



Review

Somatic alterations and dysregulation of epigenetic modifiers in cancers



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ABSTRACT

Genomic discovery efforts in patients with cancer have been critical in identifying a recurrent theme of mutations in epigenetic modifiers. A number of novel and exciting basic biological findings have come from this work including the discovery of an enzymatic pathway for DNA cytosine demethylation, a link between cancer metabolism and epigenetics, and the critical importance of post-translational modifications at specific histone residues in malignant transformation. Identification of cancer cell dependency on a number of these mutations has quickly resulted in the development of therapies targeting several of these genetic alterations. This includes, the development of mutant-selective IDH1 and IDH2 inhibitors, DOT1L inhibitors for MLL rearranged leukemias, EZH2 inhibitors for several cancer types, and the development of bromodomain inhibitors for many cancer types—all of which are in early phase clinical trials. In many cases, however, specific genetic targets linked to malignant transformation following mutations in individual epigenetic modifiers are not yet known. In this review we present functional evidence of how alterations in frequently mutated epigenetic modifiers promote malignant transformation and how these alterations are being targeted for cancer therapeutics.

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1. Introduction

Recent progress in systematic sequencing of human malignancies has identified recurrent mutations in epigenetic modifiers as a consistent theme throughout human cancer. Several of these mutated genes, or classes of genetic alterations, appear to be distinctly associated with specific disease phenotypes which have shed light on new mechanisms of malignant transformation. Moreover, many mutations in epigenetic regulatory genes result in a gain-of-function which is potentially directly targetable. Thus, identification of mutations in epigenetic regulatory genes has provided important information about disease pathogenesis as well as potential new avenues of therapy.

In this review we discuss novel classes of mutated disease alleles in genes encoding epigenetic modifying proteins. These include somatic point mutations and/or translocations in genes directly involved in DNA cytosine methylation modification (*TET2*, *IDH1/2*), genes encoding enzymes which modify histone proteins (*EZH2*, *BAP1*, *MLL1-3*, *CREBBP*, *EP300*), as well as those required for histone enzyme complexes to function (*EED*, *SUZ12*, and *ASXL1*), and genes encoding histone H3 proteins themselves. This review focuses on the epigenetic aberrations thought to be attributable to these mutations and how these epigenetic alterations might contribute to malignant transformation. In addition, we highlight the potential clinical value of understanding these mutations, as they may be therapeutically targetable in some instances.

2. Mutations in genes affecting DNA methylation

2.1. DNMT3A

The mammalian family of methyltransferases comprises three active DNA methyltransferases that enzymatically add a methyl group to cytosine in CpG dinucleotides in DNA. DNMT1 is a maintenance methyltransferase that methylates the newly synthesized CpG dinucleotides on the hemimethylated DNA during DNA

replication. DNMT3A and DNMT3B are primarily responsible for *de novo* DNA methylation, with a high expression level during embryogenesis. The catalytically inactive member of the family, DNMT3L, contributes to the regulation of DNMT3A oligomerization and enhances its methyltransferase activity.

Somatic mutations of *DNMT3A* were first identified in adult AML patients [1,2]. Recurrence studies found *DNMT3A* mutations in ~30% of normal karyotype AML cases, making it one of the most frequently mutated genes in AML [3]. Moreover, it has been demonstrated that mutations in *DNMT3A* confer poor prognosis and decreased overall survival in AML [4]. The rate of *DNMT3A* mutations varies by AML subtype, with the highest rate (20%) seen among cases with monocytic lineage (M4, M5) [5,6]. Mutations occur as a nonsense or frameshift alternation, or missense mutations.

More than 50% of *DNMT3A* mutations in AML are heterozygous missense mutations at the R882 residue within the catalytic domain, most commonly resulting in an Arginine to Histidine amino acid exchange. A murine BMT model with hematopoietic stem/progenitor cells transduced by DNMT3A R882H acquired a chronic myelomonocytic leukemia (CMML)-like disease phenotype, with clinical features reminiscent of human AML with *DNMT3A* mutation [7]. The findings of this study suggest that this mutation alone is capable of initiating leukemia. However, in AML cells, R882 mutations always occur with retention of the wild-type allele, suggesting that the R882 mutant may serve as a dominant-negative regulator of wild-type DNMT3A. To establish this assumption, it has been shown that when exogenously expressed in murine embryonic stem (ES) cells, mouse DNMT3A R878H (corresponding to human R882H) proteins fail to mediate DNA methylation, but interact with wildtype proteins. When the wildtype and mutant forms were coexpressed in the murine ES cells, the wildtype DNA methylation ability was inhibited [8]. Furthermore, in a recent study of this mutation's mechanism, size-exclusion chromatography analysis demonstrated that the mutant enzyme inhibits the ability of the wildtype enzyme to form

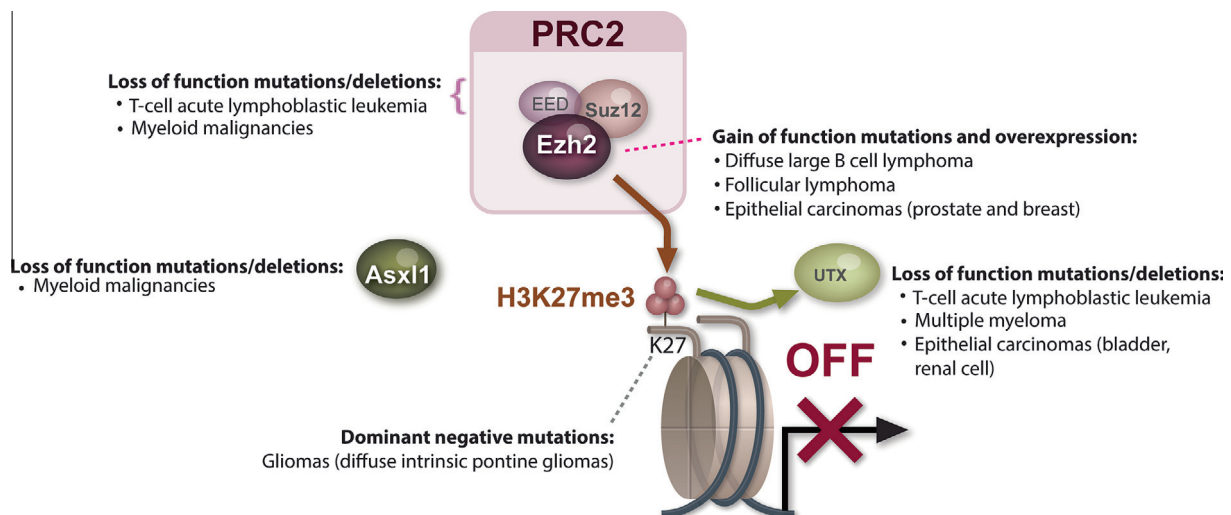


Fig. 1. Cancer associated changes regulating histone H3 lysine 27 (H3K27) methylation. In order to illustrate the wide variety of epigenetic alterations converging on a single epigenetic mechanism in cancer, the genetic alterations associated with alterations in H3K27 methylation are illustrated. Each of the genes portrayed are mutated in cancer and encode proteins which directly or indirectly affect H3K27me3 (in addition to possible additional effects in the cell). For instance, *EZH2* is affected by both loss-of-function mutations and deletions in T-cell acute lymphoblastic leukemia (T-ALL) as well as in myeloid malignancies. In contrast, somatic point mutations which confer increased enzymatic activity to *EZH2* are found in diffuse large B cell lymphoma (DLBCL) and follicular lymphoma (FL). *SUZ12* and *EED*, which form an enzymatic complex with *EZH2*, known as the Polycomb Repressive Complex 2 (PRC2) are also occasionally deleted and/or affected by loss-of-function mutations in myeloid malignancies. The Polycomb associated protein *ASXL1* has been found to be associated with global abundance of H3K27 methylation and is frequently deleted and/or affected by loss-of-function mutations in myeloid malignancies as well. *UTX*, which encodes an enzyme which demethylates di- and trimethyl groups on H3K27 (H3K27me2/3), is frequently deleted and/or affected by loss-of-function mutations in multiple myeloma, T-ALL, and several epithelial carcinomas including renal cell carcinoma and bladder urothelial carcinoma. Finally, as evidence of the importance of H3K27 methylation, this exact residue of histone H3.3 is occasionally mutated in cancer. Histone H3.3 mutations are most enriched in a specific subtype of pediatric gliomas known as diffuse intrinsic pontine gliomas.

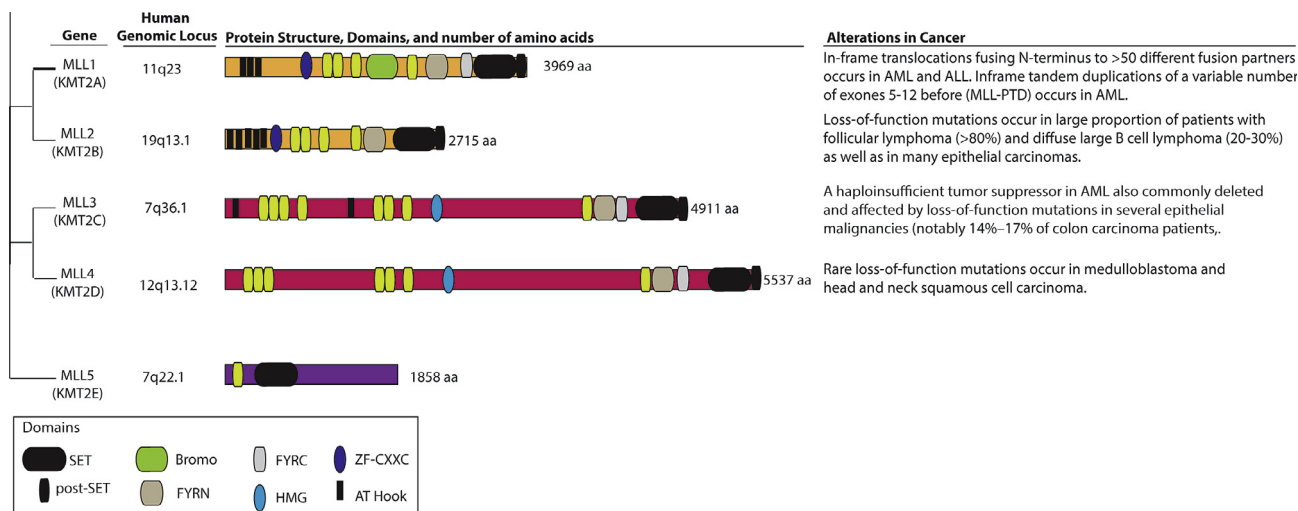


Fig. 2. Shown above are the genomic loci of each MLL family member in humans. *MLL1* and *MLL2* (also known as *KMT2A* (gene ID: 4297) and *KMT2B* (gene ID: 9757), respectively) are highly homologous as are *MLL3* and *MLL4* (also known as *KMT2C* (gene ID: 58508) and *KMT2D* (gene ID: 8085), respectively). All four members (*MLL1*–*4*) share a common cluster of domains (PHD-FYRN-FYRC-SET-postSET domain), notably including a SET domain which imparts histone H3 lysine 4 (H3K4) methyltransferase activity. In contrast to *MLL1*–*4*, *MLL5* is more distantly related and contains only a PHD and a SET domain. The founding member of the family, *MLL1*, undergoes a translocation event fusing the N-terminus of MLL to one of >50 fusion partners. This translocation event removes the PHD domain but results in recruitment of the H3K79 methyltransferase DOT1L to the C-terminus of the chimeric protein. In addition to translocations, *MLL1* also undergoes internal inframe tandem duplications which results in hyperactive H3K4 methyltransferase activity and promotes leukemogenesis *in vivo*. Somatic mutations and copy number alterations of *MLL2*–*4* are quite common in cancer, but as shown above, the genes encoding these proteins are quite large calling into question whether all of the somatic mutations describe impact a functional impact on gene function. Ongoing functional studies attempting to characterize how loss of MLL members *MLL2*–*4* contributes to tumorigenesis will be very enlightening.

functional tetramers, which are required for maximal *de novo* methylation activity [9]. This may explain the protein intrinsic mechanism through which R882H DNMT3A function as a dominant-negative inhibitor of *de novo* DNA methylation. Nevertheless, ~40% of *DNMT3A* mutations occur outside of the R882 missense mutation. Many of these alterations are predicted to cause haploinsufficiency of *DNMT3A*, with potentially no significant alterations in DNA methylation. The mechanisms of these mutations' contribution to leukemogenesis remain to be elucidated.

2.2. TET2

The Ten-Eleven Translocation (TET) family, consisting of three proteins (TET 1–3), is named after the rare t(10;11)(q22;q23) translocation that was demonstrated in a subset of AML patients harboring *TET1* translocated with *MLL1* [10]. TET proteins are mammalian DNA hydroxylases which catalyze the conversion of the methyl group at the 5-position of cytosine of DNA (5-methylcytosine (5mC)) to 5-hydroxymethylcytosine (5hmC), in a reaction which requires Fe(II) and α -ketoglutarate (α -KG) as substrates [11]. The TET family of enzymes then perform iterative oxidation of 5hmC to produce 5-formylcytosine (5fC) followed by 5-carboxylcytosine (5caC). These derivatives of 5mC oxidation are likely to be intermediates in the DNA demethylation process, through an active and passive manner. Moreover, they may affect the activity of different Methyl-CpG Binding Domain (MBD) proteins and thus alter the recruitment of chromatin regulation, or have direct effects on transcription. Genome-wide mapping of 5hmC in ES cells has identified that 5hmC is distinctly distributed at transcription start sites and within gene bodies [12,13]. It is also more commonly present in gene exons than introns.

In parallel with studies that initially described the catalytic activity of the TET family of enzymes, mutations in *TET2* were found in 8–23% patients with myeloid hematopoietic malignancies [14–16]. Mutations in *TET2* are especially enriched in CMML where they occur in ~50% of such patients and in cytogenetically normal AML (CN AML) where the frequency of *TET2* mutations is 18–23%

[17]. Given the frequency and clinical importance of *TET2* mutations in myeloid malignancies, the global and site-specific levels of 5hmC in patients bearing these mutations have been studied. Although several studies have reported a decrease in global 5hmC levels in patients with myeloid malignancies with mutations in *TET2* [18,19], there is no conclusive evidence regarding the 5mC site-specific levels. The effect of *TET2* mutations on 5mC, 5hmC, and the relationship of these modified bases to gene transcription at specific gene targets are an area of active investigation.

In order to understand the role of *TET2* in hematopoiesis, multiple *Tet2* knockout mouse models have been created. Through analysis of 5 different murine models, it is clear that *Tet2* knockout mice develop progressive expansion of the hematopoietic stem progenitor compartment, increased hematopoietic stem cell (HSC) self-renewal, and finally a proliferative myeloid malignancy, reminiscent of human CMML [20–22]. Deletion of *Tet2* alone does not seem to result in AML in mice.

3. Mutations in genes affecting both DNA methylation and histone modifications

3.1. IDH 1/2

Isocitrate Dehydrogenase 1 and 2 (IDH 1/2) are NADP-dependent enzymes that catalyze the oxidative decarboxylation of Isocitrate to α -Ketoglutarate (α -KG) while reducing NADP⁺ to NADPH. *IDH1/2* are mutated in a range of myeloid malignancies, specifically in AML, where *IDH1* and *IDH2* mutations occur in up to 16–19% of adult CN-AML patients, respectively [14,23,24]. Mutations in *IDH1/2* are also present in ~70% of secondary glioblastoma mutiforme patients, as well as in colorectal cancer, cholangiocarcinoma, thyroid cancer and other solid tumors. These mutations are always heterozygous, and occur at 3 specific residues: R132 in *IDH1*, and either R140 (Arginine to Glutamine substitution) or R172 in *IDH2*. The mutant form of *IDH1/2* enzymes result in a neomorphic activity resulting in the ability to convert α -KG into 2-Hydroxyglutarate (2HG) through oxidation of NADP [25,26]. This, in turn,

results in abnormal accumulation of 2HG in cells. Due to the similarity of 2HG to α -KG, 2HG, when present in high levels, competes with α -KG and inhibits α -KG-dependent reactions. α -KG-dependent reactions include the oxidation of 5mC and its derivatives by the Tet family of enzymes. Accordingly, the biological implication of 2-HG exposure is impaired myeloid differentiation and cytokine-independent growth in TF-1 cells which normally depend on granulocyte macrophage–colony-stimulating factor for growth. A conditional IDH1 (R132H) knockin (KI) mouse model has since been reported to display an age-dependent blockade of hematopoietic differentiation, similar to the phenotype of *Tet2* null mice. Nevertheless, expression of this IDH1 mutant form in the hematopoietic system solely did not result in AML *in vivo*. Among other α -KG-dependent enzymatic reactions that are inhibited by accumulation of 2HG, noteworthy are the Jumonji-C domain-containing (JMJC) family of histone lysine demethylases, specifically those demethylating lysines 9 and 36 of histone H3 (H3K9, H3K36) [27].

Prognostic relevance of mutations in *IDH1/2* have been examined in multiple large cohorts of AML patients. *IDH2* mutations at the R140 residue were specifically associated with a favorable outcome in AML patients from the Eastern Cooperative Oncology Group (ECOG) E1900 cohort, both in the entire cohort without regard to the cytogenetic subset as well as in CN AML patients [14]. Moreover, the subset of patients with both *IDH1/2* and *NPM1* mutations, showed to significantly co-occur in multiple clinical correlative studies, had a particularly favorable outcome, superior to that of the cytogenetically favorable subset of AML patients.

Based on progress in understanding the altered metabolic function of the mutant IDH1/2 enzymes, studies targeting these enzymes with specific drugs have emerged. Rohle et al. [28] used a selective R132H-IDH1 inhibitor to block the ability of the mutant enzyme to produce R-2HG in multiple *in vitro* and *in vivo* models of gliomas with *IDH1* mutations. The R-2HG inhibition resulted in H3K9 demethylation and expression of gliogenic-differentiation-associated genes that were suppressed with the presence of the active mutant enzyme. Moreover, the R132-IDH1 inhibitor impaired IDH1-mutant glioma cell growth without an effect on IDH1 wildtype cell growth. Surprisingly, there were no significant DNA-methylation changes genome wide in the presence of the mutant-enzyme inhibitor. This finding raises the need of further investigations of the pathway in which glioma growth is promoted by mutant IDH1.

In parallel to the work on R132-IDH1 inhibition, Wang et al. [29] developed a selective inhibitor of the mutant R140Q-IDH2 enzyme. *In vitro* treatment of TF-1 erythroleukemia and primary human AML cells with this molecule resulted in induction of cell differentiation, supporting the relevance of the mutant enzyme as a therapeutic drug target. To enhance the understanding of mutant IDH1/2's role in AML progression, Kats et al. [30] generated a transgenic IDH2-R140Q KI mouse model in an on/off- and tissue-specific manner using a tetracycline-inducible system. They examined the oncogenic potential of mutant IDH2 concurrent with *FLT3* mutations and other transformation related over-expressed proteins. They found that the IDH2-R140Q mutation could cooperate with other mutations to initiate AML. Furthermore, the growth of the leukemic cells in these mice was highly affected by genetic deinduction of the IDH2 mutation, suggesting this mutant enzyme to be an excellent potential therapeutic target in AML.

At the 2014 American Association of Cancer Research (AACR) annual meeting, early phase clinical trials results of the first IDH inhibitor to enter clinical trials, AG-221, were presented [31]. Early results of the phase I dose escalation study of AG-221 treatment for patients with *IDH2*-mutant hematologic malignancies revealed initial clinical and pharmacodynamic activity of the drug, which also appeared to be well tolerated. Six of seven evaluable patients had

objective responses which are ongoing, including three who had a complete remission (CR) and two who had a CR with incomplete platelet recovery. Moreover, there was >90% reduction in the levels of 2-HG, providing proof-of-principle for the drug's mechanism of action at doses in this phase I trial. Further results of this ongoing study are anticipated in the near future.

4. Mutations in genes affecting histone modifications

4.1. UTX

The methylation and demethylation of histone proteins at specific residues is essential for maintenance of active and silent states of gene expression in developmental processes. KDM6A, also named UTX (Ubiquitously Transcribed Tetratricopeptide Repeat on Chromosome X), is a member of the JMJC family of histone lysine demethylases. These are Fe(II)- and α -KG-dependent oxygenases which constitute important components of regulatory transcriptional chromatin complexes [32,33]. UTX, located on Xp11.2, encoding a protein which demethylates di- and trimethyl groups on lysine 27 of histone encodes a (H3K27me2/3) [34,35] (See Fig. 1). UTX plays essential roles in normal development, as it is critically required for correct reprogramming, embryonic development and tissue-specific differentiation [36]. Constitutional inactivation of UTX causes a specific hereditary disorder, Kabuki syndrome [37].

Exome- and genome-wide sequencing strategies identified recurrent inactivating UTX mutations and deletions in multiple cancer types including multiple myeloma (MM), leukemias, as well as multiple solid tumor types including esophageal and renal cancer [38–46]. Noteworthy is the high frequency of UTX mutations in bladder carcinoma, as reported by Gui et al. [41] and Ross et al. [47], most commonly consisting of truncating mutations in the functional JmJC domain coding region.

Due to its high association with disease and well-defined catalytic mechanism, UTX is an attractive target for drug development. The use of structure-guided design has led to the first highly potent and selective inhibitor of JmJC-domain containing enzymes including UTX and JMJD3 (also known as KDM6B) [48]. This study provided proof of concept for generating specific JmJC-domain inhibitors. As research progresses, the role of UTX as bona fide tumor suppressor is anticipated to be confirmed, and the potential of JmJC-domain small molecule inhibitors as a therapeutic option for cancers will be investigated.

4.2. The Polycomb Repressive Complex 2

The Polycomb Repressive Complex 2 (PRC2) is one of the classes of Polycomb-group proteins (PcG) which are transcriptional repressors with a crucial function in the maintenance of cell identity and regulation of differentiation in different cellular contexts. This complex is evolutionarily conserved throughout vertebrates, and consists of four core members: Embryonic Ectoderm Development (EED), Suppressor of Zeste 12 Homologue (SUZ12), RbAp48 (also named RBBP4), and Enhancer of Zeste Homolog 1 or 2 (EZH1/EZH2) [49] (See Fig. 1). PRC2 plays an essential role in the initiation and maintenance of transcriptional silencing of specific histones through methylation of H3K27 [49,50] by the catalytic component EZH1 or EZH2. Whereas EZH1 abnormalities are not known to have a role in human malignancies, alterations in EZH2 have been implicated in transformation of human malignancies. The identification of somatic mutations in EZH2 was first established through exome sequencing in follicular and diffuse large B-cell lymphomas of germinal-center origin (follicular lymphoma (FL) and germinal center B-cell like diffuse large B-cell lymphomas (DLBCL)) by Morin et al. [51], followed by additional descriptions of

somatic heterozygous mutations in the SET domain of EZH2. These studies identified missense alterations at Tyrosine 641, Alanine 687 or Alanine 677 in lymphoid malignancies. Sneeringer et al., Yap et al. and Majer et al. demonstrated that the catalytic efficiency and the enzyme turnover number of the Y641 or Y687 mutant EZH2 increases with the H3K27 methylation status [52–54]. This suggests that alterations of Y641 in EZH2 are gain-of-function mutations, as the mutant enzyme has increased enzymatic activity to methylate mono- and dimethylated H3K27. Given that the mutation is consistently heterozygous, co-existence of mutant and wildtype EZH2 results in increased H3K27me3. The A677 mutant of EZH2 was shown to enhance EZH2 enzymatic methylation regardless of H3K27 methylation state [55]. In order to understand the biological consequence and transcriptional targets of this gain-of-function mutation in EZH2, a transgenic conditional KI model of *Ezh2* Y641F has been studied [56]. Conditional expression of mutant EZH2 in this model was found to suppress the expression of germinal center exit genes, resulting in germinal center hyperplasia. Moreover, expression of EZH2 Y641F accelerated lymphomagenesis in cooperation with BCL2.

Interestingly, while *EZH2* is affected by gain-of-function mutations in lymphomas, somatic missense, nonsense and frameshift mutations predicted to result in loss of function were found throughout the open reading frame of *EZH2* in patients with T-cell acute lymphoblastic leukemia (T-ALL) and chronic myeloid malignancies [57–60]. Among myeloid malignancies patients, mutations in *EZH2* are most commonly found in myelodysplastic syndrome (MDS) [61], myelofibrosis [62,63] and MDS/myeloproliferative neoplasm (MPN) overlap syndrome patients [63], and rarely found in primary acute myeloid leukemia (AML) [14]. In MDS and myelofibrosis patients, *EZH2* mutations confer adverse prognosis [61,64]. Recent work by Muto et al. identified the potential contribution of *Ezh2* loss to myeloid malignancy pathogenesis [65]. The authors studied mice with conditional homozygous deletion of *Ezh2* in the hematopoietic compartment alone and in combination with *Tet2* deletion. *Ezh2* and *Ezh2/Tet2* double knockout mice developed MDS/MPN like disease. Gene expression profiling and H3K27me3 ChIP-Seq analysis of progenitor cells from these mice identified prominent upregulation of *Myc* and associated genes with *Ezh2* loss as well as upregulation of many direct PcG targets which are potential oncogenes, including *Hmga2*, *Pbx3*, and *Lmo1*. This work suggests that derepression of PcG-targeted oncogenes in conjunction with the up-regulation of the *Myc* module could function as the major drivers of *EZH2*-mutant MDS/MPN disease.

In contrast to myeloid malignancies, NOTCH1 is established as a key oncogene driving T-ALL, and oncogenic NOTCH1 appears to oppose PRC2-mediated gene silencing when activated in the pathogenesis of T-ALL [58]. *EZH2* among other PRC2 members are displaced from the promoters of some NOTCH1 known target genes. Furthermore, increased tumorigenic potential was demonstrated in T-ALL xenografted cell lines with loss of *EZH2* [58].

The explanation for differences between loss of function mutations in *EZH2* in some malignancies and gain-of-function and overexpression in others remains unclear. However, these data do suggest that *EZH2* can serve as either a tumor suppressor or an oncogene depending on tissue context.

Similar to mutations in *EZH2*, loss-of-function mutations and deletions in *EED* and *SUZ12* have also been in myeloid malignancies [66,67] and in T-ALL [58,59]. These mutations are typically heterozygous and loss-of-function in nature, suggesting that they function as haploinsufficient tumor suppressors.

4.3. ASXL1

Additional sex combs (*Asx*) gene encodes a chromatin-binding protein required for normal determination of segment identity in

the developing embryo in *Drosophila*. The human homolog of this gene, *ASXL1* (*Asx*-like), functions in a dense network of physical interactions, interacts with the PRC2 complex in myeloid hematopoietic cells, and is associated with global abundance of H3K27 methylation [68].

Gelsi-Boyer et al. [69] were the first to report somatic deletion and mutations in *ASXL1* in MDS and CMML patients. *ASXL1* somatic mutations are also observed in myelofibrosis, MDS/MPN overlap disorders, and AML transformed from MDS [63]. Multiple studies found these mutations to confer adverse overall survival in AML and MDS [14,70,71]. Due to the high prevalence of *ASXL1* mutations (occurring in 15–20% of MDS and 40–60% MDS/MPN overlap syndrome patients [69,72,73]), and clinical importance of these mutations, we [68] investigated the mechanisms of transformation by *ASXL1* mutations. Myeloid leukemia cells with endogenous *ASXL1* mutations were associated with loss of *ASXL1* expression. In addition, a positive correlation between *ASXL1* expression and global H3K27 mono-, di- and trimethylation was observed (See Fig. 1). Finally, targets of *ASXL1* repression were identified, notably including the posterior *HOXA* cluster, known to contribute to myeloid transformation.

The generation of a mouse model for conditional deletion of *Asxl1* has allowed further understanding the *in vivo* effects of *ASXL1* loss. Whereas constitutive loss of *Asxl1* resulted in severe developmental abnormalities, hematopoietic-specific deletion of the gene resembled characteristic features of human MDS. Additionally, serial transplantation of *Asxl1*-null hematopoietic cells caused lethal myeloid disorder at a shorter latency than primary *Asxl1* knockout (KO) mice. Interestingly, reduces hematopoietic stem cell self-renewal caused by *Asxl1* deletion, was reversed by concomitant deletion of *Tet2*, that is commonly co-mutated with *ASXL1* in MDS patients. Moreover, the phenotype of compound *Asxl1/Tet2* deletion was MDS with hastened death in comparison to single-gene KO mice [74].

In addition to interactions with PRC2, *ASXL1* is also an essential cofactor for the nuclear deubiquitinase enzyme BAP1. BAP1 and *ASXL1* function together to deubiquitinate the transcriptional regulator HCF-1 and the O-GlcNAc transferase enzyme OGT. Conditional deletion of *Bap1* from the hematopoietic compartment of mice results in an MDS/MPN overlap syndrome [75]. Loss of HCF-1 and OGT is seen in BAP1 deficient cells, suggesting that *ASXL1*–BAP1 play an essential role in regulation of HCF-1 and OGT expression. Further work to understand the effects of *ASXL1*/BAP1 loss may yield therapeutic insight for myeloid malignancies.

5. Mutations in genes encoding histone proteins

Mutations in genes encoding histone proteins in cancer were first discovered in colon cancer (*HIST1H1B*, 4%) and Non-Hodgkin's lymphoma (NHL; *HIST1H1C*, 7%) through exome sequencing, but frequencies were low and no recurrent mutations were identified [76,77]. However, Wu et al. [78] and Schwartzentruber et al. [79] recently identified a high frequency of heterozygous mutations in *HIST1H3B* and *H3F3A* in a subtype of pediatric glioma, diffuse intrinsic pontine glioma (DIPG). *H3F3A* mutations were reported in 78% of DIPG and 22–31% of other pediatric glioblastomas (GBMs) whereas *HIST1H3B* mutations were almost solely reported in DIPG (18%). Interestingly, these mutations occur at amino acid residues K27M and G34 (G/R, G/V), a residue critical for post-translational modification through methylation and acetylation on H3K27 and H3K36. Several sporadic mutations at these residues were reported in osteosarcoma (G34W) and MDS (K27N) [80–82], but the vast majority of these mutations are found in pediatric high-grade gliomas, including central nervous system primitive neuroectodermal tumor (11%, G34R). *H3F3A* G34 mutations tend to co-occur with

ATRX/DAXX, *PDGFRA*, and *TP53* alterations, and are often exclusive with *IDH1* Mutations [79,83].

Histone H3 K27 and G34 mutations are mutually exclusive, which implies a possible redundant function, as well as always heterozygous, which suggests that they might result in a gain-of-function. At the same time, K27M mutations predict worse overall survival in contrast to G34 and wildtype H3 patients, and are associated with younger patients [83–85]. Moreover, *H3F3AK27*-mutant GBMs occurs in midline of brain, whereas *H3F3AG34* mutant GBMs tend to occur in the hemispheric area. In recent studies, K27 and G34 tumor samples exhibited separate methylation profiles associated with divergences in gene expression [79,83,86]. For example, *H3F3AK27*-mutant samples were associated with silencing of *FOXG1* and *MICA* and elevated expression of *PDGFRA*, while *H3F3AG34* – mutant samples were associated with silencing of *OLIG1/2* [83,87]. Global DNA hypomethylation and globally reduced H3K27 di-/tri-methylation were seen at many loci in *H3F3AK27M* mutant patient samples and cell lines suggesting that these mutations functions in a dominant-negative manner [83,84,87,88]. *In vitro* overexpression of H3.3 K27M reduced H3K27me2/me3 levels by K27M mediated binding of EZH2 and SUZ12 and consequently inhibition of PRC2 [87,89], consistent with a dominant negative function of histone H3 mutations.

In contrast to studies of *H3F3AK27* mutations, the mechanism behind *H3F3A G34R/V* induced tumorigenesis is less explored. *G34R/V* mutations appear to interfere with methylation at H3K36, and there are transcriptional differences between *H3F3A G34* mutant and wildtype forms. Aberrant activation and repression of several known oncogenes is an important feature of H3.3 mutant tumors, and its understanding will help to identify additional subtypes and driver genes. An example of this is the recent identification of G34-induced MYCN activation in pediatric GBM cell line KNS42 [86]. Targeting this oncogene in *H3F3AG34* mutated GBM patient could have vast therapeutic benefit.

5.1. MLL

The Mixed Lineage Leukemia (MLL) family of genes consists of 5 members (MLL1–5) which share a SET domain and plant homeodomain (PHD) which mediates interactions between specific proteins (See Fig. 2). While MLL5 is a distantly related member of the family, the SET domain of MLL1–4 encodes a specific H3K4 methyltransferase which positively regulates gene expression. MLL1–4 additionally share several structural characteristics, with MLL1–2 and MLL3–4 being highly related architecturally and functionally [90]. *MLL1* (also named *HRX*, *KMT2A* or *ALL1*), located on 11q23, is implicated in over 50 translocation events which results in loss of the H3K4 methyltransferase domain. These translocations, found in ~10% of all human leukemia and most commonly in infant leukemia and therapy-related leukemia, identify a unique group of acute leukemia often associated with poor outcome [91]. Discoveries of missense and truncating *MLL1* mutations in bladder, lung and breast carcinomas [41,92] suggest a tumor suppressive role for MLL1 in some solid tumors along with its dominant oncogene role in leukemias mentioned above [93].

The most frequent *MLL1* translocations are *MLL-AF4*, *MLL-AF9*, *MLL-AF10*, and *MLL-ENL*, which result in recruitment of the Disruptor of Telomeric silencing 1-Like (DOT1L) to the fusion protein. These translocations cause loss of MLL1's H3K4 methyltransferase activity but result in recruitment of the H3K79 methyltransferase activity from DOT1L to the fusion protein. Multiple studies have linked H3K79 methylation to positive transcriptional activation and as a unique mark for leukemogenic transformation [94]. Accordingly, interest has arisen in targeting DOT1L's enzymatic activity to therapeutically treat MLL fusion malignancies. EPZ004777 is a methyltransferase inhibitor that was designed as

a competitive inhibitor of S-adenosylmethionine (SAM), the universal donor of the methyltransferase enzymatic reaction. Nevertheless, it has preferential selectivity for DOT1L over other histone methyltransferases, and results in selective inhibition of leukemia cell lines with specific MLL1 translocations compared with cell lines without MLL1 translocations [95]. There is currently an ongoing phase I study of the DOT1L inhibitor EPZ5676 (NCT01684150) for patients with relapsed/refractory hematologic malignancies to establish maximum tolerated dose and safety. The study is currently in a restricted/expansion phase for patients with MLL rearrangements or with partial tandem duplications in MLL.

In addition to DOT1L, MLL1 is dependent on a large number of protein–protein interactions for transcriptional regulation as well as leukemogenesis. One example is the interaction between MLL1 and PAFc, which plays a critical role initiating, elongating and terminating mRNA transcription as well as in histone H2B monoubiquitination. Through its interactions with PAFc, MLL1 interact with BRD3 and BRD4 [96]. Multiple investigators have converged recently on the therapeutic efficacy of small molecular inhibitors of the acetyl lysine binding pocket of BRD4 [97–99]. These molecules have been found to be efficacious in a diverse array of human disorders including patients with BRD4-NUT translocated midline carcinomas [100], multiple myeloma [97] and AML [101]. Bromodomain inhibition as a therapeutic strategy is an important proof-of-concept of the utility of targeting protein–protein interactions to reverse epigenetic alterations in malignancies.

The second member of the family, *MLL2* (also named *KMT2D*), is mutated in the majority of patients with follicular lymphoma (FL) as well as in almost third of DLBCL patients. After translocation t(14;18)(q32;q21), *MLL2* mutation is the most common genetic alteration in FL, present in 89% of patients [76,102]. *MLL2* mutations also appear to cluster with the GCB-like subtype of DLBCLs, where they are present in 24–32% of patients [103]. *MLL2* mutations are associated with loss of *MLL2* expression, yet their mechanism of contribution to lymphomagenesis remains unclear [104]. Further investigation of these mutations using both *in vitro* and *in vivo* methods will hopefully give insights into their role in lymphomagenesis.

MLL3 (also known as *HALR* or *KMT2C*), has been implicated as a tumor suppressor due to its frequent mutations in multiple types of tumors including hepatocellular carcinoma, fluke-associated cholangiocarcinoma, gastric cancer, colon cancer, transitional carcinoma of the bladder, and others [41,105–109]. *MLL3* mutations are frequently nonsense or frameshift, resulting in a truncated protein lacking the SET domain [93]. In colon cancer, *MLL3* mutations are reported in 14–17% of the cases and appear to be associated with increased microsatellite instability (MSI) through an unknown mechanism [110]. Examination of the expression of *MLL3* mRNA in breast tumors revealed reduced expression in cancer tissue in 40% of the samples [111]. Recently, Chen et al. utilized RNAi and CRISPR/Cas9 approaches to validate that *MLL3* is a haploinsufficient tumor suppressor in myeloid malignancies involving 7q deletions [112]. Moreover, this work identified that *MLL3*-deleted AML may be responsive to BET inhibition, a possibility that should be pursued in clinical trials of BET inhibitors in early phase investigation in AML.

5.2. NSD2

The Nuclear receptor-binding SET Domain (NSD) family consists of three members (NSD1–3) which share a SET domain. NSD2 (also known as WHSC1 or MMSET) is a histone methyltransferase which catalyzes mono or dimethylation of unmodified H3K36. Alterations of NSD2 are implicated in different cancers. Aberrant upregulation of this protein results from the t(4;14)(p16.3;q32) translocation

found in 15–20% of MM patients [113]. Global increase in H3K36me2 levels with concomitant decrease in H3K27me3, which results from this upregulation of NSD2, appears to be the dominant mechanism driving NSD2 – associated oncogenic reprogramming [114]. Recently, recurrent NSD2 E1099K mutations were identified in 7.5% of pediatric ALL patients [115]. *In vitro* examination of this mutation revealed global increases in H3K36me2 levels and decreases in H3K27me3, as seen in the overexpression of the enzyme in MM [116]. These discoveries suggest NSD2 as a potential target for development of targeted epigenetic therapy.

Another H3K36 methyltransferase that was implicated with ALL is the H3K36 trimethylase *SETD2*, which is also recurrently mutated in clear cell renal cell carcinoma, gliomas and breast cancer. The mutations recognized so far in this gene are truncation alterations resulted from frameshift or nonsense mutations [93]. In addition, Mar et al. [117] recently identified enrichment of *SETD2* mutations in pediatric ALL at relapse. This suggests involvement of *SETD2* mutations in chemotherapy resistance, and warrants further studies of this gene and its mutation in the context of ALL.

5.3. CREBPP and EP300

CREB-binding protein (CREBPP) and E1A binding protein p300 (EP300) are highly homologous transcriptional coactivators with multiple functions in development and hematopoiesis. They interact with diverse range of transcription factors, acetylate histones and other proteins (such as P53, Rb, and E2F) and affect protein turnover [118,119]. Mutations in *CREBPP* and *EP300*, which are thought to result in their inactivation, are implicated in a variety of cancers. These mutations are mutually exclusive, and for the most part heterozygous which imply haploinsufficiency of these tumor suppressors. *CREBPP* mutations have been described in almost third of the patients in several lymphomas (FL, DLBCL, NHL), and in a lower, yet significant, percentage of patients with lymphoid leukemias and epithelial carcinomas. Mutations in *EP300* were somewhat less frequent but also described in these same disease entities [41,46,76,120–122]. The oncogenic mechanism of these mutations is not yet clear, but as the most frequently mutated region in both proteins is the shared lysine acetyltransferase domain which catalyzes acetylation of histones and other essential proteins, aberrant acetyltransferase activity may be a key feature. *In vitro* studies demonstrated reduced H3K18 acetylation, as well as decreased ability to acetylate P53 and BCL6, in *CREBPP/EP300*-mutated cells [121,122]. Though both *CREBPP* and *EP300*, and their association to cancers, were identified long ago, the effect of these mutations on cancer biology is still being revealed. Due to their multiple functions and diverse interactions, many mechanisms may play a role in the different mutations' effects, some may not be through epigenetic mechanisms.

6. Conclusion

In the last decade, recurrent mutations in nearly every chromatin regulatory complex have been identified in cancer patients. This includes loss- and gain-of-function mutations in genes encoding DNA methylating enzymes, the DNA demethylation machinery, enzymatic complexes which enzymatically modify chromatin, the histone proteins themselves, and proteins which bind to modifications in chromatin. In clear cases of gain-of-function mutations in enzymes, several clinical-grade mutant-selective inhibitors have already rapidly been developed and entered early phase clinical trials. Future efforts to integrate functional genetic studies with epigenomic and transcriptomic profiling may help to delineate

genetic targets responsible for malignant transformation following perturbations in a large host of additional epigenetic modifiers.

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