Ji et al. Molecular Cancer (2025) 24:66
https://doi.org/10.1186/s12943-025-02255-4

Molecular Cancer

REVIEW

Open Access

# The epigenetic hallmarks of immune cells in cancer

Yu Ji[1,2†], Chu Xiao[1†], Tao Fan[1†], Ziqin Deng[1], Di Wang[1], Wenpeng Cai[1], Jia Li[1], Tianle Liao[1], Chunxiang Li[1*] and Jie He[1*]

## Abstract

Targeting the dysregulation of epigenetic mechanisms in cancer has emerged as a promising therapeutic strategy. Although the significant rationale progress of epigenetic therapies in blocking cancer cells, how epigenetic regulation shapes tumor microenvironment (TME) and establishes antitumor immunity remains less understood. Recent study focus has been put on the epigenetic-mediated changes in the fate of immune cells, including the differentiation, expansion, recruitment, functionalization, and exhaustion of T cells, natural killer (NK) cells, tumor-associated macrophages (TAMs), dendritic cells (DCs), myeloid-derived suppressor cells (MDSCs), and B cells within the TME. Here, we review the latest molecular and clinical insights into how DNA modifications, histone modification, and epitranscriptome-related regulations shape immune cells of various cancers. We also discuss opportunities for leveraging epigenetic therapies to improve cancer immunotherapies. This review provides the epigenetic foundations of cancer immunity and proposes the future direction of combination therapies.

**Keywords** Epigenetics, Immune cells, Cancer immunity, Immunotherapy

## Introduction

Epigenetics focuses on the heritable and reversible regulation of a wide range of cellular biological functions without DNA sequence changes, extensively engages in health and diseases, and is primarily attributed to modulating gene expression and chromatin structures [1]. Especially, epigenetic dysregulation is recognized as one of the hallmarks of cancer, and continuously emerging new epi-therapies are under testing or in clinical application [2].

The immune system is a key factor in controlling and preventing cancer progression. Notably, epigenetic mechanisms dominate the differential trajectories and functional evolutions of immune cells in the development of the immune system, as well as in TME. The immune cell members subject to close attention in cancer immunity include T cells, B cells, tumor-associated macrophages (TAMs), natural killer (NK) cells, dendritic cells(DCs), and myeloid-derived suppressor cells (MDSCs). These cells chemotactically enter TME, interact with each other and cancer cells in multiple ways, and play cancer-inhibiting or cancer-protective functions determined by multilayered factors. Numerous studies have demonstrated that epigenetic modifications of these immune cells are essential in regulating their roles in cancer [3]. Therefore, harnessing the epigenetic programming of immune cells are promising strategy to boost cancer-killing and improve outcomes.

†Yu Ji, Chu Xiao and Tao Fan contributed equally to this work and share the first authorship.

*Correspondence:
Chunxiang Li
lichunxiang@cicams.ac.cn
Jie He
prof.jiehe@gmail.com
[1] Department of Thoracic Surgery, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100021, China
[2] 4+4 Medical Doctor Program, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100730, China

Several epigenetic agents have been approved for hematological cancer indications, and multiple clinical trials are exploring their use in solid cancers. For example, histone deacetylase (HDAC) inhibitors vorinostat and romidepsin have been approved to treat T-cell lymphoma [4], and their application is being investigated in multiple solid cancers including pelvic cancer, non-small cell lung cancer (NSCLC), myeloma, breast cancer, and hepatocellular cancer [5–8]. Notably, some combinations of epi-drugs and immunotherapies achieve favorable responses in clinical trials. DNA methyltransferase (DNMTs) inhibitors or zeste homolog 2 (EZH2) inhibitors combined with immune checkpoint blockers (ICBs) are being evaluated for both hematological malignancy and solid tumors [9]. These attempts suggest that understanding the epigenetic regulation of immune cells in the TME provides the rationale for improving the immunotherapy outcome.

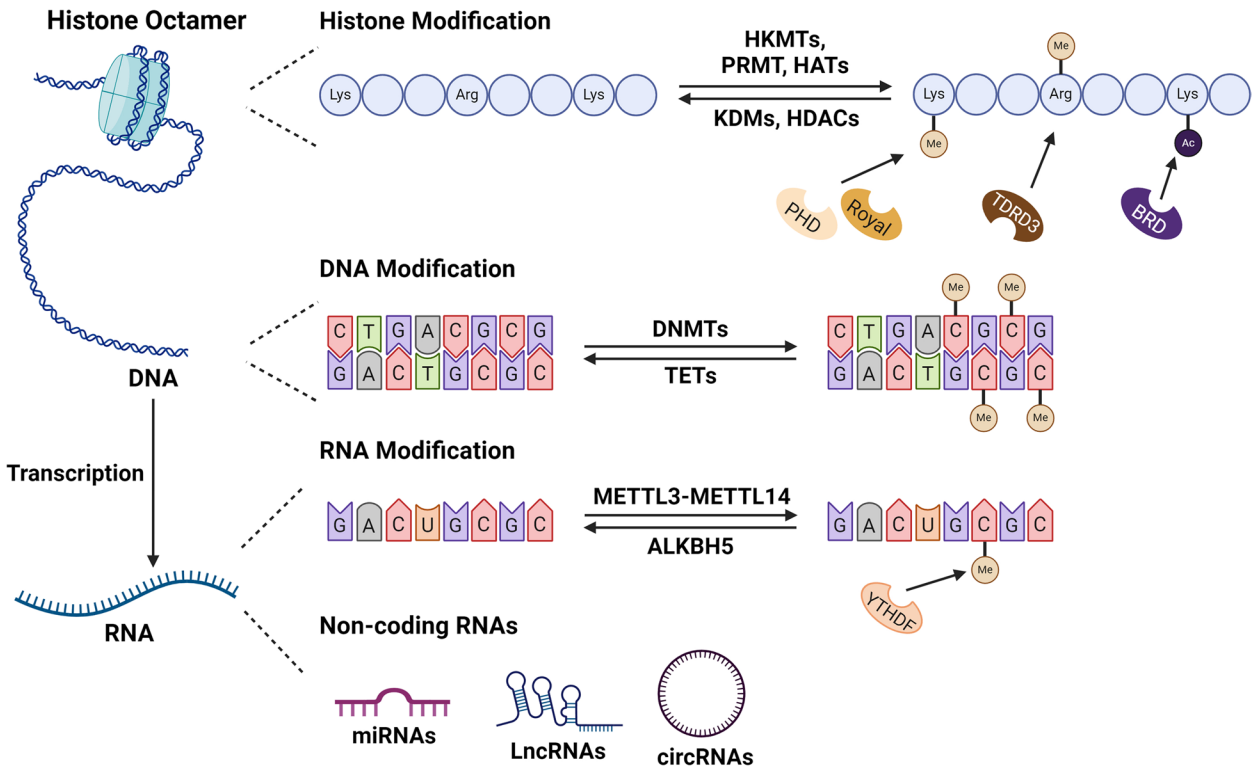
In this review, we introduce the latest studies on molecular pathways and therapeutic prospects of epigenetic strategies in regulating cancer immunity-effective immune cells for malignancy control. We provide an outlook on future clinical applications of epigenetic agents and discuss the potential limitations that need to be addressed.

## Overviews of epigenetics

DNA modifications, histone modification, and epitranscriptomic modification are the key mechanisms that determine immune cell fates and functional evolutions in the TME (Fig. 1).

### DNA methylation

DNA methylation commonly occurs at cytosine-guanine (CpG) dinucleotides and generally leads to gene silencing, with a few cases related to gene activation. DNMTs methylate DNA by transferring methyl groups from




Overview of Epigenetic Processes. The key epigenetic process includes DNA methylation, histone methylation and acetylation, RNA methylation, and non-coding RNA regulations. Histone methylation (Me) and acetylation (Ac) are catalyzed by HMTs and HATs and are removed by KDMs and HDACs, respectively. DNMTs mediate DNA methylation on CpG islands which TETs reverse. Post-transcriptional regulation includes RNA methylation regulated by METTL3-METTL14 complex and ALKBH5, and non-coding RNA targeting mRNA to affect translation. Abbreviations: HKMTs, histone lysine methyltransferases; PRMTs, protein arginine methyltransferases; HATs, histone acetyltransferases; KDMs, histone lysine demethylases; HDACs, histone deacetylases; PHD, the PHD finger group; Royal, the Royal family; TDRD3, Tudor domain-containing protein 3; BRD, Bromodomain containing; DNMTs, DNA methyltransferases; TETs, ten-eleven translocation family enzymes; METTL3-METTL14, methyltransferase-like 3- methyltransferase-like 14 complex; ALKBH5, alkB homologue 5; YTHDF, YTH domain family; miRNAs, microRNAs; LncRNAs, long non-coding RNAs; circRNAs, circular RNAs. Created with BioRender.com

S-adenosyl methionine (SAM) to the C5 position of cytosine (5mC) within CpG dinucleotides. CpG dinucleotides are highly concentrated near transcription start sites (TSS) or promoters [10], regulating 60% of promoters in the human genome [11]. Mechanistically, hypermethylated DNA represses gene expression either by recruiting methyl-CpG-binding domain (MBD) proteins to alter genome accessibility or by blocking transcription-related proteins from binding to DNA strands [11]. In humans, the DNMT family consists of DNMT1, DNMT3a, DNMT3b, and DNMT3L. DNMT1, with the assistance of ubiquitin-like, containing PHD and RING finger domains 1 (UHRF1) in maintaining methylation and induces the methylation on the newly formed DNA strand during replication [12]. DNMT3L supports DNMT3a and DNMT3b in de novo methylation during development [13].

DNA demethylation is primarily catalyzed by ten-eleven translocation (TET) family enzymes. TET oxidizes 5mC to 5-hydroxymethylcytosine (5hmC), followed by active or passive removal of the methyl group [14]. 5hmC acts as a DNMT1 inhibitor to prevent methylation on newly formed strands during replication, known as passive demethylation [15]. In contrast, active demethylation refers to TET-mediated demethylation [16].

#### Histone modification

Within chromatins, DNA strands wrap around an octamer composed of histone H2A, H2B, H3, and H4, while H1 mostly acts as a linker histone, forming a special three-dimensional nucleosome structure. Histone modifications mainly include histone methylation, acetylation, ubiquitination, phosphorylation, and lactylation, and profoundly contribute to transcription regulation [17]. Herein, histone methylation and acetylation are dominant regulatory mechanisms in the cancer course.

Histone methylation has pleiotropic effects on genetic expression depending on the methylation patterns and stoichiometry [18]. For example, trimethylation of histone H3 lysine 4 is the marker of the active promoter, while H3K27me3 signifies gene silencing [19]. Several histone methyltransferases (HMTs) are implicated in malignant processes and cancer immunity [20–23], such as EZH2, have been well-established in shaping cancer immunity [24].

Histone lysine demethylases (KDMs) are divided into the flavin adenine dinucleotide (FAD)-dependent KDM1 family, includes two homologs: lysine-specific demethylase 1 (LSD1, or KDM1a) and LSD2/KDM1b, and the oxygen-dependent JmjC domain-containing protein (JMJD, or KDM2-7) family [25–27]. Notably, strategies targeting several KDMs had shown significant immune-activated effects in cancer, such as LSD1 inhibitors, a promising option for combination therapies with ICBs [28, 29]. Taken together, targeting histone methylation modulators holds great potential for novel therapeutic strategies.

Histone acetylation increases genetic accessibility by adding acetyl group from acetyl-coenzyme A (acetyl-CoA) to the N-terminal of lysine to neutralize the positive charge on histone and reduce its interaction with negatively charged DNA [1], Upregulated expression of histone acetyltransferases (HATs), such as p300/CBP, and altered histone acetylation patterns are linked to malignant behaviors of some cancers like hepatocellular carcinoma (HCC) [30] and leukemia [31, 32]. HAT inhibitors have shown pre-clinical success in treating several solid tumors [33, 34].

HDACs inhibit gene expression by reversing histone acetylation [35]. Aberrant expression of HDACs is a well-established pro-cancer factor, and inhibiting HDAC function provides multiple antitumor effects [4, 36]. Importantly, different HDAC subtypes may play opposing roles in tumor and cancer immunity [37, 38], necessitating careful consideration when targeting HDACs.

In addition to the aforementioned histone modifiers, reader proteins that recognize epigenetic markers on histones and recruit other effectors, are also implicated in cancer immunity. Readers of histone acetylation, known as bromodomain and extra-terminal (BET) proteins including BRD2, BRD3, BRD4, and testis-specific BRDT, contain two tandem bromodomains [39, 40]. Methyllysine-specific readers, divided into the Royal Family and the PHD finger group, contain an aromatic cage to bind methylated histone [41]. The knowledge about readers of methylated arginine is limited. Readers are promising therapeutic targets in multiple cancers, and BET proteins represent [42–45].

#### RNA Regulation

Non-coding RNAs (ncRNAs), categorized into small ncRNAs and long ncRNAs (lncRNAs), are crucial epigenetic regulators targeting messenger RNAs (mRNAs) or proteins to regulate cell functions and fates [1]. Small ncRNAs include microRNA (miRNA), small interfering RNA (siRNA), circular RNA (circRNA), and piwi-interacting RNA (piRNA). Among these, miRNA and circRNA are intensively studied in cancer processes. miRNAs target the 3′-untranslated regions (3'-UTR) of specific mRNAs [46]. circRNAs sponge miRNA to affect gene expression. For example, overexpression of circRNA fibroblast growth factor receptor 1 (circFGFR1) acts as a miR-381-3p sponge, subsequently increasing C-X-C motif chemokine receptor 4 (CXCR4) and enhances the malignancy of NSCLC by excluding the cytotoxic T cells [47]. LncRNAs also have been shown to modulate cancer immunity by transcriptional regulation [48].

RNA modification is another important epigenetic regulation pathway. RNA modifiers modulate genetic expression by adding methyl groups to RNA strands to induce posttranscriptional regulation. The most well-studied modification is $N^6$-methyladenosine (m6A), regulated by methyltransferase-like 3 (METTL3)–METTL14 complex [49]. Methylated RNA can be reversed by the RNA demethylase alkB homologue 5 (ALKBH5) and recognized by YTH domain-containing reader proteins, such as YTH domain family 1 (YTHDF1) and YTHDF2 [50]. Abnormal expression of METTL3, ALKBH5, and YTHDF are associated with cancers [51, 52].

## Epigenetic regulation of immune cells

The epigenetic mechanisms-handled regulations of the differential trajectories and functional evolutions of immune cells are one of the decisive factors in cancer immunity. Here, we mainly refer to T lymphocytes, B lymphocytes, macrophages, NK cells, DCs, and MDSCs which infiltrate TME and perform predominant immunological effects to kill or protect cancer cells. A plethora of studies also validate the feasibility of epigenetic drugs in cancer treatment. Nowadays, therapeutic strategies targeting epigenetic mechanisms have broad prospects in immunotherapy regimens, either as monotherapy or in combination.

### Adaptive immune cells

Adaptive immune cells are the mainstay in executing antitumor immunity, mainly including multiple T lymphocyte subtypes with continuous functionality transition phenotypes or characteristics, and B cells. Understanding how epigenetic mechanisms handle adaptive immune cells in TME may provide novel insights into cancer therapy.

#### *T Cells*

T lymphocytes are the most important and complicated immune players in tumor immunity. After positive selection in thymus, T cells are divided into $CD4^+$ and $CD8^+$ T cells. Epigenetic regulation drives the differentiation of both $CD4^+$ and $CD8^+$ T cells into various functional subtypes during co-evolution with cancers [53, 54]. Importantly, the reversion of immunosuppressive immune cells' differentiation such as regulatory T cells (Tregs), and the reactivation of incapacitated immune cells like exhausted cytotoxic T cells are feasibly achieved by epigenetic harnessing.

**Epigenetic regulation of $CD4^+$ T cells** Cancer-related $CD4^+$ subtypes include T helper 1 (Th1) cells, Th2 cells, Th17 cells, follicular helper T (Tfh) cells, Treg cells, Th9 cells, and Th22 cells. Different $CD4^+$ T lymphocyte subsets secrete various cytokines that impact tumor immunity, as extensively reviewed in previous studies [53, 55]. Th1 cells contribute to inhibiting cancer progress. The T-box transcription factor TBX21 (T-BET) is the major regulator promoting Th1 cell differentiation and cytokines secretion [56], while other factors such as Eomesodermin (EOMES) and STAT family are also implicated [57]. For Treg cells, the determinant is the lineage-specific transcription factor Forkhead box protein P3 (FOXP3), whose expression is mainly regulated by the epigenetic modulation of four regulatory non-coding sequences (CNS0-3) upstream of *Foxp3* locus [58, 59]. Other subsets also show dichotomous functions in different cancer contexts, depending on the specific external stimuli.

Antitumor $CD4^+$ T cell subtypes can either directly activate cytotoxic $CD8^+$ T cells through CD40-CD40L signaling or support the antigen presentation of common DC precursors (CDPs)-derived conventional DC 1 (cDC1) and priming cytotoxic $CD8^+$ T cells [60, 61]. Whereas Treg cells repress antitumor immunity by expressing immune checkpoint molecules on its surface to inhibit DCs and cytotoxic T cells, and by secreting suppressive cytokines TGF-β and IL-10, or suppressive metabolites such as indoleamine 2,3-dioxygenase (IDO) to block T cells function [62]. Therefore, epigenetic regulation of transcription factors affecting $CD4^+$ T cell differentiation and cytokine secretion forms the cornerstone of therapeutic strategies targeting epigenetics [63] (Fig. 2).

The lineage differentiation and cytokine secretion of $CD4^+$ T cell subtypes are partially determined by DNA methylation. TET2 is required for the expression of T-BET, RUNX family transcription factor 2 (RUNX2), and other lineage-specific transcription factors during Th1 differentiation and functionalization [64, 65].

Notably, DNA methylation in shaping Treg cells is important. DNMT1 and TET2 govern DNA methylation within the CNS region of the FOXP3 gene during $CD4^+$ T cell differentiation. A study found that TGF-β could promote FOXP3 expression correlated with hypomethylation of the CpG intronic island, while DNMT1 inhibitor 5-azacytidine (5-aza) or DNMTi knockdown also led to similar Treg-differentiation response of $CD4^+$ T cells [66], while the inhibition or knockout of TET1 and TET2 fail to demethylate CNS2, blocking FOXP3 expression and impairing Treg differentiation and function [67, 68]. Methylation also occurs directly on the *Foxp3* promoter. Especially, the Treg-associated immunosuppressive phenotypes are

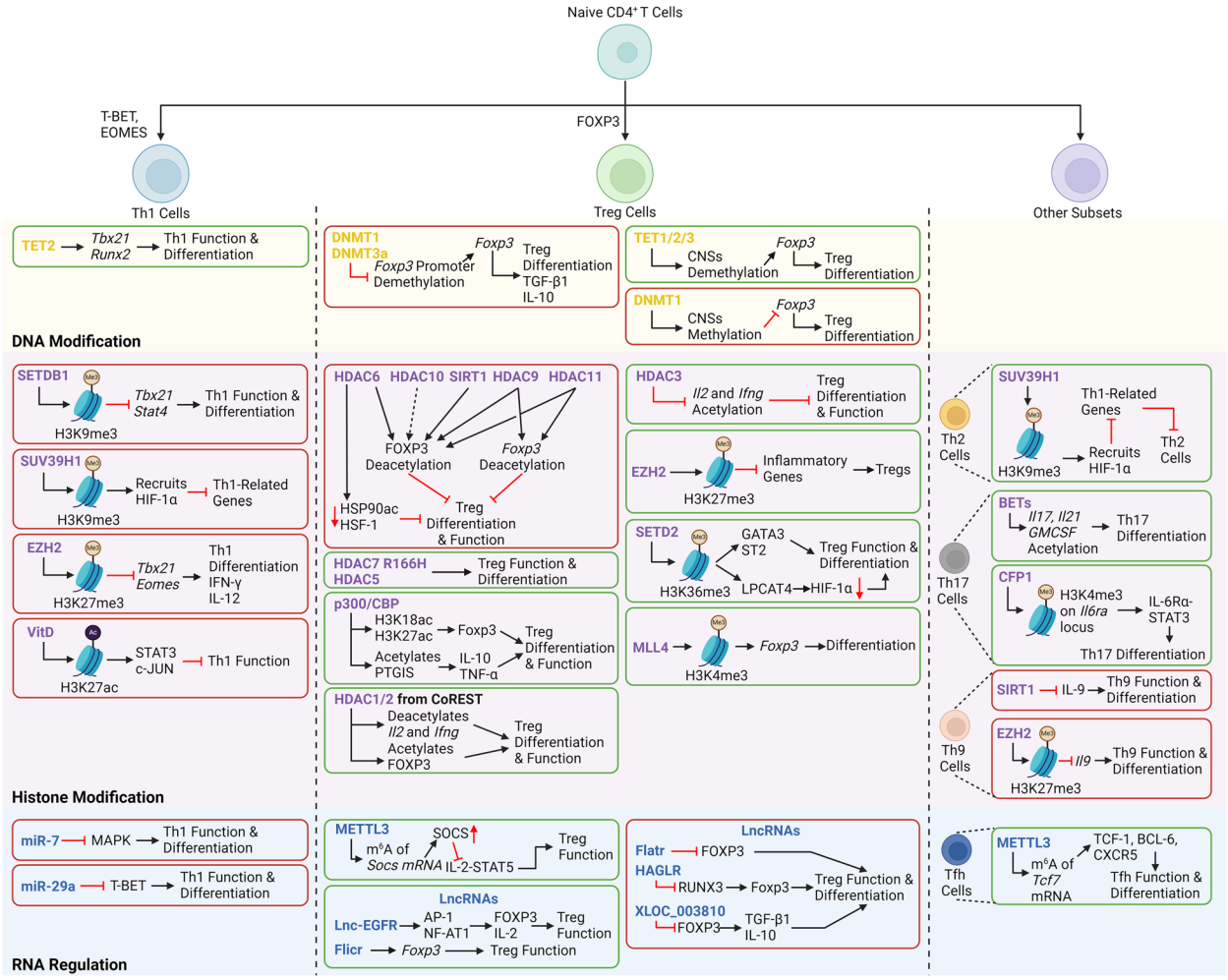



**Fig. 2** Epigenetic regulations of CD4⁺ T Cells. The red and green borders represent the inhibiting- and promoting-effects on the corresponding cell type, respectively. Yellow texts are DNA modifiers, Purple texts are histone modifiers, and Blue texts are RNA modifiers or non-coding RNAs. DNA methylation modifiers such as TETs can promote Th1 and Treg cell functions while DNMTs impair Treg cells' functions. Histone regulators have dual effects on regulating different subtypes of CD4⁺ T cells. miRNAs including miR-7 and miR-29a block Th1 function while other ncRNAs have different roles in Treg cells. Created with BioRender.com

inducible when CD4⁺ T cells coculturing with cancer cells [69]. The unfavorable effect of 5-aza in stimulating Treg cell production should be paid attention to, and two studies regarding leukemia have reported it [70, 71]. Therefore, how to interrupt the effect axis between 5-aza and Treg cells requires more investigation.

Crosstalk among various histone methylation patterns regulates the formation and effects of CD4⁺ T cell subtypes. For example, SETDB1, SUV39H1, and EZH2 respectively induce H3K9me3 and H3K27me3 deposition on cis-acting element regions of *Tbx21*, *Stat4*, and *Eomes* to repress Th1 differentiation and the expression of Th1 lineage-specific genes [63, 72, 73]. Consequently, the high expression of these histone modifiers impairs the antitumor ability of Th1 cells.

The histone methylation patterns on the cis-acting elements of *Foxp3* also regulate Treg cell differentiation, including H3K4me1 at the CNS3, promoter, and 3'UTR of *Foxp3*, as well as H3K4me3 at its promoter to facilitate gene expression [74–76]. In addition, inactive markers H3K27me3 also reduce inflammatory gene expression to promote immune escape [77]. Thus, histone methylation modulators are potential therapeutic targets. MLL4, EZH2, and SETD2 inhibition have been reported to compromise Treg cells in different cancer contexts [78, 79].

Histone methylation is also present in other CD4⁺ T cell subsets, but their roles in cancer remain controversial. For example, Th2 cells secrete IL-4, IL-5, and IL-13 to promote cancer progression [80]. The Th2 lineage is stabilized by SUV39H1-induced H3K9me3 and HIF-α

recruitment through silencing Th1-related genes [72]. For Th17 cells, CFP1 maintains proper H3K4me3 on the *Il6rα* locus, ensuring the activation of the IL-6Rα/STAT3 signaling pathway in Th17 cell differentiation [81]. EZH2 regulates IL-9 expression in Th9 cells, and TGF-β induces Th9 differentiation by activating SMAD2 and SMAD4 which segregate EZH2 from *Il9* locus [82, 83].

Histone acetylation generally represents permissive chromatin structure and transcriptional activation. H3K27 acetylation is a canonical modification marker to represent active enhancers. In Th1 cells, genome-wide H3K27ac generates super-enhancers covering STAT3 and c-JUN to repress Th1-functions [84]. In addition, histone acetylation readers BRD2 and BRD4 also engage in stimulating Th17-related cytokine expression [85].

Extensive studies regarding the role of histone acetylation in $CD4^+$ T Cells focus on Treg cells. HDAC6, HDAC9, HDAC10, HDAC11, and SIRT1 participate in Treg cell differentiation by repressing effector gene expressions and restricting Treg cell-mediate immunosuppression. Intriguingly, they all constrain Treg cell development by deacetylating FOXP3, particularly SIRT1 drives naïve $CD4^+$ T cells into Th1 cells instead of Treg cells [86–89].

In contrast, most type I HDACs are reported to promote Treg cells' function. For example, the CoREST complex containing HDAC1, HDAC2, LSD1, and scaffolding protein RCOR 1, mediates histone deacetylation of *Il2* and *Ifng* and interacts with the FOXP3 protein to maintain Treg cells' function [90]. Moreover, HDAC7 epigenetically maintains FOXP3 expression during Treg cell development [91]. HDAC5 deficiency also weakens the immunosuppressive functions of Treg cells via reducing *Foxp3* transcription. Interestingly, no antitumor effect was observed in HDAC5-knockout mice, attributed to HDAC5 is indispensable for IFN-γ expression in $CD8^+$ T cells, suggesting the dual effects of HDAC5 on tumor immunity [92].

Other acetylation modulators also play roles in Treg cells. Inhibition of the HATs p300/CBP represses H3K18ac and H3K27ac, leading to downregulated *Foxp3* and deacetylated FOXP3 proteins in Treg cells [93, 94]. Similarly, the upregulation of IL-10 during Treg cell differentiation is related to p300/CBP-mediated-prostacyclin synthase acetylation [95]. Therefore, targeting p300/CBP has significant potential for antitumor therapy.

Finally, RNA-targeted regulation has been unrevealed in various $CD4^+$ T cell subtypes. For Th1 cells, miR-7 deficiency enhances the subtypes' differentiation and antitumor effect [96], while miR-29a is important in limiting Th1 cells' function and formation to prevent colitis-to-cancer conversion [97].

RNA modification alters the expression of effect genes that mediate $CD4^+$ T cell function reprogramming. METTL3 catalyzes m6A of mRNA have been reported in several $CD4^+$ T cell subtypes, including the *Socs* gene family in Treg cells and Tcf7 gene in Tfh cells, and lead to the reorganization of downstream signaling pathways to regulate T cell phenotypes [98, 99]. Moreover, some studies focused on the roles of Lnc-RNAs in modulating the growth and differentiation of Treg cells by targeting EGFR, FOXP3, IL-2, and other critical regulatory molecules [100–104].

Overall, the significant involvement of epigenetic regulators in the differentiation and function of $CD4^+$ T cells suggests the promising potential of targeting epigenetics to improve antitumor immunity.

**Epigenetic regulation of $CD8^+$ T cells** Tumor-infiltrating $CD8^+$ T cells comprise various differentiation subtypes, including stem cell memory T (Tscm) cells, central memory T (Tcm) cells, effector memory T (Tem) cells, effector T (Teff) cells, and exhausted T (Tex) cells. Two universally acknowledged models explain $CD8^+$ T cell differentiation: in the circular model, Teff cells either differentiate into memory T cells or get into exhaustion; in the linear model, naïve T cells differentiate step-by-step into Tex cells [54].

Teff cells are activated when recognizing the MHC-I-antigen complex presented by cancer cells or antigen-presenting cells (APCs) and secrete cytotoxic cytokines including IFN-γ, TNF-α, granzymes, and perforin to kill cancer cells [105]. Tex cells signify dysfunctional T cells, differentiating under the stimulation of suppressive cytokines or immune checkpoint molecules in TME [106]. Memory subsets are either a subtype of $CD8^+$ T cells (in the circular model) or an intermediate stage of differentiation (in the linear model), which holds the potential for rapid response to secondary antigen stimulation. Regardless of the models, Epigenetic mechanisms are the essential drivers [54]. Therefore, understanding how epigenetic regulation affects $CD8^+$ T cells can advance therapy strategies for manipulating cancer-infiltrating $CD8^+$ T cells to enhance tumoricidal activity (Fig. 3).

Programming DNA methylation of differentiation and effect genes play fundamental roles in the $CD8^+$ T cell life cycle. During naïve-to-effector differentiation of $CD8^+$ T cells, DNA hypermethylation occurs at the TSS of naïve-related genes, such as *Cxcr2*, *C–c*

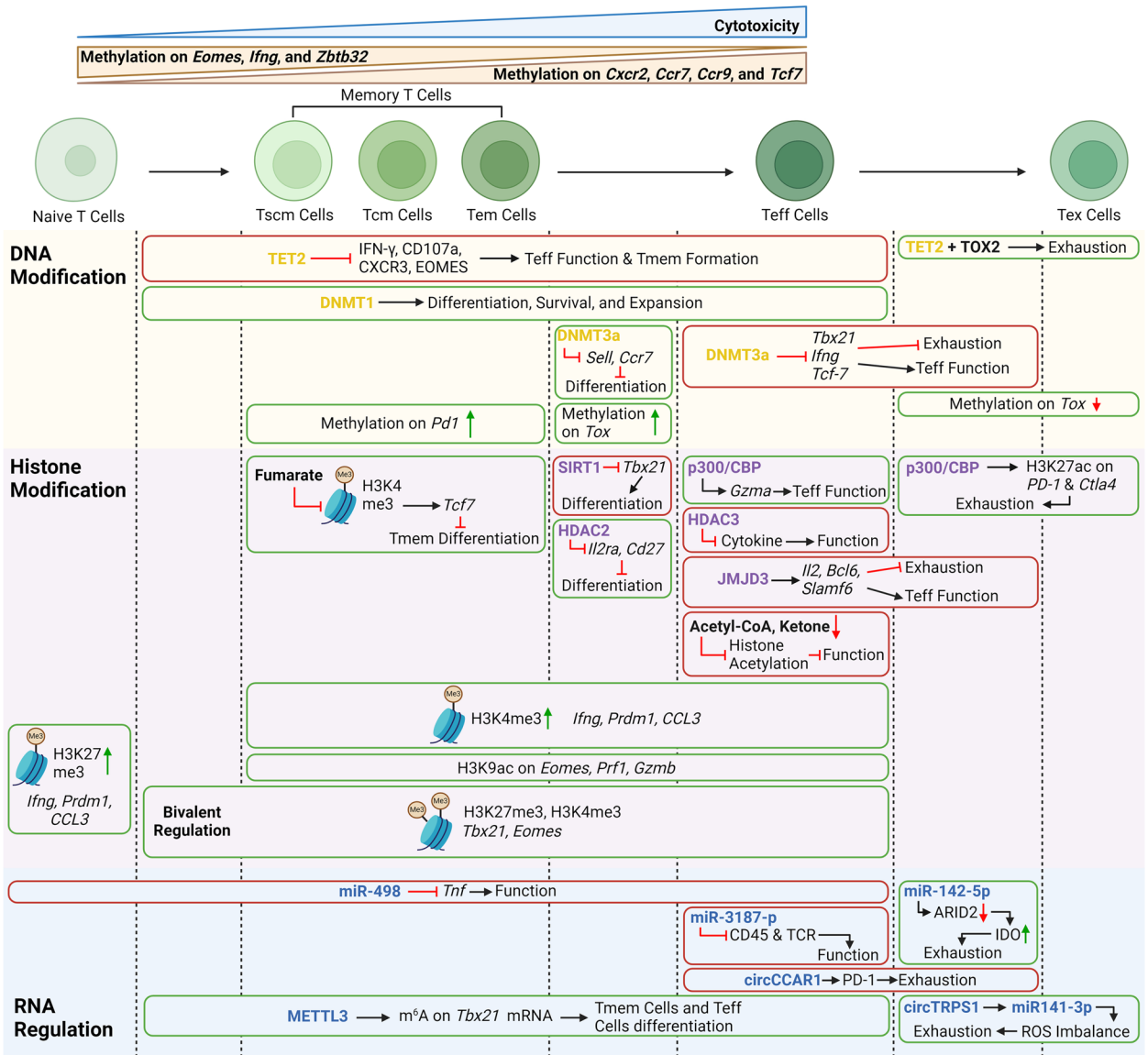



**Fig. 3** Epigenetic regulations of CD8$^+$ T Cells. The different colored borders and modifier texts have the same meanings as Fig. 2. TET2 impairs Teff function and Tmem formation while promoting T cell exhaustion. DNMTs' function in CD8$^+$ T cells should be discussed case-by-case. Histone modifications and their regulators showed complex roles in different stages of the differentiation and functionalization of CD8$^+$ T cells. miRNAs such as miR-498, miR3187-p, and miR-142-5p impair Teff function and accelerate T cell exhaustion, while METTL3 modifies mRNA of Tbx21 to promote Tmem and Teff differentiation. Created with BioRender.com

*motif chemokine receptor 7 (Ccr7)*, *Ccr9*, and *Tcf7*, accompanied by extensively DNA demethylation on effector-associated cytokines or transcription factors, such as *Eomes*, *Ifng*, and *Zinc finger and BTB domain-containing protein 32 (Zbtb32)* [107–109]. Two subsets of Teff cells, terminal Teff (TEs) cells and memory precursors (MPs), also have different DNA methylation landscapes on differentiation-determinant genes such as *PR/SET domain 1 (Prdm1)*, *Runx2*, and *Runx3*. Compared to TEs, *Prdml* locus and gene encoding B lymphocyte-induced maturation protein-1 (Blimp-1) are highly methylated in MPs, whereas *Runx3* has less methylation, aligning with the gain or impairment of memory potential in Blimp-1-deficient or RUNX3-deficient Teff cells, respectively [110–112]. Characteristic DNA methylation landscapes were observed in exhausted T cells [113], linked to upregulated *Dnmt1*, *Dnmt3*, and *Ezh2* expression during the early stage of T cell exhaustion [114]. The anti-programmed cell death 1 (PD-1) promoter region also keeps demethylated in

Tex cells while turning to hypermethylation in functional Tmem cells [115].

When considering specific DNA methylation regulators, DNMT1 is important to $CD8^+$ T lymphocyte differentiation, viability, and expansion [116, 117]. DNMT3a induces de novo DNA methylation at promoter regions of naïve-related genes loci *Sell*, *Ccr7*, and *Tcf7* in early fate decision. DNMT3a deletion fails to repress these genes and impairs naïve-to-Teff formation, thereby diminishing antitumor immunity [112, 118]. In contrast, during or after activation of Teff cells, knocking out *Dnmt3a* causes demethylation on *T-bet*, *Tcf7*, *Ifng*, and *Tbx21*, and renders $CD8^+$ T cells with strengthened effector properties [119]. Segregated DNMT1 diminishes DNA methylation on *Ifng* promoter regions, upregulating *Ifng* and IDO expression to induce T cell exhaustion [120]. Similarly, thymocyte selection-associated high mobility group box protein (TOX), an indispensable regulator in T cell exhaustion, is uniquely methylated during Tex cell formation [121, 122].

TET2 inhibition limits T cell exhaustion by blocking its interaction with TOX2 [123]. Moreover, knocking out MBD2, which targets methylated DNA, postpones MP formation and impairs Tmem cell function by affecting cytokine secretion, leading to an alternative pathway of DNA methylation affecting $CD8^+$ T cell differentiation [124]. Taken together, DNMTs are essential epigenetic regulators in determining the lineage development of $CD8^+$ T cells.

Histone methylation modulates key transcription events for $CD8^+$ T cell differentiation. Primary modulators, such as EZH2, JMJD3, and KDM5 had been stressed in mastering $CD8^+$ T cell regulation. EZH2 expression is upregulated in effector lineages but not memory lineages, corresponding to the increased H3K27me3 levels of NOTCH repressors genes *Numb* and *Fbxw7* in Teff cells [125, 126]. EZH2 inhibition is correlated with impaired Teff cell differentiation and active cell apoptosis, leading to diminished antitumor immunity [125]. In contrast to EZH2, overexpression of JMJD3 reduces H3K27me3 and facilitates the expression of both effector- and memory-associated genes including *Il2*, *Bcl6*, and *Signaling lymphocytic activation molecule family member 6 (Slamf6)*, persisting the effector functions of T cells [127]. Additionally, Tmem cells produce fumarate to metabolically suppress KDM5-mediated H3K4 demethylation on the *Tcf7* promoter to sustain Tmem cell differentiation and antitumor effect [128].

Histone acetylation also regulates phenotype transformations of $CD8^+$ T cells. During differentiation, Tmem and Teff cells gain higher H3K9ac at promoter regions of *Eomes*, *Perforin 1 (Prf1)*, and *Gzmb* compared to naïve T cells [129]. These molecules contribute to the intensive cytotoxic effects of T cells. Consistently, H3K9ac deposition and p300 binding occur at the *Gzma* locus in Teff cells and are less frequent in naïve T or Tmem cells [130]. However, p300 activates the exhaustion program by inducing H3K27ac at *Pd1* and *Ctla4* promoters [131]. Therefore, modifier-targeted strategies should be judiciously selected for different cancer-immune co-evolution states.

Histone deacetylases inactivate gene expression to block $CD8^+$ T cell subtype conversion. Basic leucine zipper transcription factor-ATF-like (BATF) transcriptionally inhibits SIRT1, preventing its deacetylase function, increasing *Tbx21* expression, and benefiting Teff cell differentiation [132]. HDAC3 and loss of acetylation fuel play negative roles in the cancer-killing functionalization of $CD8^+$ T cells. HDAC3 inhibition significantly increases the number of Teff cells secreting cytotoxic cytokines during early activation [133]. Loss of acetylation fuels, including acetyl-CoA and ketones, leads to the deregulation of histone acetylation and impedes effector functions [134, 135].

In conclusion, inhibitors of histone modifiers are potential candidates for reshaping $CD8^+$ T cells in a cancer context to improve patients' outcomes. The specific therapy combinations, doses, and types of cancer to be treated, or even eligible cancer immunity states warrant more studies.

Furthermore, many epigenetic RNA-related regulations have been found in $CD8^+$ T cells. For example, cancer cells initiate immune escape through producing exosomes that contain specific immunosuppressive miRNAs to hamper tumor-infiltrating $CD8^+$ T cells. Advanced CSCC secretes exosomes carrying miR-142-5p to accelerate T-cell exhaustion by reducing AT-rich interactive domain-containing protein 2 (ARID2) [120]. Similarly, melanoma-secreted exosomes contain miR-498 and miR-3187-3p which are internalized by $CD8^+$ T cells, where miR-498 interacts with the 3'UTR of *Tnf* (encoding tumor necrosis factor alpha, TNF-α) mRNA to reduce TNF-α secretion by T cells and miR-3187-3p binds with 3'UTR of *protein tyrosine phosphatase receptor type C (Ptprc)* mRNA, impairing CD45 production and T cell receptor (TCR) signaling in $CD8^+$ T cells [136]. Therefore, inhibiting these evil miRNAs is promising in maintaining an active tumor immune microenvironment. Notably, cancer-derived circRNAs also can be excreted into TME in exosomes and adjust T cell functions [137, 138]. In addition, similar to $CD4^+$ T cells, METTL3 is a modifier for $CD8^+$ T cell differentiation. It targets and stabilizes *Tbx21* mRNA to promote TBX21 expression and subsequent Teff differentiation [139, 140]. Therefore, harnessing RNA-related regulation is a promising target in the field of cancer immunotherapy.

### *B cells*

The role of B lymphocytes in cancer immunity has been underestimated. Recently, studies revealed that B cells are also integral participants in the onco-immune cycle. Antitumor B cells are primarily observed in tertiary lymphoid structures (TLS) where they are associated with DCs to form germinal centers and surrounded by T cells [141]. Especially, the presence of TLS correlates with improved cancer prognosis, and CXCL13 and its receptor CXCR5 are essential for B cell infiltration and TLS formation [142].

Some B cell subtypes perform cancer-inhibiting functions by producing tumor-specific antibodies to induce antibody-dependent cellular cytotoxicity (ADCC) or presenting antigens to T cells. In contrast, regulatory B cells (Breg) are the subtype that produces IL-10 and express anti-programmed cell death ligand 1 (PD-L1) on membranes to drive the differentiation of immunosuppressive T cells [143]. A deep understanding of epigenetic regulations of B cells in cancer may provide novel therapeutic candidates to regulate immunity (Fig. 4).

*Epigenetic regulation of regulatory B cells* Regulators of DNA methylation and histone modification have been found to regulate the immunosuppressive phenotypes of Breg cells. A specific DNA methylation pattern modulates the quick-response IL-10-secreting in Breg cells by establishing a demethylated region at 4.5 kb upstream of *Il10* TSS [144]. TET2 demethylates the promoter of the *Il10* locus in IL-10 secreting Breg cells, and blocking TET2 promotes antitumor immunity against cancer such as HCC [145]. In contrast, HDAC1 inhibition has been reported to limit histone deacetylation on *Il10* promoter regions, enabling nuclear factor kappa B (NF-κB)-mediated IL-10 transcription in Breg cells [146]. Taken together, epigenetic strategies aiming to compromise Breg cells may benefit antitumor immunity.

*Epigenetic regulation of antitumor B cells* The knowledge of epigenetic regulation in antitumor effects of B cells focuses on antigen presentation and ADCC. Increasing H3 and H4K8 acetylation at the *HLA-II* promoter region in B cells ensures they present tumor antigens to $CD4^+$ T cells [147]. CARM1, which methylates H3R17, is also essential for MHC-II expression in B cells [148]. Additionally, HDAC1/2, DNMT1/3a, or HATs recruit to CIITA promoter III (CIITApIII) to promote MHC-II production in B cells, but the detailed mechanisms remain unknown [149].

Plasma cells can secrete antibodies to induce ADCC for cancer-killing, suggesting that epigenetic regulation of

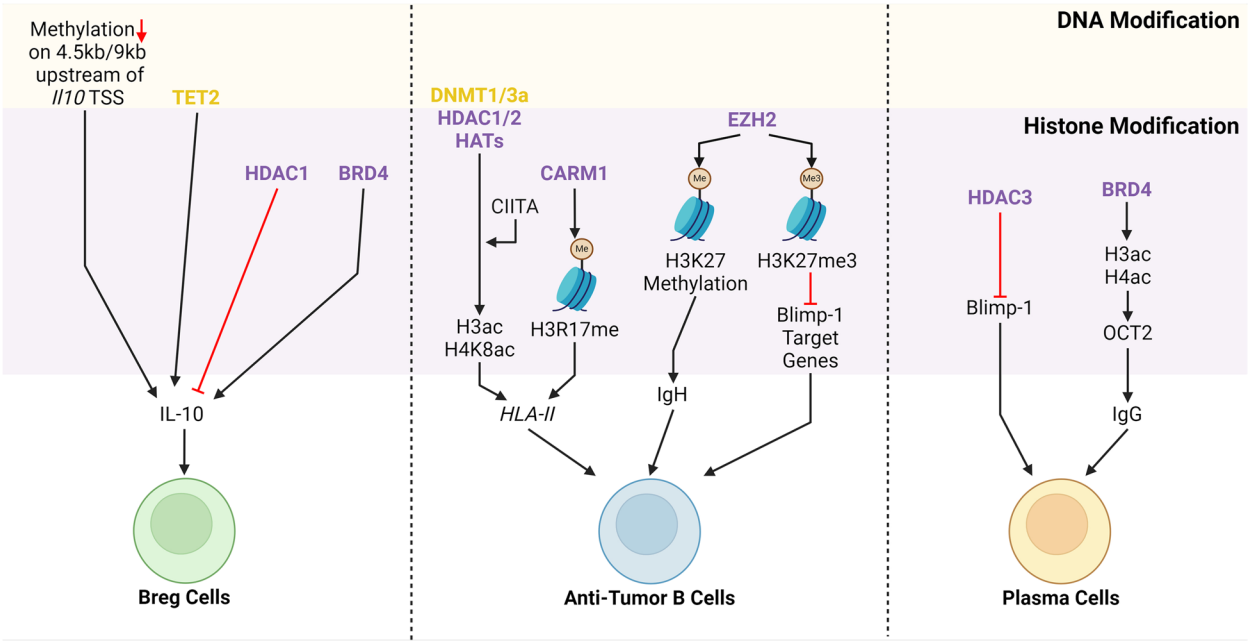



**Fig. 4** Epigenetic regulations of B cells. The different colored modifier texts have the same meanings as Fig. 2. For Breg cells, special methylation patterns are observed at the TSS of *Il10* to facilitate the expression of IL-10. Other epigenetic regulators including TET2 and BRD4 promote Breg cell function while HDAC1 impairs it. In antitumor B cells, DNMT1/3a, HDAC1/2, HATs, CARM1, and EZH2 enhance the cancer-inhibiting effects of antitumor B cells. Similarly, BRD4 promotes the antibody secreted by plasma cells but HDAC3 impairs their function by limiting Blimp-1 expression. Created with BioRender.com

'B-to-plasma' differentiation may provide novel targets for antitumor treatment. Blimp-1 is a crucial regulator during B-to-plasma differentiation [150]. EZH2 trimethylates H3K27 on Blimp-1 target genes to inhibit plasma cell development, whereas EZH2 deficiency-inducible high expression of these genes reduces antibody production in plasma cells [151]. Moreover, HDAC3 inhibition rescues Blimp-1 expression and B cell differentiation [152].

Histone modification readers also regulate antibodies secreted by plasma cells, whereas associated with poor prognosis in some cancer types [153, 154]. For example, BRD4 recognizes the acetyl group on H3 and H4, inducing transcription factor OCT2 to bind with genes encoding IgG in plasma cells and increase IgG production [155], and the level of plasma-cell-derived IgG behaves as an indicator of poor prognosis in hepatomas [153], melanoma [156], and breast cancer [157].

Epigenetic changes of B-cell lymphomagenesis may provide insights into how epigenetics regulates B-cell development. EZH2 deposits H3K27me3 on multiple tumor suppressor genes, such as *Cdkn1b/p27* and *Ckdn1a/p21* in germinal center (GC) B cells. Some of these genes become abnormally hypermethylated and suppressed during the onset of diffuse large B-cell lymphoma (DLBCL), and EZH2 inhibition in DLBCL cells upregulated tumor suppressor genes and stalled cancer proliferation [158]. Moreover, KDM5 inhibition also relieves the suppressed gene expression against GC lymphomas caused by a loss-of-function mutation of KMT2D which fails to methylate H3K4 to the active H3K4me3 state [159]. Although these studies do not directly propose the feasibility or methodology for targeting B cells in the solid tumor TME, they offer preliminary rationales for harnessing the epigenetic modulation of B cells in malignancy.

### Innate immune cells

Serving as the fundamental contributors to cancer immunity, innate immune cells exert direct cytotoxicity against cancer cells and initiate adaptive immune responses. Here, we focus on the four major types of innate immune cells, NK cells, TAMs, DCs, and MDSCs, to give an overview of their epigenetic regulation strategies that bridge cancer courses.

#### *Epigenetic regulation of natural killer cells*

In TME, NK cells are committed to killing cancer cells that express either low or absent MHC-I molecules to escape the adaptive immune response. The NK cell population includes cytotoxic $CD56^{dim}CD16^{+}$($CD56^{dim}$) NK cells and immature $CD56^{bright}CD16^{low}$($CD56^{bright}$) NK cells [160]. NK cells mainly rely on transcription factors EOMES and T-BET. Loss of EOMES leads to NK cells' conversion into intermediate type 1 innate lymphoid cells (InteILC1s) which have low cytotoxicity. Furthermore, NK cells achieve cancer control through surface receptors, including activated and inhibitory subsets. Activated surface receptors help NK cells recognize target cells to induce ADCC, while inhibitory receptors are produced when NK cells recognize MHC-I. Besides directly killing cancer cells, NK cells also recruit cDC1s to TME and promote their differentiation and expansion [161, 162]. Therefore, exogenous interventions to enhance the formation and functionality of cytotoxic NK cell subsets are attractive approaches to strengthening antitumor immunity (Fig. 5).

DNA methylation is vital in NK cell differentiation and the development of their cytotoxic activity. Compared to $CD56^{bright}$ NK cells, $CD56^{dim}$ NK cells exhibit fewer methylated CpG sites at the TSS of the *Ifng* promoter region, conferring them with Th1-like functionality [163]. Similarly, hypermethylation of *Ifng*, *Tnf*, and *Prf1* in TET2-deficient NK cells impairs their tumoricidal capacity [164]. Additionally, *Tet2* mutation leads to hypermethylation at the killer Ig-like receptors (KIRs) locus and also impairs the cytotoxicity of NK cells [164].

Other important NK cell surface receptors include the natural killer group 2 member (NKG2) family, including activated subtypes (NKG2C, NKG2D, NKG2E) and inhibitory subtypes (NKG2A/B). Hypermethylation at the *Nkg2d* promoter occurs more frequently in NK cells from patients with HCC than in tumor-free individuals, suggesting the inhibited NKG2 receptors may impair NK cell cytotoxicity and facilitate tumor development [165]. Similarly, the higher methylation level at the natural cytotoxicity receptor (NCR) member *Nkp46* locus was observed in NK cells from patients with head and neck squamous cell carcinoma (HNSCC), reflecting the extensive dysregulation of DNA methylation in NK cells under cancer contexts [166]. However, treatment of NK cells with DNMT inhibitor will restore inhibitory receptor sialic acid-binding immunoglobulin-like lectin-7 (SIGLEC7) expression and resulting in limited NK cell activity [167]. Thus, manipulating DNA methylation by DMNT inhibitors to achieve NK cell activation is indeterminate.

Histone modification is one of the regulatory steps controlling cytokine secretion in NK cells. For example, the acetylation level at *Ifng* is high in resting NK cells and further increases upon activation [168]. HATs and acetylation readers are key modulators in this process. The impaired recruitment of p300/CBP and H3K27 acetylation to the *Ifng*, *Profilin (Pfn)*, and *Gzmb* promoters would compromise antitumor immunity [169].

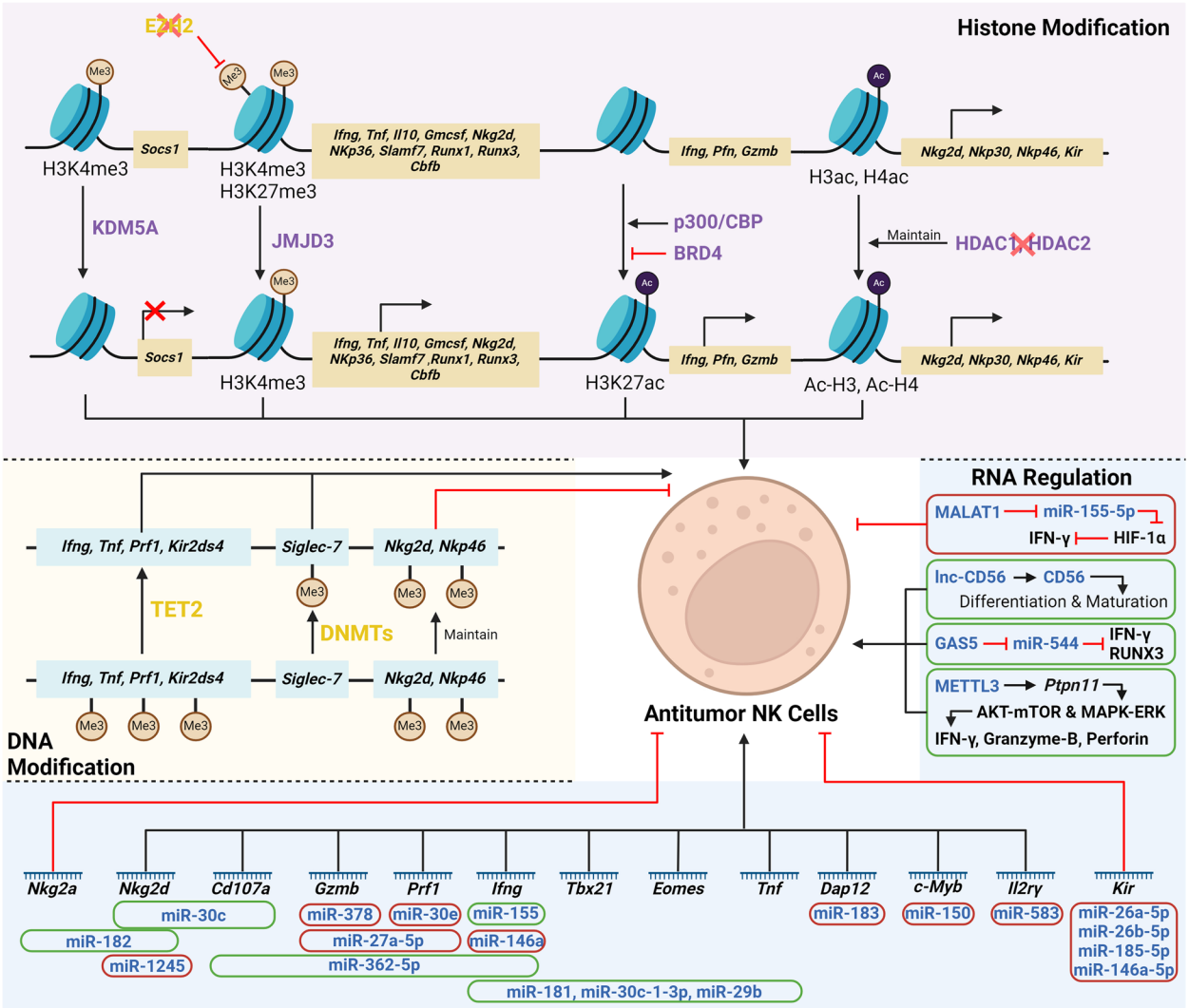



**Fig. 5** Epigenetic regulations of NK Cells. The different colored borders and modifier texts have the same meanings as Fig. 2. The demethylation on *Ifng*, *Tnf*, *Prf1*, and *Kir2ds4*, and the methylation on *Siglec-7* enhance the antitumor function of NK cells. The permissive histone modification on such genes as well as other pro-inflammatory genes also promotes antitumor immunity. RNA modification and ncRNAs exert various effects on NK cells via regulating different genes. Created with BioRender.com

Interestingly, histone acetylation has distinct effects on NK cell functions in different studies, with HDAC inhibitors serving as common methods for artificial intervention in histone acetylation processes. HDACis such as valproic acid (VPA) and vorinostat reduce NKG2D production [170], whereas trichostatin A and entinostat promote NKG2A and NKG2D expression [171, 172]. VPA and vorinostat also reduce NKP30 and NKP46 expression and then diminish NK cells' cytotoxicity [173]. These contrasting results may result from the different HDAC target spectra of each HDACi. For example, VPA and the HDAC3-specific inhibitor RGFP966 inhibit STAT3 phosphorylation which is necessary for NKG2D expression. HAT inhibitors such as curcumin also impair H3K9 acetylation at the *Nkg2d* locus leading to impaired NK cytotoxicity [174]. Conversely, entinostat specifically suppresses HDAC1 and HDAC2, preventing deacetylation on H3 and H4 at the *Nkg2d* promoter, and increasing NKG2D expression [170, 172]. Active histone patterns consisting of H4K8ac and H3K9 demethylation are elicited at *Kir* gene promoters in NK cells and $CD8^+$ T cells. However, this pattern was observed in both activating receptor *Kir2dl4* and inhibitory *Kir2dl3*, indicating the university and variability of epigenetic modulation patterns in NK cells [175]. Therefore, although targeting histone acetylation in NK cells to activate innate immunity

in cancer is theoretically feasible, evidence of clinical practice is needed to develop novel therapeutic strategies.

As for histone methylation, the "poised" state comprised by the coexistence of H3K4 methylation and H3K27me3 is essential for NK cell differentiation and functionalization. For example, terminally differentiated $CD56^{dim}$ cells contain higher levels of H3K4me3 at *Ifng* promoter regions along with high IFN-γ secretion compared to $CD56^{bright}$ cells [163]. In memory NK cells, H3K4me1 deposition at the enhancer region of *Ifng* is vital for IFN-γ production in response to secondary infection [176]. One of the mechanisms explaining H3K4me3-associated NK cell regulation involves the function of KDM5A. KDM5A recruits p50 and undergoes nuclear transportation to inhibit *Socs1* by demethylating H3K4me3. Consequently, the unblocking of JAK2/STAT4 pathways, coupled with the upregulation of IFN-γ production, represents the activation of NK cells [177]. STAT4 can also directly promote H3K4me3 deposition on the promoters of *Runx1*, *Runx3*, and *Core-binding factor subunit beta (Cbfb)*, which are essential for NK cells' clonal expansion, activation, and memory generation [178]. In the H3K27me3-regulating way, JMJD3-induced H3K27 demethylation contributes to the expression of IFN-γ, TNF-α, GM-CSF, and anti-inflammatory IL-10 in NK cells. Although both pro-inflammatory and anti-inflammatory cytokines are affected, blocking JMJD3 with its inhibitor GSK-J4 impairs NK cells' function ultimately [179]. Consistently, the deletion of UTX and JMJD3 leads to H3K27me3 deposition and diminishes NK cell development, while deleting EZH2 can partially restore NK cells' effect function [180]. Mechanistically, EZH2 inhibition increases NKG2D and NKP46 transcription and therefore promotes NK cell cytotoxicity [181]. In summary, manipulating the poised status of H3K4 methylation and H3K27me3 with mature drugs confers more potential strategies in cancer treatment.

Finally, Several RNA-related epigenetic mechanisms regulate cytokines and chemokine secretion in NK cells. miR-378, miR-30e, and miR-27a-5p were found to bind to *Gzmb* and *Prf1* mRNA to limit NK cells' cytotoxicity [182–184]. Whereas, miR-362-5p relieves inhibition of NF-κB pathway by targeting NF-κB-inhibitory modulator cylindromatosis lysine 63 deubiquitase (CYLD) to upregulate IFN-γ, perforin, granzyme-B and CD107a [185]. Other cytotoxic-stimulatory miRNAs include miR-155 and miR-181 promoting cytotoxic molecule production [186–189].

In addition, miRNA-mediated regulation also presents during NK cell differentiation and surface receptor expression, including miR-181, miR-29b, and miR-30c-1-3p promote the production of essential transcription factors like *Tbx21* and *Eomes* [187, 190–192]. Conversely, miR-150 and miR-583 respectively downregulate mRNA levels of transcription factor *c-Myb* and surface receptor *Il2rγ* [193, 194]. As for surface receptor production including NKG2 and KIR families, multiple miRNAs engage in and consist of the intricate miRNA-regulatory network to regulate the efficacy of NK cells in antitumor immunity [195–199].

Other RNA-related mechanisms cover the production of cytotoxic factors and the expression of transcription factors of NK cells' differentiation. For example, lncRNA MALAT1 impairs IFN-γ secretion and NK cell function, while lncRNAs lnc-CD56 and GAS5 exert opposite effects [196, 200, 201]. METTL3 is also indispensable for NK cell function by mediating *Ptpn11* (encoding SHP-2) m6A modification to maintain the activation of AKT-mTOR and MAPK-ERK signaling pathways [202]. Collectively, in terms of the widely developed immunotherapy strategies targeting NK cells in cancer treatment, epigenetic therapies are highly promising options for improving these immunotherapies.

#### *Epigenetic regulation of tumor associated-macrophages*

Tumor associated-macrophages can differentiate into highly heterogeneous subsets in the TME, thereby playing dual roles in cancer control. A more accessible classification terms macrophages that prefer to mediate pro-inflammatory responses M1-like macrophages, while terms another immunosuppressive subgroup activated by IL-4, IL-10, or TGF-β M2-like macrophages [203]. Notably, the growing evidence indicates that some TAM subgroups evolve diverse characteristics that are difficult to explain by the binary classification. For example, a pan-cancer study reveals TAM contains subgroups that express both M1 and M2 gene signatures [204, 205]. Within the long-term co-evolution between immune cells and cancer cells in the TME, the immunosuppressive cytokines produced by cancers, Treg cells, and MDSCs eventually come to dominate, subsequently inducing macrophages to undergo M2 polarization [206]. These immunosuppressive TAMs produce TGF-β, IL-10, and inducible nitric oxide synthase (iNOS) that impair T cells' cytotoxicity, induce Treg cells' differentiation, and suppress DCs' functions [207]. Therefore, the role of epigenetic regulation in TAM differentiation is an important topic, and understanding it holds the potential for the exploit of epigenetic therapies (Fig. 6).

DNA methylation regulates some decisive genes of macrophage polarization and activation. DNMT3b methylates the promoter region of peroxisome proliferator-activated receptor γ1 (PPARγ1), an important M2-related gene, to suppress M2 polarization [208]. In addition, DNMT1 promotes M1-like function by inducing hypermethylation at the SOCS1 promoter

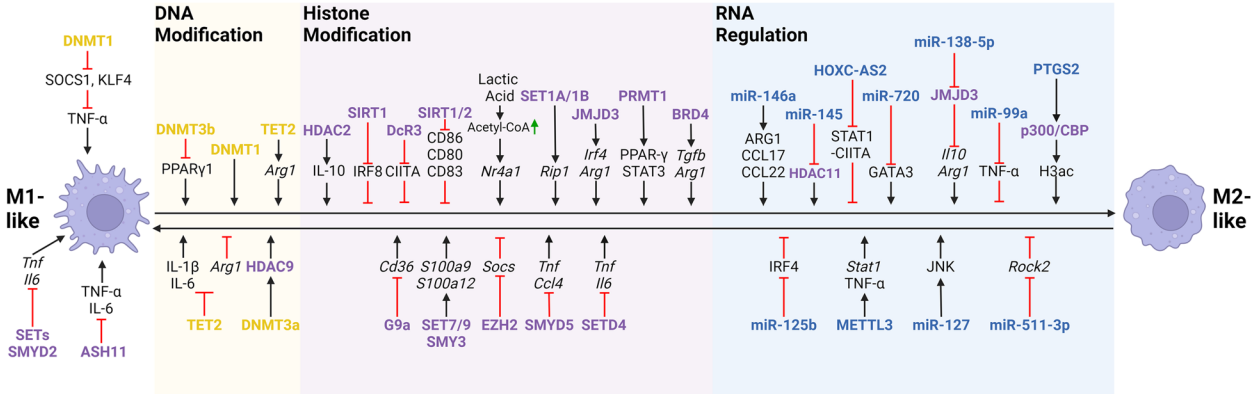



**Fig. 6** Epigenetic regulations of macrophage polarization. The different colored modifier texts have the same meanings as Fig. 2. DNA modifiers such as DNMT1 and TET2 shift TAMs to M2 polarization while DNMT3a promotes M1-like TAMs formations. Similarly, histone modification regulators including HDAC2, PRMT1, and BRD4 enhance M2 polarization and others such as SET7/9 and SMY3 polarize M1-like macrophages. ncRNAs including miRNAs and LncRNAs also perform various effects on TAMs polarization and functions. Created with BioRender.com

to upregulate TNF-α secretion [209, 210]. However, DNMT1 inhibitor 5-aza blocks DNMT1 and redirects polarization to M1-like macrophages instead of M2 polarization in mice ovarian cancer models [211]. Therefore, the noncorresponding results of DNMT1 functions and its inhibitors on TAM maturation need more investigation. TETs also mediate the differentiation induction of macrophages. For example, TAMs are converted from M2-like type to M1-like type in MyeTET2-null mice, which is attributed to the deregulation of immunosuppressive genes such as *Arginase 1* (*Arg1*), an enzyme converts arginine into orthenine and urea instead of cytotoxic NO and ROS [212]. In addition to the above mechanisms, the regulation of DNA methylation in TAMs remains a significant research gap that requires further investigation.

Some studies reported histone modification involved in TAM regulation, including core modifiers and metabolic constituents in the TME. Histone acetylation modulators p300/CBP, HDAC2, SIRT1, SIRT2, and BRD4 in TAMs have been reported to promote cancer development by inducing immunosuppressive polarization of TAMs [213–215]. p300/CBP mediates H3 acetylation at *NF-κB* and *Il6* promoter regions, which promotes M2 polarization and facilitates lung cancer progression [216]. HDAC2 regulates H3 acetylation to promote transcription factor SP-1 expression, facilitating SP-1-mediated IL-10 production, which enhances M2-like activation in lung cancer [217]. The non-traditional HDAC decoy receptor 3 (DcR3) also stimulates M2 polarization by repressing class II transactivator (CIITA) expression, a key MHC-II expression regulator in TAMs. Reduced MHC-II production impairs the tumoricidal function of TAMs, leading to uncontrolled tumor expansion [218].

Histone acetylation is closely linked with various other epigenetic components in macrophages. For instance, DNMT3a creates an active methylation pattern on the *Hdac9* promoter region, and the induced HDAC9 deacetylates tank binding kinase 1 (TBK1) to enable interferon regulatory factor 3 (IRF3) phosphorylation and subsequent type I IFN production [219]. Colorectal cancer-secreted miR-145 represses HDAC11 production in TAMs and consequently promotes IL-10 production and M2 polarization [220].

Especially, the acetyl-CoA metabolism is essential for TAM regulation. Lactic acid secreted by cancer cells can be uptaken by TAMs, fueling the TCA cycle to produce acetyl-CoA, and donating the acetyl group for H3K27ac. H3K27ac promotes transcription of immunosuppressive genes such as *Nuclear receptor subfamily 4 group A member 1 (Nr4a1)* that inhibit pro-inflammatory response and M1 polarization [221].

Several essential gene targets that determine the reprogramming of TAMs are controlled by histone methylation. As for the effector methyltransferases, HKMT G9a has been found to induce macrophages to transition into tumor-promoting phenotypes via di-methylating H3K9 on *Cd36* promoter regions to suppress CD36 transcription [222]. H3K4 methylation-associated modifiers, WDR5 subunit of SET1A/SET1B, SET itself, and ASH1l, as well as H3K36 methylation modifier MYND domain-containing 2 (SMYD2), respectively induce H3K4me3 and H3K36me2 deposition at the promoter regions of *tumor necrosis factor alpha-induced protein 3* (*Tnfaip3*), *receptor-interacting protein 1* (*Rip1*), *Tnf*, and *Il6* [223–225]. These proteins

are upregulated to maintain the M2-like phenotypes of TAMs while blocking M1 signaling. SMYD2 also upregulates TGF-β secretion in TAMs, promoting Treg differentiation and facilitating the establishment of immunosuppressive TME [224]. In addition, SYMD5 catalyzes H4K20me3 deposition on *Tnf* and *Ccl4* promoter regions which suppresses macrophage activation [226].

In contrast, some HKMTs upregulate the expression of proinflammatory factors to activate tumor-inhibiting TAMs. SET7/9 and SYMD3 catalyze H3K4 methylation at the *S100a9* (encoding S100 calcium-binding protein A9) and *S100a12* loci and the two key proteins promote M1 polarization [227]. EZH2 trimethylates H3K27 on *Socs1*, preventing the SOCS1-mediated degradation of tumor necrosis factor receptor-associated factor 6 (TRAF6), thereby allowing TRAF6-related signaling cascade to induce proinflammatory gene expression [228].

Histone demethylases also play roles in TAM differentiation. JMJD3 induces H3K27 demethylation to upregulate the expression of M2 genes including *Irf4* and *Arg1* [229, 230]. However, another study revealed that breast cancer cells produced miR-138-5p to target *Jmjd3* mRNA in TAMs, and the insufficient JMJD3 was correlated to the increasing expression of M2-related genes such as *Il10* and *Arg1* [231]. These two opposing results indicate that studies respectively focus on the upstream or downstream regulation of histone modification and may arrive at distinct conclusions. Another core histone demethylase LSD1 was downregulated during M1 polarization, consistent with the observation that LSD1 inhibition limits H3K4 and H3K9 demethylation to maintain M1 markers expression [232]. Moreover, several studies discovered less common types of histone arginine methylation in macrophages. PRMT1 catalyzes H4R3me2a on *Pparg* promoter regions to upregulate PPAR-γ expression which benefits PPAR-γ-dependent M2 polarization [233]. In human HCCs, PRMT1-mediated STAT3 activation contributes to M2-like TAM formation, while its inhibition decreases tumor burden with less IL-10 and IL-6 production and M2 polarization in mice model [234]. Collectively, targeting various histone modifiers to manipulate TAM polarization towards M1-like or M2-like subtypes may benefit patients with tumors.

Several miRNAs have been revealed to regulate TAM polarization, including miR-19a-3p and miR-720 in breast cancer growth by limiting the M2-like phenotype of TAMs [235, 236]. While miR-146a and miR-99a promote M2 polarization, miR-511-3p, miR-127, and miR-125b link to M1 polarization [237]. LncRNAs HOXC-AS2 promotes M2 polarization by repressing the STAT1-CIITA pathway in TAMs [238].

As for RNA modification, METTL3 has been found to methylate the 3′-UTR of *Stat1* mRNA thus facilitating M1 polarization [239]. Uncontrolled tumor growth occurs when intracellular METTL3 in TAM is deleted [240].

#### *Epigenetic regulation of dendritic cells*

Responsible for antigen presentation, DCs are the central immune cells of the cancer immunity cycle. DC-mediated regulation requires three signals: antigen presentation (primarily by MHC-I and MHC-II molecules), costimulatory signals (activating or inhibiting), and signaling mediated by soluble factors [241]. The major subtypes of DCs are defined as: cDC1 and cDC2, plasmacytoid DCs (pDCs) from both CDPs and lymphoid progenitors, and monocyte-derived DCs (moDCs) [241]. cDC1s engulf extracellular tumor-associated antigens (TAAs, proteins, or other molecules that express on cancer cells while they are often absent or present in much lower quantities on non-malignant cells) and present them on MHC-I molecules to stimulate $CD8^+$ T cells through cross-priming. cDC2s facilitate Th1, Th2, and Th17 differentiation through MHC-II-$CD4^+$ T lymphocyte recognition. MoDCs function similarly to cDC2s in priming $CD4^+$ T cells and are involved in inflammation [242]. pDCs accelerate cDC1 maturation and stimulate the cytotoxicity of T cells and NK cells [243]. DCs also show immune-regulatory roles in multiple physiological or pathological situations, especially in cancer [244, 245]. For example, pDCs suppress T cell activity and promote cancer immune escape via expressing PD-L1 [246]. Simple TAAs-TCR recognition without costimulatory signals also leads to T-cell dysfunction [247]. Additionally, DCs express CD80/86 with higher affinity for binding with CTLA-4 instead of CD28 on T cells, leading to T cell incompetence [248]. Thus, the epigenetic modulation of DCs may help enhance antitumor immunity (Fig. 7a).

There are relatively few studies about how DNA methylation regulates the functions of DCs but the existing findings have offered insights. During monocyte-to-DC differentiation, DNA demethylation occurs at CpG2 and CpG3 of the CD209 promoter region, indicating upregulated CD209 expression in differentiating DC cells compared to monocytes [249]. The alternative expression of DNA methylation modulators, such as DNMT1, DNMT3A, DNMT3B, and TETs, may explain these changes [250]. When responding to heat shock protein gp96, DNMT1 is recruited by NF-κB to genes loci to upregulate Neuropilin-1 (NRP1) in pDCs and lead the immunosuppressive pDCs-Treg interactions [251]. DNMT1 also promotes tumor-associated DC maturation and their antitumor ability by methylating the *Socs1* promoter and facilitating the activation of TLR signaling

[252]. Moreover, TET2 demethylates DC-specific genes or genes encoding antigen-presenting molecules, or pro-inflammatory cytokines in the presence of external IL-4 or cofactor vitamin C, promoting DC differentiation and DC-induced T cell activation [253, 254]. In summary, DNA hypomethylation is conducive to activating DCs. Targeting DNA methylation modifiers may be beneficial for establishing immune-activated TME in a DC-dependent manner.

Histone methylation modifiers EZH2 and DOT1L have been studied in the function and development of DCs. Many studies stressed the important roles of EZH2 in DC maturation [255–260]. For example, EZH2 deficiency deletes H3K27 trimethylation at the *Runx1* promoter, leading to RUNX1 upregulation which suppresses DC maturation [260].

DOT1L upregulates the expression of forkhead box transcription factor M1 (FOXM1) by di-methylating H3K79 on the promoter regions and then facilitates the downstream DC maturation suppressor Wnt family number 5A (WNT5A) upregulation. These DC-associated tumor-promoting effects are observed in pancreatic and colon cancer [261]. Moreover, H3K4me3 deposition at *Il12*, *Cd86*, *Ccr7, Cd40*, *HLA-DR*, and *Stat3* loci is vital for DC maturation and cancer containment [262–264].

Multiple histone acetylation modifiers, such as TIP60, p300/CBP, and HDACs, are involved in regulating the response of DCs to pathological conditions including infection, allergy, and inflammation [265–268]. For example, TIP60-mediated H4K12ac is upregulated in DCs upon alcoholic stimulation, restricting the expression of multiple pro-inflammatory cytokines such as IL-15 and TNF-α [268]. This mechanism may also be applied to cancer, particularly pancreatic cancer secondary to chronic alcoholic abuse.

The role of histone acetylation in DC maturation and function was also reflected in studies involving HDACis. For example, to explore how histone acetylation regulates DC development, authors utilized bone marrow cells from C57BL/6 J mice and stimulated them with different cytokines. The upregulation of PU.1, a key transcription factor in DC differentiation, is associated with H3K9 deacetylation on its promoter regions, unlike the traditional linkage between histone acetylation and increased gene expression. In TSA-treated DCs, the H3K9ac is maintained at *Sfpi1* (encoding PU.1*)*, *Fms-like tyrosine kinase 3* (*Flt3*), and *Irf8* locus, reducing their expression and blocking DCs development [269]. Moreover, VPA treatment impairs CD40, CD80, TNF-α, and IL-6 production, and reduces nuclear levels of IRF8 and IRF3 in DCs, associated with impaired differentiation and dysfunction [270].

Furthermore, METTL3 also plays an important role in DC activation by maintaining the production of costimulatory molecules like CD40 and CD80, and pro-inflammatory cytokines including IL-12 and TNF-α in DCs [271, 272]. However, the role of YTHDF1 in DC cells remains controversial. Wang et al. reported that YTHDF1 upregulates CD40 and CD80 expression in DCs, while Han et al. indicate that knocking out YTHDF1 in DC cells enhances antigens presentation and cross-primes cytotoxic $CD8^+$ T cells against tumors by recognizing m6A on mRNA for lysosomal cathepsins, which are key in process for antigen presentation [273]. Therefore, further investigation into the impact of RNA modification and its reader on DC cells would be required.

Both lncRNA and miRNA also regulate DCs in endogenous or exogenous manners. For example, miR-5119 contributes to PD-L1 elimination in DCs and rescues exhausted T cells in breast tumor-bearing mice [274]. Another study also reported the potential of miR-5119-containing cancer vaccine in cancer therapy [275]. Moreover, miR-212-3p contained in the exosomes from pancreatic cancer cells would impair the antigen-presenting ability of DCs by suppressing regulatory factor X-associated protein (RFXAP) expression, a vital transcription factor of MHC-II [276]. Moreover, lncRNAs also participate in DC regulation by controlling critical gene expression, including HOXA1, STAT3, and HIF-1α [277–280].

Taken together, although most studies exploring the epigenetic regulation of DCs are not in cancer, epigenetic therapies also offer novel strategies for reshaping DC phenotypes to establish more intensive antitumor TME.

#### *Epigenetic regulation of myeloid-derived suppressor cells*

MDSC is also a highly heterogeneous group of immunosuppressive cells within the TME. The two main

(See figure on next page.)

**Fig. 7** Epigenetic regulations of DCs and MDSCs. **A** Epigenetic regulation of DCs; B. Epigenetic regulation of MDSCs. The different colored modifier texts have the same meanings as Fig. 2. In DCs, DNMT1, EZH2, and miR-212-3p repress DCs' cancer-suppressive functions, while other epigenetic regulators such as METTL3, lnc-DC, and YTHDF1 may enhance the antigen presentation ability and antitumor functions of DCs. To regulate MDSCs, histone modifiers such as SETD1B, MLL1, and KAT6A reshape histone modification patterns to promote MDSCs' function and formation. DNMT1, DNMT3a/3b, and TET2 regulate the DNA methylation pattern on the key genes of MDSCs. Posttranscriptional regulators also exert a wide effect on MDSCs by regulating their differentiation, functions, and expansion. Created with BioRender.com

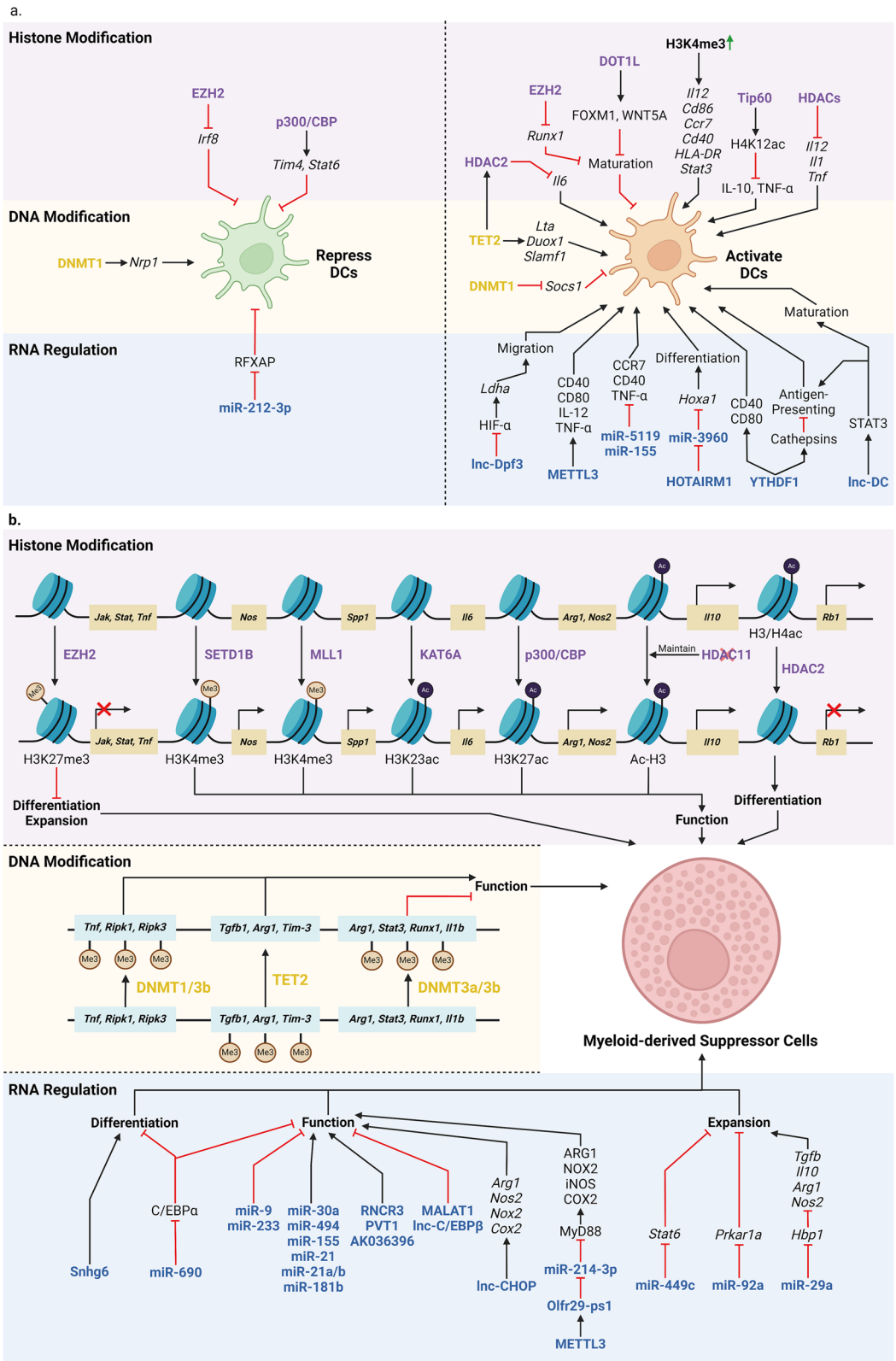



**Fig. 7** (See legend on previous page.)

subgroups include neutrophil-like polymorphonuclear MDSCs (PMN-MDSCs) and monocyte-like mononuclear MDSCs (M-MDSCs) [281]. M-MDSCs repress both antigen-dependent and antigen-independent T cell response by secreting nitric oxide (NO), IL-10, TGF-β, and ARG1, while PMN-MDSC primarily affect antigen-specific T cell response by ROS and reactive nitrogen species (RNS) [282, 283]. MDSCs also produce checkpoint molecules such as CTLA-4 and PD-L1 to attenuate T-cell activity [284, 285]. Additionally, MDSCs coordinate Treg cells and TAMs to exacerbate immunosuppression [286, 287]. Besides interacting with immune cells, MDSCs also directly facilitate cancer metastasis and angiogenesis by producing matrix metalloproteinases (MMPs) [288, 289]. Therefore, debilitating the differentiation and maintenance mechanisms of MDSCs is essential for tumor control, and here we focus on the epigenetic strategies to control MDSCs (Fig. 7b).

DNA methylation is a pivotal mechanism to inhibit the ARG1 and STAT3 expression and impair MDSC functions, and the effect methylases are DNMT3a and DNMT3b [290]. However, some studies found that DNMT1, DNMT3a, and DNMT3b contribute to MDSC-specific hypermethylation of some genes including *Runx1*, *Il1b*, *Tnf*, *Ripk1,* and *Ripk3* to maintain the immune-inhibiting effects of MDSCs and their survival [291, 292].

TET2 promotes MDSCs function and tumor growth by demethylating the promoters of immunosuppressive genes like *Tgfb1*, *Arg1*, and *T-cell immunoglobulin and mucin-domain containing-3* (*Tim-3*) [293]. TET2 deletion would reduce ARG1 expression in MDSCs and increase T cell infiltration [212]. However, another study found that *Tet2*$^{-/-}$ mice lose tumor growth control as TET2 deletion upregulated IL-6 expression and enhanced MDSC expansion in the TME [294]. Therefore, the function of DNA methylation modifiers in MDSCs may exhibit variability in a context-dependent manner and require further investigation.

Histone methylation modifiers profoundly impact MDSCs. EZH2 inhibitors GSK126 and GSK343 promote MDSC expansion by inhibiting H3K27 methylation of differentiation-essential genes and upregulating pro-expansion pathways like JAK-STAT and TNF signaling [295, 296]. Interestingly, in colitis, EZH2 inhibition alleviates symptoms and delays colon cancer onset secondary to colitis [296]. In addition, SETD1B is upregulated in MDSCs to mediate H3K4 trimethylation at the *Nitric oxide synthase 2 (Nos2)* promoter and increases iNOS production to nitrate TCR and STAT1 on T cells, inhibiting their cytotoxicity [297]. The H3K4 methylation-catalyzed protein complex consisting of MLL1, WD repeat domain 5 (WDR5), Absent, small or homeotic discs-like 2 (ASH2L), and RB binding protein 5 (RBBP5) is decreased in MDSCs from lung cancer patients [298]. This is consistent with WDR5-dependent H3K4me3 deposition on the *Secreted phosphoprotein 1 (Spp1)* promoter which enhances the osteopontin (OPN) production in MDSCs. SPP1 interacts with CD44 on T cells and then impairs T cells' function [299].

Notably, 44% of HDAC-related genes were upregulated in immature MDSCs from colorectal cancer (CRC) patients, while these genes were downregulated in PMN-MDSCs. Several HATs' expression in PMN-MDSCs and M-MDSCs are also upregulated [300]. KAT6A and p300/CBP mainly drive the immunosuppressive effects of MDSCs. KAT6A acetylates on K20/K117 of SMAD3 and H3K23, increasing the transcription of tumor-promoting genes such as *Il6* to enable breast cancer metastasis and MDSCs' infiltration [301]. P300/CBP acetylates H3K27 in MDSCs on *Arg1* and *Nos2* promoters to enhance their immunoinhibitory functions [302].

Different HDACs exhibit opposite effects on MDSCs. For example, HDAC11 knockout in mice would result in unlimited tumor growth caused by upregulated IL-10 expression and more MDSCs with intensive immunosuppressive phenotype [303]. Conversely, HDAC2-induced *Retinoblastoma 1* (*Rb1*) promoter deacetylation and gene silencing promote M-MDSC differentiation to PMN-MDSCs, correlated with fostered tumor growth [304]. This evidence supports the pharmacological use of HDACis. For example, HDACi VPA showed inhibition effects on MDSCs by decreasing *Arg1* and *Pdl1* expression [305]. More studies are warranted to explore the efficacy of drugs targeting histone modification in MDSC inhibition and cancer control.

Immunosuppressive miRNAs, such as miR-30a [306], miR-494 [307], miR155, miR-21 [308], miR-449c [309], miR-21a, miR-21b, and miR-181b [298], are upregulated in MDSCs. Take miR-449c as an example, it degrades STAT6 mRNA to activate MDSC expansion and contributes to tumor growth. Immunosuppressive miRNAs can also be taken into MDSCs via exosomal vesicles secreted by cancer cells. Glioma, for instance, produces exosomes containing miR-29a and miR-92a to target *High-mobility group box transcription factor 1 (Hbp1)* and *Protein kinase cAMP-dependent type I regulatory subunit alpha (Prkar1a)* mRNA in MDSCs respectively. HBP1 represses proliferation-related genes, while *Prkar1a* deletion upregulates *Tgfb*, *Il10*, *Arg1*, and *Nos2*. Consequently, miR-29a and miR-92a strengthen the expansion of functional MDSCs [310]. Immunostimulating miRNAs, such as miR-690 [311], miR-9 [312], and miR-223 [313], have been found to restrain MDSC function. For example, miR-690 reduces the level of CCAAT/enhancer-binding protein α (C/EBPα) during MDSC development, delaying

the terminal differentiation and immunosuppression of THC-induced MDSCs [311].

LncRNAs also contribute to the regulation of MDSCs. RNCR3 [314], PVT1 [315], and AK036396 [316] sustain the immunosuppressive function of MDSCs, while MALAT1 [317] and lnc-C/EBPβ [318] repress MDSCs. Furthermore, lncRNAs interact with other epigenetic components. LncRNA Snhg6 induces EZH2 ubiquitination thereby promoting MDSC differentiation [319]. Lnc-CHOP promotes H3K4me3 deposition on the promoter regions of *Arg1*, *Nos2*, *Nox2* (encoding NADPH oxidase 2), and *Cox2* (encoding cyclooxygenase-2) in MDSCs, enhancing their immunosuppressive effects [320]. Additionally, METTL3-induced m6A modification on lncRNA Olfr29-ps1 upregulates its expression and interaction with miR-214-3p, preventing MyD88 inhibition, a positive regulator for MDSC differentiation and function. Olfr29-ps1 overexpression is associated with the upregulation of ARG1, COX2, NOX2, and iNOS in MDSCs [321]. Therefore, targeting ncRNAs in MDSCs may help reduce tumor immune escape by limiting MDSCs' function in the TME.

## Clinical applications of epigenetics agents

Intensive mechanistic studies provide the rationale for developing epi-drugs, and various agents targeting epigenetic regulators showing favorable efficacy in clinical trials [322]. This section summarizes the development, application, and combination therapy strategies of FDA-approved epi-drugs or newly developed epi-drugs that could potentially regulate immune cells within the TME. Clinical trials in progress are also discussed in the context of combining epi-drugs with traditional immunotherapies.

### DNA methylation modulators

The major epi-drugs targeting DNA methylation are DNMTi. Azacitidine, decitabine, clofarabine, and arsenical trioxide are approved for treating hematologic tumors, while several other agents are evaluated in clinical trials [323]. For example, 5-aza-4'-Thio-2'-Deoxycytidine (aza-TdC), an inhibitor of DNMT1, is currently in a phase I study for patients with advanced solid tumors (NCT03366116) [324]. Given the extensive DNMTs-mediated regulations of immune cells within TME, it is promising to evaluate the potential of DNMTis utilized in the context of immunotherapy.

In short, DNMT inhibitors remove DNA methylation to reactivate the suppressed genes and reshape the phenotypes of immune cells. Decitabine treatment significantly inhibits MDSC infiltration and elevates T cell-mediated cytotoxicity in the mice model [292]. However, 5-aza-dC maintains the Treg population with a stable FOXP3-positive phenotype [325].

DNMT inhibitors also engage in converting suppressive M2-like macrophages into cytotoxic M1-like counterparts to enhance antitumor immunity. In the mice breast cancer model, combination treatment of 5-aza-dC and HDACi TSA upregulates M1-related cytokines such as IFN-γ while reducing M2-related cytokines such as IL-10 and IL-4 [326]. Moreover, decitabine stimulates p65 phosphorylation and IL-6 production in macrophages, inducing the formation of M1-like phenotype and T cell activation in the CRC model [327].

Moreover, azacitidine can promote KIR and IFN-γ production in NK cells to enhance NK cell-mediated antitumor immunity [328]. Both decitabine and azacitidine can inhibit suppressive receptor expression including *T cell immunoreceptors with Ig and ITIM domains* (*Tigit*) and *killer cell lectin like receptor G1* (*Klrg1*) to repress NK cells-favored breast cancer metastasis [329]. However, azacitidine or HDACi butyric acid treatment would induce SIGLEC7 expression which impaired NK cell-mediated cancer killing [167].

DCs treated by 5-aza-dC express high levels of CD40 and CD86, while the secretion of T-cell-repressing cytokines IL-10 and IL-27 is downregulated [330]. A combination of azacitidine, romidepsin (a HDACi), and IFN-α2 (ARI) upregulates IRF accessibility to IFN-stimulated genes (ISG) in DCs, increasing DC migration to tumor sites and cross-priming T cell [331]. Similarly, synergizing IFN-α, decitabine, and a DC-targeting DNA vaccine promotes the infiltration of DC, NK cells, and $CD8^+$ T cells in melanoma sites and enhances the antitumor effects [332]. Therefore, DNMT inhibitors enhance antitumor immunity by targeting multiple immune cells, and further investigation to assess the optimizing combination therapy regimens is warranted.

### Histone modification modulators

Current epi-drugs targeting histone modification with potential for clinical application mainly include HDAC inhibitors, EZH2 inhibitors, KDM inhibitors, and BET inhibitors [333, 334].

#### *HDAC and HAT inhibitors*

HDAC and HAT inhibitors reshape the genomic histone acetylation and transcriptional profiles of immune cells to build cancer immunity. Due to the highly heterogeneous functions of 18 human HDAC subtypes [8], HDACis with substrate-specificity makes distinct effects on immune cells. First, HDACis can regulate immunosuppressive components in TME. Vorinostat induces MDSCs apoptosis to strengthen antitumor immunity while treating oral squamous cell carcinoma (OSCC)-bearing mice with

HDACi TSA restricts tumor growth by limiting ARG1 and iNOS expression in MDSCs [335, 336]. Similarly, entinostat represses FOXP3 expression in Treg cells and impairs Treg-driven immunosuppression [337]. Second, HDACi also supports antitumor components. For example, panobinostat maintains H3K27ac at the promoter region of the type I IFN gene to enhance type I IFN expression in the TME [338, 339]. HDAC6 inhibitor AVS100 was shown to facilitate the formation of pro-inflammatory M1-like TAMs and Teff in melanoma and colon cancer [340]. In addition, the HDAC3-specific inhibitor RGFP966 promotes T cells to secrete proinflammatory molecules including granzyme B, IFN-γ, and TNF-α [133]. Histone acetylation modulators also target immune cells in antitumor therapy. GNE-781, an inhibitor of p300/CBP, represses ARG1 and iNOS secretion by MDSCs thereby blocking MDSC-induced immunosuppression [302]. p300/CBP inhibition also impairs Treg differentiation [95].

Nonetheless, some studies also pointed to the potential cancer-promoting effects of HDAC inhibitors. For example, TSA treatment blocks HDAC9-mediated deacetylation on *Foxp3* genes to boost Treg cells [341], while VPA promotes the distribution of H3K9ac and H3K4me3 over *Il6* promoter regions to enhance M2 polarization of macrophages [342]. HDACis such as TSA, VPA, and sodium butyrate (NaB) impair NK cell cytotoxicity [343]. Therefore, the different effect mechanisms of HDACis should be further studied.

#### *BET inhibitors*

BET acts as a reader of histone modification and functions by recruiting other effectors to regulate gene expression. JQ1 is a potent BET bromodomain inhibitor making dichotomous effects on cancer immunity. JQ1 impairs the immunosuppressive functions of Breg cells by blocking BRD4-NF-κB p65 recruitment to the *Il10* promoter region and IL-10 secretion [344]. JQ1 also reduces PD-L1 expression on both DCs and cancer cells [45]. INCB057643 is a novel BET inhibitor evaluated in phase I clinical trial and significantly reduces FOXP3 expression in Treg cells [345]. Another novel BET inhibitor PLX51107 also eliminates Treg cells in the TME and restricts melanoma growth. Notably, the combination of PLX51107 and PD-1 blockade shows remarkable efficacy compared to either single treatment [346].

#### *HKMT and KDM inhibitors*

Due to the active or inactive histone methylation patterns generally regulating gene transcription, HKMT and KDM inhibitors can switch on or off the gene expression. EZH2 is the major therapeutic target for epigenetic therapy development. The EZH2 inhibitor CPI-1205 reduces FOXP3 expression in Treg cells and reshapes them to the Th1-like phenotype [77]. Similarly, a preclinical study regarding the CPI-1205-ipilimumab (anti-CTLA-4) combination achieves favorable patients' responses in bladder cancer, as EZH2 inhibition induces Treg cells into a Teff-like phenotype [347]. This combination also overcomes anti-PD1 therapy resistance by destabilizing Treg cells in liver metastasis [348]. In the nasopharyngeal carcinoma tissue, EZH2 inhibitor DZNep inactivates Treg cells and induces TAA-specific T cell cytotoxicity [349]. Its combination with DNMT inhibitor decitabine and anti-PD-L1 treatment or adoptive T-cell therapy also achieved tumor control by inducing Th1-like chemokine secretion and subsequent cytotoxic $CD8^+$ T cell infiltration in ovarian cancer model [24]. Moreover, EZH2 inhibitors UNC1999 and EPZ005687 can promote NK cell maturation for cancer treatment in HPSCs [181]. There is some evidence for contrary results, such as the MDSC-promoting and Teff cell-inhibiting effects of EZH2 inhibitor GSK126 reported in a study [295].

The well-investigated inhibitors of histone demethylases include JMJD3 inhibitors, such as GSK-J4, and LSD1 inhibitors seclidemstat, both impair antitumor immunity by limiting NK cells' function [179, 350]. The novel nuclear LSD1 phosphorylated at serine 111 (nLSD1p)-specific inhibitor, EPI-111, targets the nLSD1p-EOMES axis in exhausted T cells from immunotherapy-resistant melanoma patients or mouse models, revitalizing dysfunctional T cells for tumoricidal immunity [351]. Overall, regulating histone methylation shows great potential in reprogramming the TME, and corresponding inhibitors have shown favorable effects in several cancer types.

### Combination therapy with epigenetic drugs and immunotherapies

In terms of the significant regulatory effects of epi-drugs, their appropriate coordination with immunotherapies rationally leads to more synergetic therapy efficacy. The most widely used immunotherapies are immune checkpoint blockades (ICBs) and adoptive cell therapy (ACT) [352].

#### *Combination with immune checkpoint blockades*

Several epi-drugs are being investigated with ICBs in clinical trials. The combination of DNMTis with ICBs enhances tumoricidal immunity by upregulating T cell and NK cell infiltration, boosting IFN-γ expression, and reducing T cell exhaustion, MDSCs, and Treg cell infiltration [119, 353]. In treating Hodgkin lymphoma, decitabine combined with anti-PD-1 blocker camerlizumab significantly increases the complete remission (CR) rate (71% versus 32%) and 6-month response rate (100% versus 76%) compared to camerlizumab monotherapy

[354]. Moreover, combining HDACis with ICBs, such as vorinostat plus pembrolizumab or entinostat plus pembrolizumab, receives promising results in NSCLC treatment [355, 356]. The synergization of HDAC6-specific inhibitor nexturastat A with an anti-PD-1 blockade promotes immune cell infiltration and reduces M2-like macrophages in the TME, enhancing antitumor immunity [357]. A regimen of entinostat plus anti-CTLA-4 or anti-PD-1, or a combination of all three, achieves prolonged tumor-free survival in mouse models of pancreatic cancer or breast cancer by suppressing MDSCs and stimulating cytotoxic T cells in the TME [358]. These findings align with molecular evidence of M2-like macrophage impairment and MDSC-mediated immunosuppression in TSA treatment. The use of anti-PD-L1 blockers targets TSA-induced PD-L1 upregulation, improving tumor control and extending survival in tumor-bearing mice [359]. Similarly, combining the EZH2 inhibitor CPI-1205 enhances ipilimumab efficacy in the mice model [347]. The combination of BETi JQ1 and PD-1 antibody reduces Treg cells and increases Th1-like T cell infiltration in mice bearing with lung cancer [360]. Other epi-drugs combined with ICBs such as BETi PLX51107 and HDACi chidamide enhance tumor control in mice models by reprogramming the immune composition of TME [346, 361].

In worth mentioning, that epigenetic drugs can not only enhance immunotherapy efficacy by directly regulating immune cells' function but also via reactivating transposable elements (TEs), a unique DNA sequence that is mobile within the genome of tumor cells and some immune cells [362, 363]. For example, LSD1 inhibitor GSK-LSD1 elevates H3K4me2 and the expression of a group of endogenous retroviruses (ERVs) which subsequently leads to increased double-stress RNA (dsRNA) stress and immunogenicity of cancer cells, along with enhanced T cell infiltration in TME and anti-PD-1 effect. The mechanism of combination therapy has been shown in multiple cancer types [28]. Similarly, the upregulation of treatment-induced neopeptides (t-neopeptides) from ERV-derived polyadenylated transcripts can be presented by MHC molecules and therefore enhances T cell-induced antitumor immunity [364]. Taken together, epi-drugs combined with ICBs elicit substantial potential as a novel therapeutic strategy.

#### *Combination with adoptive cell therapy*

ACT refers to extracorporeal pre-treating immune cells to enhance their antitumor function. The most potent example is chimeric antigen receptor T-cell therapy (CAR-T). T cells are equipped with bio-editing T-cell surface receptors to recognize specific tumor neoantigens (rises from tumor-specific mutations and not expressed in non-malignant cells) to kill cancer cells specifically [365]. Other ACTs such as CAR-NK and CAR-macrophages are under study. Since epigenetic regulation is the hallmark mechanism that reshapes immune cells within the whole cancer immunity cycle, utilizing epi-drugs to reprogram immune cells of ACT is a great potential therapy regimen (Table 1).

Combining epi-drug with ACT aligns to harness epigenetics in immune cells to regulate tumor immunity. Decitabine-treated CAR-T cells showed decreased expression of exhaustion-related genes such as *Eomes*, *Tcf7*, and *Ctla4*, alongside enhanced cytotoxicity and pro-inflammatory cytokine production, indicating the strengthened CAR-T cell function [366]. The class I HDACis M344 and chidamine promote CAR-T cell cytotoxicity by blocking HDAC1 and maintaining H3K27ac, which facilitates transcription of *Tcf4*, *Lef1*, and *Ctnnb1*. These proteins form a transcription complex that activates the H3K27ac-dependent WNT signaling pathway to promote cytokine production, tumoricidal function, and resistance to exhaustion of CAR-T cells [367]. BETi JQ1 and a p300 inhibitor block BRD4-p300 recruitment to the *Batf* promoter region to block BATF expression and maintain the antitumor function of CAR-T cells [368]. *Tet2*-deleted CAR-T cells demonstrate enhanced clinical efficacy in treating chronic lymphocytic leukemia and prostate cancer, suggesting the potential of TET2 inhibitors in sensitizing CAR-T therapy [369, 370]. Moreover, LSD1 inhibitors can used in CAR-T cell preprocessing before ACT [18]. The role of epi-drugs in combination with CAR-NK, CAR-M, or TCR-T lacks experimental evidence. In conclusion, how to utilize epi-drugs in ACT to obtain the most favorable efficacy is worthy of further exploration.

## Discussion

Substantial evidence confirms the regulatory role of epigenetics in immune cells, offering potential strategies for cancer treatment. Multiple epi-drugs are under investigation for clinical use or have been approved for treating various cancers. In this review, we summarize current knowledge of the molecular mechanisms by which epigenetic regulation mediates the development, differentiation, and functional evolution of immune cells, especially their performance in the cancer context.

Great advantages and potentials are presented in epigenetically targeting immune cells in cancer treatment. The most promising one is the epigenetic plasticity of immune cells. For example, developing agents to reactivate METTL3 could enhance antitumor immunity by activating NK cells and DCs [202, 271]. This tack can be

**Table 1** Selected clinical trials combining epigenetic targeting agents and immunotherapies

| Epigenetic Modification | Class | Agents | Cancer Type | Drugs Combination (Target) | Phase (Trial ID) |
|---|---|---|---|---|---|
| **DNA methylation** | **DNMTi** | **Azacitidine** | **MDS** | | **FDA-approved** |
| | | | | Dendritic Cells Vaccination | I (NCT04999943) |
| | | | | NKR-2 (CAR-T) | I (NCT03612739) |
| | | | | Atezolizumab (PD-L1) | Ib (NCT02508870) |
| | | | | Durvalumab (PD-L1) | I (NCT02117219) |
| | | | | Durvalumab (PD-L1) | II (NCT02281084) |
| | | | | Durvalumab (PD-L1) | II (NCT02775903) |
| | | | | Durvalumab (PD-L1) and/or Tremelimumab (CTLA-4) | I (NCT02117219) |
| | | | | Nivolumab (PD-1) | II/III (NCT03092674) |
| | | | | Nivolumab (PD-1) | I/II (NCT03259516) |
| | | | | Nivolumab (PD-1) and Lirilumab (KIR2DL1/2L3) | II (NCT02599649) |
| | | | | Nivolumab (PD-1) and/or Ipilimumab (CTLA-4) | II (NCT02530463) |
| | | | | Pembrolizumab (PD-1) | II (NCT03094637) |
| | | | | Sabatolimab (TIM-3) | II (NCT05201066) |
| | | | | Sabatolimab (TIM-3) | I (NCT03066648) |
| | | | | Tislelizumab (PD-1) | II (NCT06536959) |
| | | | **AML** | | **FDA-approved** |
| | | | | Avelumab (PD-L1) | I/II (NCT02953561) |
| | | | | Avelumab (PD-L1) and/or Gemtuzumab Ozogamicin (CD33) or PF-04518600 (OX40) | Ib/II (NCT03390296) |
| | | | | Durvalumab (PD-L1) | II (NCT02775903) |
| | | | | Lirilumab (KIR2DL1/2L3) | II (NCT02399917) |
| | | | | Nivolumab (PD-1) | I/II (NCT03825367) |
| | | | | Nivolumab (PD-1) | II/III (NCT03092674) |
| | | | | Nivolumab (PD-1) and Relatlimab (LAG-3) | II (NCT04913922) |
| | | | | Nivolumab (PD-1) and/or Ipilimumab (CTLA-4) | II (NCT02397720) |
| | | | | NKR-2 (CAR-T) | I (NCT03612739) |
| | | | | Pembrolizumab (PD-1) | II (NCT04284787) |
| | | | | Pembrolizumab (PD-1) | II (NCT03769532) |
| | | | | Pembrolizumab (PD-1) | II (NCT02845297) |
| | | | | Sabatolimab (TIM-3) | I (NCT03066648) |
| | | | | Tislelizumab (PD-1) | II (NCT06536959) |
| | | | | Vadastuximab talirine (CD33) | I (NCT01902329) |
| | | | | Vadastuximab talirine (CD33) | III (NCT02785900) |
| | | | **JMML** | | **FDA-approved** |
| | | | B-ALL | GDC-0199 (CAR-T) | II (NCT06078306) |
| | | | B-cell Non-Hodgkin Lymphoma | CD19/CD22 (CAR-T) | II (NCT05797948) |
| | | | CML | Sabatolimab (TIM-3) | II (NCT05201066) |
| | | | CRC | Pembrolizumab (PD-1) | II (NCT02260440) |
| | | | | Pembrolizumab (PD-1) with/without Romidepsin (HDAC) | I (NCT02512172) |
| | | | DLBCL | Avelumab (PD-L1) and/or Utomilumab (4-1BB) or Rituximab (CD20) | Ib (NCT02951156) |
| | | | | Obinutuzumab (CD20) and Tucidinostat (HDAC) | II (NCT05823701) |
| | | | Hodgkin Lymphoma | Nivolumab (PD-1) | I (NCT05162976) |
| | | | Melanoma | Pembrolizumab (PD-1) | II (NCT02816021) |
| | | | Microsatellite-stable CRC, Ovarian cancer, Breast cancer | Durvalumab (PD-L1) | II (NCT02811497) |

**Table 1** (continued)

| Epigenetic Modification | Class | Agents | Cancer Type | Drugs Combination (Target) | Phase (Trial ID) |
|---|---|---|---|---|---|
| | | | NSCLC | Nivolumab (PD-1) and Entinostat (HDAC) | II (NCT01928576) |
| | | | | Pembrolizumab (PD-1) | II (NCT02546986) |
| | | | NSCLC, Microsatellite-stable CRC, HNSCC, Urothelial Carcinoma, Melanoma | Pembrolizumab (PD-1) and Epacadostat (IDO-1) | I/II (NCT02959437) |
| | | | Osteosarcoma | Nivolumab (PD-1) | Ib/II (NCT03628209) |
| | | | Ovarian Cancer | Pembrolizumab (PD-1) | II (NCT02900560) |
| | | | Pancreatic Cancer | Pembrolizumab (PD-1) | II (NCT03264404) |
| | | | PTCL | Durvalumab (PD-L1) with/without Romidepsin (HDAC) | I/IIa (NCT03161223) |
| | | **Decitabine** | **MDS** | | **FDA-approved** |
| | | | | Tislelizumab (PD-1) | II/III (NCT03092674) |
| | | | | Dendritic Cells Vaccination | I (NCT04999943) |
| | | | | Ipilimumab (CTLA-4) | I (NCT02890329) |
| | | | | Pembrolizumab (PD-1) | Ib (NCT03969446) |
| | | | | Spartalizumab (PD-1) and/or Sabatolimab (TIM-3) | I (NCT03066648) |
| | | | | Spartalizumab (PD-1) with/without Sabatolimab (TIM-3) | II (NCT05201066) |
| | | | | SX-682 (CXCR1/2) | I (NCT04245397) |
| | | | **AML** | | **FDA-approved** |
| | | | | Pembrolizumab (PD-1) | I/II (NCT02996474) |
| | | | | Camrelizumab (PD-1) | II (NCT04353479) |
| | | | | Ipilimumab (CTLA-4) | I (NCT02890329) |
| | | | | Nivolumab (PD-1) | I (NCT04277442) |
| | | | | Pembrolizumab (PD-1) | Ib (NCT03969446) |
| | | | | Spartalizumab (PD-1) and/or Sabatolimab (TIM-3) | I (NCT03066648) |
| | | | | Tislelizumab (PD-1) | II/III (NCT03092674) |
| | | | | Vadastuximab talirine (CD33) | I (NCT01902329) |
| | | | | Vadastuximab talirine (CD33) | III (NCT02785900) |
| | | | Advanced Esophageal Squamous Cell Carcinoma | Tislelizumab (PD-1) | II (NCT05638984) |
| | | | Breast Cancer | Pembrolizumab (PD-1) | II (NCT02957968) |
| | | | | (With Cedazuridine in Agent ASTX727) Pembrolizumab (PD-1) | I (NCT05673200) |
| | | | CML | Spartalizumab (PD-1) with/without Sabatolimab (TIM-3) | II (NCT05201066) |
| | | | Head and Neck Cancer | Durvalumab (PD-L1) | I (NCT03019003) |
| | | | Hodgkin Lymphoma | Camrelizumab (PD-1) | II/III (NCT04510610) |
| | | | | Camrelizumab (PD-1) | II (NCT03250962) |
| | | | | Camrelizumab (PD-1) with/without Tucidinostat (HDAC) | II (NCT04514081) |
| | | | | Camrelizumab (PD-1) and Tucidinostat (HDAC) | II (NCT04233294) |
| | | | Mucosal Melanoma | Nivolumab (PD-1) | Ib/II (NCT05089370) |
| | | | NSCLC | Nivolumab (PD-1) | II (NCT02664181) |
| | | | NSCLC, Esophageal Carcinoma | Pembrolizumab (PD-1) | I/II (NCT03233724) |
| | | | PMBCL | Camrelizumab (PD-1) | I/II (NCT03346642) |
| | | | PTCL, CTCL | Pembrolizumab (PD-1) | I (NCT03240211) |
| | | **Guadecitabine** | CRC | Nivolumab (PD-1) | Ib/II (NCT03576963) |
| | | | Advanced Liver, Pancreatic, Bile Duct, Gallbladder Cancer | Durvalumab (PD-L1) | Ib (NCT03257761) |
| | | | AML | Atezolizumab (PD-L1) | Ib (NCT02892318) |
| | | | MDS, CML, AML | Atezolizumab (PD-L1) | I/II (NCT02935361) |

**Table 1** (continued)

| Epigenetic Modification | Class | Agents | Cancer Type | Drugs Combination (Target) | Phase (Trial ID) |
|---|---|---|---|---|---|
| | | | Melanoma | Ipilimumab (CTLA-4) | Ib (NCT02608437) |
| | | | NSCLC | Pembrolizumab (PD-1) and Mocetinostat (HDAC) | Ib/II (NCT03220477) |
| | | | NSCLC, Melanoma | Nivolumab (PD-1) and Ipilimumab (CTLA-4) | II (NCT04250246) |
| | | | NSCLC, Prostatic Cancer | Pembrolizumab (PD-1) | I (NCT02998567) |
| | | | Ovarian, Primary Peritoneal, Fallopian Tube Cancer | Pembrolizumab (PD-1) | II (NCT02901899) |
| | | | | Atezolizumab (PD-L1) and CDX-1401 (NY-ESO-1) | I/IIb (NCT03206047) |
| | | | Renal Cancer | Durvalumab (PD-L1) | Ib/II (NCT03308396) |
| | | | SCLC | Durvalumab (PD-L1) and Tremelimumab (CTLA-4) | I (NCT03085849) |
| | | | Urothelial Carcinoma | Atezolizumab (PD-L1) | II (NCT03179943) |
| **Histone Acetylation** | **HDACi** | **Vorinostat** | **CTCL** | | **FDA-approved** |
| | | | Neuroblastoma | Dinutuximab (GD2) | II (NCT02559778) |
| | | | Glioblastoma | Pembrolizumab (PD-1) | I (NCT03426891) |
| | | | Breast Cancer | Pembrolizumab (PD-1) | II (NCT04190056) |
| | | | | Pembrolizumab (PD-1) | II (NCT02395627) |
| | | | DLBCL, FL, Hodgkin Lymphoma | Pembrolizumab (PD-1) | I (NCT03150329) |
| | | | HNSCC, SGC | Pembrolizumab (PD-1) | I/II (NCT02538510) |
| | | | NSCLC | Pembrolizumab (PD-1) | I/II (NCT02638090) |
| | | | Prostate, Renal, Urothelial Cancer | Pembrolizumab (PD-1) | I/Ib (NCT02619253) |
| | | | Squamous Cell Carcinoma | Pembrolizumab (PD-1) | II (NCT04357873) |
| | | **Romidepsin** | **CTCL** | | **FDA-approved** |
| | | | Breast Cancer | Nivolumab (PD-1) | I/II (NCT02393794) |
| | | | CRC | Pembrolizumab (PD-1) with/without Azacitibine (DNMT) | I (NCT02512172) |
| | | | PTCL | Durvalumab (PD-L1) | I/IIa (NCT03161223) |
| | | **Belinostat** | **PTCL** | | **FDA-approved** |
| | | | B-cell Non-Hodgkin Lymphoma | Ibritumomab tiuxetan (CD20) and Rituximab (CD20) | II (NCT01686165) |
| | | | Urothelial Carcinoma | Durvalumab (PD-L1) | I (NCT05154994) |
| | | **Panobinostat** | CRC, Breast Cancer, NSCLC | Spartalizumab (PD-1) | Ib (NCT02890069) |
| | | | DLBCL | Rituximab (CD20) | II (NCT01238692) |
| | | | | Rituximab (CD20) | II (NCT01282476) |
| | | | Melanoma | Ipilimumab (CTLA-4) | I (NCT02032810) |
| | | | Myeloma | Daratumumab (CD38) | I (NCT04956302) |
| | | **Chidamide** | **PTCL** | | **Chinese FDA-apprved** |
| | | | Bladder Cancer | Tislelizumab (PD-1) | II (NCT04562311) |
| | | | DLBCL | Obinutuzumab (CD20) and Azacitidine (DNMT) | II (NCT05823701) |
| | | | Hodgkin Lymphoma | Camrelizumab (PD-1) and Decitabine (DNMT) | II (NCT04233294) |
| | | | | Camrelizumab (PD-1) and Decitabine (DNMT) | II (NCT04514081) |
| | | | CRC | Sintilimab (PD-1) | II (NCT04724239) |
| | | | Melanoma, RCC, NSCLC | Nivolumab (PD-1) | Ib/II (NCT02718066) |
| | | | NSCLC | Envafolimab (PD-L1) | II (NCT05068427) |
| | | | | Pembrolizumab (PD-1) | II (NCT05141357) |
| | | | | Nivolumab (PD-1) | III (NCT04674683) |
| | | **Entinostat** | **Breast Cancer** | | **FDA BTD** |
| | | | Advanced Solid Tumors | Pembrolizumab (PD-1) | I (NCT02909452) |
| | | | Bladder Cancer | Pembrolizumab (PD-1) | II (NCT03978624) |
| | | | Breast Cancer | Atezolizumab (PD-L1) | Ib/II (NCT03280563) |

**Table 1** (continued)

| Epigenetic Modification | Class | Agents | Cancer Type | Drugs Combination (Target) | Phase (Trial ID) |
|---|---|---|---|---|---|
| | | | | Atezolizumab (PD-L1) | II (NCT02708680) |
| | | | | Nivolumab (PD-1) and Ipilimumab (CTLA-4) | I (NCT02453620) |
| | | | | Bintrafusp Alfa (TGF-β & PD-L1) | I (NCT04296942) |
| | | | CNS Tumor, Solid Tumor | Nivolumab (PD-1) | I/II (NCT03838042) |
| | | | HPV-related Cancer, Small Bowel Cancer, Colon Cancer | Bintrafusp Alfa (TGF-β & PD-L1) and NHS-IL12 | I/II (NCT04708470) |
| | | | Lymphoma | Pembrolizumab (PD-1) | II (NCT03179930) |
| | | | MDS | Pembrolizumab (PD-1) | Ib (NCT02936752) |
| | | | Melanoma | Pembrolizumab (PD-1) | II (NCT02697630) |
| | | | | Pembrolizumab (PD-1) | II (NCT03765229) |
| | | | NSCLC | Nivolumab (PD-1) and Azacitidine (DNMT) | II (NCT01928576) |
| | | | NSCLC, Melanoma, CRC | Pembrolizumab (PD-1) | Ib/II (NCT02437136) |
| | | | Ovarian Cancer, Peritoneal Cancer, Fallopian Tube Cancer | Avelumab (PD-L1) | I/II (NCT02915523) |
| | | | Pancreatic Cancer, Cholangiocarcinoma | Nivolumab (PD-1) | II (NCT03250273) |
| | | | RCC | Nivolumab (PD-1) and Ipilimumab (CTLA-4) | II (NCT03552380) |
| | | | | Atezolizumab (PD-L1) | I/II (NCT03024437) |
| | | | SCLC | Atezolizumab (PD-L1) | I (NCT04631029) |
| | | **Mocetinostat** | Hodgkin Lymphoma | Brentuximab Vedotin (CD30) | I/II (NCT02429375) |
| | | | Melanoma | Nivolumab (PD-1) and Ipilimumab (CTLA-4) | Ib (NCT03565406) |
| | | | NSCLC | Nivolumab (PD-1) | II (NCT02954991) |
| | | | | Pembrolizumab (PD-1) and Guadecitabine (DNMT) | Ib/II (NCT03220477) |
| | | | NSCLC, Advanced Solid Tumor | Durvalumab (PD-L1) | I/II (NCT02805660) |
| | | **ACY-241** | NSCLC | Nivolumab (PD-1) | Ib (NCT02635061) |
| | | | NSCLC, Melanoma | Nivolumab (PD-1) and Ipilimumab (CTLA-4) | I (NCT02935790) |
| | | **Valproic acid** | Virus-associated Cancer | Avelumab (PD-L1) | II (NCT03357757) |
| | | | DLBCL | Rituximab (CD20) | I/II (NCT01622439) |
| | | | Glioblastoma | Nivoluman (PD-1) | I (NCT02648633) |
| | | **Tinostamustine** | Melanoma | Nivoluman (PD-1) | I (NCT03903458) |
| | | **Abexinostat** | Advanced Solid Tumors | Pembrolizumab (PD-1) | I (NCT03590054) |
| | | **Domatinostat** | Gastrointestinal Cancers | Avelumab (PD-L1) | II (NCT03812796) |
| | | | Merkel Cell Carcinoma | Avelumab (PD-L1) | II (NCT04393753) |
| | | | | Avelumab (PD-L1) | II (NCT04874831) |
| | | | Melanoma | Nivolumab (PD-1) and Ipilimumab (CTLA-4) | Ib (NCT04133948) |
| | | **Nanatinostat** | EBV + Solid Tumor | Pembrolizumab (PD-1) | Ib/II (NCT05166577) |
| **Histone Methylation** | **EZH2i** | **Tazemetostat** | **FL** | | **FDA-approved** |
| | | | **Epithelioid Sarcoma** | | **FDA-approved** |
| | | | NSCLC | Pembrolizumab (PD-1) | Ib/II (NCT05467748) |
| | | | HNSCC | Pembrolizumab (PD-1) | I/II (NCT04624113) |
| | | | Advanced Solid Tumors | Durvalumab (PD-L1) | II (NCT04705818) |
| | | | FL, DLBCL | Atezolizumab (PD-L1) | I (NCT02220842) |
| | | | Malignant Rhabdoid Tumor, Atypical Teratoid Rhabdoid Tumor, Epithelioid Sarcoma, Chordoma | Nivolumab (PD-1) and Ipilimumab (CTLA-4) | I/II (NCT05407441) |
| | | | Urothelial Carcinoma | Pembrolizumab (PD-1) | I/II (NCT03854474) |
| | | **Valemetostat** | **ATL** | | **Japanese MHLW-approved** |
| | | | FL | Rituximab (CD20) | I/II (NCT05683171) |

**Table 1** (continued)

| Epigenetic Modification | Class | Agents | Cancer Type | Drugs Combination (Target) | Phase (Trial ID) |
|---|---|---|---|---|---|
| | | | HCC | Atezolizumab (PD-L1) | I/II (NCT06294548) |
| | | | HNSCC | Pembrolizumab (PD-1) | Ib/II (NCT05879484) |
| | | | Metastatic Prostate, Urothelial, Renal Cell Cancers | Ipilimumab (CTLA-4) | I (NCT04388852) |
| | | **CPI-1205** | Advanced Solid Tumors | Ipilimumab (CTLA-4) | I/II (NCT03525795) |
| | **LSD1i** | **Seclidemstat** | **Ewing Sarcoma** | | **FDA FTD** |
| | | | Gynecologic Cancer | Pembrolizumab (PD-1) | I (NCT04611139) |
| | | **Iadademstat** | **AML** | | **FDA ODD** |
| | | | **SCLC** | | **FDA ODD** |
| | | | SCLC | Atezolizumab (PD-L1) and Durvalumab (PD-L1) | I/II (NCT06287775) |
| | | **INCB059872** | SCLC | Nivolumab (PD-1) | I/II (NCT02712905) |
| | | | | Nivolumab (PD-1) | I/II (NCT02959437) |
| | | | NSCLC, Microsatellite-stable CRC, HNSCC, Urothelial Carcinoma, Melanoma | Pembrolizumab (PD-1) and Epacadostat (IDO-1) | I/II (NCT02959437) |
| | | **Bomedemstat** | SCLC | Atezolizumab (PD-L1) | I/II (NCT05191797) |
| **Histone Modification Readers** | **BETi** | **BMS-986158** | Selected Advanced Tumours | Nivolumab (PD-1) | I/II (NCT02419417) |
| | | **ZEN-3694** | Breast Cancer | Pembrolizumab (PD-1) | I (NCT05422794) |
| | | | Prostate Cancer | Pembrolizumab (PD-1) | II (NCT04471974) |
| | | | Solid Tumor | Nivolumab (PD-1) and/or Ipilimumab (CTLA-4) | I (NCT04840589) |
| | | **INCB057643** | NSCLC, Microsatellite-stable CRC | Pembrolizumab (PD-1) | I/II (NCT02959437) |

Abbreviations: *MDS* Myelodysplastic syndrome, *AML* Acute myeloid leukemia, *JMML* Juvenile myelomonocytic leukemia, *B-ALL* B cell acute lymphoblastic leukemia, *CML* Chronic myeloid leukemia, *CRC* Colorectal carcinoma, *DLBCL* Diffuse large B cell lymphoma, *NSCLC* Non-small cell lung cancer, *HNSCC* Head and neck squamous carcinoma, *PTCL* Peripheral T-cell lymphoma, *PMBCL* Primary mediastinal large B-cell lymphoma, *CTCL* Cutaneous T-cell lymphoma, *SCLC* Small cell lung cancer, *FL* Follicular lymphoma, *SGC* Salivary gland cancer, *RCC* Renal cell carcinoma, *ATL* Adult T-cell leukaemia/lymphoma

applied to different epigenetics in various immune cells based on molecular rationales. Moreover, the epigenetic changes in cancer cells and immune cells are reversible, meaning that targeting the corresponding epigenetic modulators could re-functionalize genes, reversing cancer cells into a more normal state and immune cells into tumoricidal types [371]. By targeting epigenetic regulators instead of specific mutated proteins, epi-drugs are potentially applicable to multiple cancers.

However, disadvantages come along. As epi-drug targets epigenetic modulators to reprogram the gene expression, it would require appropriate time to observe the response. This would burden the clinical trial as long-term evaluation would be required [372]. Similarly, without a cancer-specific target, targeting epigenetic regulators that are presented in normal cells may bring unwanted side effects. Several clinical trials were terminated due to intolerant toxicity in epi-drug monotherapy or combination with other therapy. Early in 2006, a phase II study of HDACi depsipeptide for metastatic neuroendocrine tumors was terminated due to severe cardiotoxicity [373]. Even approved HDACis have side effects, including cardiotoxicity, sepsis, and myelosuppression [374]. A Phase I/II trial of the vorinostat-rituximab-CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisolone) regimen in DLBCL patients showed a high incidence of febrile neutropenia (38%) and sepsis (19%), along with a low response rate, discouraging its use in the general DLBCL population [375]. Therefore, the prediction and prevention strategies for toxicity and side effects of epi-drugs warrant more research.

The divergent and dichotomous effects of epigenetic regulation are notable. Epi-drugs will reshape immune cells, the interaction between different immune cells, or immune-cancer cell interaction, and the non-target effects are inevitable. For example, HDAC6 inhibition impairs Treg differentiation and function by destabilizing FOXP3, while HDAC10 deletion promotes FOXP3 expression by preventing histone acetylation [86, 87]. The integrated effects of epi-drugs should be considered in the complicated TME. How to balance the effects of epigenetic modulators on each component of TME must be addressed before broader clinical use.

Other limitations such as drug delivery and off-target effects also hinder the clinical use of epi-drugs. Currently approved epi-drugs are exclusively used for hematological cancers. Their applications on solid tumors are limited. Due to the complex TME, drug delivery and exposure may be disturbed, especially the contact of adoptive transferred therapeutic cells to cancer cells. Positive results from the epi-immunotherapy combination may be attributed to immunotherapy drugs converting the TME to a state conducive to epi-drug effectiveness. Further investigation into suitable epi-drug delivery methods, such as using nanoparticles or bispecific antibodies, is required.

Furthermore, off-target effects may impact the clinical use of epigenetic drugs. Metallo-β-lactamase domain-containing protein 2 (MBLAC2) is a common off-target protein of various HDACis. Although the function of MBLAC2 is not well understood, its inhibition by HDACi leads to accumulated extracellular vesicles, highlighting the presence of HDACi off-target effect [376]. Similarly, the LSD1 inhibitor SP-2509 was found to be potentially promiscuous, targeting proteins other than the intended one, leading to unexpected toxicity [377, 378]. To address these problems, CRISPR/Cas9 can be used to create more selective epigenetic modulators, minimizing toxic off-target effects and enhancing drug delivery.

In addition to directly targeting epigenetic regulators, modulating epigenetic modification-related metabolism in immune cells offers the potential for cancer treatment. The TLR4-MyD88-TRIF signaling cascade accelerates glycolysis and the TCA cycle in macrophages, providing more acetyl-CoA for histone acetylation and subsequent M1 polarization of macrophages [379]. Therefore, TLR4 agonists may aid in tumor control. Similarly, increased expression of the methionine transporter SLC43A2 in cancer cells results in greater methionine uptake than surrounding T cells, leading to decreased H3K79me2 deposition in the T cell genome and impaired T-cell cytotoxicity [380]. This finding is consistent with the reduced H3K79me2 and STAT5 in *Dot1l*-deleted $CD8^+$ T cells. Using a tumor-cell-specific SLC43A2 inhibitor may thus enhance tumoricidal T-cell function by restoring H3K79me2 levels. Therefore, manipulating metabolites essential for epigenetic regulations represents another therapeutic strategy.

Moreover, novel epigenetic processes have emerged to determine immune cell functions. For example, p300/CBP catalyzes histone acetylation in TAMs associated with glioblastoma, promoting IL-10 expression and diminishing antitumor T cells [381]. Citrullination also occurs on *Stat1* in TAMs, leading to blockage of MHC-II expression and Teff function [382]. Similarly, histone citrullination contributes to the pro-inflammatory function of T cells in the multiple sclerosis contexts, implicating its potential role in tumor immunity [383]. Therefore, targeting these epigenetic pathways understudies shows great prospects in regulating immune cells in TME.

In summary, leveraging epigenetic regulation of immune cells is feasible to reestablish antitumor immunity. Uncovering molecular mechanisms suggests significant potential for both epi-drug monotherapy and combination with immunotherapy. Enhancing the specificity, optimizing the doses and delivery of existing epigenetic modulators for cancer therapy are important to prevent toxicity and off-target effects. The development of target therapies for unachievable epigenetic components such as ncRNA will lead to further advancements in cancer therapy.

**Acknowledgements**
Not applicable.

**Authors' contributions**
J.H. and C.L. conceived the work. Y.J., C.X., and T.F. drafted the manuscript. Y.J. and C.X. performed visualization. T.F. collected materials and revised the manuscript. Z.D., D.W., W.C., J.L., and T.L. proofread the manuscripts. All authors have read and approved the final manuscript.

**Funding**
This work was supported by the Beijing Natural Science Foundation (L248050, 7242119), the National Natural Science Foundation of China (82473443), and the CAMS Innovation Fund for Medical Sciences (CIFMS) (2021–1-I2M-012).

**Data availability**
No datasets were generated or analysed during the current study.

## Declarations

**Ethics approval and consent to participate**
Not applicable.

**Consent for publications**
Not applicable.

**Competing interests**
The authors declare no competing interests.

Received: 17 November 2024 Accepted: 30 January 2025
Published online: 05 March 2025

**References**

1. Dawson MA, Kouzarides T. Cancer Epigenetics: From Mechanism to Therapy. Cell. 2012;150:12–27.
2. Lu Y, et al. Epigenetic regulation in human cancer: the potential role of epi-drug in cancer therapy. Mol Cancer. 2020;19:79.
3. Cao J, Yan Q. Cancer Epigenetics, Tumor Immunity, and Immunotherapy. Trends Cancer. 2020;6:580–92.
4. West AC, Johnstone RW. New and emerging HDAC inhibitors for cancer treatment. J Clin Invest. 2014;124:30–9.
5. Ree AH, et al. Vorinostat, a histone deacetylase inhibitor, combined with pelvic palliative radiotherapy for gastrointestinal carcinoma: the Pelvic Radiation and Vorinostat (PRAVO) phase 1 study. Lancet Oncol. 2010;11:459–64.
6. Takhar HS, et al. Phase I study evaluating the safety and efficacy of oral panobinostat in combination with radiotherapy or chemoradiotherapy

in patients with inoperable stage III non-small-cell lung cancer. Anticancer Drugs. 2015;26:1069.
7. Hontecillas-Prieto, L. et al. Synergistic Enhancement of Cancer Therapy Using HDAC Inhibitors: Opportunity for Clinical Trials. Front. Genet. 11, (2020).
8. Moran B, Davern M, Reynolds JV, Donlon NE, Lysaght J. The impact of histone deacetylase inhibitors on immune cells and implications for cancer therapy. Cancer Lett. 2023;559: 216121.
9. Chen X, et al. Epigenetic strategies synergize with PD-L1/PD-1 targeted cancer immunotherapies to enhance antitumor responses. Acta Pharm Sin B. 2020;10:723–33.
10. Lyko F. The DNA methyltransferase family: a versatile toolkit for epigenetic regulation. Nat Rev Genet. 2018;19:81–92.
11. Portela A, Esteller M. Epigenetic modifications and human disease. Nat Biotechnol. 2010;28:1057–68.
12. Sharif J, et al. The SRA protein Np95 mediates epigenetic inheritance by recruiting Dnmt1 to methylated DNA. Nature. 2007;450:908–12.
13. Okano M, Bell DW, Haber DA, Li E. DNA Methyltransferases Dnmt3a and Dnmt3b Are Essential for De Novo Methylation and Mammalian Development. Cell. 1999;99:247–57.
14. Kohli RM, Zhang Y. TET enzymes, TDG and the dynamics of DNA demethylation. Nature. 2013;502:472–9.
15. Hashimoto H, et al. Recognition and potential mechanisms for replication and erasure of cytosine hydroxymethylation. Nucleic Acids Res. 2012;40:4841.
16. He Y-F, et al. Tet-Mediated Formation of 5-Carboxylcytosine and Its Excision by TDG in Mammalian DNA. Science. 2011;333:1303–7.
17. Zhang L, Lu Q, Chang C. Epigenetics in Health and Disease. Adv Exp Med Biol. 2020;1253:3–55.
18. Hogg SJ, Beavis PA, Dawson MA, Johnstone RW. Targeting the epigenetic regulation of antitumour immunity. Nat Rev Drug Discov. 2020;19:776–800.
19. Xiao C, et al. H3K4 trimethylation regulates cancer immunity: a promising therapeutic target in combination with immunotherapy. J Immunother Cancer. 2023;11: e005693.
20. Yang Y, Bedford MT. Protein arginine methyltransferases and cancer. Nat Rev Cancer. 2013;13:37–50.
21. Liu J, et al. PRMT1 mediated methylation of cGAS suppresses anti-tumor immunity. Nat Commun. 2023;14:2806.
22. Hu, R. et al. PRMT5 Inhibition Promotes PD-L1 Expression and Immuno-Resistance in Lung Cancer. Front. Immunol. 12, (2022).
23. Fan T, et al. CXXC finger protein 1 (CFP1) bridges the reshaping of genomic H3K4me3 signature to the advancement of lung adenocarcinoma. Signal Transduct Target Ther. 2023;8:369.
24. Peng D, et al. Epigenetic silencing of Th1 type chemokines shapes tumor immunity and immunotherapy. Nature. 2015;527:249–53.
25. Shi Y, et al. Histone Demethylation Mediated by the Nuclear Amine Oxidase Homolog LSD1. Cell. 2004;119:941–53.
26. Huang J, et al. p53 is regulated by the lysine demethylase LSD1. Nature. 2007;449:105–8.
27. Kontaki H, Talianidis I. Lysine methylation regulates E2F1-induced cell death. Mol Cell. 2010;39:152–60.
28. Sheng W, et al. LSD1 Ablation Stimulates Anti-tumor Immunity and Enables Checkpoint Blockade. Cell. 2018;174:549-563.e19.
29. Cai W, et al. Targeting LSD1 in cancer: Molecular elucidation and recent advances. Cancer Lett. 2024;598: 217093.
30. Tsang FH-C, et al. Aberrant Super-Enhancer Landscape in Human Hepatocellular Carcinoma. Hepatology. 2019;69:2502.
31. Mansour MR, et al. An oncogenic super-enhancer formed through somatic mutation of a noncoding intergenic element. Science. 2014;346:1373–7.
32. Garcia-Carpizo V, et al. CREBBP/EP300 bromodomains are critical to sustain the GATA1/MYC regulatory axis in proliferation. Epigenetics Chromatin. 2018;11:30.
33. Yan G, et al. Selective Inhibition of p300 HAT Blocks Cell Cycle Progression, Induces Cellular Senescence, and Inhibits the DNA Damage Response in Melanoma Cells. J Invest Dermatol. 2013;133:2444–52.
34. Lasko LM, et al. Discovery of a selective catalytic p300/CBP inhibitor that targets lineage-specific tumours. Nature. 2017;550:128–32.
35. Seto E, Yoshida M. Erasers of Histone Acetylation: The Histone Deacetylase Enzymes. Cold Spring Harb Perspect Biol. 2014;6:a018713.
36. Falkenberg KJ, Johnstone RW. Histone deacetylases and their inhibitors in cancer, neurological diseases and immune disorders. Nat Rev Drug Discov. 2014;13:673–91.
37. Buglio D, et al. HDAC11 plays an essential role in regulating OX40 ligand expression in Hodgkin lymphoma. Blood. 2011;117:2910–7.
38. Bhaskara S, et al. Hdac3 Is Essential for the Maintenance of Chromatin Structure and Genome Stability. Cancer Cell. 2010;18:436–47.
39. Dai E, et al. Epigenetic modulation of antitumor immunity for improved cancer immunotherapy. Mol Cancer. 2021;20:171.
40. VanDemark AP, et al. Autoregulation of the Rsc4 Tandem Bromodomain by Gcn5 Acetylation. Mol Cell. 2007;27:817–28.
41. Musselman CA, Lalonde M-E, Côté J, Kutateladze TG. Perceiving the epigenetic landscape through histone readers. Nat Struct Mol Biol. 2012;19:1218–27.
42. Mertz JA, et al. Targeting MYC dependence in cancer by inhibiting BET bromodomains. Proc Natl Acad Sci. 2011;108:16669–74.
43. Faivre EJ, et al. Selective inhibition of the BD2 bromodomain of BET proteins in prostate cancer. Nature. 2020;578:306–10.
44. Andrikopoulou A, Liontos M, Koutsoukos K, Dimopoulos M-A, Zagouri F. Clinical perspectives of BET inhibition in ovarian cancer. Cell Oncol. 2021;44:237–49.
45. Zhu H, et al. BET Bromodomain Inhibition Promotes Anti-tumor Immunity by Suppressing PD-L1 Expression. Cell Rep. 2016;16:2829–37.
46. Calin GA, Croce CM. MicroRNA signatures in human cancers. Nat Rev Cancer. 2006;6:857–66.
47. Zhang P-F, et al. Circular RNA circFGFR1 promotes progression and anti-PD-1 resistance by sponging miR-381-3p in non-small cell lung cancer cells. Mol Cancer. 2019;18:179.
48. Statello L, Guo C-J, Chen L-L, Huarte M. Gene regulation by long non-coding RNAs and its biological functions. Nat Rev Mol Cell Biol. 2021;22:96–118.
49. Liu J, et al. A METTL3–METTL14 complex mediates mammalian nuclear RNA N6-adenosine methylation. Nat Chem Biol. 2014;10:93–5.
50. Barbieri I, Kouzarides T. Role of RNA modifications in cancer. Nat Rev Cancer. 2020;20:303–22.
51. Zhang S, et al. m6A Demethylase ALKBH5 Maintains Tumorigenicity of Glioblastoma Stem-like Cells by Sustaining FOXM1 Expression and Cell Proliferation Program. Cancer Cell. 2017;31:591-606.e6.
52. Paris J, et al. Targeting the RNA m6A Reader YTHDF2 Selectively Compromises Cancer Stem Cells in Acute Myeloid Leukemia. Cell Stem Cell. 2019;25:137-148.e6.
53. Speiser DE, Chijioke O, Schaeuble K, Münz C. CD4+ T cells in cancer. Nat Cancer. 2023;4:317–29.
54. Henning AN, Roychoudhuri R, Restifo NP. Epigenetic control of CD8+ T cell differentiation. Nat Rev Immunol. 2018;18:340–56.
55. Sun L, Su Y, Jiao A, Wang X, Zhang B. T cells in health and disease. Signal Transduct Target Ther. 2023;8:1–50.
56. Szabo SJ, et al. A Novel Transcription Factor, T-bet, Directs Th1 Lineage Commitment. Cell. 2000;100:655–69.
57. Zhu J, Yamane H, Paul WE. Differentiation of Effector CD4 T Cell Populations. Annu Rev Immunol. 2010;28:445–89.
58. Lee W, Lee GR. Transcriptional regulation and development of regulatory T cells. Exp Mol Med. 2018;50:e456–e456.
59. Zheng Y, et al. Role of conserved non-coding DNA elements in the Foxp3 gene in regulatory T-cell fate. Nature. 2010;463:808–12.
60. Lei X, et al. CD4+ helper T cells endow cDC1 with cancer-impeding functions in the human tumor micro-environment. Nat Commun. 2023;14:217.
61. Schoenberger SP, Toes REM, van der Voort EIH, Offringa R, Melief CJM. T-cell help for cytotoxic T lymphocytes is mediated by CD40–CD40L interactions. Nature. 1998;393:480–3.
62. Ohue Y, Nishikawa H. Regulatory T (Treg) cells in cancer: Can Treg cells be a new therapeutic target? Cancer Sci. 2019;110:2080–9.
63. Tumes DJ, et al. The Polycomb Protein Ezh2 Regulates Differentiation and Plasticity of CD4+ T Helper Type 1 and Type 2 Cells. Immunity. 2013;39:819–32.
64. Baessler A, et al. Tet2 deletion in CD4+ T cells disrupts Th1 lineage commitment in memory cells and enhances T follicular helper cell recall responses to viral rechallenge. Proc Natl Acad Sci. 2023;120:e2218324120.

65. Ichiyama K, et al. The Methylcytosine Dioxygenase Tet2 Promotes DNA Demethylation and Activation of Cytokine Gene Expression in T Cells. Immunity. 2015;42:613–26.
66. Kim H-P, Leonard WJ. CREB/ATF-dependent T cell receptor–induced FoxP3 gene expression: a role for DNA methylation. J Exp Med. 2007;204:1543–51.
67. Yang R, et al. Hydrogen Sulfide Promotes Tet1- and Tet2-Mediated Foxp3 Demethylation to Drive Regulatory T Cell Differentiation and Maintain Immune Homeostasis. Immunity. 2015;43:251–63.
68. Yue X, et al. Control of Foxp3 stability through modulation of TET activity. J Exp Med. 2016;213:377–97.
69. Ke X, et al. Non-small-cell lung cancer-induced immunosuppression by increased human regulatory T cells via Foxp3 promoter demethylation. Cancer Immunol Immunother. 2016;65:587–99.
70. Costantini B, et al. The effects of 5-azacytidine on the function and number of regulatory T cells and T-effectors in myelodysplastic syndrome. Haematologica. 2013;98:1196–205.
71. Stübig, T. et al. 5-Azacytidine Promotes an Inhibitory T-Cell Phenotype and Impairs Immune Mediated Antileukemic Activity. (2014) https://doi.org/10.1155/2014/418292.
72. Allan RS, et al. An epigenetic silencing pathway controlling T helper 2 cell lineage commitment. Nature. 2012;487:249–53.
73. Adoue V, et al. The Histone Methyltransferase SETDB1 Controls T Helper Cell Lineage Integrity by Repressing Endogenous Retroviruses. Immunity. 2019;50:629-644.e8.
74. Feng Y, et al. A mechanism for expansion of regulatory T-cell repertoire and its role in self-tolerance. Nature. 2015;528:132–6.
75. Placek K, et al. MLL4 prepares the enhancer landscape for Foxp3 induction via chromatin looping. Nat Immunol. 2017;18:1035–45.
76. Floess S, et al. Epigenetic Control of the foxp3 Locus in Regulatory T Cells. Plos Biol. 2007;5:e38.
77. Wang D, et al. Targeting EZH2 Reprograms Intratumoral Regulatory T Cells to Enhance Cancer Immunity. Cell Rep. 2018;23:3262–74.
78. Xiao X, et al. EZH2 deficiency attenuates Treg differentiation in rheumatoid arthritis. J Autoimmun. 2020;108:102404.
79. Ding Z, et al. Setd2 supports GATA3+ST2+ thymic-derived Treg cells and suppresses intestinal inflammation. Nat Commun. 2022;13:7468.
80. Hong S, et al. Roles of Idiotype-Specific T Cells in Myeloma Cell Growth and Survival: Th1 and CTL Cells Are Tumoricidal while Th2 Cells Promote Tumor Growth. Cancer Res. 2008;68:8456–64.
81. Lin, F. et al. Epigenetic initiation of the TH17 differentiation program is promoted by Cxxc finger protein 1. Sci. Adv. 5, eaax1608 (2019).
82. Wang Y, et al. Histone Deacetylase SIRT1 negatively regulates the differentiation of Interleukin-9-producing CD4+ T Cells. Immunity. 2016;44:1337–49.
83. Wang A, et al. Cutting Edge: Smad2 and Smad4 Regulate TGF-β–Mediated Il9 Gene Expression via EZH2 Displacement. J Immunol. 2013;191:4908–12.
84. Chauss D, et al. Autocrine vitamin D signaling switches off pro-inflammatory programs of TH1 cells. Nat Immunol. 2022;23:62–74.
85. Mele DA, et al. BET bromodomain inhibition suppresses TH17-mediated pathology. J Exp Med. 2013;210:2181–90.
86. Beier, U. H. et al. Histone Deacetylases 6 and 9 and Sirtuin-1 Control Foxp3+ Regulatory T Cell Function Through Shared and Isoform-Specific Mechanisms. Sci. Signal. 5, ra45–ra45 (2012).
87. Dahiya S, et al. HDAC10 deletion promotes Foxp3+ T-regulatory cell function. Sci Rep. 2020;10:424.
88. Huang J, et al. Histone/protein deacetylase 11 targeting promotes Foxp3+ Treg function. Sci Rep. 2017;7:8626.
89. Daenthanasanmak A, et al. Targeting Sirt-1 controls GVHD by inhibiting T-cell allo-response and promoting Treg stability in mice. Blood. 2019;133:266–79.
90. Xiong Y, et al. Inhibiting the coregulator CoREST impairs Foxp3$^{+}$ Treg function and promotes antitumor immunity. J Clin Invest. 2020;130:1830–42.
91. Axisa PP. et al. A multiple sclerosis–protective coding variant reveals an essential role for HDAC7 in regulatory T cells. Sci Transl Med. 2022;14:eabl3651.
92. Xiao H, et al. HDAC5 controls the functions of Foxp3+ T-regulatory and CD8+ T cells. Int J Cancer. 2016;138:2477–86.
93. Liu Y, et al. Inhibition of p300 impairs Foxp3+ T regulatory cell function and promotes antitumor immunity. Nat Med. 2013;19:1173–7.
94. Ghosh S, et al. Regulatory T Cell Modulation by CBP/EP300 Bromodomain Inhibition *. J Biol Chem. 2016;291:13014–27.
95. Castillo J, et al. CBP/p300 Drives the Differentiation of Regulatory T Cells through Transcriptional and Non-Transcriptional Mechanisms. Cancer Res. 2019;79:3916–27.
96. Chang X, et al. MiR-7 deficiency promotes Th1 polarization of CD4+T cells and enhances the antitumor effect in adoptive cell therapy for lung cancer. Immunol Res. 2024;72:134–46.
97. Czopik AK, et al. HIF-2α-dependent induction of miR-29a restrains TH1 activity during T cell dependent colitis. Nat Commun. 2024;15:8042.
98. Tong J, et al. m6A mRNA methylation sustains Treg suppressive functions. Cell Res. 2018;28:253–6.
99. Yao Y, et al. METTL3-dependent m6A modification programs T follicular helper cell differentiation. Nat Commun. 2021;12:1333.
100. Jiang R, et al. The long noncoding RNA lnc-EGFR stimulates T-regulatory cells differentiation thus promoting hepatocellular carcinoma immune evasion. Nat Commun. 2017;8:15129.
101. Zemmour D, Pratama A, Loughhead SM, Mathis D, Benoist C. Flicr, a long noncoding RNA, modulates Foxp3 expression and autoimmunity. Proc Natl Acad Sci. 2017;114:E3472–80.
102. Yan W, et al. Knockdown of lncRNA HAGLR promotes Treg cell differentiation through increasing the RUNX3 level in dermatomyositis. J Mol Histol. 2022;53:413–21.
103. Chen Z, Ke X, Wang X, Kang H, Hong S. LncRNA JPX contributes to Treg/Th17 imbalance in allergic rhinitis via targeting the miR-378g/CCL5 axis. Immunopharmacol Immunotoxicol. 2022;44:519–24.
104. Niu L, Jiang J, Yin Y, Hu B. LncRNA XLOC_003810 modulates thymic Th17/Treg balance in myasthenia gravis with thymoma. Clin Exp Pharmacol Physiol. 2020;47:989–96.
105. Raskov H, Orhan A, Christensen JP, Gögenur I. Cytotoxic CD8+ T cells in cancer and cancer immunotherapy. Br J Cancer. 2021;124:359–67.
106. Jiang Y, Li Y, Zhu B. T-cell exhaustion in the tumor microenvironment. Cell Death Dis. 2015;6:e1792–e1792.
107. Scharer CD, Barwick BG, Youngblood BA, Ahmed R, Boss JM. Global DNA Methylation Remodeling Accompanies CD8 T Cell Effector Function. J Immunol. 2013;191:3419–29.
108. Rodriguez RM, et al. Epigenetic Networks Regulate the Transcriptional Program in Memory and Terminally Differentiated CD8+ T Cells. J Immunol. 2017;198:937–49.
109. Scott-Browne JP, et al. Dynamic Changes in Chromatin Accessibility Occur in CD8+ T Cells Responding to Viral Infection. Immunity. 2016;45:1327–40.
110. Wang D, et al. The Transcription factor Runx3 establishes chromatin accessibility of cis-regulatory landscapes that drive memory cytotoxic T lymphocyte formation. Immunity. 2018;48:659-674.e6.
111. Rutishauser RL, et al. Transcriptional Repressor Blimp-1 Promotes CD8+ T Cell Terminal Differentiation and Represses the Acquisition of Central Memory T Cell Properties. Immunity. 2009;31:296–308.
112. Youngblood B, et al. Effector CD8 T cells dedifferentiate into long-lived memory cells. Nature. 2017;552:404–9.
113. Belk JA, Daniel B, Satpathy AT. Epigenetic regulation of T cell exhaustion. Nat Immunol. 2022;23:848–60.
114. Schietinger A, et al. Tumor-Specific T Cell Dysfunction Is a Dynamic Antigen-Driven Differentiation Program Initiated Early during Tumorigenesis. Immunity. 2016;45:389–401.
115. Ahn E, et al. Demethylation of the PD-1 Promoter Is Imprinted during the Effector Phase of CD8 T Cell Exhaustion. J Virol. 2016;90:8934–46.
116. Lee PP, et al. A Critical Role for Dnmt1 and DNA Methylation in T Cell Development, Function, and Survival. Immunity. 2001;15:763–74.
117. Chappell C, Beard C, Altman J, Jaenisch R, Jacob J. DNA Methylation by DNA Methyltransferase 1 Is Critical for Effector CD8 T Cell Expansion1. J Immunol. 2006;176:4562–72.
118. Ladle BH, et al. De novo DNA methylation by DNA methyltransferase 3a controls early effector CD8+ T-cell fate decisions following activation. Proc Natl Acad Sci. 2016;113:10631–6.
119. Ghoneim HE, et al. De Novo Epigenetic Programs Inhibit PD-1 Blockade-Mediated T Cell Rejuvenation. Cell. 2017;170:142-157.e19.

120. Zhou C, et al. Exosome-derived miR-142-5p remodels lymphatic vessels and induces IDO to promote immune privilege in the tumour microenvironment. Cell Death Differ. 2021;28:715–29.
121. Alfei F, et al. TOX reinforces the phenotype and longevity of exhausted T cells in chronic viral infection. Nature. 2019;571:265–9.
122. Khan O, et al. TOX transcriptionally and epigenetically programs CD8+ T cell exhaustion. Nature. 2019;571:211–8.
123. Collins, S. M. et al. TOX2 coordinates with TET2 to positively regulate central memory differentiation in human CAR T cells. Sci. Adv. 9, eadh2605 (2023).
124. Kersh EN. Impaired Memory CD8 T Cell Development in the Absence of Methyl-CpG-Binding Domain Protein 2. J Immunol. 2006;177:3821–6.
125. Kakaradov B, et al. Early transcriptional and epigenetic regulation of CD8+ T cell differentiation revealed by single-cell RNA sequencing. Nat Immunol. 2017;18:422–32.
126. Zhao E, et al. Cancer mediates effector T cell dysfunction by targeting microRNAs and EZH2 via glycolysis restriction. Nat Immunol. 2016;17:95–103.
127. Ford, B. R. et al. Tumor microenvironmental signals reshape chromatin landscapes to limit the functional potential of exhausted T cells. Sci. Immunol. 7, eabj9123 (2022).
128. Yang, Y. et al. ECSIT facilitates memory CD8+ T cell development by mediating fumarate synthesis during viral infection and tumorigenesis. Nat. Cell Biol. 1–14 (2024) https://doi.org/10.1038/s41556-024-01351-9.
129. Gujral P, Mahajan V, Lissaman AC, Ponnampalam AP. Histone acetylation and the role of histone deacetylases in normal cyclic endometrium. Reprod Biol Endocrinol. 2020;18:84.
130. Nguyen MLT, et al. Dynamic regulation of permissive histone modifications and GATA3 binding underpin acquisition of granzyme A expression by virus-specific CD8+ T cells. Eur J Immunol. 2016;46:307–18.
131. Wang Z, et al. Modulation of SRSF2 expression reverses the exhaustion of TILs via the epigenetic regulation of immune checkpoint molecules. Cell Mol Life Sci. 2020;77:3441–52.
132. Kuroda S, et al. Basic leucine zipper transcription factor, ATF-like (BATF) regulates epigenetically and energetically effector CD8 T-cell differentiation via Sirt1 expression. Proc Natl Acad Sci. 2011;108:14885–9.
133. Tay RE, et al. Hdac3 is an epigenetic inhibitor of the cytotoxicity program in CD8 T cells. J Exp Med. 2020;217: e20191453.
134. Vodnala, S. K. et al. T cell stemness and dysfunction in tumors are triggered by a common mechanism. Science 363, eaau0135 (2019).
135. Luda KM, et al. Ketolysis drives CD8+ T cell effector function through effects on histone acetylation. Immunity. 2023;56:2021-2035.e8.
136. Vignard V, et al. MicroRNAs in Tumor Exosomes Drive Immune Escape in Melanoma. Cancer Immunol Res. 2020;8:255–67.
137. Yang C, et al. Exosome-derived circTRPS1 promotes malignant phenotype and CD8+ T cell exhaustion in bladder cancer microenvironments. Mol Ther. 2022;30:1054–70.
138. Hu Z, et al. Exosome-derived circCCAR1 promotes CD8 + T-cell dysfunction and anti-PD1 resistance in hepatocellular carcinoma. Mol Cancer. 2023;22:55.
139. Li X, Ma S, Deng Y, Yi P, Yu J. Targeting the RNA m6A modification for cancer immunotherapy. Mol Cancer. 2022;21:76.
140. Guo W, et al. Mettl3-dependent m6A modification is essential for effector differentiation and memory formation of CD8+ T cells. Sci Bull. 2024;69:82–96.
141. Helmink BA, et al. B cells and tertiary lymphoid structures promote immunotherapy response. Nature. 2020;577:549–55.
142. Workel HH, et al. A Transcriptionally Distinct CXCL13+CD103+CD8+ T-cell Population Is Associated with B-cell Recruitment and Neoantigen Load in Human Cancer. Cancer Immunol Res. 2019;7:784–96.
143. Downs-Canner SM, Meier J, Vincent BG, Serody JS. B Cell Function in the Tumor Microenvironment. Annu Rev Immunol. 2022;40:169–93.
144. Tonon S, et al. IL-10-producing B cells are characterized by a specific methylation signature. Eur J Immunol. 2019;49:1213–25.
145. Lu Z, et al. Ten-eleven translocation-2 inactivation restrains IL-10-producing regulatory B cells to enable antitumor immunity in hepatocellular carcinoma. Hepatology. 2023;77:745.
146. Min KY, et al. Entinostat, a histone deacetylase inhibitor, increases the population of IL-10+ regulatory B cells to suppress contact hypersensitivity. BMB Rep. 2021;54:534–9.
147. Beresford GW, Boss JM. CIITA coordinates multiple histone acetylation modifications at the HLA-DRA promoter. Nat Immunol. 2001;2:652–7.
148. Zika E, Ting JP-Y. Epigenetic control of MHC-II: interplay between CIITA and histone-modifying enzymes. Curr Opin Immunol. 2005;17:58–64.
149. Wright KL, Ting JP-Y. Epigenetic regulation of MHC-II and CIITA genes. Trends Immunol. 2006;27:405–12.
150. Shapiro-Shelef M, et al. Blimp-1 Is Required for the Formation of Immunoglobulin Secreting Plasma Cells and Pre-Plasma Memory B Cells. Immunity. 2003;19:607–20.
151. Guo M, et al. EZH2 Represses the B Cell Transcriptional Program and Regulates Antibody-Secreting Cell Metabolism and Antibody Production. J Immunol. 2018;200:1039–52.
152. Tanaka H, et al. Epigenetic Regulation of the Blimp-1 Gene (Prdm1) in B Cells Involves Bach2 and Histone Deacetylase 3 *. J Biol Chem. 2016;291:6316–30.
153. Wei Y, et al. Plasma Cell Polarization to the Immunoglobulin G Phenotype in Hepatocellular Carcinomas Involves Epigenetic Alterations and Promotes Hepatoma Progression in Mice. Gastroenterology. 2019;156:1890-1904.e16.
154. Biswas S, et al. IgA transcytosis and antigen recognition govern ovarian cancer immunity. Nature. 2021;591:464–70.
155. Shim JM, et al. BET proteins are a key component of immunoglobulin gene expression. Epigenomics. 2017;9:393–406.
156. Karagiannis P, et al. IgG4 subclass antibodies impair antitumor immunity in melanoma. J Clin Invest. 2013;123:1457.
157. Gu Y, et al. Tumor-educated B cells selectively promote breast cancer lymph node metastasis by HSPA4-targeting IgG. Nat Med. 2019;25:312–22.
158. Velichutina I, et al. EZH2-mediated epigenetic silencing in germinal center B cells contributes to proliferation and lymphomagenesis. Blood. 2010;116:5247–55.
159. Heward J, et al. KDM5 inhibition offers a novel therapeutic strategy for the treatment of KMT2D mutant lymphomas. Blood. 2021;138:370–81.
160. Xia, M., Wang, B., Wang, Z., Zhang, X. & Wang, X. Epigenetic Regulation of NK Cell-Mediated Antitumor Immunity. Front. Immunol. 12, (2021).
161. Barry KC, et al. A natural killer–dendritic cell axis defines checkpoint therapy–responsive tumor microenvironments. Nat Med. 2018;24:1178–91.
162. Böttcher JP, et al. NK Cells Stimulate Recruitment of cDC1 into the Tumor Microenvironment Promoting Cancer Immune Control. Cell. 2018;172:1022-1037.e14.
163. Luetke-Eversloh M, et al. NK cells gain higher IFN-γ competence during terminal differentiation. Eur J Immunol. 2014;44:2074–84.
164. Boy M, et al. Myelodysplastic Syndrome associated TET2 mutations affect NK cell function and genome methylation. Nat Commun. 2023;14:588.
165. Zhao N-H, et al. Diagnostic value of NKG2D promoter methylation in hepatitis B virus-associated hepatocellular carcinoma. Biomark Med. 2019;13:1093–105.
166. Accomando WP, et al. Decreased NK Cells in Patients with Head and Neck Cancer Determined in Archival DNA. Clin Cancer Res. 2012;18:6147–54.
167. Huang H-T, et al. DNA methylation-mediated Siglec-7 regulation in natural killer cells via two 5′ promoter CpG sites. Immunology. 2020;160:38–51.
168. Chang S, Aune TM. Histone hyperacetylated domains across the Ifng gene region in natural killer cells and T cells. Proc Natl Acad Sci. 2005;102:17095–100.
169. Jiao, D. et al. Lipid accumulation-mediated histone hypoacetylation drives persistent NK cell dysfunction in anti-tumor immunity. Cell Rep. 42, (2023).
170. Ni L, et al. The histone deacetylase inhibitor valproic acid inhibits NKG2D expression in natural killer cells through suppression of STAT3 and HDAC3. Sci Rep. 2017;7:45266.
171. Rogers SL, Rouhi A, Takei F, Mager DL. A Role for DNA Hypomethylation and Histone Acetylation in Maintaining Allele-Specific Expression of Mouse NKG2A in Developing and Mature NK Cells1. J Immunol. 2006;177:414–21.
172. Zhu S, et al. The Narrow-Spectrum HDAC Inhibitor Entinostat Enhances NKG2D Expression Without NK Cell Toxicity, Leading to Enhanced Recognition of Cancer Cells. Pharm Res. 2015;32:779–92.

173. Ogbomo H, Michaelis M, Kreuter J, Doerr HW, Cinatl J. Histone deacetylase inhibitors suppress natural killer cell cytolytic activity. FEBS Lett. 2007;581:1317–22.
174. Fernández-Sánchez A, et al. DNA demethylation and histone H3K9 acetylation determine the active transcription of the NKG2D gene in human CD8+ T and NK cells. Epigenetics. 2013;8:66–78.
175. Santourlidis S, Graffmann N, Christ J, Uhrberg M. Lineage-Specific Transition of Histone Signatures in the Killer Cell Ig-Like Receptor Locus from Hematopoietic Progenitor to NK Cells1. J Immunol. 2008;180:418–25.
176. Rasid O, et al. H3K4me1 Supports Memory-like NK Cells Induced by Systemic Inflammation. Cell Rep. 2019;29:3933-3945.e3.
177. Zhao D, et al. H3K4me3 Demethylase Kdm5a Is Required for NK Cell Activation by Associating with p50 to Suppress SOCS1. Cell Rep. 2016;15:288–99.
178. Rapp, M. et al. Core-binding factor β and Runx transcription factors promote adaptive natural killer cell responses. Sci. Immunol. 2, eaan3796 (2017).
179. Cribbs A, et al. Inhibition of histone H3K27 demethylases selectively modulates inflammatory phenotypes of natural killer cells. J Biol Chem. 2018;293:2422–37.
180. Northrup D, et al. Histone demethylases UTX and JMJD3 are required for NKT cell development in mice. Cell Biosci. 2017;7:25.
181. Yin J, et al. Ezh2 regulates differentiation and function of natural killer cells through histone methyltransferase activity. Proc Natl Acad Sci. 2015;112:15988–93.
182. Wang P, et al. Identification of Resting and Type I IFN-Activated Human NK Cell miRNomes Reveals MicroRNA-378 and MicroRNA-30e as Negative Regulators of NK Cell Cytotoxicity. J Immunol. 2012;189:211–21.
183. Kim T-D, et al. Human microRNA-27a* targets Prf1 and GzmB expression to regulate NK-cell cytotoxicity. Blood. 2011;118:5476–86.
184. Liu S, et al. Suppressed expression of miR-378 targeting gzmb in NK cells is required to control dengue virus infection. Cell Mol Immunol. 2016;13:700–8.
185. Ni F, et al. MicroRNA transcriptomes of distinct human NK cell populations identify miR-362-5p as an essential regulator of NK cell function. Sci Rep. 2015;5:9993.
186. Trotta R, et al. miR-155 regulates IFN-γ production in natural killer cells. Blood. 2012;119:3478–85.
187. Cichocki F, et al. Cutting Edge: MicroRNA-181 Promotes Human NK Cell Development by Regulating Notch Signaling. J Immunol. 2011;187:6171–5.
188. Wang, H., Zhang, J., Peng, Y. & Yu, J. Regulation of Human Natural Killer Cell IFN-γ Production by MicroRNA-146a via Targeting the NF-κB Signaling Pathway. Front. Immunol. 9, (2018).
189. Kim N, et al. MicroRNA-150 regulates the cytotoxicity of natural killers by targeting perforin-1. J Allergy Clin Immunol. 2014;134:195-203.e4.
190. Mundy-Bosse BL, et al. MicroRNA-29b mediates altered innate immune development in acute leukemia. J Clin Invest. 2016;126:4404–16.
191. Steiner DF, et al. MicroRNA-29 Regulates T-Box Transcription Factors and Interferon-γ Production in Helper T Cells. Immunity. 2011;35:169–81.
192. Gong J, et al. miR-30c-1* promotes natural killer cell cytotoxicity against human hepatoma cells by targeting the transcription factor HMBOX1. Cancer Sci. 2012;103:645–52.
193. Bezman NA, Chakraborty T, Bender T, Lanier LL. miR-150 regulates the development of NK and iNKT cells. J Exp Med. 2011;208:2717–31.
194. Yun S, et al. Integrated mRNA-MicroRNA Profiling of Human NK Cell Differentiation Identifies MiR-583 as a Negative Regulator of IL2Rγ Expression. PLoS ONE. 2014;9: e108913.
195. Ma Y, et al. MicroRNA-30c promotes natural killer cell cytotoxicity via up-regulating the expression level of NKG2D. Life Sci. 2016;151:174–81.
196. Pesce S, et al. New miRNA Signature Heralds Human NK Cell Subsets at Different Maturation Steps: Involvement of miR-146a-5p in the Regulation of KIR Expression. Front Immunol. 2018;9:2360.
197. Nutalai R, Gaudieri S, Jumnainsong A, Leelayuwat C. Regulation of KIR3DL3 Expression via miRNA. Genes. 2019;10:603.
198. Espinoza JL, et al. Human microRNA-1245 down-regulates the NKG2D receptor in natural killer cells and impairs NKG2D-mediated functions. Haematologica. 2012;97:1295–303.
199. Donatelli SS, et al. TGF-β–inducible microRNA-183 silences tumor-associated natural killer cells. Proc Natl Acad Sci. 2014;111:4203–8.
200. Guo F, et al. Downregulation of the long non-coding RNA MALAT1 in tenofovir-treated pregnant women with hepatitis B virus infection promotes immune recovery of natural killer cells via the has-miR-155-5p/HIF-1α axis. Int Immunopharmacol. 2022;107: 108701.
201. Fang P, et al. LncRNA GAS5 enhanced the killing effect of NK cell on liver cancer through regulating miR-544/RUNX3. Innate Immun. 2019;25:99–109.
202. Song H, et al. METTL3-mediated m6A RNA methylation promotes the anti-tumour immunity of natural killer cells. Nat Commun. 2021;12:5522.
203. Wang N, Liang H, Zen K. Molecular Mechanisms That Influence the Macrophage M1–M2 Polarization Balance. Front Immunol. 2014;5:614.
204. Pittet MJ, Michielin O, Migliorini D. Clinical relevance of tumour-associated macrophages. Nat Rev Clin Oncol. 2022;19:402–21.
205. Cheng S, et al. A pan-cancer single-cell transcriptional atlas of tumor infiltrating myeloid cells. Cell. 2021;184:792-809.e23.
206. Binnewies M, et al. Understanding the tumor immune microenvironment (TIME) for effective therapy. Nat Med. 2018;24:541–50.
207. Shen, M., Du, Y. & Ye, Y. Tumor-associated macrophages, dendritic cells, and neutrophils: biological roles, crosstalk, and therapeutic relevance. Med. Rev. 1, 222–243.
208. Yang X, et al. Epigenetic Regulation of Macrophage Polarization by DNA Methyltransferase 3b. Mol Endocrinol. 2014;28:565–74.
209. Cheng C, et al. SOCS1 hypermethylation mediated by DNMT1 is associated with lipopolysaccharide-induced inflammatory cytokines in macrophages. Toxicol Lett. 2014;225:488–97.
210. Tang R-Z, et al. DNA methyltransferase 1 and Krüppel-like factor 4 axis regulates macrophage inflammation and atherosclerosis. J Mol Cell Cardiol. 2019;128:11–24.
211. Travers M, et al. DFMO and 5-Azacytidine Increase M1 Macrophages in the Tumor Microenvironment of Murine Ovarian Cancer. Cancer Res. 2019;79:3445–54.
212. Pan W, et al. The DNA methylcytosine dioxygenase Tet2 sustains the immunosuppressive function of tumor-infiltrating myeloid cells to promote melanoma progression. Immunity. 2017;47:284-297.e5.
213. Jia Y, et al. IRF8 is the target of SIRT1 for the inflammation response in macrophages. Innate Immun. 2017;23:188–95.
214. Li T, et al. SIRT1/2 orchestrate acquisition of DNA methylation and loss of histone H3 activating marks to prevent premature activation of inflammatory genes in macrophages. Nucleic Acids Res. 2020;48:665–81.
215. Joshi S, et al. SF2523: Dual PI3K/BRD4 Inhibitor Blocks Tumor Immunosuppression and Promotes Adaptive Immune Responses in Cancer. Mol Cancer Ther. 2019;18:1036–44.
216. Wang Y-C, et al. USP24 induces IL-6 in tumor-associated microenvironment by stabilizing p300 and β-TrCP and promotes cancer malignancy. Nat Commun. 2018;9:3996.
217. Zheng X, et al. The HDAC2-SP1 Axis Orchestrates Protumor Macrophage Polarization. Cancer Res. 2023;83:2345–57.
218. Chang Y-C, et al. Epigenetic control of MHC class II expression in tumor-associated macrophages by decoy receptor 3. Blood. 2008;111:5054–63.
219. Li X, et al. Methyltransferase Dnmt3a upregulates HDAC9 to deacetylate the kinase TBK1 for activation of antiviral innate immunity. Nat Immunol. 2016;17:806–15.
220. Shinohara H, et al. Regulated Polarization of Tumor-Associated Macrophages by miR-145 via Colorectal Cancer-Derived Extracellular Vesicles. J Immunol. 2017;199:1505–15.
221. Shi, W., Cassmann, T. J., Bhagwate, A. V., Hitosugi, T. & Ip, W. K. E. Lactic acid induces transcriptional repression of macrophage inflammatory response via histone acetylation. Cell Rep. 43, (2024).
222. Wang X, et al. Histone methyltransferases G9a mediated lipid-induced M1 macrophage polarization through negatively regulating CD36. Metabolism. 2021;114: 154404.
223. Zhang Y, et al. Activation of MAT2A-RIP1 signaling axis reprograms monocytes in gastric cancer. J Immunother Cancer. 2021;9: e001364.
224. Xu G, et al. The Histone Methyltransferase Smyd2 Is a Negative Regulator of Macrophage Activation by Suppressing Interleukin 6 (IL-6) and Tumor Necrosis Factor α (TNF-α) Production. J Biol Chem. 2015;290:5414–23.

225. Xia M, et al. Histone Methyltransferase Ash1l Suppresses Interleukin-6 Production and Inflammatory Autoimmune Diseases by Inducing the Ubiquitin-Editing Enzyme A20. Immunity. 2013;39:470–81.
226. Stender JD, et al. Control of Proinflammatory Gene Programs by Regulated Trimethylation and Demethylation of Histone H4K20. Mol Cell. 2012;48:28–38.
227. Mossel, D. M. et al. Epigenetic Regulation of S100A9 and S100A12 Expression in Monocyte-Macrophage System in Hyperglycemic Conditions. Front. Immunol. 11, (2020).
228. Zhang X, et al. Macrophage/microglial Ezh2 facilitates autoimmune inflammation through inhibition of Socs3. J Exp Med. 2018;215:1365–82.
229. Satoh T, et al. The Jmjd3-Irf4 axis regulates M2 macrophage polarization and host responses against helminth infection. Nat Immunol. 2010;11:936–44.
230. Ishii M, et al. Epigenetic regulation of the alternatively activated macrophage phenotype. Blood. 2009;114:3244–54.
231. Xun J, et al. Cancer-derived exosomal miR-138-5p modulates polarization of tumor-associated macrophages through inhibition of KDM6B. Theranostics. 2021;11:6847–59.
232. Boulding T, et al. LSD1 activation promotes inducible EMT programs and modulates the tumour microenvironment in breast cancer. Sci Rep. 2018;8:73.
233. Tikhanovich I, et al. Protein arginine methyltransferase 1 modulates innate immune responses through regulation of peroxisome proliferator-activated receptor γ-dependent macrophage differentiation. J Biol Chem. 2017;292:6882–94.
234. Zhao J, O'Neil M, Vittal A, Weinman SA, Tikhanovich I. PRMT1-Dependent Macrophage IL-6 Production Is Required for Alcohol-Induced HCC Progression. Gene Expr. 2019;19:137–50.
235. Yang J, et al. MicroRNA-19a-3p inhibits breast cancer progression and metastasis by inducing macrophage polarization through downregulated expression of Fra-1 proto. Oncogene. 2014;33:3014–23.
236. Zhong Y, Yi C. MicroRNA-720 suppresses M2 macrophage polarization by targeting GATA3. Biosci Rep. 2016;36: e00363.
237. Larionova I, Kazakova E, Patysheva M, Kzhyshkowska J. Transcriptional, Epigenetic and Metabolic Programming of Tumor-Associated Macrophages. Cancers. 2020;12:1411.
238. Yin C, et al. LncRNA-HOXC-AS2 regulates tumor-associated macrophage polarization through the STAT1/SOCS1 and STAT1/CIITA pathways to promote the progression of non-small cell lung cancer. Cell Signal. 2024;115: 111031.
239. Liu, Y. et al. The N6-methyladenosine (m6A)-forming enzyme METTL3 facilitates M1 macrophage polarization through the methylation of STAT1 mRNA. Am. J. Physiol.-Cell Physiol. 317, C762–C775 (2019).
240. Tong J. Pooled CRISPR screening identifies m6A as a positive regulator of macrophage activation. Sci Adv. 2021;7:eabd4742.
241. Wculek SK, et al. Dendritic cells in cancer immunology and immunotherapy. Nat Rev Immunol. 2020;20:7–24.
242. Segura E, et al. Human Inflammatory Dendritic Cells Induce Th17 Cell Differentiation. Immunity. 2013;38:336–48.
243. Brewitz A, et al. CD8+ T Cells Orchestrate pDC-XCR1+ Dendritic Cell Spatial and Functional Cooperativity to Optimize Priming. Immunity. 2017;46:205–19.
244. Del Rio M-L, Bernhardt G, Rodriguez-Barbosa J-I, Förster R. Development and functional specialization of CD103+ dendritic cells. Immunol Rev. 2010;234:268–81.
245. Lai WK, et al. Hepatitis C is associated with perturbation of intrahepatic myeloid and plasmacytoid dendritic cell function. J Hepatol. 2007;47:338–47.
246. Swiecki M, Colonna M. The multifaceted biology of plasmacytoid dendritic cells. Nat Rev Immunol. 2015;15:471–85.
247. Steinman RM. Decisions About Dendritic Cells: Past, Present, and Future. Annu Rev Immunol. 2012;30:1–22.
248. Rowshanravan B, Halliday N, Sansom DM. CTLA-4: a moving target in immunotherapy. Blood. 2018;131:58–67.
249. Bullwinkel J, Lüdemann A, Debarry J, Singh PB. Epigenotype switching at the CD14 and CD209 genes during differentiation of human monocytes to dendritic cells. Epigenetics. 2011;6:45–51.
250. Zhang X, et al. DNA methylation dynamics during ex vivo differentiation and maturation of human dendritic cells. Epigenetics Chromatin. 2014;7:21.
251. Kinner-Bibeau LB, Sedlacek AL, Messmer MN, Watkins SC, Binder RJ. HSPs drive dichotomous T-cell immune responses via DNA methylome remodelling in antigen presenting cells. Nat Commun. 2017;8:15648.
252. Liu L, et al. Integrated Nanovaccine with MicroRNA-148a Inhibition Reprograms Tumor-Associated Dendritic Cells by Modulating miR-148a/DNMT1/SOCS1 Axis. J Immunol. 2016;197:1231–41.
253. Vento-Tormo R, et al. IL-4 orchestrates STAT6-mediated DNA demethylation leading to dendritic cell differentiation. Genome Biol. 2016;17:4.
254. Morante-Palacios O, et al. Vitamin C enhances NF-κB-driven epigenomic reprogramming and boosts the immunogenic properties of dendritic cells. Nucleic Acids Res. 2022;50:10981–94.
255. Gunawan M, et al. The methyltransferase Ezh2 controls cell adhesion and migration through direct methylation of the extranuclear regulatory protein talin. Nat Immunol. 2015;16:505–16.
256. Li H, et al. Epigenetic Modification of Enhancer of Zeste Homolog 2 Modulates the Activation of Dendritic Cells in Allergen Immunotherapy. Int Arch Allergy Immunol. 2019;180:120–7.
257. Sun, S., Yu, F., Xu, D., Zheng, H. & Li, M. EZH2, a prominent orchestrator of genetic and epigenetic regulation of solid tumor microenvironment and immunotherapy. Biochim. Biophys. Acta BBA - Rev. Cancer 1877, 188700 (2022).
258. Loh JT. Ezh2 Controls Skin Tolerance through Distinct Mechanisms in Different Subsets of Skin Dendritic Cells. iScience 2018;10:23-39.
259. Zerif E, et al. Elucidating the Role of Ezh2 in Tolerogenic Function of NOD Bone Marrow-Derived Dendritic Cells Expressing Constitutively Active Stat5b. Int J Mol Sci. 2020;21:6453.
260. Wang Y, et al. Inhibition of EZH2 ameliorates bacteria-induced liver injury by repressing RUNX1 in dendritic cells. Cell Death Dis. 2020;11:1–13.
261. Zhou Z, et al. Epigenetically modulated FOXM1 suppresses dendritic cell maturation in pancreatic cancer and colon cancer. Mol Oncol. 2019;13:873–93.
262. Yi L, et al. Intracellular HSP70L1 inhibits human dendritic cell maturation by promoting suppressive H3K27me3 and H2AK119Ub1 histone modifications. Cell Mol Immunol. 2020;17:85–94.
263. Shinde P, Melinkeri S, Santra MK, Kale V, Limaye L. Autologous Hematopoietic Stem Cells Are a Preferred Source to Generate Dendritic Cells for Immunotherapy in Multiple Myeloma Patients. Front Immunol. 2019;10:1079.
264. Guenther C, et al. β2-Integrin Adhesion Regulates Dendritic Cell Epigenetic and Transcriptional Landscapes to Restrict Dendritic Cell Maturation and Tumor Rejection. Cancer Immunol Res. 2021;9:1354–69.
265. Yang B, et al. Histone acetyltransferease p300 modulates TIM4 expression in dendritic cells. Sci Rep. 2016;6:21336.
266. López-Bravo M, et al. IL-4 blocks TH1-polarizing/inflammatory cytokine gene expression during monocyte-derived dendritic cell differentiation through histone hypoacetylation. J Allergy Clin Immunol. 2013;132:1409-1419.e13.
267. Zhang Q, et al. Tet2 is required to resolve inflammation by recruiting Hdac2 to specifically repress IL-6. Nature. 2015;525:389–93.
268. Parira T, et al. Novel detection of post-translational modifications in human monocyte-derived dendritic cells after chronic alcohol exposure: Role of inflammation regulator H4K12ac. Sci Rep. 2017;7:11236.
269. Chauvistré H, et al. Dendritic cell development requires histone deacetylase activity. Eur J Immunol. 2014;44:2478–88.
270. Nencioni A, et al. Histone Deacetylase Inhibitors Affect Dendritic Cell Differentiation and Immunogenicity. Clin Cancer Res. 2007;13:3933–41.
271. Wang H, et al. Mettl3-mediated mRNA m6A methylation promotes dendritic cell activation. Nat Commun. 2019;10:1898.
272. Wu H, et al. Dendritic cells with METTL3 gene knockdown exhibit immature properties and prolong allograft survival. Genes Immun. 2020;21:193–202.
273. Han D, et al. Anti-tumour immunity controlled through mRNA m6A methylation and YTHDF1 in dendritic cells. Nature. 2019;566:270–4.
274. Zhang M, et al. miRNA-5119 regulates immune checkpoints in dendritic cells to enhance breast cancer immunotherapy. Cancer Immunol Immunother. 2020;69:951–67.

275. Huang KC-Y, et al. A Novel Engineered AAV-Based Neoantigen Vaccine in Combination with Radiotherapy Eradicates Tumors. Cancer Immunol Res. 2023;11:123–36.
276. Ding G, et al. Pancreatic cancer-derived exosomes transfer miRNAs to dendritic cells and inhibit RFXAP expression via miR-212-3p. Oncotarget. 2015;6:29877–88.
277. Liu J, et al. CCR7 Chemokine Receptor-Inducible lnc-Dpf3 Restrains Dendritic Cell Migration by Inhibiting HIF-1α-Mediated Glycolysis. Immunity. 2019;50:600-615.e15.
278. Wang P, et al. The STAT3-Binding Long Noncoding RNA lnc-DC Controls Human Dendritic Cell Differentiation. Science. 2014;344:310–3.
279. Xin J, et al. Downregulation of long noncoding RNA HOTAIRM1 promotes monocyte/dendritic cell differentiation through competitively binding to endogenous miR-3960. OncoTargets Ther. 2017;10:1307–15.
280. Liu X, et al. Long non-coding RNA: Multiple effects on the differentiation, maturity and cell function of dendritic cells. Clin Immunol. 2022;245: 109167.
281. Li K, et al. Myeloid-derived suppressor cells as immunosuppressive regulators and therapeutic targets in cancer. Signal Transduct Target Ther. 2021;6:1–25.
282. Rodríguez, P. C. & Ochoa, A. C. Arginine Metabolism, a Major Pathway for the Suppressive Function of Myeloid-Derived Suppressor Cells. in Tumor-Induced Immune Suppression: Mechanisms and Therapeutic Reversal (eds. Gabrilovich, D. I. & Hurwitz, A. A.) 369–386 (Springer, New York, NY, 2014). https://doi.org/10.1007/978-1-4899-8056-4_13.
283. Yang, Y., Li, C., Liu, T., Dai, X. & Bazhin, A. V. Myeloid-Derived Suppressor Cells in Tumors: From Mechanisms to Antigen Specificity and Microenvironmental Regulation. Front. Immunol. 11, (2020).
284. de Coaña YP, et al. Ipilimumab Treatment Results in an Early Decrease in the Frequency of Circulating Granulocytic Myeloid-Derived Suppressor Cells as well as Their Arginase1 Production. Cancer Immunol Res. 2013;1:158–62.
285. Antonios JP, et al. Immunosuppressive tumor-infiltrating myeloid cells mediate adaptive immune resistance via a PD-1/PD-L1 mechanism in glioblastoma. Neuro-Oncol. 2017;19:796–807.
286. Schlecker E, et al. Tumor-Infiltrating Monocytic Myeloid-Derived Suppressor Cells Mediate CCR5-Dependent Recruitment of Regulatory T Cells Favoring Tumor Growth. J Immunol. 2012;189:5602–11.
287. Lasser SA, Ozbay Kurt FG, Arkhypov I, Utikal J, Umansky V. Myeloid-derived suppressor cells in cancer and cancer therapy. NatRev Clin Oncol. 2024;21:147–64.
288. Ahn G-O, Brown JM. Matrix Metalloproteinase-9 Is Required for Tumor Vasculogenesis but Not for Angiogenesis: Role of Bone Marrow-Derived Myelomonocytic Cells. Cancer Cell. 2008;13:193–205.
289. Yang L, et al. Abrogation of TGFβ Signaling in Mammary Carcinomas Recruits Gr-1+CD11b+ Myeloid Cells that Promote Metastasis. Cancer Cell. 2008;13:23–35.
290. Sido JM, Yang X, Nagarkatti PS, Nagarkatti M. Δ9-Tetrahydrocannabinol-mediated epigenetic modifications elicit myeloid-derived suppressor cell activation via STAT3/S100A8. J Leukoc Biol. 2015;97:677–88.
291. Rodríguez-Ubreva J, et al. Prostaglandin E2 Leads to the Acquisition of DNMT3A-Dependent Tolerogenic Functions in Human Myeloid-Derived Suppressor Cells. Cell Rep. 2017;21:154–67.
292. Smith AD, et al. Autocrine IL6-Mediated Activation of the STAT3–DNMT Axis Silences the TNFα–RIP1 Necroptosis Pathway to Sustain Survival and Accumulation of Myeloid-Derived Suppressor Cells. Cancer Res. 2020;80:3145–56.
293. Saleh R, et al. DNA methylation in the promoters of PD-L1, MMP9, ARG1, galectin-9, TIM-3, VISTA and TGF-β genes in HLA-DR– myeloid cells, compared with HLA-DR+ antigen-presenting cells. Epigenetics. 2020;15:1275–88.
294. Li S, et al. TET2 promotes anti-tumor immunity by governing G-MDSCs and CD8+ T-cell numbers. EMBO Rep. 2020;21: e49425.
295. Huang S, et al. EZH2 Inhibitor GSK126 Suppresses Antitumor Immunity by Driving Production of Myeloid-Derived Suppressor Cells. Cancer Res. 2019;79:2009–20.
296. Zhou J, et al. Targeting EZH2 histone methyltransferase activity alleviates experimental intestinal inflammation. Nat Commun. 2019;10:2427.
297. Redd PS, et al. SETD1B Activates iNOS Expression in Myeloid-Derived Suppressor Cells. Cancer Res. 2017;77:2834–43.
298. Zhang Z, Huang X, Wang E, Huang Y, Yang R. Suppression of Mll1-Complex by Stat3/Cebpβ–Induced miR-21a/21b/181b Maintains the Accumulation, Homeostasis, and Immunosuppressive Function of Polymorphonuclear Myeloid-Derived Suppressor Cells. J Immunol. 2020;204:3400–15.
299. Lu C, et al. WDR5-H3K4me3 epigenetic axis regulates OPN expression to compensate PD-L1 function to promote pancreatic cancer immune escape. J Immunother Cancer. 2021;9: e002624.
300. Sasidharan Nair, V., Saleh, R., Toor, S. M., Alajez, N. M. & Elkord, E. Transcriptomic Analyses of Myeloid-Derived Suppressor Cell Subsets in the Circulation of Colorectal Cancer Patients. Front Oncol. 2020;10.
301. Yu B, et al. KAT6A Acetylation of SMAD3 Regulates Myeloid-Derived Suppressor Cell Recruitment, Metastasis, and Immunotherapy in Triple-Negative Breast Cancer. Adv Sci. 2021;8:2100014.
302. Nagata DE de A. et al. Regulation of Tumor-Associated Myeloid Cell Activity by CBP/EP300 Bromodomain Modulation of H3K27 Acetylation. Cell Rep. 2019;27:269-281.e4.
303. Sahakian E, et al. Histone deacetylase 11: A novel epigenetic regulator of myeloid derived suppressor cell expansion and function. Mol Immunol. 2015;63:579–85.
304. Youn J-I, et al. Epigenetic silencing of retinoblastoma gene regulates pathologic differentiation of myeloid cells in cancer. Nat Immunol. 2013;14:211–20.
305. Xie Z, Ago Y, Okada N, Tachibana M. Valproic acid attenuates immunosuppressive function of myeloid-derived suppressor cells. J Pharmacol Sci. 2018;137:359–65.
306. Xu Z, et al. MiR-30a increases MDSC differentiation and immunosuppressive function by targeting SOCS3 in mice with B-cell lymphoma. FEBS J. 2017;284:2410–24.
307. Liu Y, et al. MicroRNA-494 Is Required for the Accumulation and Functions of Tumor-Expanded Myeloid-Derived Suppressor Cells via Targeting of PTEN. J Immunol. 2012;188:5500–10.
308. Li L, et al. MicroRNA-155 and MicroRNA-21 Promote the Expansion of Functional Myeloid-Derived Suppressor Cells. J Immunol. 2014;192:1034–43.
309. Han X, et al. MicroRNA 449c Mediates the Generation of Monocytic Myeloid-Derived Suppressor Cells by Targeting STAT6. Mol Cells. 2020;43:793–803.
310. Guo X, et al. Glioma exosomes mediate the expansion and function of myeloid-derived suppressor cells through microRNA-29a/Hbp1 and microRNA-92a/Prkar1a pathways. Int J Cancer. 2019;144:3111–26.
311. Hegde VL, et al. Distinct MicroRNA Expression Profile and Targeted Biological Pathways in Functional Myeloid-derived Suppressor Cells Induced by Δ9-Tetrahydrocannabinol in Vivo: REGULATION OF CCAAT/ENHANCER-BINDING PROTEIN α BY MicroRNA-690 *. J Biol Chem. 2013;288:36810–26.
312. Tian J, et al. MicroRNA-9 Regulates the Differentiation and Function of Myeloid-Derived Suppressor Cells via Targeting Runx1. J Immunol. 2015;195:1301–11.
313. Liu Q, et al. miR-223 suppresses differentiation of tumor-induced CD11b+Gr1+myeloid-derived suppressor cells from bone marrow cells. Int J Cancer. 2011;129:2662–73.
314. Shang W, et al. LncRNA RNCR3 promotes Chop expression by sponging miR-185-5p during MDSC differentiation. Oncotarget. 2017;8:111754–69.
315. Zheng Y, et al. Long noncoding RNA Pvt1 regulates the immunosuppression activity of granulocytic myeloid-derived suppressor cells in tumor-bearing mice. Mol Cancer. 2019;18:61.
316. Tian X, et al. LncRNA AK036396 Inhibits Maturation and Accelerates Immunosuppression of Polymorphonuclear Myeloid-Derived Suppressor Cells by Enhancing the Stability of Ficolin B. Cancer Immunol Res. 2020;8:565–77.
317. Zhou Q, et al. LncRNA MALAT1 negatively regulates MDSCs in patients with lung cancer. J Cancer. 2018;9:2436–42.
318. Gao Y, et al. Lnc-C/EBPβ Negatively Regulates the Suppressive Function of Myeloid-Derived Suppressor Cells. Cancer Immunol Res. 2018;6:1352–63.
319. Lu W, et al. LncRNA Snhg6 regulates the differentiation of MDSCs by regulating the ubiquitination of EZH2. J Hematol Oncol. 2021;14:196.

320. Gao Y, Wang T, Li Y, Zhang Y, Yang R. Lnc-chop Promotes Immunosuppressive Function of Myeloid-Derived Suppressor Cells in Tumor and Inflammatory Environments. J Immunol. 2018;200:2603–14.
321. Shang W, Gao Y, Tang Z, Zhang Y, Yang R. The Pseudogene Olfr29-ps1 Promotes the Suppressive Function and Differentiation of Monocytic MDSCs. Cancer Immunol Res. 2019;7:813–27.
322. Davalos V, Esteller M. Cancer epigenetics in clinical practice. CA Cancer J Clin. 2023;73:376–424.
323. Zhang, Z. et al. Recent progress in DNA methyltransferase inhibitors as anticancer agents. Front. Pharmacol. 2022;13.
324. Thottassery JV, et al. Novel DNA methyltransferase-1 (DNMT1) depleting anticancer nucleosides, 4′-thio-2′-deoxycytidine and 5-aza-4′-thio-2′-deoxycytidine. Cancer Chemother Pharmacol. 2014;74:291–302.
325. Freudenberg K. et al. Critical Role of TGF-β and IL-2 Receptor Signaling in Foxp3 Induction by an Inhibitor of DNA Methylation. Front Immunol. 2018;9.
326. Vadevoo SMP. et al. Epigenetic therapy reprograms M2-type tumor-associated macrophages into an M1-like phenotype by upregulating miR-7083–5p. Front Immunol. 2022;13.
327. Shi R, et al. 5-aza-2′-deoxycytidine potentiates anti-tumor immunity in colorectal peritoneal metastasis by modulating ABC A9-mediated cholesterol accumulation in macrophages. Theranostics. 2022;12:875–90.
328. Sohlberg E, et al. Imprint of 5-azacytidine on the natural killer cell repertoire during systemic treatment for high-risk myelodysplastic syndrome. Oncotarget. 2015;6:34178–90.
329. Chan IS, et al. Cancer cells educate natural killer cells to a metastasis-promoting cell state. J Cell Biol. 2020;219: e202001134.
330. Frikeche J, et al. Impact of the hypomethylating agent 5-azacytidine on dendritic cells function. Exp Hematol. 2011;39:1056–63.
331. Fragale A, et al. Antitumor Effects of Epidrug/IFNα Combination Driven by Modulated Gene Signatures in Both Colorectal Cancer and Dendritic Cells. Cancer Immunol Res. 2017;5:604–16.
332. Gordy JT. et al. IFNα and 5-Aza-2′-deoxycytidine combined with a dendritic-cell targeting DNA vaccine alter tumor immune cell infiltration in the B16F10 melanoma model. Front Immunol. 2023;13.
333. Yang J, et al. Epigenetic regulation in the tumor microenvironment: molecular mechanisms and therapeutic targets. Signal Transduct Target Ther. 2023;8:1–26.
334. Xie Z, Zhou Z, Yang S, Zhang S, Shao B. Epigenetic regulation and therapeutic targets in the tumor microenvironment. Mol Biomed. 2023;4:17.
335. Wang H-F, et al. Histone deacetylase inhibitors deplete myeloid-derived suppressor cells induced by 4T1 mammary tumors in vivo and in vitro. Cancer Immunol Immunother. 2017;66:355–66.
336. Mahale A, et al. Pharmacological blockade of HDAC6 attenuates cancer progression by inhibiting IL-1β and modulating immunosuppressive response in OSCC. Int Immunopharmacol. 2024;132: 111921.
337. Shen L, et al. Class I Histone Deacetylase Inhibitor Entinostat Suppresses Regulatory T Cells and Enhances Immunotherapies in Renal and Prostate Cancer Models. PLoS ONE. 2012;7: e30815.
338. Salmon JM, et al. Epigenetic Activation of Plasmacytoid DCs Drives IFNAR-Dependent Therapeutic Differentiation of AML. Cancer Discov. 2022;12:1560–79.
339. Inamoto T, et al. Short-chain fatty acids stimulate dendrite elongation in dendritic cells by inhibiting histone deacetylase. FEBS J. 2023;290:5794–810.
340. Kovalovsky D, et al. The HDAC6 inhibitor AVS100 (SS208) induces a pro-inflammatory tumor microenvironment and potentiates immunotherapy. Sci Adv. 2024;10:eadp3687.
341. Tao R, et al. Deacetylase inhibition promotes the generation and function of regulatory T cells. Nat Med. 2007;13:1299–307.
342. Hu L. et al. Epigenetic Regulation of Interleukin 6 by Histone Acetylation in Macrophages and Its Role in Paraquat-Induced Pulmonary Fibrosis. Front Immunol. 2017;7.
343. Rossi LE, et al. Histone deacetylase inhibitors impair NK cell viability and effector functions through inhibition of activation and receptor expression. J Leukoc Biol. 2012;91:321–31.
344. Lee MB, et al. JQ1, a BET inhibitor, controls TLR4-induced IL-10 production in regulatory B cells by BRD4-NF-κB axis. BMB Rep. 2017;50:640–6.
345. Leal AS, Liu P, Krieger-Burke T, Ruggeri B, Liby KT. The Bromodomain Inhibitor, INCB057643, Targets Both Cancer Cells and the Tumor Microenvironment in Two Preclinical Models of Pancreatic Cancer. Cancers. 2021;13:96.
346. Nikbakht N, Tiago M, Erkes DA, Chervoneva I, Aplin AE. BET Inhibition Modifies Melanoma Infiltrating T Cells and Enhances Response to PD-L1 Blockade. J Invest Dermatol. 2019;139:1612–5.
347. Goswami S, et al. Modulation of EZH2 expression in T cells improves efficacy of anti–CTLA-4 therapy. J Clin Invest. 2018;128:3813–8.
348. Lee JC, et al. Regulatory T cell control of systemic immunity and immunotherapy response in liver metastasis. Sci Immunol. 2020;5:eaba0759.
349. Sun W, et al. Targeting EZH2 depletes LMP1-induced activated regulatory T cells enhancing antitumor immunity in nasopharyngeal carcinoma. J Cancer Res Ther. 2020;16:309.
350. Bailey CP, Figueroa M, Gangadharan A, Lee DA, Chandra J. Scaffolding LSD1 Inhibitors Impair NK Cell Metabolism and Cytotoxic Function Through Depletion of Glutathione. Front Immunol. 2020;11.
351. Tu, W. J. et al. Targeting Nuclear LSD1 to Reprogram Cancer Cells and Reinvigorate Exhausted T Cells via a Novel LSD1-EOMES Switch. Front. Immunol. 2020;11.
352. Waldman AD, Fritz JM, Lenardo MJ. A guide to cancer immunotherapy: from T cell basic science to clinical practice. Nat Rev Immunol. 2020;20:651–68.
353. Amaro A, et al. Guadecitabine increases response to combined anti-CTLA-4 and anti-PD-1 treatment in mouse melanoma in vivo by controlling T-cells, myeloid derived suppressor and NK cells. J Exp Clin Cancer Res. 2023;42:67.
354. Nie J, et al. Addition of Low-Dose Decitabine to Anti–PD-1 Antibody Camrelizumab in Relapsed/Refractory Classical Hodgkin Lymphoma. J Clin Oncol. 2019;37:1479–89.
355. Gray JE, et al. Phase I/Ib Study of Pembrolizumab Plus Vorinostat in Advanced/Metastatic Non-Small Cell Lung Cancer. Clin Cancer Res. 2019;25:6623–32.
356. Hellmann MD, et al. Entinostat plus Pembrolizumab in Patients with Metastatic NSCLC Previously Treated with Anti–PD-(L)1 Therapy. Clin Cancer Res. 2021;27:1019–28.
357. Knox T, et al. Selective HDAC6 inhibitors improve anti-PD-1 immune checkpoint blockade therapy by decreasing the anti-inflammatory phenotype of macrophages and down-regulation of immunosuppressive proteins in tumor cells. Sci Rep. 2019;9:6136.
358. Christmas BJ, et al. Entinostat Converts Immune-Resistant Breast and Pancreatic Cancers into Checkpoint-Responsive Tumors by Reprogramming Tumor-Infiltrating MDSCs. Cancer Immunol Res. 2018;6:1561–77.
359. Li X, et al. HDAC inhibition potentiates anti-tumor activity of macrophages and enhances anti-PD-L1-mediated tumor suppression. Oncogene. 2021;40:1836–50.
360. Adeegbe DO, et al. BET Bromodomain Inhibition Cooperates with PD-1 Blockade to Facilitate Antitumor Response in Kras-Mutant Non-Small Cell Lung Cancer. Cancer Immunol Res. 2018;6:1234–45.
361. Que Y, et al. Frequent amplification of HDAC genes and efficacy of HDAC inhibitor chidamide and PD-1 blockade combination in soft tissue sarcoma. J Immunother Cancer. 2021;9: e001696.
362. Wells JN, Feschotte C. A Field Guide to Eukaryotic Transposable Elements. Annu Rev Genet. 2020;54:539–61.
363. Jones PA, Ohtani H, Chakravarthy A, De Carvalho DD. Epigenetic therapy in immune-oncology. Nat Rev Cancer. 2019;19:151–61.
364. Goyal A, et al. DNMT and HDAC inhibition induces immunogenic neoantigens from human endogenous retroviral element-derived transcripts. Nat Commun. 2023;14:6731.
365. Maalej KM, et al. CAR-cell therapy in the era of solid tumor treatment: current challenges and emerging therapeutic advances. Mol Cancer. 2023;22:20.
366. Wang Y, et al. Low-dose decitabine priming endows CAR T cells with enhanced and persistent antitumour potential via epigenetic reprogramming. Nat Commun. 2021;12:409.
367. Zhu M. et al. Class I HDAC inhibitors enhance antitumor efficacy and persistence of CAR-T cells by activation of the Wnt pathway. Cell Rep. 2024;43.
368. Kagoya Y, et al. BET bromodomain inhibition enhances T cell persistence and function in adoptive immunotherapy models. J Clin Invest. 2016;126:3479–94.

369. Jain N, et al. TET2 guards against unchecked BATF3-induced CAR T cell expansion. Nature. 2023;615:315–22.
370. Fraietta JA, et al. Disruption of TET2 promotes the therapeutic efficacy of CD19-targeted T cells. Nature. 2018;558:307–12.
371. Ahuja N, Sharma AR, Baylin SB. Epigenetic Therapeutics: A New Weapon in the War Against Cancer. Annu Rev Med. 2016;67:73–89.
372. Azad N, Zahnow CA, Rudin CM, Baylin SB. The future of epigenetic therapy in solid tumours—lessons from the past. Nat Rev Clin Oncol. 2013;10:256–66.
373. Shah MH, et al. Cardiotoxicity of Histone Deacetylase Inhibitor Depsipeptide in Patients with Metastatic Neuroendocrine Tumors. Clin Cancer Res. 2006;12:3997–4003.
374. Shah RR. Safety and Tolerability of Histone Deacetylase (HDAC) Inhibitors in Oncology. Drug Saf. 2019;42:235–45.
375. Persky DO, et al. A phase I/II trial of vorinostat (SAHA) in combination with rituximab-CHOP in patients with newly diagnosed advanced stage diffuse large B-cell lymphoma (DLBCL): SWOG S0806. Am J Hematol. 2018;93:486–93.
376. Lechner S, et al. Target deconvolution of HDAC pharmacopoeia reveals MBLAC2 as common off-target. Nat Chem Biol. 2022;18:812–20.
377. Sonnemann J, et al. LSD1 (KDM1A)-independent effects of the LSD1 inhibitor SP2509 in cancer cells. Br J Haematol. 2018;183:494–7.
378. Mould DP, McGonagle AE, Wiseman DH, Williams EL, Jordan AM. Reversible Inhibitors of LSD1 as Therapeutic Agents in Acute Myeloid Leukemia: Clinical Significance and Progress to Date. Med Res Rev. 2015;35:586–618.
379. Lauterbach MA, et al. Toll-like Receptor Signaling Rewires Macrophage Metabolism and Promotes Histone Acetylation via ATP-Citrate Lyase. Immunity. 2019;51:997-1011.e7.
380. Bian Y, et al. Cancer SLC43A2 alters T cell methionine metabolism and histone methylation. Nature. 2020;585:277–82.
381. De Leo A, et al. Glucose-driven histone lactylation promotes the immunosuppressive activity of monocyte-derived macrophages in glioblastoma. Immunity. 2024;57:1105-1123.e8.
382. Pitter MR. et al. PAD4 controls tumor immunity via restraining the MHC class II machinery in macrophages. Cell Rep. 2024;43.
383. Sharma P, et al. Citrullination of Histone H3 Interferes with HP1-Mediated Transcriptional Repression. PLOS Genet. 2012;8: e1002934.


## Publisher's Note