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REVIEW ARTICLE

Epigenetic alterations and advancement of lymphoma treatment

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Abstract

Lymphomas, complex and heterogeneous malignant tumors, originate from the lymphopoietic system. These tumors are notorious for their high recurrence rates and resistance to treatment, which leads to poor prognoses. As ongoing research has shown, epigenetic modifications like DNA methylation, histone modifications, non-coding RNA regulation, and RNA modifications play crucial roles in lymphoma pathogenesis. Epigenetic modification–targeting drugs have exhibited therapeutic efficacy and tolerability in both monotherapy and combination lymphoma therapy. This review discusses pathogenic mechanisms and potential epigenetic therapeutic targets in common lymphomas, offering new avenues for lymphoma diagnosis and treatment. We also discuss the shortcomings of current lymphoma treatments, while suggesting potential areas for future research, in order to improve the prediction and prognosis of lymphoma.

Keywords Epigenetics · Lymphoma · Pathogenesis · Epigenetic drugs · Therapeutic advances

Background

Lymphoma, a malignant tumor group, originates from lymph nodes and extralymphatic tissues [1]. There are two categories: Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL). HL, which constitutes approximately 5 to 10% of lymphomas, branches into classical and nodular lymphocyte-predominant types. In contrast, NHL is further divided into B cell, T cell, and natural killer (NK) cell types [2]. The most prevalent type of aggressive NHL is diffuse large B cell lymphoma (DLBCL) [3], accounting for approximately 40% of adult NHL in China [4]. The most common type of low-grade lymphoma, follicular lymphoma (FL), represents 2.5 to 6.6% of NHL in China [5]. According to a survey [6], in 2020, there were 544,352 new NHL cases globally, ranking it 13th in terms of new malignant tumor cases worldwide, with 55.9% of cases in males and 44.1% in females. Its overall mortality rate was 28.1%. There were 83,087 HL cases (males: 59.1%; females: 40.9%), with an overall mortality rate of 47.7%. Each lymphoma type differs in pathogenesis, clinical manifestations, treatment modalities, and prognosis assessment [7]. Therefore, lymphoma treatments need to be tailored according to the patient's age, physical condition, clinical stage, pathological type, and molecular genetic characteristics [8].

Recently, targeted therapies for lymphoma have seen significant expansion [9]. B cell lymphoma (BCL)–targeted therapies include rituximab targeting CD20, chimeric antigen receptor–modified T cell (CAR-T) therapy targeting CD19, targeted small-molecule drugs such as ibrutinib [10], and therapies targeting the tumor microenvironment like bortezomib and lenalidomide [11]. The first-line treatment for common lymphomas remains cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) or a CHOP-like regimen (CHOEP) [12]. However, due to drug resistance, some patients do not respond well,

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leading to high failure and relapse rates [13]. Hematopoietic stem cell transplantation (SCT) has become a vital tool for treating relapsed/refractory (R/R) lymphoma. Notwithstanding, the source and quality of hematopoietic stem cells, along with their post-transplantation developmental and functional status, are still limiting outcome factors [14]. Therefore, finding new lymphoma treatment targets and developing new, more effective drug combinations are critical for reducing lymphoma relapse and mortality rates.

Epigenetic modifications play a significant role in hematological tumor cell regulation [15]. Epigenetics encompasses heritable modifications that alter gene activation, independent of nucleotide sequence changes. These include DNA methylation, histone modifications, non-coding RNA regulation, and RNA modifications. They mediate gene transcription and translation changes, regulate gene expression, and play a role in trait inheritance and disease pathology [28].

The term "epigenetic landscape," introduced by Waddington in 1939, describes the mechanisms of translating genetic traits into phenotypes [29]. Recently, epigenetics has become a key research area, aiming to understand how social conditions, the environment, psychosocial factors, and nutrition can impact gene expression [30]. Numerous studies have demonstrated that epigenetics is crucial to lymphoma development and progression. DNA methylation and histone modifications have been implicated in tumor pathogenesis and are considered important targets for treating different types of lymphoma and many other tumors (Fig. 1) [31]. Furthermore, epigenetic targets have shown promising therapeutic results in clinical treatment [32]. For instance, DNA methylation–blocking antibodies have been developed, and combinations of drugs like decitabine, a DNA methylation

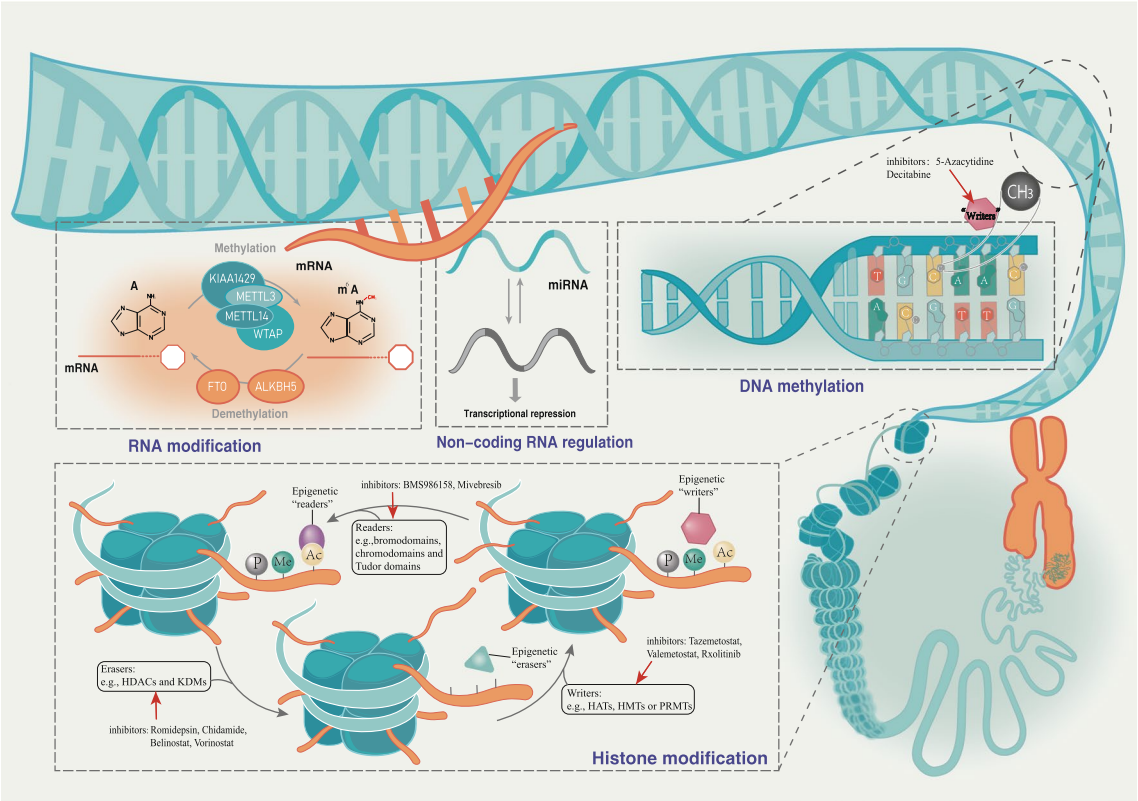

Fig. 1 Epigenetic mechanisms and treatment schemes in lymphoma. The pathogenesis of lymphoma is multi-disciplinary. Here, four epigenetic abnormalities associated with the lymphoma development are displayed: histone modifications (mainly including histone methylation and histone acetylation), DNA methylation, non-coding RNA regulation, and RNA modifications. Among them, DNA methylation mainly involves the selective addition of methyl to cytosines at specific sites on the DNA sequence, catalyzed by DNA methyltransferases (DNMTs), to form 5-methylcytosine. It regulates gene expression by recruiting proteins involved in gene repression or inhibiting the binding of transcription factors to DNA, causing further development and progression of lymphoma. In the histone modification, aberrant histone modifications can be reversed by inhibiting the activity of histone methyltransferases (HMTs) and histone deacetylases (HDACs), which then further inhibit tumor cell proliferation and induce apoptosis. The red arrows represent epigenetic-based approaches for lymphoma treatment. For example, in the DNA methylation, DNMT inhibitors azacitidine and decitabine are representative drugs. In terms of histone modifications, drugs like romidepsin, chidamide, and tazemetostat have been approved by the Food and Drug Administration (FDA) for some specific types of lymphoma

inhibitor, and chidamide, a histone acetylase inhibitor, can significantly inhibit lymphoma progression [9]. Current therapeutic approaches for the cancer epigenome include FDA-approved therapies and investigational agents in clinical trials. These target regulators of histone acetylation, histone methylation, DNA methylation, and histone phosphorylation (Table 1). This review focuses on the research progress on epigenetic modifications, their roles in the pathogenesis, and targeted therapy of common clinical lymphomas.

DNA methylation and lymphoma

DNA methylation predominantly involves the selective addition of a methyl group to cytosine (C) at certain points within the DNA sequence. This process is facilitated by DNMTs to form 5-methylcytosine (5mC). This resultant structure, 5mC, is involved in the regulation of DNA binding, either through recruiting proteins that suppress gene expression or by preventing the expression of transcription factors [33]. The primary enzymes known for transferring methylation are DNMT3A, DNMT3B, and DNMT3L, which are responsible for the initial methylation process. DNMT1, another vital enzyme, maintains the methylation patterns [34]. DNA methylation, one of the most intensely studied epigenetic alterations in mammals, aids in precise gene control and long-term gene silencing [35]. Throughout development, the patterns of DNA methylation within the genome undergo dynamic changes through a balance of methylation and demethylation processes [36]. Therefore, differentiated cells generate stable and unique DNA methylation patterns that control gene transcription specific to certain tissues [37].

It is widely recognized that hypermethylation within promoter regions results in the inactivation of particular oncogenes, with DNMTs having a critical role in the progression of lymphoma [38]. In some lymphomas associated with the Epstein-Barr virus (EBV), there are significantly high levels of genomic DNA methylation, which are connected to a decrease in tumor suppressor gene expression. Consequently, intentional reduction of DNA methylation levels could potentially stimulate viral gene expression, exposing the cells to the immune system. Additionally, this process could enhance tumor suppressor gene expression, possibly inhibiting cancer cell growth or inducing apoptosis. As such, understanding the regulation of DNA methylation levels could pave the way for novel therapies for EBV-associated lymphoma [39]. Dalton et al. [40] have illustrated the potential of decitabine in driving viral genome hypomethylation, resulting in the re-expression of immunogenic viral genes in lymphoma cells associated with EBV. However, it is important to note that not all EBV genomes reactivate in all lymphoma cells. Epigenetic drugs are occasionally combined with T cell therapy to boost the expression of tumor antigens that bind to identical T cell receptors. For instance, decitabine and 5-azacytidine are potent stimulants of immunogenic EBV antigens in EBV-associated tumors at latent stage I. A combination of decitabine and EBV-CTL results in T cell homing to the tumor and the suppression of tumor growth in a Burkitt lymphoma (BL) xenograft model.

Guo et al. [41] conducted a genetic screen in both EBV and BL cells and discovered the UHRF1 protein, containing ubiquitin-like, PHD, and RING finger domains, and its chaperone DNMT1 to be crucial in controlling the expression of EBNA and LMP. They further found that the levels of UHRF1, DNMT1, and DNMT3B are elevated in germinal center (GC) B cells, which are the origin cells of BL. This provides a molecular connection between B cell status and EBV latency. In preclinical models of T cell lymphoma, the inhibitors of DNMTs and HDACs demonstrated synergy in vitro. The theoretical combination of azacytidine (AZA) and romidepsin (ROMI) could stimulate the expression of multiple cancer testis antigens (CTAs), thereby increasing tumor immunogenicity. In a multicenter phase II clinical trial, Falchi et al. reported that the combination therapy with AZA and ROMI was both safe and effective for treating peripheral T cell lymphoma (PTCL), particularly for patients who are treatment-naive (TN) and T follicular helper (TFH) cells. Consequently, AZA and ROMI could be adopted as a first-line combination therapy for PTCL and R/R PTCL, as well as a bridging therapy [16].

Histone modifications

The role of histone modifications in lymphoma pathogenesis

In eukaryotic cells, genetic information stored in DNA exists in a well-structured chromatin organization. The fundamental unit of chromatin is the nucleosome, comprising a histone octamer and 146–147 nucleotide base pairs. Post-translational modifications including acetylation, methylation, phosphorylation, sulfonylation, and ubiquitination can occur at both the N- and C-termini of histones [42]. These modifications, taking place at the R and K residues of histones, can be regulated by various enzymes. Typically, enzymes that add chemical groups to histone tails are termed "writers," proteins that recognize these specific epigenetic marks are called "readers," and other proteins that contribute to removing marks are known as "erasers" [43]. Notably, these modifications change the structure and charge of the histone tails bound to DNA, thereby modulating the state of chromatin and the signaling pathways of DNA-binding proteins, which in turn impacts gene expression [44]. Furthermore, histone modifications can create a binding platform for proteins involved in chromatin remodeling, histone chaperones,

Table 1 Summary of key epigenetic therapies by target category

Epigenetic mechanisms		Target	Drug		Key result	
					Monotherapy	Combination therapy
DNA methylation	Writers	DNMT1 DNMT2	5-Azacytidine Decitabine		Data not yet available	PTCL (AZA + DOMI): ORR 61%, CR 48% [16] R/R DLBCL (AZA + vorinostat + gemcitabine/busulfan/melphalan): ORR 78% [17]
Histone methylation	Writers	EZH1		Valemetostat	$EZH2^{MUT}$ FL (tazemetostat): ORR 69% [18] TCL (valemetostat): ORR 80% [19] R/R ATL (valemetostat): ORR 48% [20]	Data not yet available
		EZH2	Tazemetostat, CPI-0209, CPI-1205, SHR2554, GSK2816126, PF-06821497			
		PRMT3	GSK3368715		DLBCL: terminated as the benefit/risk assessment did not favor (NCT03666988)	No studies
		PRMT5	GSK3326595 JNJ-64619178		NHL: Data not yet available (NCT02783300) NHL: Data not yet available (NCT03573310)	No studies
Histone acetylation	Readers	BRD2 BRD3 BRD4	BMS986158 CPI-0610 Mivebresib OTX015	Abexinostat, belinostat, fimepinostat, givinostat, panobinostat, tinostamustine, vorinostat	Lymphoma (BMS986158): Data not yet available (NCT03936465) Progressive lymphoma (CPI-0610): Data not yet available (NCT01949883) NHL (Mivebresib): Data not yet available (NCT02391480) Lymphoma (OTX015): No clinical benefit [21]	NHL (mivebresib + venetoclax): Data not yet available (NCT02391480)
	Erasers	HDAC1 HDAC2 HDAC3 HDAC8 HDAC4 HDAC5 HDAC7 HDAC9	Chidamide, romidepsin, entinostat, mocetinostat, nanatinostat		R/R PTCL (chidamide): ORR 58.6%, DCR 21.1% [22] R/R PTCL (ROMI): ORR 25%, CR 15% [23] R/R DLBCL (mocetinostat): ORR 18.9% [24] FL (mocetinostat): ORR 11.5% [24] R/R PTCL (belinostat): ORR 25.8% [25] R/R HL (panobinostat): ORR 27.2% (NCT00742027) FL (vorinostat): ORR 48.7%; non-FL B-NHL (vorinostat): ORR 27.3% (NCT00875056)	PTCL (chidamide + CHOP): ORR 89.3%, CR 57.1% [26] R/R PTCL (ROMI + pralatrexate): ORR 71% [27] R/R HL (panobinostat + lenalidomide): ORR 16.7% (NCT01460940)
		HDAC6	Ricolinostat		Lymphoma (ricolinostat): Data not yet available (NCT02091063)	
		HDAC10	Chidamide			
Histone phosphorylation	Writers	JAK2	Ruxolitinib		R/R DLBCL after HSCT: ORR 8.5% R/R PTCL after HSCT: ORR 15.4%	Data not yet available

Abbreviations: *DNMT* DNA methyltransferase, *EZH1* enhancer of zester homolog 2, *EZH2* enhancer of zester homolog 2, *PRMT* protein arginine methyltransferase, *BRD* bromodomain, *HDAC* histone deacetylases, *JAK* Janus kinase, *AZA* 5-azacytidine, *ROMI* romidepsin, *mut* mutant, *FL* follicular lymphoma, *TCL* T cell lymphoma, *R/R* relapsed/refractory, *ATL* adult T cell leukemia/lymphoma, *DLBCL* diffuse large B cell lymphoma, *NHL* non-Hodgkin's lymphoma, *PTCL* peripheral T cell lymphoma, *HL* Hodgkin's lymphoma, *HSCT* hematopoietic stem cell transplantation, *CR* complete response, *ORR* objective response rate, *DCR* disease control rate, *CHOP* cyclophosphamide, doxorubicin, vincristine, and prednisone. Retrieved from: http://clinicaltrials.gov/

DNA/histone modifying enzymes, and general transcription factors [43]. These histone modifications are crucial for various cellular processes, and their dysregulation is linked to cancer development and developmental defects [45]. They are currently a significant area of epigenetic research [46, 47]. Histone acetylation and methylation are the most commonly studied types of histone modifications.

Histone methylation primarily occurs at residues K or R of H3 and H4. This process is instrumental in forming and maintaining heterochromatin's structure and genome, and in regulating blotting, DNA repair, X-chromatin inactivation, and transcription. Three main factors regulate histone methylation: HMT, histone methylation recognition proteins, and histone demethylases. HMT is classified into histone lysine methyltransferase (HKMT) and protein arginine methyltransferase (PRMT). Meanwhile, histone demethylases are generally divided into two types: lysine-specific demethylase (LSD) and jumonji domain–containing histone demethylase. H3K at positions 4, 9, 27, 36, and 79 and H4K at position 20 can be methylated [48]. H3K4 and H3K9 are common modification sites. The N-terminal of L residues can undergo mono-, di-, or tri-methylation modifications, while R residues can undergo only mono- and asymmetric di-methylation modifications. Interactions between histone lysine methylation and other histone modifications may regulate gene expression. For instance, H3K4 and H3K79 methylation requires prior H2B ubiquitination in yeast. Acetylation and methylation on the same lysine residue can act as antagonists, leading to crosstalk between different histone marks [42]. Histone acetylation is a reversible process primarily maintained by histone acetyltransferases (HATs) and HDACs. Histone acetylation can occur at sites 9, 14, 18, and 23 of H3 and sites 5, 8, 12, and 16 of H4, facilitating transcription on the one hand, and weakening the interaction between histones and DNA by reconfiguring higher chromatin structure on the other [49].

Relationship between histone methylation and lymphoma development

Histone methylation, one of the most significant post-translational modifications, typically refers to the addition of methyl groups to the lysine (K) residues of histones H3 and H4 [50]. Histone lysine residues can be mono-, di-, or tri-methylated, acting as active or repressive marks for gene expression [51]. Unlike other histone modifications, which specify active or repressed chromatin states, histone lysine methylations confer active or repressive transcription depending on their positions and methylation states. Generally, H3K4, H3K36, and H3K79 methylation are often considered markers of active transcription, while H3K9, H3K27, and H4K20 methylation are associated with silent chromatin states [43]. Under normal circumstances, activation and inhibition of methylation modifications maintain a dynamic equilibrium [49].

KMT2D (also known as MLL2) triggers methylation on lysine 4 of histone H3 (H3K4me). This methylation at promoters and enhancers acts as a marker for transcriptional activation. Zhang et al. [52] discovered that mutations in the gene encoding KMT2D methyltransferase could decrease KMT2D enzyme activity. Such a reduction led to a decrease in overall H3K4 methylation in GC B cells and DLBCL cells, thereby increasing the incidence of GC-derived lymphomas. Decitabine also synergistically enhanced the interaction between KMT2D and PU.1. This interaction affected H3K4me-related signaling pathways, rendering lymphoma cells more responsive to chidamide. Dual therapy with chidamide and decitabine significantly slowed tumor growth and promoted apoptosis in a KMT2D-mutated heterozygous T cell lymphoma model. This therapeutic effect occurred via modulation of the KMT2D/H3K4me axis [53].

Moreover, SETD2 is the sole methylation transferase responsible for the trimethylation of lysine 36 on histone 3 (H3K36me3). The involvement of H3K36me3 in RNA splicing occurs not only through the recruitment of MRG15 and ZMYND11 but also through multiple pathways, such as mismatch repair (MMR), the recruitment of LEDGF, and the subsequent activation of DNA damage perception through homologous recombination (HR) [54–56]. In various solid tumors and leukemias, the exclusive subunit functional deficiency of SETD2 results in defective DNA damage repair and impaired transcription. However, recent findings indicate that heterozygous SETD2 deficiency in DLBCL can cause GC proliferation, increased competitive fitness, reduced DNA damage checkpoint activity, and decreased apoptosis, all of which contribute to expedited lymphoma formation [57].

PRMT serves as the catalytic subunit of the polycomb repressor complex 2 (PRC2), which represses gene expression via the trimethylation of histone H3 lysine 27 (H3k27me3). Somatic mutations in residues Y641 and A677 of the EZH2 SET domain correlate with poor prognosis in DLBCL and FL [58]. Epigenomic studies have revealed that inappropriate H3k27me3 deposition is a key determinant of aberrant transcriptomes in malignant lymphomas and various solid tumors [59]. Given that H3k27me3 is an enzymatic product, its reversibility provides an excellent foundation for the development of epigenetic drugs. Numerous preclinical studies have confirmed the efficacy of EZH2 in BCL. Tazemetostat, one of the most promising compounds, was granted accelerated approval by the FDA in June 2020. It was sanctioned for the treatment of adult patients with R/R FL, particularly those who had previously received at least two standard-of-care systemic therapies or had no suitable alternative treatment options [60, 61]. Tazemetostat, a selective EZH2 inhibitor, curbs tumor growth by reducing H3k27

methylation levels [62]. A multicenter, open-label, single-arm, phase II study involving 99 adult patients with R/R FL demonstrated that tazemetostat monotherapy exhibited good single-agent activity, a durable response, and good tolerability in patients with R/R FL [18]. With the results of this study, tazemetostat is expected to be a new promising treatment option for FL patients. Furthermore, a phase I study conducted in Japanese patients with R/R B cell NHL showed that tazemetostat, at a dosage of 800 mg twice daily, also exhibited an acceptable safety profile and promising antitumor activity [63]. Despite the underwhelming efficacy of EZH2 inhibition in the current clinical exploration of DLBCL, EZH2 inhibitors have proven to be well-tolerated. Therefore, numerous studies are investigating combination therapy options to augment the efficacy of EZH2 in DLBCL. Scholze et al. [64] discovered the synergistic effects of tazemetostat and venetoclax in DLBCL cells and 3-dimensional lymphoma organoids carrying EZH2 mutations and IGH/BCL2 translocations. Tazemetostat treatment upregulated pro-apoptotic proteins, and it is postulated that venetoclax enhances the BH3-mediated apoptosis thereby triggered. A short course of combination therapy with tazemetostat and venetoclax achieved complete remission and improved overall survival in DLBCL patient–derived xenografts (PDXs) compared to either monotherapy. Other studies have also confirmed the synergistic effects of tazemetostat in combination with R-CHOP regimens and drugs such as lenalidomide and atezolizumab for their antitumor effects in DLBCL [65–67].

Several ongoing clinical trials are investigating the use of tazemetostat and other EZH2 inhibitors in various malignant lymphomas (more details are shown in Table 2). Yamagishi et al. discovered that aggressive lymphomas often co-express EZH1 and EZH2, which can interfere with and compensate for each other's function, suggesting a principle of dual targeting of EZH1/2 [68]. Moreover, Honma et al. showed that EZH1/2 dual inhibitors outperform EZH2 selective inhibitors in terms of antitumor efficacy in both in vitro and in vivo studies, without causing severe hematological side effects [69]. In September 2022, valemetostat became the first dual EZH1/2 inhibitor approved in Japan for treating aggressive adult T cell leukemia (ATL) [70]. There are ongoing phase I and II clinical trials of valemetostat for treating malignant lymphomas, such as BCL and R/R PTCL (see Table 2). These trials have shown promising safety and antitumor activity against lymphomas.

Furthermore, histone modifications and DNA methylation are functionally linked. Specifically, the removal of histone H3 lysine 4 methylation (H3K4me0) correlates with an increase in H3K9 methylation[45]. Selker et al. confirmed, using a yeast model, that DNA methylation requires histone H3K9 methylation [71]. In mammalian cells, a structural domain typically connects histone methylation to DNA methylation. For instance, the H3K4 methyltransferase MLL1 contains a CpG-interacting CXXC structural domain that couples the H3K4 methylation reaction to unmethylated DNA.

Relationship between histone acetylation and lymphoma development

Reversible acetylation, mediated by HDACs, influences a variety of physiological processes, many of which are aberrantly regulated in tumor cells [72]. In various lymphomas, HDAC inhibitors (HDACi) inhibit cell cycle progression and induce apoptosis. To safeguard and/or boost NK cell function, the specific function of individual HDACs often needs to be determined. For instance, HDAC8, a known target in T cell lymphomas, can inhibit mantle cell lymphoma (MCL) growth without changing NK cell viability, receptor expression, and antibody-dependent cell-mediated cytotoxicity (ADCC). This does not limit the therapeutic activity of rituximab in MCL patients due to impaired NK cell function [73]. Niklas et al.'s discovery that PD-404182 acts as a "molecular trigger" by forming an additional intramolecular disulfide bond between Cys102 and Cys153, thereby inhibiting HDAC8 activity, provides theoretical support for developing selective inhibitors [47].

In addition to HDACs, the HDACi target HSP72 can increase the sensitivity of Hut78 cells from the cutaneous T cell lymphoma (CTCL) cell line to vorinostat [74]. Recently, HDACi has been found to induce autophagy, increase the expression of autophagy factor LC3d, and inhibit the trophic-sensing kinase of mammalian target of rapamycin (mTOR) protein, thereby improving the drug's therapeutic effect [75].

Additionally, HDACs regulate the G1–S transition, while Aurora A kinase (AAK) regulates mitosis through its role at the G2–M transition point. HDACi leads to AAK and Aurora B kinase (ABK) degradation and kinetochore assembly modification, providing a preclinical rationale for their interaction with AAK inhibitors. In a preclinical model of T cell NHL, Strati et al. [76] discovered that romidepsin (HDACi) and alisertib (AAKi) displayed a synergistic effect secondary to cytoplasmic fission failure, which was not observed in B cells. However, phase I clinical studies of romidepsin combined with alisertib in patients with R/R BCL (14 patients), PTCL (4 patients), and HL (7 patients) revealed that the combination treatment was inferior to the single agent regimen. HDACi combined with Janus kinase inhibitors (JAKi) showed significant antitumor effects on CTCL cells [77]. For example, resminostat (HDACi) combined with ruxolitinib (JAKi) effectively inhibits key cellular pathways in MyLa and SeAx cells, providing a new potential therapeutic approach for CTCL patients [78].

Table 2 Ongoing clinical trials of EZH2 inhibitors for lymphoma treatment

EZH2i	Approved by	Clinical phases, status	Co-treatment	Primary outcome	Cancer specificity	Clinical trial identifier
Tazemetostat	FDA (FTD)	-, R	None	Number of participants with ADRs and serious ADRs	R/R FL	NCT05228158
		II, C	None	ORR	R/R B cell NHL	NCT03456726
		II, R	None	Efficiency of Tazemetostat in $EZH2^{MT}$	R/R FL with EZH2	NCT05467943
		I/II, R	Rituximab, bendamustine	Phase I: MTD Phase II: CMR	High tumor burden FL	NCT05551936
		II, R	HMPL-689	DLT, ORR, DCR, DOR, PFS	R/R lymphoma	NCT05713110
		III, R	Lenalidomide, rituximab	PR3D, PFS	R/R FL, FL, refractory FL	NCT04224493
		I, R	Belinostat	MTD	Recurrent B cell NHL, recurrent DLBCL	NCT05627245
		I, C	Itraconazole, rifampin	PK	FL, NHL, DLBCL, etc	NCT04537715
		I/II, R	CC-99282	DLT, MTD, AEs	R/R NHL	NCT03930953
CPI-0209		I/II, R	None	Phase I: DLTs Phase II: ORR	DLBCL, TCL, etc	NCT04104776
SHR2554		I/II, R	Monotherapy and with SHR1701	Phase I: AEs Phase I/II: CRR	R/R HL	NCT05896046
		I/II, R	Monotherapy and with SHR1701	PFS	Lymphoma	NCT04407741
		I/II, R	None	ORR	R/R PTCL	NCT05559008
PF-06821497		I, R	None	DLT, MTD, overall safety profile including AEs	FL	NCT03460977
Valemetostat	Japan	II, R	None	ORR	BCL	NCT04842877
		II, ANR	None	ORR, AEs	R/R PTCL, ATL	NCT04703192
		I/II, R	Rituximab, lenalidomide	AEs	Lymphoma	NCT05683171
		II, ANR	None	ORR	ATL	NCT04102150

Abbreviations: EZH2: enhancer of zester homolog 2, FTD: Fast Track Designation, R: Recruiting, C: Completed, ANR: Active, not recruiting, ADRs: Adverse Drug Reactions, CMR: Complete Metabolic Response, DLT: Dose-Limiting Toxicity, ORR: Objective Response Rate, DCR: disease control rate, DOR: Duration of Response, PFS: Progression-Free-Survival, PR3D: Recommended Phase 3 Dose, MTD: Maximum Tolerable Dose, AEs: Incidence of adverse events, CRR: Complete response rate, FL: follicular lymphoma, R/R: Relapsed/Refractory, NHL: Non-Hodgkin's Lymphoma, DLBCL: diffuse large B-cell lymphoma, ATL: Adult T-cell leukemia/Lymphoma. Retrieved from: http://clinicaltrials.gov/

Epigenetic drugs

Romidepsin, a cyclic tetrapeptide intravenous HDACi primarily targeting the enzymatic activity of class I HDACs, induces cell cycle arrest through the upregulation of p21. This substance has shown synergistic effects with novel agents such as bortezomib [79]. In 2011, the FDA gave its approval for romidepsin to be used in the treatment of patients with PTCL who had received at least one prior treatment. Subsequent clinical trials revealed that romidepsin provided durable responses and long-term tolerance in patients with R/R PTCL. Accordingly, the National Comprehensive Cancer Network recommends romidepsin for the second-line and subsequent treatment of patients, whether or not they intend to receive high-dose therapy or SCT [80]. Combination regimens with romidepsin and other drugs such as pralatrexate [81], bendamustine [82], or azacitidine [83] have demonstrated better effectiveness and manageable toxicity for PTCL treatment compared to romidepsin monotherapy. To enhance treatment regimens, phase II studies of lenalidomide and romidepsin are currently being conducted for patients with untreated PTCL. These studies are driven by the promising results of lenalidomide monotherapy in similar patient cohorts, including longer median progression-free survival (PFS), overall survival (OS), and duration of response (DOR). Phase II clinical trials in refractory CTCL implied the clinical efficacy and safety of romidepsin. In patients with CTCL who have received at least one

systemic therapy, romidepsin responses were observed in all stages of the disease and in all sites, including the blood, lymph nodes, and skin [84]. However, a phase III study of untreated PTCL indicated that the combination of romidepsin and CHOP failed to significantly improve PFS and remission rates compared to the CHOP regimen alone. This combination was also associated with an increased frequency of grade ≥ 3 treatment-emergent adverse events [23].

Belinostat, a pan-HDACi derived from hydroxypentanoic acid, broadly inhibits all zinc independent HDAC enzymes. This includes class I HDACs (HDAC1, HDAC2, and HDAC3), class II HDACs (HDAC6, HDAC9, and HDAC10), and the class IV HDAC (HDAC11). In 2014, the FDA approved belinostat for the treatment of PTCL. A phase II study involving 129 patients with R/R PTCL showed an objective response rate (ORR) of approximately 26% and a complete response (CR) rate of 11% following belinostat administration [85]. Twelve patients subsequently received a hematopoietic SCT, 10 of whom were still alive at the time of statistical data cutoff (OS range 9.4 to 22.9 months). Furthermore, the occurrence of grade 3–4 hematologic toxicity made it possible to include belinostat in combination regimens with other agents (thrombocytopenia, 7%; neutropenia, 6.2%; anemia, 10.9%). Johnston et al. [86] conducted a trial with belinostat combined with the CHOP regimen, yielding promising results. Out of 23 patients, the overall ORR was 86%, including an 89% response in patients with angioimmunoblastic T cell lymphoma (AITL) and a 90% response in patients with bone marrow involvement. The CR at the maximum tolerated dose was 71%. The optimal dose of belinostat in the belinostat-CHOP regimen was found to be the same as that for belinostat monotherapy, with no additional toxicity identified. Although combination regimens with belinostat appear promising, further validation is needed to establish their efficacy and safety.

Vorinostat, another hydroxyvalerate derivative, was approved by the FDA in 2006 for the treatment of CTCL. It is a broad inhibitor of class I and class II HDACs. A phase I study of vorinostat combined with CHOP in PTCL patients reported an OS of 82%, a median PFS of 79%, and a median response duration of 29 months. However, further studies are needed to confirm the effectiveness of this combination and its impact on patient survival [87]. In a phase I/II clinical study, vorinostat combined with rituximab-CHOP achieved an ORR of 81% ($n = 63$) in patients with R/R DLBCL. However, due to high rates of febrile neutropenia (38%) and sepsis (19%), this regimen is not recommended for routine clinical use [88]. Other substances such as abexinostat and fimepinostat have been granted fast track designation (FTD) by the FDA for patients with R/R FL and R/R DLBCL respectively. Another HDACi, panobinostat, was approved by the FDA in 2015 for use in combination with bortezomib and dexamethasone in the treatment of multiple myeloma in patients who had received at least two prior therapies. A phase I clinical trial showed good tolerability of panobinostat in patients with CTCL [89].

In 2017, the China Food and Drug Administration (CFDA) authorized chidamide, an independently developed Chinese drug, as a standalone therapy for R/R PTCL. Selectively inhibiting the activity of HDAC1, 2, 3, and 10, chidamide blocks the AKT/mTOR and MAPK signaling pathways while activating the ATM-Chk2-p53-p21 pathway, thus exerting antitumor effects in NK/TCL cells [90]. Additionally, chidamide inhibits the HDACs/STAT3/Bcl-2 pathway, which triggers apoptosis in DLBCL cells [91]. Chidamide enhances OS in DLBCL patients by upregulating OTUD7B expression and synergizing with low-dose adriamycin [92]. A clinical study involving 383 PTCL patients validated the safety and effectiveness of chidamide monotherapy, particularly for AITL patients with an international prognostic index (IPI) score of 2 or more. Furthermore, combining chidamide with chemotherapy—specifically CHOP-like or platinum-containing regimens—yielded higher ORR and DOR in AITL patients [93]. This indicates that the combination of chidamide with chemotherapy is effective in R/R PTCL, especially in young patients with a high IPI who are negative for CD30 expression [94]. Combining chidamide with the CPET regimen (prednisone, etoposide, thalidomide) in a multicenter phase II clinical trial involving 71 newly diagnosed AITL patients (with 51 completing eight cycles) resulted in a 90.2% ORR and a median PFS of 42.6 months [95]. In a retrospective study, Wang et al. [96] evaluated the combination of chidamide with the PEL regimen (prednisone, etoposide, lenalidomide) for R/R DLBCL patients who were not eligible for aggressive chemotherapy or autologous SCT. Furthermore, a patient with EZB/C3 subtype DLBCL who relapsed post-R-CHOP treatment achieved complete remission following the combined treatment with lenalidomide, chidamide, and R-CHOP. This case report supports the feasibility of combining chidamide with the R2-CHOP regimen. In addition to the findings about chidamide's potential use in treating NK/T cell lymphoma (NKTCL) [90], Zhou et al. also highlighted its potential as a therapeutic target against the EBV.

Beyond its direct anticancer activity, HDACi can influence immune regulation [97]. Evidence indicates that epigenetic factors can enhance the efficacy of anti-programmed cell death protein (PD-1) or anti-PD1-ligand 1 (PD-L1) therapy [98]. Numerous studies have shown that HDACi can amplify the antitumor activity and persistence of PD-1 antibodies by mediating immune recognition and upregulating NKG2D ligand and HSP70 genes [99]. Moreover, HDACi can promote tumor suppression by activating p53 acetylation to stimulate PD-1, inherent in cancer cells [100]. Combining sintilimab and chidamide yielded a durable response with minimal toxicity in a patient with R/R NKTCL resistant to

pegaspargase and immunotherapy [101]. Additional case reports endorse the potential of combining anti-PD-1 antibodies with HDACi for treating R/R lymphoma [102–104]. The side effects of PD-L1 antibodies are less significant compared to those of PD-1 antibodies. Mocetinostat (MGCD0103), a specific benzamide histone deacetylase inhibitor [24], can elevate PD-L1 levels by reducing BCL-2 levels. One patient with refractory extranodal NKTCL responded well to a treatment regimen that combined radiotherapy, chidamide, and the PD-L1 antibody atezolizumab [105]. Thus, combining HDACi with PD-L1 shows promise for R/R lymphoma treatment. Moreover, Bissonnette et al. highlighted in preclinical studies that chidamide can trigger epigenetic modifications in the tumor microenvironment to amplify the effectiveness of immune checkpoint inhibitors (ICIs) [106]. This finding provides a theoretical basis for combining chidamide and ICIs in treating various tumors, including lymphoma. Consequently, HDACi may be most beneficial when combined with other drugs—such as protein kinase inhibitors, Bcl-2 inhibitors, and other epigenetic agents—or with other therapies like immunotherapy, as is being examined in ongoing clinical trials (Table 3).

Non-coding RNA regulation

Non-coding RNAs (ncRNAs), which do not code for proteins, constitute a significant portion of the human genome. High-throughput genome sequencing and array-based studies estimate that around 90% of the human genome can potentially be transcribed [107]. However, only about 2% of this transcribed genome encodes proteins, totaling around 20,000 proteins [108]. For a long time, this small protein-coding part of the genome was the primary focus of medical research, and ncRNAs were disregarded as "evolutionary junk" [109]. Recent studies have highlighted the vital role ncRNAs can play in various human diseases, notably cancer, as well as in regulating fundamental biological processes

Table 3 HDACi combination therapies under investigation started after 2018 for lymphoma treatment

HDACi	Approved by	Clinical phases, status	Co-treatment	Primary outcome	Cancer specificity	Clinical trial identifier
Romidepsin	FDA	II, C	Tenalisib (RP650)	DLT	R/R TCL	NCT03770000
		I/II, ANR	Ixazomib	MTD, CRR	R/R PTCL	NCT03547700
		II, ANR	Venetoclax	AEs, ORR	MTCL	NCT03534180
Chidamide	CFDA	II, C	Chiauranib	DLT	NHL	NCT03974243
		II, C	Sintilimab	DLT, MTD, CRR, PRR	R/R ENKTCL	NCT03820596
		II, C	Sintilimab	ORR, CRR, PRR	Newly diagnosed ENK-TCL	NCT04994210
		II, R	Sintilimab	PFS	PTCL	NCT04512534
		II, R	Mitoxantrone, liposome	ORR	R/R PTCL	NCT05495100
		II, R	Lenalidomide	ORR	R/R PTCL	NCT04329130
		II, R	CHOP	CRR	Previously untreated PTCL with TFH	NCT05572983
		II, R	Sintilimab	ORR	R/R CTL	NCT04296786
		II, ANR	CHOP	CRR	ATCL	NCT03853044
		I/II, R	Decitabine, anti-PD1/PD-L1/CTLA4 antibodies)	ORR	ATCL	NCT05320640
Vorinostat	FDA	II, ANR	Busulfan, clofarabine, cyclophosphamide, cyclophosphamide, gemcitabine, mycophenolate mofetil, rituximab, tacrolimus	PFS	Relapsed aggressive B cell or T cell non-Hodgkin lymphoma	NCT04220008
Abexinostat	FDA (FTD)	I, ANR	Ibrutinib	MTD	DLBCL, MCL	NCT03939182

Abbreviations: C: Completed, R: Recruiting, ANR: Active, not recruiting, CHOP: Cyclophosphamide, Doxorubicin, Vincristine and Prednisone, DLT: Dose-Limiting Toxicity, CRR: Complete Response Rate, MTD: Maximum Tolerable Dose, ORR: Objective Response Rate, PRR: Partial Response Rate, PFS: Progression-Free-Survival, AEs: Incidence of adverse events, NHL: Non-Hodgkin's Lymphoma, PTCL: Peripheral T-Cell Lymphoma, MTCL : Mature T-cell lymphoma, TFH: Follicular Helper of T Cell, R/R: Relapsed/Refractory, ENKTCL: extranodal Natural Killer Cell/T-cell Lymphoma, CTL: Cutaneous T-cell lymphoma, ATCL: Angioimmunoblastic T Cell Lymphoma, TCL: T Cell Lymphoma, MCL: mantle cell lymphoma. Retrieved from: http://clinicaltrials.gov/

such as growth, development, and organ function [110–112]. ncRNAs, due to their smaller molecular weight, ability to carry multiple negative charges, and excellent histocompatibility, are promising candidates as therapeutic targets [113]. ncRNAs can be classified into small non-coding RNAs (sncRNA, 18–200 nt) and long-stranded non-coding RNAs (lncRNA, > 200 nt) based on their length. sncRNAs include types such as rRNA, tRNA, miRNA, and piRNA, all of which play a critical role in gene expression regulation [114]. Long-stranded non-coding RNAs (lncRNAs) often function similarly to miRNAs, regulating cancer progression. Cyclic RNA, another type of ncRNA, differs structurally from linear RNA and performs complex functions that are still being explored [115].

miRNAs, the most studied type of ncRNA, are small (18–24 nucleotide) molecules that mainly bind recognition sites in the 3′UTRs of genes, thereby limiting post-transcriptional gene expression [116]. They can also down-regulate protein levels through sequence-specific binding to target mRNAs, leading to translation inhibition or mRNA degradation [117]. Additionally, miRNAs can regulate tumor cell interactions with the microenvironment, contributing to lymphoma progression [118]. Table 4 presents various dysregulated miRNAs reported in lymphoma. Lin et al. [119] identified 20 potential miRNA biomarkers in PTCL-not otherwise specified (PTCL-NOS) using PCR alignment and gene ontology analysis. Thirteen miRNAs were upregulated, and 7 miRNAs were downregulated. Notably, the overexpression of miR187 was linked to PTCL-NOS tumor progression and poor prognosis in patients by regulating the Ras-mediated ERK/AKT/MYC axis. The proteasome inhibitor bortezomib suppressed miR187 overexpression during tumor progression [120]. For instance, miR-340-5p enhances the infiltration and antitumor function of CD8 + tumor-infiltrating T lymphocytes by regulating lysine methyltransferase 5A and constitutive photomorphogenesis protein 1, which activate CD73 ubiquitination. This miRNA also directly regulates DLBCL cells [121], suggesting a potential target for DLBCL immunotherapy. miR155, a BCL biomarker, is associated with poor prognosis in DLBCL patients and is implicated in tumor progression by regulating PD-1/PD-L1-mediated interactions with CD8 + T cells in the tumor microenvironment [118]. Other miRNAs like let-7f, miR-9, and miR-27a are specifically expressed and consistently upregulated in classical HL [122]. Furthermore, miR-21 is regarded as a biomarker for HIV-associated lymphoma [123].

lncRNAs represent the most diverse group of ncRNAs. They typically contain long sequences that exceed 200 nucleotides. Unlike short ncRNAs, primarily associated with gene regulation, lncRNAs demonstrate a broad array of mechanistic functions. For instance, the EBV supports BCL progression by suppressing the novel p53-responsive lncRNA, IGFBP7-AS1. However, the exogenous introduction of IGFBP7 or wt-p53 can restore the tumorigenic properties affected by the deletion of IGFBP7-AS1 [147]. One study involving DLBCL patients and healthy controls employed bioinformatics analysis to construct a lymphoma, drug, and lncRNA protein–protein interaction network. This study suggested lncRNAs HOTAIR, GAS5, and XIST as potential diagnostic tools for DLBCL, and HOTAIR and GAS5 as indicators for evaluating treatment efficacy [148]. Zhu et al. [149] conducted a comprehensive genome-wide analysis of lncRNA expression in five DLBCL cell lines and normal B cells. The goal was to identify potential DLBCL-related targets via gene ontology and pathway analysis. The study revealed that a total of 1053 lncRNAs and 4391 mRNAs were aberrantly regulated in DLBCL cells compared to normal B cells. Pathways highly relevant included cell cycle/apoptosis/B cell receptors and the nuclear factor B signaling pathway. Table 5 lists specific dysregulated lncRNAs and their functions in various prevalent lymphoma subtypes. The differing lncRNA activity profiles align with the classification of PTCL subtypes [150].

RNA modification

While the triplet code of the open reading frame is well understood for mRNAs, some functions of non-coding RNAs remain unknown, and advances in genome sequencing technologies have revolutionized our understanding of the genome and its transcription [164]. Many studies have begun to provide a clearer picture of RNA modifications, and more than 160 RNA modifications, including N7-methyluracil (m^7G), N6-methyladenosine (m^6A), and 5-methylcytosine (m^5C), have been identified [165–167].

In eukaryotes, m^6A is the most abundant mRNA modification, accounting for more than 80% of all RNA methylation modifications. M^6A is mainly regulated by methyltransferases (METTL3, METTL14, WTAP, and VIRMA), demethylase proteins (FTO, ALKBH5), and reading proteins (YTH family proteins) [168, 169] that are expressed in a variety of tumors and play a major part in promoting tumor progression, especially in lymphomas [170]. In DLBCL, the m^6 A regulatory genes piRNA-30473 and WTAP prolong DLBCL patient survival and it has been demonstrated that the piRNA-30473/WTAP/HK2 axis promotes tumorigenesis by regulating m^6A RNA methylation [171]. In addition, m^6A-modified mRNAs mediate multiple cellular and viral functions. In lymphoma, m^6A-modified EBV transcripts are disrupted by the UTUDF1 protein, leading to the downregulation of m^6A-dependent EBV infection and replication, which could provide a new target for the treatment of EBV-associated lymphoma [172].

Furthermore, m^6A mRNA modification was associated with histone modification. m^6A modification increased

Table 4 List of miRNAs with dysregulated expression in lymphoma

MiRNA	Target	Lymphoma subtype	Biological significance	References
Up-regulation				
miR-21	C1RL, TCAP	BL	It promotes the progression of BL through the PI3K/AKT signaling pathway	[124]
miR130b	OX40L	DLBCL	1. It promotes lymphoma progression by recruiting Th17 cells through down-regulation of OX40L expression and further promoting their immunosuppressive function 2. It inhibits autophagy of lymphoma cells	[125]
miR-155	STAT3/VEGFC	NKTCL	1. It upregulates VEGFC and promotes lymphangiogenesis 2. Targeting miR-155 in NKTCL cells enhances apoptosis	[126]
	C1RL, TCAP	BL	It promotes the progression of BL through the PI3K/AKT signaling pathway	[124]
	FOCXO3	BCL	It promotes the proliferation of BCL cells and suppresses apoptosis	[127]
miR-378a-3p	IRAK4, MNT	BL	Its inhibition reduces the growth of multiple BL cells	[128]
miR-425-5p	PTEN	DLBCL	It is associated with the progression and relapse of tumorigenesis by the PTEN/PI3K signaling pathway	[129]
miR-584	FOXO1	NKTCL	Its overexpression suppresses proliferative and invasive abilities in NKTCL cells	[130]
Down-regulation				
miR-100	mTOR	MCL	1. Its upregulation inhibits cell proliferation and accelerates cell apoptosis 2. It restrains the cell cycle in the G1 phase via targeting the mTOR gene 3. It is associated with tumor suppression	[131]
miR-101	KDM1A	DLBCL	It regulates cell proliferation and apoptosis by targeting KDM1A	[132]
miR-135a	GATA-3	CTCL	It leads to T cell deregulation and proliferation through GATA-3/TOX regulation	[133]
miR-145-5p	S1PR1	DLBCL	It restrains DLBCL cell growth and movement by suppressing the S1PR1/STAT3/AKT pathway	[134]
miR-152	DNMT1	NHL	It increases the expression of SOCS3 and SHP-1 It inhibits the cell proliferation and induces cell apoptosis	[135]
miR-214	PD-L1	DLBCL	It inhibits tumor growth by targeting PD-L1	[136]
miR-212-3p	SOX11	MCL	It inhibits lymphoma cell proliferation and migration, and promotes their apoptosis by regulating SOX11	[137]
miR-337	STAT3	CTCL	It promotes apoptosis in CTCL cell lines and inhibits cell invasion	[138]
miR-363	SIRT6	NKTCL	It inhibits cell proliferation and promotes cell apoptosis through suppressing the SIRT6/PI3K/AKT pathway	[139]
miR-363-3p	DUSP10	DLBCL	1. It is associated with tumorigenesis and drug resistance 2. The miRNA-363-3p/DUSP10/JNK axis is correlated with the negative regulation of HR and DNA repair pathways	[140]
miR-383	ZEB2	Gastric MALT lymphoma	1. It inhibits cell division by downregulating the ZEB2 expression 2. It is associated with tumor suppression	[141]
miR-383-5p		DLBCL	1. Its upregulation inhibits cell expansion and invasion 2. It may predict a favorable prognosis, and can be used as a prognostic biomarker	[142]
miR-506	B7H3	MCL	It reduces MCL cell proliferation, invasion, and migration It restrains the cell cycle in the G0/G1 phase	[129]
	IL22	CTCL	It is associated with tumor invasion and the metastasis of advanced CTCL via regulating the IL-22-STAT3-CCL20 cascade	[143]
miR-532-3p	β-Catenin	Lymphoma	1. Its overexpression inhibits cell proliferation and promotes cell apoptosis 2. It is associated with tumor suppression by targeting β-catenin	[144]
miR-665	LASP1	DLBCL	It inhibits cell proliferation and invasion and induces apoptosis via targeting LASP1 and MYC and further suppresses DLBCL progression	[145]
miR-1250-5p	MAPK1, DR1	NHL	1. It is responsible for inhibiting the MAPK/ERK signaling pathway and SDF-1-dependent cell migration 2. It is associated with tumor suppression	[146]

Abbreviations: miRNA: microRNA, HR: homologous recombination, SOX11: sex-determining region Y-box 11, IL22: interleukin-22, LASP1: LIM and SH3 protein 1, BL: Burkitt lymphoma, DLBCL: diffuse large B-cell lymphoma, NKTCL: NK/T cell lymphoma, MCL: mantle cell lymphoma, CTCL: cutaneous T-cell lymphoma, MALT: mucosa-associated lymphoid tissue, NHL: Non-Hodgkin's Lymphoma

H3K36me3 levels, and m^6A was significantly reduced when H3K36me3 was depleted in cells. H3K36me3 levels showed the importance of m^6A in terms of specificity and dynamic deposition in mRNA and revealed the interaction between histone and RNA methylation during gene expression regulation [173]. In DLBCL tumors and cell lines, the m^6A and methyltransferase 3, N6-adenosine-methyltransferase complex catalytic subunit (METTL3) levels were upregulated,

Table 5 LncRNAs with dysregulated expression in lymphoma

Lymphoma subtype	Dysregulated lncRNA	Biological significance	References
BCL	IGFBP7	Restores the tumorigenic properties caused by EBV-induced IGFBP7 deletion	[147]
DLBCL	NKILA	1. Hypermethylation frequently occurs in DLBCL 2. Associated with tumor suppression	[151]
	NORAD	1. Participates in the miR-345-3p/TRAF6/PI3K/Akt axis 2. Its downregulation inhibits DLBCL cell proliferation, blocks the cell cycle, and induces apoptosis	[152]
	SNHG5	Highly expressed in DLBCL	[153]
	SNHG14	1. SNGH14 upregulates ZEB1 by inhibiting miR-5590-3p 2. ZEB1 transcription promotes immune escape of DLBCL cells through activation of SNHG14 and PD-L1	[154]
	SMAD5-AS1	1. Its downregulation promotes DLBCL cell proliferation 2. Inhibits DLBCL proliferation by sponging miR-135b-5p to upregulate APC expression and inactivate the Wnt/β-catenin pathway	[155]
	PEG10	1. Significantly downregulated in DLBCL 2. Downregulates miR-101-3p levels (miR-101-3p upregulation has an inhibitory effect on DLBCL progression) 3. Associated with tumor proliferation	[156]
	TRERNA1	1. Regulation by the demethylation enzyme ALKBH5 2. Regulates cell proliferation in vivo and ex vivo through m6A methylation	[157]
	NBAT1	1. Reduces APOBEC3A expression 2. Targeting NBAT1 reduces resistance to chemotherapeutic agents (methotrexate or cytarabine) in HBV-infected DLBCL patients	[158]
HL	H19	1. Overexpressed in HL 2. Upregulates AKT protein expression 3. Negative correlation with HL patient prognosis	[159, 160]
	NEAT1	Associated with tumor proliferation	[161]
ENKTCL	BCYRN1	1. Overexpressed in NKTCL 2. Promotes apoptosis and autophagy in ENKTCL cells by affecting the PI3K/AKT/mTOR and p53/mTOR pathways 3. Interferes with the inhibitory effect of ASP on tumor proliferation	[162]
	TP73-AS1	1. High TP73-AS1 blood levels in NKTCL patients 2. TP73-AS1 potentiates the malignant progression of NKTCL by inducing DKK1 promoter methylation	[163]

Abbreviations: BCL: B Cell Lymphoma, HL: Hodgkin's Lymphoma, ENKTCL: Extranodal Natural Killer Cell/T-cell Lymphoma, NKTCL: NK/T cell lymphoma, CTL: Cutaneous T-cell lymphoma, ATCL: Angioimmunoblastic T Cell Lymphoma

and silencing METTL3 decreased cell proliferation and reduced m^6A methylation and pigment epithelium-derived factor (PEDF) total mRNA levels. High levels of PEDF eliminated the inhibitory effect of METTL3 silencing on DLBCL cell proliferation, demonstrating that METTL3 promotes DLBCL development via moderating m^6A levels of PEDF mRNA [174]. The m^6A methyltransferase complex, which brings the m6A methyltransferases METTL3 and METTL14 to their respective mRNA targets and is involved in catalyzing the formation of m^6A, is made up in key part of the nuclear protein known as WT1-associated protein (WTAP). WTAP is overexpressed in various types of malignancies, and it functions as an oncogene. It has been demonstrated that WTAP is upregulated in human NKTCL and silencing WTAP inhibits NK/T cell proliferation while enhancing apoptosis of tumor cells. WTAP also enhances the chemoresistance of NK/T cells to cisplatin by increasing dual specificity phosphatase 6 mRNA levels in an m^6A-dependent manner. Sustained upregulation of WTAP promoted the proliferative capacity of DLBCL cells and improved tumor resistance to apoptosis, and downregulation of WTAP resulted in a significant increase in apoptosis after etoposide treatment [175].

There are two classes of modifying enzymes involved in m^5C: the methyltransferase family (DNMT2/TRDMT1) and the NOP2/Sun domain (NSUN) family (NSUN1-7) [176]. DNMT2 is one of the first identified RNA m^5C methyltransferases, and it was considered a DNA methyltransferase because it has all the structural features of a DNA methyltransferase, except a specific nucleic acid binding region. DNMT2 has important regulatory roles in tissue and organ development, hematopoiesis, and external stress responses [177]. In addition, synergistic interactions between m^5C and m^6A may regulate protein expression. In tumor cells,

NSUN2 catalyzes the m^5C modification, and METTL3 and METTL14 catalyze the m^6A modification, which synergistically increases p21 translation, leading to elevated p21 expression and oxidative stress–induced cellular senescence [178]. NSUN2 is a nucleoprotein that plays a significant role in tissue homeostasis, spindle stability, and early embryogenesis. NSUN2 promotes mRNA stability, regulates miRNA expression, enhances protein synthesis and translation, and influences the expression and translation of key cell cycle regulators [179]. NSUN2 and METTL1 silencing in tumor cells significantly enhanced their sensitivity to 5-fluorouracil. NSUN2 and METTL1 were phosphorylated by ABK and AKT, tRNA modification activity was inhibited by phosphorylation, and overexpression reduced 5-FU sensitivity. Thus, interfering with tRNA methylation may provide a new direction for treatment with 5-FU [180].

Conclusion and outlook

Lymphoma represents a group of malignant tumors that originate from the lymphopoietic system. These tumors are characterized by high recurrence rates, high mortality, and short survival time. DLBCL, the most common clinical malignant lymphoma, is traditionally treated with the R-CHOP regimen as the standard first-line chemotherapy. Although the treatment has high response rates, 30–40% of DLBCL patients ultimately progress to R/R DLBCL and face a fatal outcome. Therefore, identifying new targets for lymphoma treatment and developing new drugs and more effective combination regimens are of clinical importance.

Epigenetics has provided a novel perspective compared to classical genetic theories, paving the way for precision medicine in oncology. Currently, substantial progress has been made in studying lymphoma pathogenesis and targeted drugs. Beyond genetic variants, primarily gene mutations, epigenetic changes play an essential role in lymphoma pathogenesis. Epigenetics-based targeted treatments, such as decitabine and chidamide, have been well received clinically. Additionally, while some epigenetic drugs like pan-HDACi vorinostat and EZH2 selective inhibitor tazemetostat have limited efficacy alone, their combination with other drugs such as immunostimulatory monoclonal antibodies, proteasome inhibitors, or multiple epigenetic drugs has demonstrated high response rates and good tolerability. Nevertheless, in clinical and preclinical studies, investigators should carefully monitor whether combination regimens can manage the incidence of adverse effects.

In summary, the evolution and investigation of epigenetics are crucial to the future realization of more effective precision therapy. However, epigenetic studies alone are insufficient to fully comprehend lymphoma pathogenesis. Integration of multidimensional clinical data with transcriptomics, proteomics, metabolomics, and epigenomics datasets could unveil superior treatment targets and therapeutic regimens with enhanced clinical efficacy. Minimizing the toxic side effects of chemotherapy and other treatments will enhance patient's quality of life.

Abbreviations HL: Hodgkin's lymphoma; NHL: Non-Hodgkin's lymphoma; DLBCL: Diffuse large B cell lymphoma; CAR-T: Chimeric antigen receptor-modified T cell; CHOP: Cyclophosphamide, doxorubicin, vincristine, and prednisone; CHOEP: CHOP-like regimen; SCT: Stem cell transplantation; DNMT: DNA methyltransferases; 5mC: 5-Methylcytosine; EBV: Epstein-Barr virus; BL: Burkitt lymphoma; UHRF1: Ubiquitin-like, containing PHD and RING finger domains, 1; AZA: 5-Azacytidine; ROMI: Romidepsin; CTAs: Cancer testis antigens; PTCL: Peripheral T cell lymphoma; TN: Treatment-naïve; TFH: T follicular helper cell; GC: Germinal center; PRC2: Polycomb repressor complex 2; HDAC: Histone deacetylase; HDACi: Histone deacetylase inhibitors; MCL: Mantle cell lymphoma; ADCC: Antibody-dependent cell-mediated cytotoxicity; MTCL: Mature T cell lymphoma; CTCL: Cutaneous T cell lymphoma; mTOR: Mammalian target of rapamycin; AAK: Aurora A kinase; ABK: Aurora B kinase; AAKi: Aurora A kinase inhibitors; JAKi: Janus kinase inhibitors; C: Completed; R: Recruiting; ANR: Active, not recruiting; DLT: Dose-limiting toxicity; CRR: Complete response rate; MTD: Maximum tolerable dose; ORR: Objective response rate; PRR: Partial response rate; PFS: Progression-free survival; PTCL: Previously untreated peripheral T cell lymphoma; R/R: Relapsed/refractory; ENKTCL: Extranodal natural killer cell/T cell lymphoma; CTL: Cutaneous T cell lymphoma; ATCL: Angioimmunoblastic T cell lymphoma; TCL: T cell lymphoma; MCL: Mature cell lymphoma; AITL: Angioimmunoblastic T cell lymphoma; CFDA: The China Food and Drug Administration; IPI: International prognostic index; CPET regimen: Prednisone, etoposide, and thalidomide; PEL regimen: Prednisone, etoposide, lenalidomide; PD-1: Programmed death-1; PD-L1: Anti-PD1-ligand 1; ICIs: Immune checkpoint inhibitors; ncRNAs: Non-coding RNAs; sncRNA: Small non-coding RNAs; lncRNA: Long-stranded non-coding RNAs; PTCL-NOS: PTCL-not otherwise specified; BCL: B cell lymphoma; m7G: N7-methyluracil; m6A: N6-methyladenosine; m5C: 5-Methylcytosine; METTL3: Methyltransferase 3, N6-adenosine-methyltransferase complex catalytic subunit; PEDF: Pigment epithelium-derived factor; WTAP: WT1-associated protein

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Declarations

Ethics approval and consent to participate Not applicable.

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