Review

MOZ and MORF acetyltransferases: Molecular interaction, animal development and human disease

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ABSTRACT

Lysine residues are subject to many forms of covalent modification and one such modification is acetylation of the ε-amino group. Initially identified on histone proteins in the 1960s, lysine acetylation is now considered as an important form of post-translational modification that rivals phosphorylation. However, only about a dozen of human lysine acetyltransferases have been identified. Among them are MOZ (monocytic leukemia zinc finger protein; a.k.a. MYST3 and KAT6A) and its paralog MORF (a.k.a. MYST4 and KAT6B). Although there is a distantly related protein in *Drosophila* and sea urchin, these two enzymes are vertebrate-specific. They form tetrameric complexes with BRPF1 (bromodomain- and PHD finger-containing protein 1) and two small non-catalytic sub-units. These two acetyltransferases and BRPF1 play key roles in various developmental processes; for example, they are important for development of hematopoietic and neural stem cells. The human *KAT6A* and *KAT6B* genes are recurrently mutated in leukemia, non-hematologic malignancies, and multiple developmental disorders displaying intellectual disability and various other abnormalities. In addition, the *BRPF1* gene is mutated in childhood leukemia and adult medulloblastoma. Therefore, these two acetyltransferases and their partner BRPF1 are important in animal development and human disease.

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1. Introduction

Since identification of the very first histone acetyltransferases such as Hat1 (histone acetyltransferase 1), Gcn5 (general control non-derepressible 5), PCAF (p300/CBP-associated factor), p300 (adenoviral E1A-binding protein of 300 kDa) and CBP (CREB-binding protein) in 1996 [1–6], various other proteins with such enzymatic activity have been described [7–9]. According to sequence similarity, known mammalian histone acetyltransferases are organized into three major groups [10–12]. One such group is the GCN5/PCAF family, consisting of GCN5, PCAF and related proteins [10–12]. The p300/CBP family is another group that has been extensively characterized [13–15]. Also initially identified in 1996 [16,17], the MYST family of proteins forms a third major group [10,18,19]. The acronym MYST was derived from the four founding members: human MOZ [17], yeast Ybf2 (renamed Sas3, for something about silencing 3) [16,20], yeast Sas2 [16] and human TIP60 (HIV Tat-interacting 60 kDa protein) [21–23]. There are five MYST proteins in humans, and the other three members are hMOF (human males-absent on the first) [24], HBO1 (HAT bound to ORC1) [25] and MORF [26]. Members of this family only share the MYST domain [10]. Compared to the GCN5/PCAF and p300/CBP groups, this family is more diverse in domain organization, complex formation, and biological function [10,18,19]. In the past two decades, these proteins have been systematically renamed twice. In the first nomenclature system, MYST1, MYST2, MYST3 and MYST4 were given to HBO1, hMOF, MOZ and MORF, respectively; incidentally, TIP60 was omitted in this system. The second nomenclature system is part of the 'lysine (K) acetyltransferase (KAT)' proposal adopted in 2007 [11]. According to this, TIP60, MOZ, MORF, HBO1 and hMOF were renamed KAT5, KAT6A, KAT6B, KAT7 and KAT8, respectively. It should be noted that mouse Morf was also identified as Querkopf ('squarhead' in German) after the head shape of mutant mice deficient in Morf [27]. While the KAT nomenclature system is gradually being adopted in the literature, traditional names such as MOZ, MORF, HBO1, hMOF and TIP60 are still being widely used. Hereafter we will use acronyms in both systems mainly according to how the names are cited in original publications.

2. MOZ and MORF as transcriptional coactivators with intrinsic enzymatic activity

These two acetyltransferases have similar domain organizations (Fig. 1A) [10,28]. In the yeast, there are three MYST members, Esa1 (essential Sas2-related acetyltransferase 1), Sas2 and Sas3 [29]. Gcn5, Hat1,

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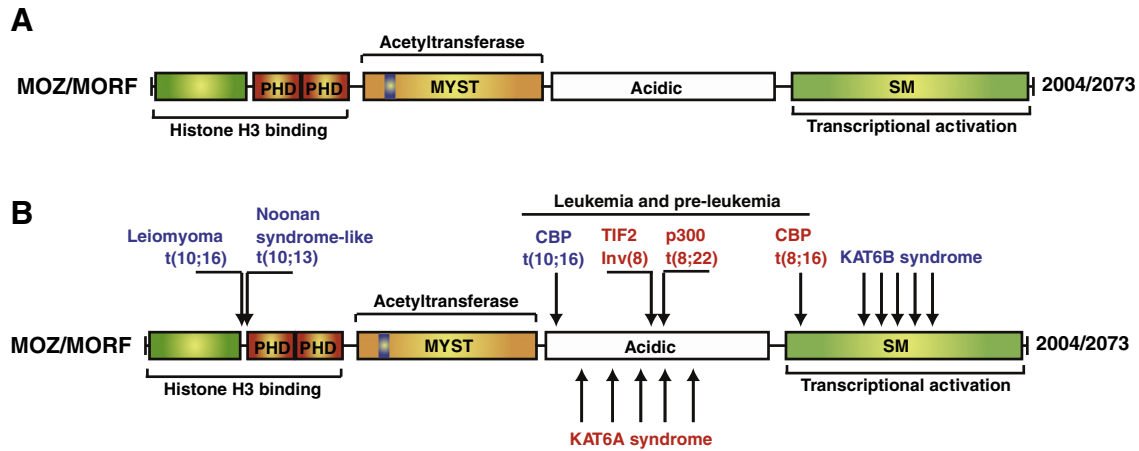E-mail address: xiang-jiao.yang@mcgill.ca.

Fig. 1. Domain organization of MOZ/MORF and their disease-cauding mutations. (A) Both MOZ and MORF are composed of tandem PHD fingers, a MYST domain, an acidic region and a Ser/Met (SM)-rich domain. In addition to the PHD fingers and MYST domain, the region N-terminal to the PHD finger is also conserved in *Drosophila* Enok, so this region has been referred to as the NEMM (N-terminal part of Enok, MOZ and MORF) domain [28]. This domain shows some sequence similarity to histones H1 and H5, thus also known as the H15 domain [28]. (B) The *MOZ* and *MORF* genes are recurrently mutated in leukemia, non-hematologic malignancies, and developmental disorders with the common characteristics of intellectual disability and developmental delay. Vertical arrows pointing to locations of disease-causing chromosomal translocations and point mutations affecting MOZ (brown) and MORF (blue). For leukemia-associated translocations, the corresponding fusion partners are also indicated. Except the two translocations at the very N-terminal region, many other mutations remove the SM domain but leave the very N-terminal region and the MYST domain intact. KAT6A (a.k.a. MOZ) syndrome refers to a new syndrome characteristic of microcephaly and global developmental delay, whereas KAT6B (a.k.a. MORF) syndrome includes genitopatellar syndrome and related developmental disorders. For simplicity, only a few arrows are used to illustrate mutation positions related to KAT6A/B syndromes; refer to several published reports for complete list of mutations [78,79,130,134]. Abbreviations: CBP, CREB-binding protein; p300, E1A-associated p300 kDa protein (paralogous to CBP); TIF2, transcription intermediary factor 2 (known to bind p300 and CBP).

ELP3 (elongator protein3), Rtt109 (Ty1 transposition gene product 109) and Eco1 (establishment of cohesion 1) are the other five lysine acetyltransferases known in yeast [11,29,30], so the MYST family is important for controlling yeast histone acetylation. There are about a dozen lysine acetyltransferases in mammals [10,11] and the mammalian MYST family contains five members, so this family is critical for maintaining histone acetylation and lysine acetylome in general [30]. The defining feature for members of this family is the MYST domain (Fig. 1A), which confers intrinsic acetyltransferase activity [10,28]. This domain shares an acetyl-CoA binding motif with GCN5, but displays no similarity to p300 and CBP [10,11]. In addition to the MYST domain, the N-terminal part of MOZ or MORF is highly similar to *Drosophila* Enok (named after 'enoki mushroom bodies' in mutant flies lacking this protein), which is crucial for neuroblast proliferation [31] and oocyte development in the female germline [32,33]. This N-terminal part contains the very N-terminal region, tandem PHD fingers and the MYST domain (Fig. 1A) [28].

As shown with other members of this family, the MYST domains of MOZ and MORF confer intrinsic acetyltransferase activities [26,27,34,35]. While MOZ and MORF acetylate histone H3 at Lys-9 and -14 [36,37], Enok specifically targets Lys-23 [33]. The tandem PHD fingers of human KAT6A are important for histone H3 binding (Fig. 1A) [38–40]. Arg-2 or Lys-4 methylation inhibits, but Lys-14 acetylation promotes, this binding, thereby providing a mechanism for crosstalk between modifications at different sites [38–40]. This also serves as a potentially important mechanism to survey the gene locus-specific modification status and control its acetylation by the MYST domain [40].

C-terminal to the MYST domain of MOZ or MORF are an acidic region and a serine/methionine (SM)-rich domain (Fig. 1A). Both are present in two zebrafish orthologs but not in *Drosophila* Enok or a related sea urchin protein [28], indicating that MOZ and MORF are vertebrate-specific. While little is known about the function of the acidic region, the SM domain possesses potent transcriptional activation potential (Fig. 1A) [26,28,34]. MOZ and MORF do not bind DNA directly, so they function as coactivators for DNA-binding transcription factors [28]. Consistent with this, MOZ and MORF interact with RUNX transcription factors (Fig. 2A) [35,41,42], and MOZ also acetylates p53 to activate p21 transcription (Fig. 2B) [43]. Thus, MOZ and MORF are transcriptional coactivators with intrinsic acetyltransferase activity.

3. MOZ and MORF form tetrameric complexes with BRPF1 and two other subunits

In 2006, purification of ING5 (inhibitor of growth 5) from HeLa cell extracts identified a tetrameric complex containing BRPF1, MOZ and EAF6 (homolog of yeast Esa1-associated factor 6) (Fig. 3A & C) [44]. In the complex, MOZ can be replaced with MORF [44]. Recent purification of BRPF1 from HeLa cell extracts revealed that it also forms a tetrameric complex with HBO1, ING4/5 and EAF6 (Fig. 3B & D) [45,46].

BRPF1 was formerly known as BR140 (bromodomain protein of 140 kDa), incidentally cloned in 1994 as a zinc finger protein containing a bromodomain similar to two such domains on the 250-kDa subunit of the transcription initiation factor TFIID [47]. Subsequent cloning of two leukemia-associated fusion partners on chromosomes 10 and 17 unraveled a Cys/His-rich domain that the fusion partners share with BR140 [48–50]. This domain harbors two PHD (plant homeodomain-linked) fingers joined by a C_2HC zinc knuckle and is thus named the PZP (PHD-zinc knuckle-PHD) module (Fig. 4A) [51]. In BRPF1, this module is located in the middle part but N-terminal to the bromodomain (Fig. 4A). In light of this PZP module and the bromodomain, new proteins similar to BRPF1 were sought after, leading to the identification of BRL (BR140-like protein), now known as BRPF2 or BRD1 (bromodomain protein 1) (Fig. 4B) [52]. BRPF3 is a third paralog (Fig. 4B), which was uncovered during genome annotation. These three proteins form a small but unique family of multidomain chromatin regulators (Fig. 4A–B) [28,53,54].

The PZP module is also present in other chromatin modifiers such as the leukemia-associated methyltransferase NSD1 and the demethylase GASC1 [51], further supporting a role in chromatin regulation. Moreover, this module is found in three JADE [protein encoded by gene (J) for apoptosis and differentiation in epithelia] proteins (Fig. 4C) [44,55]. Flanking the PZP module of BRPF1 are two small motifs similar to EPC (enhancer of polycomb) proteins (Fig. 4A & D) [44,51,56]. The N-terminal motif contributes to interaction with MOZ and MORF, while the C-terminal motif binds to ING5 and EAF6 (Fig. 3C) [36,44], indicating that BRPF1 serves as a scaffold for complex formation (Fig. 3A) [36]. The bromodomain of BRPF1 has acetyllysine-binding ability [57], whereas the PZP modules of BRPF1 and BRPF2 recognize the unmodified N-terminus of histone H3 [46,58] and the second PHD finger of BRPF2 is also known to bind directly
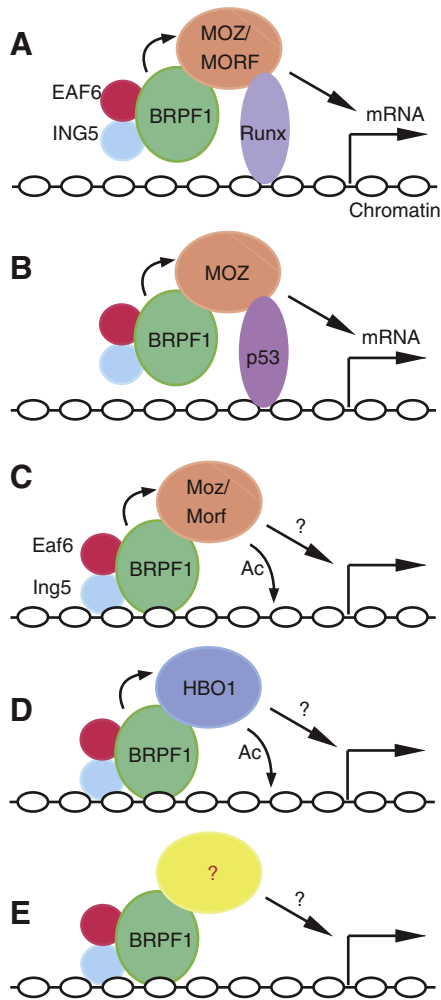
Fig. 2. Models showing how BRPF1 is targeted to chromatin for specific transcriptional regulation. (A) RUNX transcription factors bind to DNA and recruit the MOZ or MORF histone acetyltransferase, along with the trimeric complex composed of BRPF1, ING5 and EAF6. It is unclear whether MOZ/MORF, BRPF1 and ING5 also utilize their histone-binding domains to interact with chromatin [132]. (B) The tumor suppressor p53 binds to DNA and recruits the MOZ/MORF histone acetyltransferases, which in turn form tetrameric complexes with BRPF1, ING5 and EAF6. As in (A), it remains unclear whether MOZ/MORF, BRPF1 and ING5 also utilize their histone-binding domains to recognize chromatin. (C–D) BRPF1 forms a trimeric complex with ING5 and EAF6 to recruit the histone acetyltransferase MOZ, MORF (C) or HBO1 (D) to regulate gene expression. Dark question marks denote unknown consequences of recruitment of Moz/Morf and Hbo1. Ac, acetylation. (E) It remains possible that BRPF1 also acts through an unknown partner(s) as indicated by a yellow oval along with a red question mark.

to DNA [59]. The PZP module interacts specifically with the unmodified N-terminus of histone H3 in a manner sensitive to modifications at Lys-4 [46,58], thereby indirectly 'reading' histone modifications. Located at the C-terminal part of BRPF1 is a highly conserved PWWP domain (Fig. 4A), which forms a specific pocket for lysine-methylated histone H3 [60,61].

Interestingly, despite their high sequence similarity to BRPF1, both BRPF2 and BRPF3 (Fig. 4A) preferentially form complexes with HBO1, rather than with MOZ and MORF (Kezhi Yan & X.J.Y., unpublished data) [45,46]. Thus, even at the molecular level, BRPF1 can function quite differently from BRPF2 and BRPF3. Strikingly, BRPF1 association switches the substrate specificity of HBO1 from nucleosomal histone H4 to H3 [46], indicating a dominant role of BRPF1 in controlling the substrate specificity [46,62]. Notably, BRPF1 does not interact with other acetyltransferases such as hMOF [63] and p300 [45], supporting that association with MOZ, MORF and HBO1 is specific (Fig. 2A–B). Thus, BRPF1 specifically interacts with three different acetyltransferases to govern their enzymatic properties.

4. MOZ and MORF in vertebrate development

Inactivation of the mouse *Moz* gene leads to embryonic lethality around embryonic (E) day 14.5 [64]. Mutant embryos at E14.5 are bloodless and have small liver, indicating defective hematopoiesis. Analyses of two different knockout strains lead to the conclusion that Moz is required for maintaining fetal hematopoietic stem cells [64,65]. In addition, a knock-in mutant mouse strain has been engineered [66] to express the point mutant G657E, known to be defective in histone acetylation [67]. Compared to wild-type littermates, the resulting homozygotes display shortened lifespan, low body weight, small thymus and spleen, and proliferation defects in various hematopoietic progenitors [66], supporting the importance of the acetyltransferase activity of Moz *in vivo*. Moreover, the mouse *Moz* gene is required for normal B cell development, as well as for optimal lymphoma development induced by Myc [68,69]. In addition, loss of Moz leads to senescence of mouse embryonic fibroblasts and neural stem cells [70,71]. The requirement for lymphoma development and cell proliferation suggests that Moz has an oncogenic role.

The biological function of mouse Morf has been investigated in a gene-trap strain possessing ~10% residual mRNA [27]. Heterozygous mutant animals are normal, but the homozygotes die at weaning (*i.e.*, ~3 weeks of age) and display dwarfism, craniofacial abnormalities and cerebral defects [27]. Related to the cerebral defects, Morf is important for regulating neural stem cells [72,73]. These findings shed some light on defects characteristic of developmental disorders due to mutations in the *MOZ* and *MORF* genes [74–79]. The phenotypes observed with these mutant mice indicate that although they are interchangeable in various molecular and cell-based studies *in vitro* [26,34,36], MOZ and MORF have quite distinct functions *in vivo*.

While MOZ and MORF are large (~240 kDa, Fig. 3C), HBO1 is much smaller (Fig. 3D). Its N-terminal domain is different from those of MOZ and MORF (Fig. 3A & D). No direct links to diseases have been uncovered yet for human HBO1, but mouse Hbo1 is essential for embryo development [80]. Inactivation of the mouse gene leads to embryonic lethality at E10.5 [80]. Importantly, it is a major acetyltransferase for Lys-14 acetylation of histone H3 in mouse embryonic fibroblasts [80] and other cells [45,81]. This is slightly different in budding and fission yeast, where both Sas3 (similar to HBO1) and Gcn5 contribute to histone H3 acetylation at Lys-14 [82,83]. This histone mark (H3K14ac) is important. For example, it controls cell cycle progression [82,83], factor recruitment to chromatin [38], H3K4me3 demethylation [84] and RNAi-mediated gene silencing [85]. Studies using human cells indicate a key role of HBO1 in DNA replication [86,87], but the mouse gene is not required [80]. Whether this discrepancy is due to species difference awaits further investigation.

5. MOZ and MORF in leukemia, solid tumors and developmental disorders

In 1996, the *MOZ* gene was first identified as a fusion partner in the recurrent chromosome translocation t(8;16)(p11;p13) associated with acute myeloid leukemia (Fig. 1B) [17]. This gene is fused to that of CBP, producing an aberrant transcript encoding the fusion protein MOZ-CBP [10,17]. Similarly, in the leukemia-associated chromosome translocation t(8;22)(p11;q13), the *MOZ* gene is fused to that of p300, producing the fusion protein MOZ-p300 [88]. The *MOZ* gene is also rearranged in hematologic malignancies with the inversion inv(8)(p11q13), generating fusion proteins with TIF2 (transcription intermediary factor 2, a known partner of p300/CBP) (Fig. 1B) [89,90]. The resulting MOZ-TIF2 fusion proteins promote self-renewal of leukemic stem cells [67,91, 92]. In addition, the *MOZ* gene is fused to a novel partner, *LEUTX* (leucine twenty homeobox), in therapy-related acute myeloid leukemia with t(8;19)(p11;q13) [93]. Reminiscent of the *MOZ* gene, the *MORF* gene is fused to the *CBP* gene in translocation t(10;16)(q22;p13) associated with acute myeloid leukemia (Fig. 1B) [94,95].
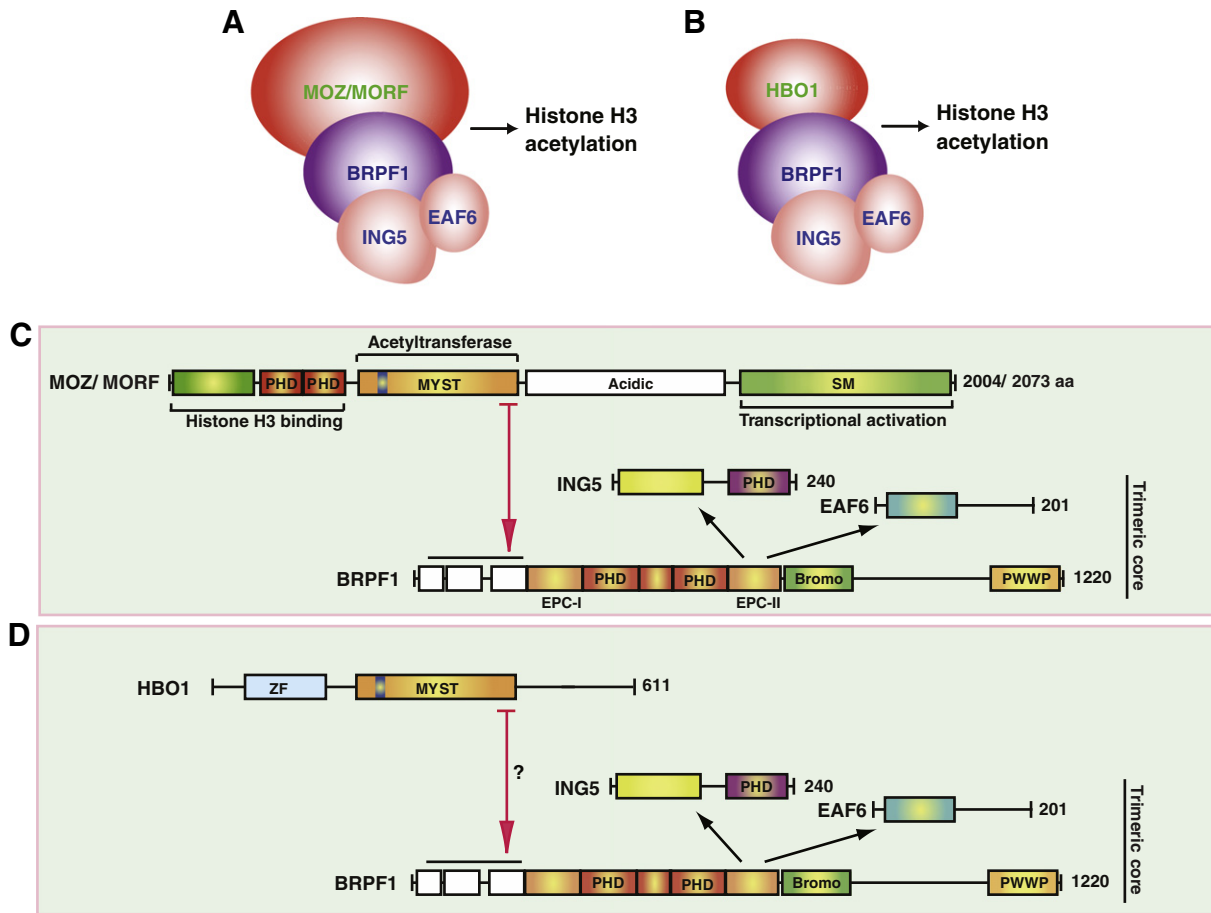
Fig. 3. Architecture of BRPF1 complexes and links of MOZ/MORF to cancer and other diseases. (A) Cartoon showing a tetrameric complex composed of MOZ (or MORF), BRPF1, ING5 and EAF6. BRPF1 serves as a scaffold, to promote complex formation and stimulate acetylation of nucleosomal histone H3. In the complex, ING5 can be replaced with ING4. (B) Same as (A) except that the catalytic subunit is HBO1 instead of MOZ or MORF. (C) Molecular architecture showing how different domains are involved in tetrameric complex formation. MOZ and MORF are two paralogs, each comprising multiple domains: tandem PHD fingers, a MYST domain, and a transcriptional activation domain. It is striking that only a small region of MOZ and MORF (red vertical arrow) is required for interaction with BRPF1. EPC-II of BRPF1 serves as the binding surface for ING5 and EAF6. BRPF1 forms a trimeric core with ING5 and EAF6 for interaction with MOZ and MORF. (D) Molecular architecture illustrating how different domains are involved in tetrameric HBO1 complex formation. HBO1 is much smaller than MOZ or MORF, and does not have the PHD fingers and SM domain of MOZ or MORF. However, it possesses an uncharacterized zinc finger (ZF) and a serine-rich domain (not depicted here). It is unclear whether the C-terminal region of the MYST domain mediates HBO1 interaction with BRPF1 as shown for MOZ and MORF (C).

In addition to hematologic malignancies, the *MOZ* and *MORF* genes are altered in solid tumors. The *MOZ* gene is mutated in esophageal adenocarcinoma [96] and abnormal expression of mouse Moz contributes to metastasis of medulloblastoma [97]. The *MORF* gene is altered in leiomyomata [98,99], breast cancer [100] and castration-resistant prostate cancer [101]. In leiomyomata with the chromosomal translocation t(10;17)(q22;q21), the *MORF* gene is fused to the gene of KANSL1 (KAT8 regulatory NSL complex subunit 1), leading to expression of a fusion protein containing the NEMM domain of MORF (Fig. 1A) and a KANSL1 domain able to interact with KAT8 [99]. This suggests that mistargeted acetylation is oncogenic, which is reminiscent of fusion of MOZ and MORF to p300, CBP and TIF2 in leukemia (Fig. 2B). Moreover, the *MOZ* and *MORF* genes have both been identified as top-ranking targets amplified in different types of cancer [102]. Mouse studies indicate that Moz is required for lymphoma development induced by Myc [68] and its loss leads to senescence of mouse embryonic fibroblasts and neural stem cells [70,71]. All of these support that MOZ has an oncogenic role.

In addition to cancer, the *MORF* gene is mutated in four different developmental disorders (Fig. 1B): Noonan syndrome-like disorder [103], Ohdo syndrome [74,104], genitopatellar syndrome [75,76] and blepharophimosis–ptosis–epicanthus inversus syndrome [77]. A boy with the Noonan syndrome-like disorder displays reduced growth, cardiac defects, distinctive facial dysmorphism, and variable cognitive deficits [103]. Patients with Ohdo syndrome exhibit eyelid dysplasia, mask-like facial appearance and severe intellectual disability [74]. Genitopatellar syndrome is associated with patellar aplasia or hypoplasia, external genital abnormalities and severe intellectual disability [75, 76]. Blepharophimosis–ptosis–epicanthus inversus syndrome is characterized with abnormal eyelid development and distinct facial features, and some female patients also exhibit ovarian insufficiency [77]. Diverse defects in patients of these four genetic diseases support that MORF functions as a pleiotropic regulator in various biological processes [26]. Importantly, two recent studies have also identified recurrent *MOZ* gene mutations in previously unrecognized syndromes that display intellectual disability and global developmental delay (Fig. 1B) [78,79].

A key issue is what molecular mechanisms underlie cancer and developmental disorders caused by mutations in the *MOZ* and *MORF* genes. These developmental disorders share the common characteristics of intellectual disability and craniofacial abnormalities. Related to this, Morf-deficient mice show defects in cerebral and bone development [27]. Morf is required for adult neurogenesis [72,73] and Moz is also important for NSCs [71]. In addition, Moz regulates neural crest development and craniofacial morphogenesis [105]. Moreover, both fish and mouse Moz proteins modulate skeletal development [37, 106–108]. The pleiotropic effects of the human *MOZ* and *MORF* gene mutations are also consistent with the molecular studies that both
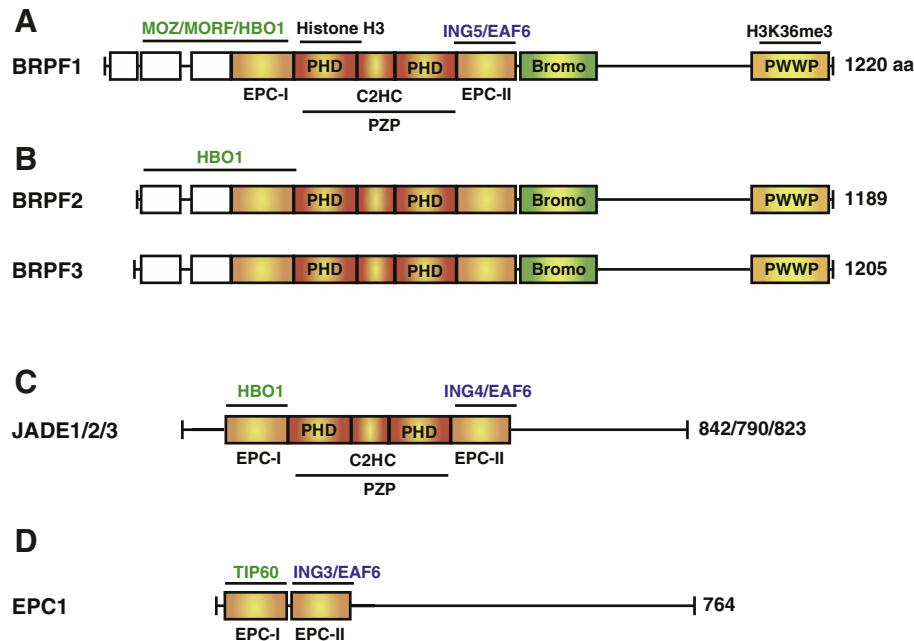
Fig. 4. Domain organization of BRPF1 and its comparison with related proteins. (A–B) Domain organization of BRPF1, BRPF2 and BRPF3. These three proteins are highly homologous to each other except that BRPF1 possesses a small N-terminal extension. Enhancer of polycomb (EPC)-like domains and PZP (PHD-zinc knuckle-PHD) modules are similar to those of JADE proteins (C). However, unlike BRPF proteins, JADEs do not have the bromodomain (Bromo) and PWWP domain. MOZ, MORF and HBO1 bind to BRPF1 through its N-terminal region, whereas ING5 and EAF6 interact with EPC-II. Unlike BRPF1, both BRPF2 and BRPF3 prefer to bind HBO1 rather than MOZ and MORF, indicating the functional difference of BRPF1 from BRPF2 and BRPF3. (C–D) Domain organization of three JADE proteins and EPC1. These proteins share EPC-I and -II domains with BRPFs. While JADEs interact with HBO1, EPC1 binds to a similar histone acetyltransferase, TIP60. In both cases, the interaction is mediated by EPC-I domains. EPC-II domains of EPC1 and JADEs target ING3 and ING4, respectively. EAF6 binds to this domain through ING3 or ING4.

MOZ and MORF function as transcriptional coactivators for RUNX transcription factors, the p53 tumor suppressor and perhaps others (Fig. 2A–B).

6. BRPF1 and its paralogs in animal development and human disease

BRPF1 is conserved from *Caenorhabditis elegans* to humans [28]. In budding and fission yeast, there is one related protein (Nto1, for NuA three ORF 1), but it is an ortholog of JADEs [62,83,109,110]. Although the biological function of *Drosophila* Brpf1 remains unclear, the *C. elegans* ortholog Lin-49 is known to regulate neuron asymmetry, hindgut development and reproduction [111–113]. Lin-49 genetically interacts with two proteins distantly related to MOZ and EAF6 [113]. Inactivation of zebrafish *Brpf1* affects anterior *Hox* gene expression and alters pharyngeal segmental identity [114]. Such a phenotype is reminiscent of what was reported for inactivation of zebrafish *Moz* [106]. Moreover, inactivation of medaka *Brpf1* reduces expression of anterior and posterior *Hox* genes, thereby altering craniofacial and caudal skeletons, respectively [115]. Therefore, fish Brpf1 interacts with Moz to regulate *Hox* gene expression. While there is only one ortholog in *C. elegans* or *Drosophila*, Brpf1 has two paralogs (Brpf2 and Brpf3) in fish and other vertebrates (Fig. 4A–B). Functions of fish Brpf2 and Brpf3 remain to be determined.

We have characterized a mouse strain containing two LoxP sites and a *LacZ* reporter cassette inserted at the mouse *Brpf1* locus [116]. Using the *LacZ* reporter, we determined the expression atlas and the results suggest an important role of mouse Brpf1 in different developmental processes [116]. Total knockout embryos die at E9.5, indicating an essential role in embryogenesis [116,117]. Because of high expression in the brain [116], we have recently generated forebrain-specific knockouts and discovered that Brpf1 is key to development of the cerebral cortex and hippocampus [63,118]. Notably, Brpf1 is crucial for dentate gyrus development by regulating neural stem cells [63,118]. To understand the underlying mechanisms, we have utilized microarray-based gene expression analysis to investigate how Brpf1 loss alters the transcriptome, discovering that mouse Brpf1 regulates expression of *Hox* and multiple other genes in the mouse forebrain [63,118].

Phenotypes of *Brpf1*$^{-/-}$ embryos are much more severe than those of *Moz*$^{-/-}$ embryos and *Morf*-deficient mice [27,64,65]. It may be related to the ability of Brpf1 to regulate both Moz and Morf (Fig. 2C) [36,44]. Alternatively, Brpf1 has functions independent of them. Of relevance, Brpf1 also interacts with Hbo1 (Fig. 2D) [45,46]. Also, it is still possible that Brpf1 acts independently of Moz, Morf and Hbo1 *in vivo*; if so, Brpf1 may interact with an unidentified factor(s) (Fig. 2E). Inactivation of mouse *Brpf2* leads to embryonic lethality at E15.5, with neural tube defects, abnormal eye development and faulty erythropoiesis [45]. In contrast, mouse *Brpf3* is non-essential (Kezhi Yan & X.J.Y., unpublished data). Thus, despite their sequence similarity (Fig. 4A–B), mouse Brpf1, Brpf2 and Brpf3 have quite distinct roles *in vivo*.

As illustrated in Fig. 5A, the human *BRPF1* gene is recurrently mutated in childhood leukemia [119] and adult medulloblastoma [120]. The mutations appear to diminish the function of BRPF1, suggesting that it plays a tumor-suppressor role. Both BRPF2 and BRPF3 are also altered in cancer (Fig. 5A–B) [119–121]. One leukemia-associated chromosomal translocation leads to expression of a fusion protein containing a DNA binding domain of the PAX5 transcription factor and entire BRPF2, suggesting that mistargeted BRPF2 is oncogenic. ING5 is a part of the ING (inhibitor of growth) family, whose founding members were initially identified as inhibitors of cell growth [122]. The *EAF6* gene is rearranged in endometrial stromal sarcoma [123,124]. Thus, like MOZ and MORF, the BRPF1–ING5–EAF6 subcomplex plays a direct role in cancer. The crucial role of mouse Brpf1 in development [63,116–118], as well as its close partnership with MOZ and MORF (Fig. 2A) [36,44,46], suggests that human BRPF1 may also be important in different developmental disorders.

7. Conclusions and future directions

It is now widely recognized that both genetic and epigenetic mechanisms are critical in human development and disease [125,126].
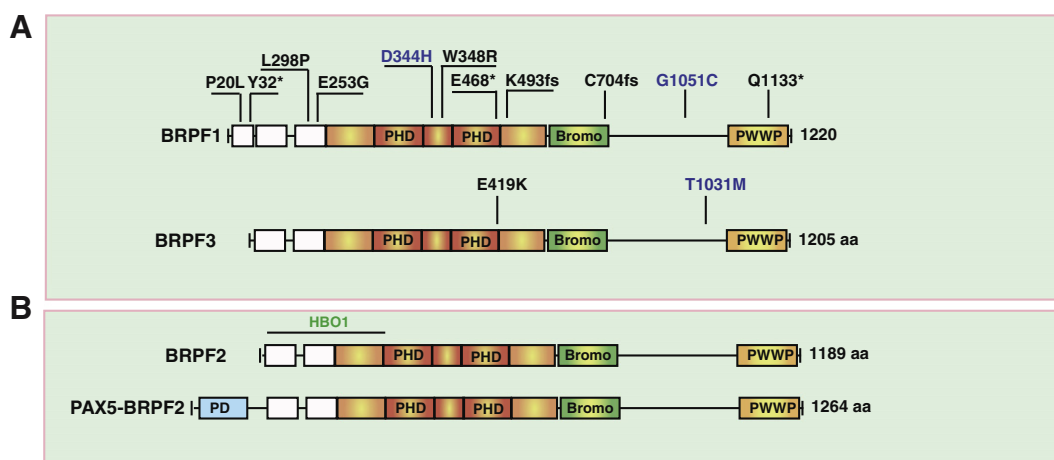
Fig. 5. The *BRPF1* gene is recurrently mutated in childhood leukemia and adult medulloblastoma. (A) Illustrated are mutations that have been discovered in the *BRPF1* and *BRPF3* genes. The mutations present in adult medulloblastoma are indicated with dark letters, whereas those found in pediatric leukemia are shown in blue. fs, reading frame shift; *, translational termination. The mutations are composed from data published in two recent studies [119,120]. Neither study has uncovered any point mutations on the *BRPF2* gene. (B) Comparison of BRPF2 with a leukemia-associated fusion protein containing a part of the transcription factor PAX5. In childhood acute lymphoblastic leukemia, the paired domain (PD) of PAX5 is fused to entire BRPF2. This paired domain confers specific DNA binding and is thus able to recognize certain enhancers, so discovery of this fusion protein in leukemia suggests that mistargeted BRPF2 may lead to leukemogenesis.

Related to the epigenetic angle, hundreds of chromatin regulators have been identified and characterized at the molecular level [11,127–129], so an important research direction is to pinpoint pathophysiological roles of different chromatin regulators. In this regard, the *MOZ* and *MORF* genes are recurrently mutated in cancer [28,96,97,101,102] and multiple developmental disorders [74–79,103,130]. In addition, both MOZ and MORF interact with—and their acetyltransferase activities are stimulated by—the multivalent chromatin regulator BRPF1 [28,36,44]. Mouse Brpf1 is important for regulating different developmental processes [63,116–118], and the human *BRPF1* gene is mutated in pediatric lymphoma and adult meduloblastoma [119,120]. Related to the biological functions, mouse Brpf1 regulates different developmental processes, including mouse embryo survival [116,117] and forebrain development [63,118], suggesting the intriguing possibility that the human *BRPF1* gene is also mutated in developmental disorders. Therefore, since the initial identification in 1996 and 1999 [17,26], MOZ and MORF have emerged as two unique chromatin regulators with important roles in animal development and human diseases.

As for future directions, how to correlate information from molecular studies in cell-free and cell-based systems, and fish and mouse genetic analyses, with symptoms in human diseases with mutations in the *MOZ, MORF* and *BRPF1* genes remains an important question deserving continued research attention. While good progress has been made about the molecular and biological functions of these proteins, how their functions are regulated, *e.g.*, by cellular signaling networks, remains a question that little is known about. How different histone-binding domains of MOZ/MORF–BRPF1 complexes (Fig. 3A & C) cooperate with each other, as well as with other epigenetic regulators, to confer genome-wide actions is another important question awaiting further investigation. In addition to histones, numerous non-histone proteins have been identified [131]. For example, ~5% bacterial and mammalian proteins are acetylated on lysine residues [30]. In contrast to numerous protein kinases maintaining the human kinome, only over a dozen lysine acetyltransferases have been identified. In this context, an important question is whether MOZ and MORF acetylate various non-histone proteins. The last important question is how to translate the knowledge that we have acquired and will acquire to the clinics. Related to this, different domains of MOZ, MORF and BRPF1 are potential drug targets (Figs. 1 & 4) [132]. In this regard, a highly-specific compound targeting the bromodomain of BRPF1 has been developed [133]. Overall, through dedicated efforts from multiple research laboratories with complementary expertise, we have learned a lot about MOZ, MORF and their binding partners. However, there are still a lot of very important questions awaiting even more concerted research attention.

Conflict of interest

The author declares no conflict of interests.

Acknowledgements

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