZ and the KAT8 MOF. The MOF C₂HC zinc finger

recognizes the histone H4 tail (73). Therefore, it was proposed that the transforming activity of MOZ-TIF2 is mainly mediated through recruiting CBP to the MOZ-binding sites on chromatin. However, the MOZ mutant with a mutated acetyl-CoA binding site used in reference 70 still has some residual HAT activity (5 to 10% of wild-type levels) (74). By using a Q654E (Q-to-E change at position 654)/G657E double mutation in the acetyl-CoA binding pocket that decreased the MOZ HAT activity to background control levels, a recent study demonstrated that the HAT activity of MOZ is also required for the ability of MOZ-TIF2 to induce AML in mice (74). In support of these findings, wild-type MOZ was recently shown to be specifically upregulated by an oncogenic p53 mutant (75). Furthermore, MOZ is critical for the proliferation of B-cell progenitors, and therefore, *Moz* haploinsufficiency delays the development of MYC-induced lymphoma (76). In addition to hematopoietic malignancy, recurrent amplification of the *MOZ* and/or *MORF* genes has been identified in solid tumors, including breast cancer, ovarian cancer, uterine cervix cancer, lung adenocarcinoma, colon and rectal adenocarcinomas, and medulloblastoma (13, 14). Furthermore, MORF is fused to KANSL1, a subunit of both the methyltransferase MLL1 and the acetyltransferase NSL1 complexes, in retroperitoneal leiomyoma (77). Taken together, current data generally support the notion that misregulation of MOZ/MORF is an important contributing factor in tumorigenesis.

Consistent with the roles of Enok and MOZ/BRPF1 in the proliferation of neuroblasts and neural stem cells, respectively, mutations of MOZ and MORF are associated with several disorders exhibiting intellectual disability. Heterozygous mutations in *MOZ* have been identified in patients with microcephaly and global developmental delay, including intellectual disability and cardiac defects (5, 6). Notably, MOZ has also been shown to play important roles in cardiac septum development (78). Dominant mutations in *MORF* are associated with Noonan syndrome, Say-Barber-Biesecker-Young-Simpson syndrome, genitopatellar syndrome, and blepharophimosis-ptosis-epicanthus inversus syndrome (7–12). The common phenotypes shared between at least two of these four syndromes include abnormal facial features, intellectual disability, congenital heart defects, and genital anomalies. Therefore, the involvement of *MOZ/MORF* mutations in these developmental disorders further highlights the importance of KAT6 HATs in the development of the heart and the neural and genital systems.

PROSPECTS

As misregulation of MOZ/MORF results in tumorigenesis and developmental disorders, better understanding the regulation of KAT6 functions would contribute significantly to our knowledge of human health and diseases. While recent studies have revealed targets for individual reader domains (PHD finger, bromodomain, and PWWP domain) in the KAT6 complexes, how these domains dynamically coordinate with each other to mediate the function of KAT6 under different conditions is an important question that remains to be answered. Also, KAT6 HATs are critical for the maintenance of different stem cells in both flies and mammals. However, the underlying mechanisms are still largely unclear. Since KAT6 HATs can acetylate both histones and non-histone proteins, they may have transcription-dependent and -independent roles in stem cell maintenance, and it will be intriguing to identify nonhistone substrates for KAT6 on a proteome-wide scale. Finally, although the majority of studies to date suggest on-

cogenic roles for MOZ/MORF, MORF has been reported to act as a tumor suppressor in small cell lung cancer (44). Therefore, understanding whether MOZ/MORF has different roles in tumor development in a tissue-specific manner may provide important insights into cancer therapies.

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