Chromatin-Remodeled State in Lymphoma

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Abstract

Purpose of Review Emerging evidence has shown that epigenetic derangements might drive and promote tumorigenesis in various types of malignancies and is prevalent in both B cell and T cell lymphomas. The purpose of this review is to explain how the epigenetic derangements result in a chromatin-remodeled state in lymphoma and contribute to the biology and clinical features of these tumors.

Recent Findings Studies have explored on the functional role of epigenetic derangements in chromatin remodeling and lymphomagenesis. For example, the haploinsufficiency of CREBBP facilitates malignant transformation in mice and directly implicates the importance to re-establish the physiologic acetylation level. New findings identified 4 prominent DLBCL subtypes, including EZB-GC-DLBCL subtype that enriched in mutations of CREBBP, EP300, KMT2D, and SWI/SNF complex genes. EZB subtype has a worse prognosis than other GCB-tumors. Moreover, the action of the histone modifiers as well as chromatin-remodeling factors (e.g., SWI/SNF complex) cooperates to influence the chromatin state resulting in transcription repression. Drugs that alter the epigenetic landscape have been approved in T cell lymphoma. In line with this finding, epigenetic lesions in histone modifiers have recently been uncovered in this disease, further confirming the vulnerability to the therapies targeting epigenetic derangements.

Summary Modulating the chromatin state by epigenetic-modifying agents provides precision-medicine opportunities to patients with lymphomas that depend on this biology.

Keywords Chromatin · Lymphoma · Epigenetics

Introduction

DNA, carrying our genetic code, is packaged in the nucleus around histone proteins H1, H2A, H2B, H3, and H4. This tight complex is known as chromatin. Chromatin structure is regulated by two general classes of complexes: those that covalently modify histone tails and those that remodel nucleosomes in an ATP-dependent manner. Together, these classes cooperate to dynamically regulate the structure of chromatin, and thus have essential roles in the control of gene expression, DNA repair, cell division, and apoptosis. Not surprisingly, these processes are often mutated in cancer. Diseases characterized by a chromatin-remodeled state often have inherent resistance to chemotherapy and therefore tend to be highly aggressive.

Epigenetic regulation of the chromatin state and transcription is a dynamic process coordinated by the interplay of multiple complexes working in concert. Three main groups of enzymes and proteins control these processes: writers, erasers, and readers (Fig. 1). Writers include enzymes that add acetyl groups such as histone acetyltransferases (HATs) and methyl groups such as histone and DNA methyltransferases. Acetylation of histone leads to an open, active chromatin state. HAT enzymes that are known to influence the chromatin state in the context of lymphoma are p300 and CBP. New efforts to target HATs are underway. Methylation of histone or DNA can have either an activating or repressive role, depending on the location of the modification. The histone methyltransferase EZH2 is commonly mutated in lymphoma. This

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Fig. 1 Epigenetic regulation of the chromatin state. Three main groups of enzymes and proteins control these processes: writers, erasers, and readers. Me, Fmethylation; Ac, acetylation; Ub, ubiquitination; SWI/SNF, switch/sucrose non-fermentable
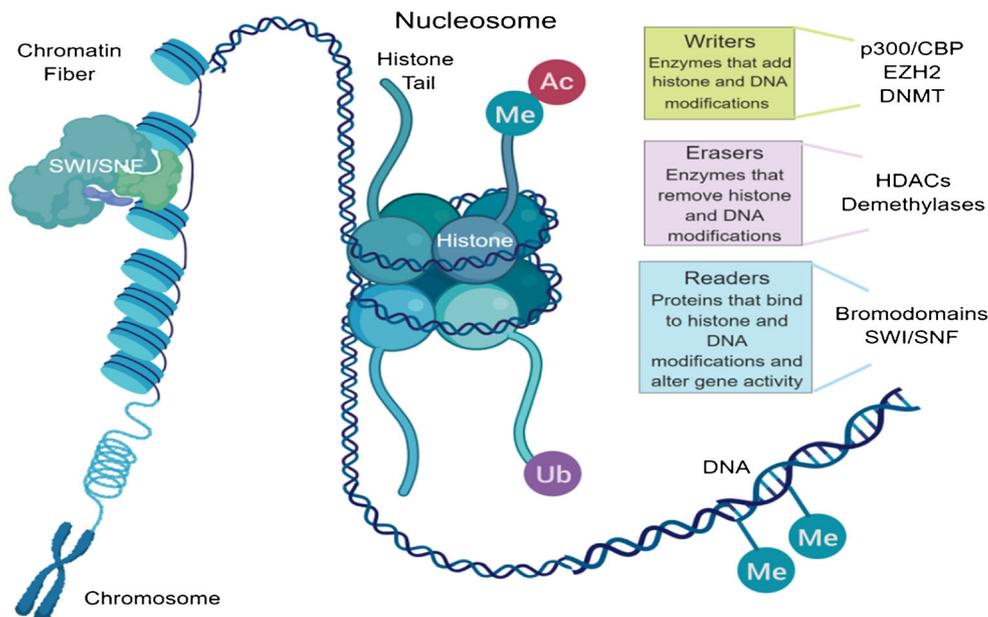
derangement contributes to lymphomagenesis by enforcing trimethylation of histone. Drugs targeting EZH2 are now in clinical development. Erasers are enzymes that remove post-translational marks on histone and DNA. Histone deacetylases (HDACs) are a large family of erasers that remove acetyl groups from histone. Targeting of HDACs with inhibitors leads to increased acetylation on histone. HDAC inhibitors have demonstrated successful clinical application in T cell lymphomas. Readers are proteins that recognize and bind to specific histone acetylation marks. This recognition and binding contribute to chromatin remodeling by co-activating the signal carried by the lysine state. There is a large family of these readers which are called bromodomains. Bromodomains are contained within HAT enzymes and members of the SWI/ SNF complex to name a few. Bromodomain inhibitors are being studied across a broad range of cancers including lymphomas and have shown promise.

Old and new insights into these derangements and their interplay have opened the possibility of directing treatment toward epigenetic processes. By modulating the chromatin state, there is an opportunity to restore normal physiological epigenetic controls and thus reverse malignant phenotypes. Herein, we will discuss epigenetic controls of the nucleosome that lead to a chromatin-remodeled state and methods for targeting specific derangements driving lymphoma.

Histone Lysine Methylation

EZH2

Chromatin modifying gene (CMG) mutations have led to altered effects of key enzymes driving lymphoma. Many of

these enzymes are being studied as therapeutic targets in follicular lymphoma (FL) and diffuse large B cell lymphoma (DLBCL), including CBP, EZH2, and KMT2D (alias, ALR/ MLL2). EZH2 (enhancer of zeste homolog 2) has a multifaceted role as a catalytic histone methyltransferase of histone H3 on lysine 27 (H3K27). It is the catalytic subunit of the polycomb repressive complex 2 (PRC2). The PRC2 contains multiple subunits including EZH2, EED, and SUZ12, and together they play an essential role in transcriptional regulation. There are two PRC2 complexes containing either EZH2 or EZH1 [1]. PRC2 catalyzes trimethylation of H3K27 (H3K27me3) that leads to chromatin silencing, suppressing the expression of genes regulating cell proliferation and differentiation in the normal physiologic state (Fig. 2). EZH2 activity is upregulated during the germinal center (GC) reaction, where B cells undergo somatic hypermutation; this allows DNA damage to go unchecked and prevents programmed cell death. Abnormal, hyperactive PRC2 activity as identified in lymphomas has been attributed to trimethylation of histone [2]. This enforces a condensed chromatin state that prohibits normal transcriptional processes from occurring. Alterations in EZH2 at Ala677 and Tyr641 have been recognized in both FL and DLBCL [3]. As a subunit of the PRC2 complex, EED brings the N-terminal activation loop of EZH2 proximal to the catalytic SET domain; together, these cofactors enable PRC2 basal activity and further contribute to transcriptional repression [4]. In fact, many histone methyltransferases, like MLL2 and EZH2, have been linked to the development of lymphomas, predominantly GC-derived lymphomas, including DLBCL and FL. Several EZH2 inhibitors have been tested in preclinical models, including GSK 343, EPZ-6438, ZLD10A, DZNep, and CPI 1205, as a way of targeting aberrant histone methylation.

Fig. 2 Interplay between EZH2 and MLL2 in normal hematopoietic cells
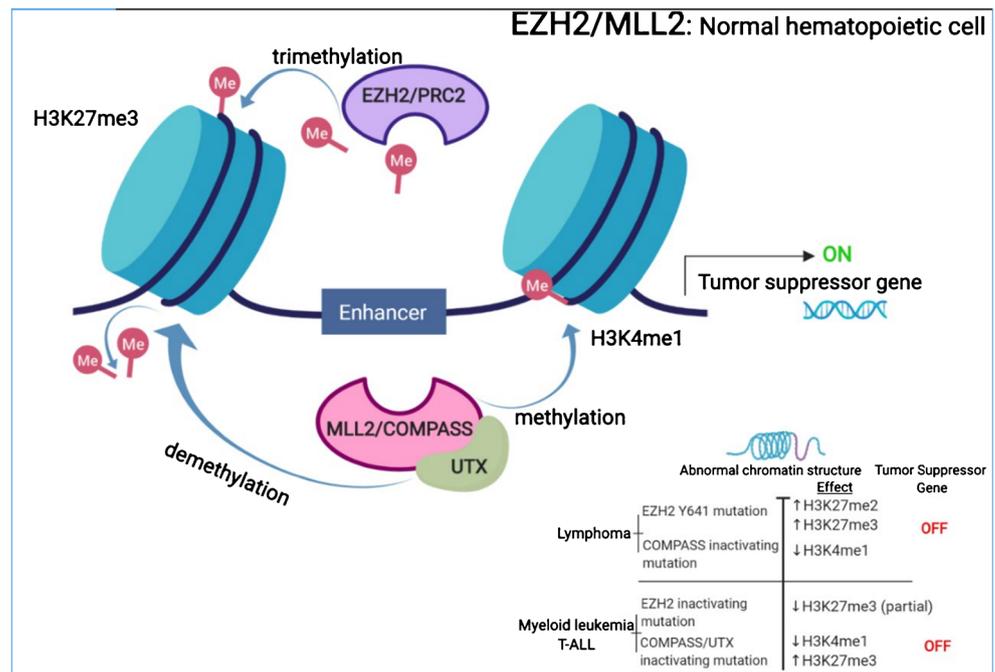
Results conclude that EZH2 inhibitors show strong anti-tumor effects by suppressing the overall methylation of H3K27 and cause an anti-proliferation effect in a concentration and time-dependent manner in DLBCL cell lines [3]. The clinical development of EZH2 inhibitors for the treatment of lymphoma has revealed that EHZ2 is a bona fide target. A phase 2 study of tazemetostat in patients with FL demonstrated an objective response rate in 74% (29/39) of relapsed/refractory patients harboring EZH2 mutations. A complete response was achieved in 10% of the responders. In contrast, the response rate in the wild-type group was only 34%. Stable disease was achieved in both groups at a rate of 26% and 30%, respectively. Tazemetostat was very well tolerated and therefore has a potential role in the treatment of FL [5•].

EZH2 has been found to lead to a chromatin-condensed state even in the absence of its mutational status. In T cell lymphomas (TCL) such as adult T cell leukemia/lymphoma (ATLL), there is immunohistochemistry evidence demonstrating a correlation between increased activity of EZH2 and increased levels of H3K27me3. Additionally, EZH2 upregulation is facilitated by MYC-induced suppression of its regulatory microRNAs (miRNAs) [6]. Both miRNAs, miR-26a and miR-548, are repressed by MYC, which contributes to lymphoma cell survival by silencing EZH2 [7]. Furthermore, MYC regulation of miRNA expression is further supported by miRNA array data showing that EZH2 inhibition induced expression of a number of MYC-regulated miRNAs [7].

With that in mind, in TCL cell lines, the EZH2 inhibitor, DZNep, in combination with daunoblastine inhibited cell growth and increased apoptosis by decreasing EZH2 protein expression levels [8]. Moreover, the inhibitor DS-3201b,

targeting EZH1 and EZH2, has shown anti-tumor activity in 80% of TCL patients with an overall response rate of about 53% [9]. Taken together, the in vitro and clinical data demonstrate the effectiveness of the inhibiting EZH2 in TCL, which may be a therapeutic target in these diseases.

In addition, the EZH2 protein has been demonstrated to be overexpressed in mantle cell lymphoma (MCL). This has led to abnormal methylation patterns on H3K27me3, which is thought to be linked to proliferation of MCL cell lines [10]. This suggests that MCL cell lines may be susceptible to EZH2 inhibition despite not possessing the mutations in EZH2. Recent studies have demonstrated that treatment with GSK 343 inhibited binding between EZH2 and its cofactor EED in MCL cell lines. To analyze the outcome of EED inhibition alongside EZH2, an immunoprecipitation was performed on transfected cells overexpressed with EED and EZH2, which revealed that it caused an increase in cell proliferation and resulted in increased H3K27 trimethylation [10]. Exposure to the EZH2 inhibitor, GSK 343, significantly inhibited cell growth (more than 90%) at 20 μM concentration in the MCL cell lines Mino, Granta, and Z138 [10]. Together, these outcomes propose that wild-type EZH2 is an epigenetic target for MCL. Although EZH2 inhibition has been correlated with a greater cytotoxic impact on mutated EZH2 in the setting of DLBCL and FL, this example seen with MCL indicates that lymphomas with wild-type EZH2 may also have sensitivity to EZH2 inhibitor agents [10].

In our laboratory, we studied the impact of combining EZH2 inhibition and pan-HDAC inhibition. Our hypothesis was that dual epigenetic targeting would induce greater modulation in the histone state and therefore lead to increased

programmed cell death. The combination exhibited synergy in lymphoma cell lines with both EZH2 mutations as well as wild-type EZH2 cell lines with overexpression of the enzyme. The combination of EZH2 and HDAC inhibitors led to both modification of acetylation and methylation of H3K27. Additionally, the combination disrupts the PRC2 complex possibly due to acetylation of the RBAP subunit [11•]. With combined increased histone acetylation induced by HDAC inhibition and reduced histone methylation induced by EZH2 inhibition, chromatin is likely less compact and more accessible allowing for the expression of differentiation factors and tumor suppressors.

MLL2

Chromatin modifying genes play an essential part in modifying normal B cell differentiation programs and inhibiting germinal center exit [12]. The mutated KMT2D (MLL2) gene is frequently found in FL (approximately 72% of cases) and in a lower frequency found in DLBCL (approximately 24% of cases) [12]. Among the mixed lineage leukemia (MLL) family of proteins, KMT2D has a role in the SET1 methyltransferases through the methylation of histone 3 lysine 4 (H3K4).

KMT2D also functions as a scaffolding protein. It forms a complex with H3K27 demethylase UTX. The mutations of KMT2D, which are frameshift or stop codons, are deleterious to protein abundance and function. This results in the loss of KMT2D and subsequently leads to a reduction of the KMT2D/KMT2C-UTX complex. This KMT2D-UTX complex is responsible for the removal of trimethylation of H3K27. Because KMT2D is part of the complex, the loss of KMT2D leads to the accumulation of H3K27me3 (Fig. 3) [12]. Like EZH2, KMT2D protein's function is responsible for cell differentiation and embryonic development. KMT2D gene deletion increased levels of sister chromatid exchange, gross chromosomal aberrations, and micronuclei [13, 14]. This is an example of opposing effects of histone methylation on chromatin status.

The first gene in this family, KMT2A (alias, MLL1), was initially discovered because of its translocation (11q23 with more than 80 different partners) in a majority of lymphoid and myeloid leukemias arising in infants [15]. These translocations generate fusion proteins that aberrantly activate oncogenes such as HOXA9 and EV11 [16, 17]. Many of the MLL translocation partners such as ENL, AF9, AFF1, and AFF4 are found in a super elongation complex (SEC) with elongation factors eleven-nineteen Lys-rich leukemia (ELL) and the RNA polymerase II elongation factor P-TEFb [18]. MLL2KMT2D expression is controlled in part by PTEFbP-TEFb following the misrecruitment of SEC to MLL target genes, perturbing transcription elongation checkpoints at these loci, and resulting in leukemic pathogenesis. Accordingly, in preclinical models, CDK9/PTEFbP inhibitors

have shown efficacy in MLL rearranged models of AML [19]. Further evaluation in lymphomas with MLL2 mutations may be merited.

DOT1L

Disruptor of telomeric silencing 1-like (DOT1L) is the only known H3 lysine 79 (H3K79) methyltransferase in mammals. Genetic silencing of DOT1L leads to complete loss of H3K79 methylation, which affects mitotic spindle formation and cell cycle progression. Genome-wide analysis has demonstrated H3K79 methylation is a marker of active euchromatin and highly correlated to transcriptional activity [20, 21]. The efficacy of DOT1L inhibition has been reported in AML preclinical models. The DOT1L-containing complex is present as a frequent translocation partner of MLL fusions in AML, which have aberrant H3K79 methylation patterns. Pinometostat (EPZ-5676), a DOT1L inhibitor, is currently being evaluated in clinical trials in AML. It demonstrated sensitivity in AML models harboring recurrent mutations of IDH1/2 and DNMT3A. Given these mutations are also frequent in T cell lymphomas, it would be interesting to determine the vulnerability of TCL to the DOT1L inhibition. Thus far, pinometostat has been shown to decrease cell viability in PTEN-inactivated TCL preclinical models [22, 23].
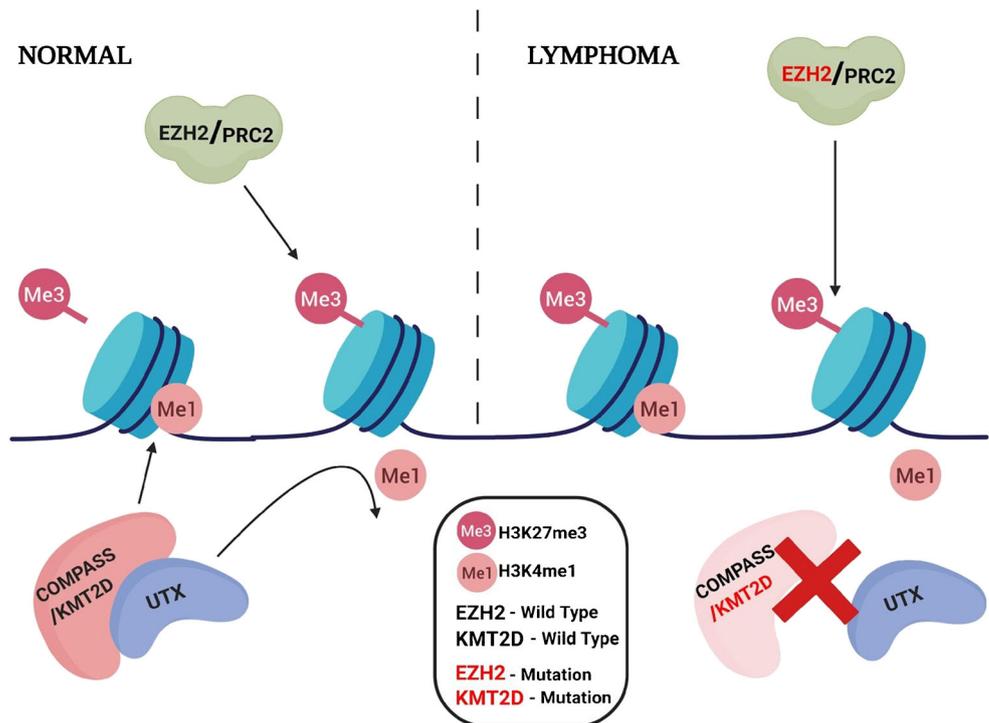
Histone Acetylation

Histone Acetyltransferases

CBP/p300

The acetylation of histone lysine residues is a dynamic process regulated by the balance between the activity of histone acetyltransferases (HATs) and histone deacetylases (HDACs) [24]. Acetylation mediated by HATs leads to an open chromatin structure and recruitment of bromodomain protein "readers" to induce an open chromatin state and subsequent transcriptional activation [25, 26]. Besides altering histone acetylation patterns, HATs also acetylate and affect the activity of non-histone substrates that directly regulate transcription, including a diverse array of transcription factors [27]. Choudhary and colleagues discovered 1750 proteins in addition to histones are modified by lysine acetylation in leukemia cells, indicating that HATs play widespread roles in regulating cellular activities [28].

Among 17 HATs in four different HAT families, CBP and p300 are the best-characterized HATs in relation to lymphomas. Several studies have demonstrated that HAT proteins CBP and p300 act as tumor suppressors in B cell lymphomas. CBP and p300 function as co-activators of transcription factors and acetylation proteins relevant to lymphomagenesis,

Fig. 3 As part of the COMPASS complex, KMT2D has a role as a SET1 methyltransferase leading to the mono-methylation of H3K4, which opposes H3k27me3. UTX, part of the KMT2D/COMPASS complex, is a demethylase responsible for the demethylation of H3K4. Removal of the H3K4 methyl group allows for trimethylation of H3K27me3 by the EZH2/PRC2 complex

such as p53, NF-kB, BCL6, and Hsp90 [29, 30, 31••, 32]. Inhibition of BCL6 induces p300 expression and acetyltransferase activity, which is lethal to DLBCL cells [31••].

Multiple findings suggest that histone acetylation has a key role in lymphoid malignancies and particularly in germinal center–derived tumors. Mono-allelic inactivating mutations in CREBBP harbor frequently in 39% in a cohort of 134 DLBLCs, and 33% and 68%, respectively, in another 2 different studies of follicular lymphoma (FL) as well as in 17% of ocular marginal zone lymphoma [33, 34••]. Less commonly, somatic mutations truncating or disrupting the HAT domain of p300 were identified in 20% of ATLLs [35], 10% in 2 different studies of DLBCLs [31••, 34••], and 9% in a cohort of above 46 FLs [34••]. CREBBP mutations are relatively rare in PTCL and other T-lymphoid malignancies compared with B cell lymphomas [36–39]. CREBBP mutations cluster within the substrate-binding pocket and decrease the affinity for acetyl-CoA, resulting in a reduction of acetylation in the H3K18 and H3K27 residue [40]. The reduced histone acetylation changes the electrical charge of the core histone, and thereby transforms chromatin structure to a resting closed conformation and less accessible to transcriptional factors. Pasqualucci and colleagues discovered that mutated CBP led to the impaired ability to acetylate BCL6, a transcriptional repressor and master regulator of the germinal center. Acetylation of BCL6 abrogates its effects, whereas the lack of acetylation allows for transcriptional repression imposed by BCL6 [34••]. Activated BCL6 can recruit PRC1-like BCOR complexes and SMRT/HDAC3 complexes in B cell promoters to

most effectively repress transcription and deacetylate H3K27 resulting in a repressed chromatin environment [41]. In addition, mutations led to impaired acetylation of p53, which compromised its effects as a tumor suppressor. Mutations of CREBBP may be related to chemotherapy resistance. CREBBP mutations were identified in 18% of relapsed pediatric B-acute lymphoblastic leukemia patients but only half of these were present at diagnosis, indicating these mutations may be induced by chemotherapy possibly contributing to chemo-resistance [40]. Although GC-specific loss of CREBBP was insufficient to initiate malignant transformation, compound CREBBP-haploinsufficient/BCL2-transgenic mice, mimicking the genetics of FL and DLBCL, develop clonal lymphomas recapitulating the features of the human diseases. It further suggests CREBBP loss contribute to lymphomagenesis indicating itself as a haplosufficient tumor suppressor in GC-B cells [42]. In FL patients, 94% of CREBBP mutations were identified in progenitor cells indicating they are early event in the genomic evolution of FL. CREBBP mutant FLs have significantly lower expression of HLA class II and thus less number of infiltrating T cell compared with wild-type tumors, suggesting CREBBP mutations play a role in promoting immune invasion in FL [43].

Loss of function of HAT genes in germinal center–derived B cell lymphomas shifts the balance toward a condensed chromatin state and transcriptional repression of differentiation genes. HAT mutations are mono-allelic suggesting that their activity could be restored if the wild-type allele's function can be enhanced in some way, providing a strong rationale to

induce HAT activity through therapeutic approaches. HAT activators have been reported [44, 45], but their therapeutic application has been limited by their lack of solubility and membrane permeability. We recently reported a HAT activator [46]; YF2 induces p300-mediated acetylation of histone and p53 and demonstrates selective cytotoxic effect in EP300-mutated DLBCLs. We observed strong synergistic effect when combining HAT activator with HDAC inhibitor in vitro and in vivo [46]. Conversely, CBP/p300 has been detected in several oncogenic fusions and acts as co-activator for leukemogenic proteins in leukemia. In line with this, a CBP/p300 bromodomain inhibitor, I-CBP112, impairs aberrant self-renewal of leukemic cells [47]. More recently, a second p300/CBP inhibitor, A-485, targeting the catalytic domain of p300/CBP, demonstrated potent activity in a subset of multiple myeloma, acute myeloid leukemia, and non-Hodgkin's lymphoma cell lines [48]. However, it is unclear if the killing effect of the compounds is associated with HAT mutation status and the long-term effect of the treatment. Taken together, these preclinical data point toward the potential therapeutic advantage to targeting HAT enzymes in hematologic malignancies.

MYST Family (TIP60, KAT6A)

Among the genes coding for the MYST family of KATs (KAT5–KAT8), the acetyltransferases implicated in lymphoma include TIP60 (alias, KAT5) and KAT6A (alias, MYST4, MOZ). Tip60 is a haploinsufficient tumor suppressor which suffers mono-allelic loss and reduced expression in a small fraction of FLs and DLBCLs. The key function of Tip60 is to protect cells from genomic instability and to suppress potential transforming events which can lead to cancer. Tip60 participates in two pathways, chromatin modeling at DNA-strand double breaks (DSBs) via NuA4-Tip60 complex and acetylation and activation of the ATM kinase. The NuA4-Tip60 complex acetylates histones H2AX and H4 at DSBs, modifying the chromatin structure to facilitate DSB repair. In line with it, the haploinsufficiency of Tip60 accelerates the tumor development in Eμ-myc mice and abrogates a MYC-induced DNA damage response [49].

KAT6A has an essential role in normal hematopoietic stem cells [50–52]. Chromosomal translocation of this gene with CREBBP has been identified in multiple cancer types, indicating it is the oncogene [53, 54]. Loss of one allele of KAT6A prolongs the median survival of mice with MYC-induced lymphoma from 103 to 413 days [55], indicating that the progression of lymphoma is highly dependent on KAT6A. A KAT6A inhibitor, WM-1119, demonstrated significant anti-tumor efficacy in a xenograft model of lymphoma [56]. Although inhibition of KAT6A may provide a therapeutic benefit in lymphoma, careful study will be required to determine if KAT6A contributes to lymphomagenesis via aberrant chromatin acetylation state.

GCN5 Family (PCAF)

Histone acetyltransferase PCAF belonging to the GCN5 family regulates various epigenetic events for transcriptional regulation through alterations in the chromatin structure. Kikuchi and colleagues revealed that Bcl-6 and Pax5 were downregulated in PCAF-deficient immature B cell line DT40 cells. PCAF-deficiency caused remarkable decrease in acetylation levels of both H3K9 and H3K14 residues within chromatin surrounding the 5′-flanking regions of Bcl-6 and Pax5 genes in vivo [57]. It suggests that PCAF is essential in epigenetic regulation in transcription factors for normal development of B cells.

HDACs

Human HDACs are categorized into four major groups based on sequence homology to yeast proteins and function: class I (HDAC1, HDAC2, HDAC3, and HDAC8); class II (HDAC4, HDAC5, HDAC6, HDAC7, HDAC9, and HDAC10), class III (NAD-dependent protein deacetylase sirtuin 1 (SIRT1)–SIRT7); and class IV (HDAC11) [58]. HDACs generally act as transcriptional corepressors by deacetylating nucleosomal histones, which can lead to chromosomal condensation and the exclusion of transcriptional activating complexes [59, 60]. In addition, large HDAC-containing repressor complexes can localize to specific gene loci and exclude activating molecules from interacting with transcriptional factors.

Mutations in genes encoding HDACs have not been found in any B and T cell lymphoid malignancies. However, non-mutant HDACs have been reported to be dysregulated (usually increased) in various types of leukemia and lymphomas [61]. HDACs tend to be recruited by oncoproteins to support repressive malignant gene expression. For example, multiple studies demonstrated that the inhibition of HDAC induces apoptosis in cancer cells by modulating the expression of c-myc and BCL2 family proteins [62–65]. Several HDAC inhibitors (vorinostat, romidepsin, panobinostat, belinostat) are currently approved by the FDA for relapsed T cell lymphomas or in combination for multiple myeloma [66–70]. Despite approval in T cell lymphoma, single-agent HDAC inhibitors have demonstrated limited activity in relapsed DLBCL. Our previous work has demonstrated that the combination of niacinamide, a sirtuin inhibitor, and HDAC inhibitors (romidepsin, vorinostat, belinostat, or panobinostat) leads to synergistic cytotoxicity in GC-DLBCL but not in ABC-DLBCL [71]. Following exposure to romidepsin and niacinamide, mouse lymphoid tissue demonstrated acetylation of both Bcl6 and p53 as well as modulation of downstream targets BLIMP1 and p21. This proof-of-principle study

demonstrates a potential role of combined HDAC inhibition therapy in B cell lymphomas [71]. In addition, it suggests that the cumulative epigenetic derangements of GC-DLBCL may be amenable to targeted therapy through modulation of the acetylation state.

Given the conversely biological effect of HDAC and HAT, it is intriguing to determine if the presence of HAT mutations can predict the clinical activity of HDAC inhibitors. In B cell lymphoma, HDAC inhibitors have been shown to rescue deficits in histone acetylation induced by EP300/CREBBP mutations [72]. Although in other studies, the sensitivity to romidepsin was not associated with HAT mutation status in a panel of lymphoma cell lines [11•]. The HDAC inhibitor chidamide has shown favorable efficacy in PTCL-NOS patients bearing EP300/CREBBP mutations [39], indicating such mutations may alter the protein function on chromatin state regulation, sensitizing PTCL-NOS patients to HDAC inhibitors. PTCL-NOS commonly displays mutations in genes involved in histone methylation and acetylation. The presence of histone modifier gene mutations was associated with decreased progression-free survival in a cohort of 125 PTCL-NOS patients. PTCL-NOS cells were shown to experience growth inhibition when treated with a HDAC inhibitor, chidamide, and a DNA methyltransferase (DNMT) inhibitor decitabine, both in vitro and in vivo [39]. Dual therapy enhanced the interaction of KMT2D with the transcription factor PU.1, consequently inactivating the MAPK, which tends to be constitutively activated in TCL. PU.1 interacts with DNMTs to control hematopoiesis and suppress leukemia, via the histone modifier KMT2D. In addition, clinical response to HDAC inhibitors is strongly associated with a concurrent gain in chromatin accessibility in CTCL. HDAC inhibitors cause distinct chromatin responses in leukemic and host CD4+ T cells, reprogramming host T cells toward normalcy [73•].

BET

Bromodomains are protein motifs that recognize and bind to acetylated lysine moieties located on histone tails. BETs consist of two amino-terminal tandem **b**romodomains and an **e**xtra-**t**erminal (non-bromodomain) region. The BET family includes BRD2, BRD3, BRD4, and bromodomain testis-specific protein. Upon binding to the acetylated lysine residues on histones, BETs promote gene transcription either directly by recruiting and stabilizing transcription effectors or indirectly by interacting with gene super enhancers [74]. Therefore, BETs contribute to the tumor development and progression by activating and potentiating the expression of key oncogenes.

Although BET mutations or translocations are rare, the overexpression of BETs is common [75]. Consequently, BET inhibition has been demonstrated to be effective in preclinical studies in different types of cancers, including breast, ovarian, neuroendocrine, glioma, sarcoma, and hematological malignancies [76–80]. In B cell lymphomas, BRD4 was found to preferentially bind in the proximity of critical lymphoma-related oncogenes, such as c-Myc and CD79B, and enhancers essential for B cell fate determination, such as Pax5 and IRF8 [81]. BETs activate the MYC oncogene and the BCL2 anti-apoptotic signaling pathways. The BET inhibitor, JQ1, results in a decreased expression of MYC in myeloma cells [82]. JQ1 has also been shown to prolong the survival duration of xenograft models of MYC-driven lymphoma, including those that were resistant to etoposide and those carrying TP53 deletions [83]. In patients with double-hit DLBCL, resistance to venetoclax can be overcome by administration of the BET inhibitor CPT-203, likely due to downregulation of BCL2-like-protein (BFL1) [84]. High concentration of BRD4 has been observed in the site of super enhancers known to regulate genes involved in B cell receptor signaling pathways as well as that of genes with oncogenic effects in CLLs. BET inhibition was further shown to downregulate the expression of those genes and reduce tumor burden in vivo [75]. BET proteolysis-targeting chimeras (PROTACs) are hetero-bifunctional compounds which induce the profound deletions of BET proteins by promoting their ubiquitylation through E3 ligases. They have been shown to work more effectively than BET inhibitor (OTX015) in ibrutinib-resistant mantle cell lymphoma [85]. In the context of T cell lymphomas, BET inhibition by JQ1 resulted in the downregulation of c-myc expression, induced cell cycle arrest in vitro, and inhibited tumor growth in vivo [86]. OTX015, an oral BRD2/3/4 inhibitor, induced cell cycle arrest in 5/8 ALCL cell lines. ALK status had no impact on likelihood of response. OTX015 was found to suppress the transcription of the MYC gene in 4/4 cell lines [87]. Moreover, several other BET inhibitors were found synergistically induced cell death in combination with HDAC or BCL2 inhibition in 4 CTCL cell lines. MYC and BCL2 expressions were repressed when CTCL cells were treated with JF1 and HDAC inhibitors, indicating cooperative activities at the level of epigenetic regulation [86].

Higher Order Chromatin Structure

SWI/SNF

Among the families of ATP-dependent chromatin remodelers, SWI/SNF chromatin-remodeling complex (also known as BAF complex) was originally described (in yeast) as the complex is critical for cellular responses to mating type switching (SWI) or sucrose fermentation (SNF) [88, 89]. SWI/SNF complex containing more than 15 subunits [90–92] utilizes the energy from ATP to remodel chromatin by shuffling nucleosomes along the DNA [93]. [93]. It is capable in regulating the accessibility of DNA to other proteins involved in

replication or repair as well as allowing for the activation or suppression of gene expression [94].

Specific inactivating mutations in subunits of SWI/SNF chromatin-remodeling complexes occur at a high frequency in several types of cancer [93, 95–98], including SNF5 (alias, SMARCB1, INI1, and BAF47), ARID1A (alias, BAF250A, and SMARCF1), BRM/SWI2-related gene 1 (BRG1; alias, SMARCA4), and BCL7A/B/C subunits (Table 1). Mutations of these genes are largely mutually exclusive and are commonly small deletions that introduce stop codon or frameshift resulting in loss of function in protein [99]. In detail, loss of SNF5 was first described in rhabdoid sarcomas [95, 96] and the list of SNF5-deficient tumors has since expanded to include several types of cancers [93, 98]. Notably, conditional knockout of SNF5 in mice results in mature CD8+ T cell lymphoma or rare rhabdoid tumors with a median onset of only 11 weeks, indicating SNF5 is a bona fide tumor suppressor [100]. In addition, *ARID1A* is the most commonly mutated subunit. In the context of Burkitt lymphoma, truncated mutations in ARID1A were observed in 17% of 29 cases [101]. Krysiak and colleagues identified recurrent mutations in 9 SWI/SNF complex genes affecting 32 (30.5%) patients in a cohort of 105 follicular lymphoma patients at mutation frequencies ranging from 0.95 to 19.4% [102]. Among these was ARID1A (5.7%), a modifier gene in the m7-FLIPI associated with longer failure-free survival [103].

SMARCA4 mutation was observed significantly more frequently in endemic Burkitt lymphomas harboring EBV type 2 latency and those without EBV than tumors with EBV type 1 latency, whereas ARID1A was mutated in roughly equivalent levels in either categorization [99]. BCL7A-MYC

translocation has been previously reported in a Burkitt lymphoma cell line [104]. Overexpression of BCL-7A was associated with germinal center-DLBCL.

In a cohort of 24 mantle cell lymphoma patients, chromosome 9p21.1-p24.3 loss and/or mutations in components of the SWI-SNF chromatin-remodeling complex, i.e., SMARCA2, ARID2, and SMARCA4, were present in all patients who were primarily refractory to ibrutinib plus venetoclax treatment and two-thirds of patients with relapsed disease [105]. Interestingly, SMARCA4-deficient and ARID1A-mutant cancers are particularly vulnerable when the other components of SWI/SNF complex are inhibited [106, 107]. This implication points to the rationale of combinatorial therapeutic approaches targeting these components in lymphoma and other disease harboring these mutations.

EZB-GC-DLBCL was recently defined as a distinct subtype of DLBCL, which has a worse prognosis than its former designation of GC-DLBCL [108••]. The signature includes discrete genetic signatures including BCL2 translocation and mutations of EZH2, CREBBP, EP300, TNFRSF14, KMT2D, and MEF2B [108••]. Mutations of two SWI/SNF complex genes, ARID1A and BCL7A, were enriched in this subtype of patients.

Inactivating mutations of members of the SWI/SNF complex lead to unfettered activity of EZH2 and the PRC2 complex. Both disruption of the PRC2 complex and inhibition of the EZH2 SET domain have been demonstrated to lead to cellular demise in cell lines harboring mutations in the SWI/SNF complex [109]. Consistently, tumors carrying SWI/SNF inactivating mutations are particularly vulnerable to genetic and pharmacological inhibition of PRC2 [110, 111]. This

Table 1 Frequency of chromatin modifying and organizing gene mutations in B cell and T cell lymphomas. Data from genome, exome, and transcriptome sequencing studies of FL [43, 113, 114, 116, 117•, 119], BL [99, 120], DLBCL [34••, 117•, 118•, 121, 122], and TCL [35, 123] with sufficient data quality are summarized

Epigenetic modifiers	Function	Mutation frequency				Mutation type	Protein activity	Histone state (as a consequence of mutations)
		FL, % [43, 114, 116]	GCB-like, %	BL, %	TCL, %			
EZH2	H3K27 methyltransferase	25	15–20 [117•]	2	ATLL, 3 CTCL, 0	Gain of function	Active	H3K27me3 ↑
KMT2D	H3K4 methyltransferase	72	25 [118•]	2	CTCL, 2	Loss of function	Inactive	H3K4me1/me2 ↓
CREBBP	Lysine acetyltransferase	65	32 [34••]	6	CTCL, 5	Loss of function	Inactive	H3K27ac ↓ H3K18ac ↓
EP300	Lysine acetyltransferase	15	10 [34••]	0	ATLL, 20 [35]	Loss of function	Inactive	H3K27ac ↓ H3K18ac ↓
ARID1A	SWI/SNF component	11	10	7	CTCL,5	Loss of function	Inactive	
SMARCA4	SWI/SNF component	1	10	21	CTCL,5	Loss of function	Inactive	
HIST1H1E	Linker histone	14	17	0	0	Loss of function	Inactive	

has been demonstrated in epithelioid sarcomas, where patients with mutations in *SMARCB1* have an enriched response to EZH2 inhibitors [112].

Linker Histone Genes

Linker histones bind to DNA at the entry and exit sites of the nucleosome, and are generally required to achieve chromatin condensation in the nucleus. Mutations in linker histone family genes (HIST1H1 B-E) are identified as recurrent mutated genes in follicular lymphoma and less frequent in DLBCL [113, 114]. The most commonly mutated linker histone, HIST1H1E, can be methylated at lysine 26 by EZH2 to facilitate the formation of transcriptionally inactive heterochromatin. Linker histone can also recruit DNA methyltransferases and recruitment DNMT3B is impaired by somatic mutations [113]. Inactivating somatic mutations of linker histone genes may lead to greater accessibility of chromatin, which is in opposite effect of heterochromatin formation by activating EZH2 mutations and loss-of-function KMT2D or CREBBP mutations. However, acetylation of HIST1H1E at lysine 34 by GCN5 can also lead to recruitment of TAF1 and promote transcriptional activation, meaning that loss-of-function mutations may have a transcriptionally repressive effect. Given that each of the linker histone family genes may have unique biological function in gene transcription [115], future studies will be required to understand the precise role of these mutations in lymphomas.

Conclusion

Recurrent mutations leading to a chromatin-remodeled state have been identified as pathogenic in lymphoma. These mutations can occur across multiple enzyme mechanisms affecting the control of chromatin condensation. As such, there is likely not one Achilles heel in these diseases. New therapies targeting histone methyltransferase, deacetylases, and bromodomains have successfully targeted each of these individual derangements. Clinical therapeutic success will likely be best achieved with combined targeting of these epigenetic derangements.

Compliance with Ethical Standards

Conflict of Interest Dr. Amengual declares that she has received a grant from Appia Pharmaceuticals and has been paid to speak by Epizyme. Dr. Yuxuan and Dr. Rosario have no conflicts to disclose.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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