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REVIEW

Regulation of T cell differentiation and function by epigenetic modification enzymes

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Abstract

Peripheral naive $CD4^+$ and $CD8^+$ cells are developed in the thymus and proliferate and differentiate into various specialized T cell subsets upon activation by peptide-major histocompatibility complexes in periphery to execute different functions during immune responses. Cytokines, transcription factors, and a large number of intracellular molecules have been shown to affect T cell development, activation, and function. In addition, epigenetic modifications, such as histone modification and DNA methylation, regulate T cell biology. The epigenetic modifications are regulated by a range of DNA methyltransferases, DNA demethylation enzymes, and histone modification enzymes. Dysregulations of epigenetic modifications are closely associated with autoimmune diseases and tumorigenesis. Here, we review the current literature about the functions of DNA and histone modification enzymes in T cell development, activation, differentiation, and function.

Keywords T cell · Epigenetic regulation · DNA methylation · 5mC demethylation · Histone modification enzymes

Introduction

T cells are crucial components of host adaptive immune responses against invading pathogens, self-antigens, and tumors. T cells recognize pMHC complexes presented by antigen-presenting cells (APC) and are activated. In combination with the local cytokine milieu, activated T cells undergo rapid proliferation and differentiation into different subsets [1]. For $CD4^+$ T helper cells, there are multiple T helper subsets that are identified: Th1, Th2, Th9, and Th17 cells that are defined by the cytokines they express and the roles they play in combatting specific types of infection and regulatory T cells (Treg) that are defined by the expression of the transcription factor FoxP3 and the ability to inhibit other cells of the immune system [2, 3]. During the resolution of immune responses, most of these activated T cells die off, but a small proportion of activated $CD4^+$ cells differentiate into long-lived memory $CD4^+$ T cells [4]. Similarly, $CD8^+$ T cells can differentiate into short-lived cytotoxic T effector cells or long-lived memory T cells [4]. Differentiated T cells play specialized functions in immune responses against infections and tumors. Dysregulation of T cell differentiation and function is often associated with autoimmunity and tumorigenesis.

The processes of T cell activation, differentiation, and acquisition of the specialized functions are regulated by cytokines, transcriptional factors, and other intracellular molecules. These topics have been intensively reviewed in the literature [5, 6]. In this review, we will discuss the part played by epigenetic regulation, including DNA methylation status and histone modifications by various histone modification enzymes.

DNA methylation involves the covalent transfer of a methyl group to the C-5 position of the cytosine ring of DNA by DNA methyltransferases (DNMTs), which alter the regulation of gene expression. This methylation is usually heritable and tends to silence gene expression [7]. The long chain of

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negatively charged DNA is packed with positively charged proteins collectively known as chromatin. Chromatin is composed of numerous nucleosomes, which consists of ~ 147 bp deoxyribonucleic acids that wrapped around an octamer of the four core histones (H3, H4, H2A, and H2B). A striking feature of histones is that they can be post-translationally modified at specific amino acid residues with a diverse set of chemical modifications, such as acetylation, methylation, phosphorylation, ubiquitination, sumoylation, ADP-ribosylation, deamination, and proline isomerization [8, 9]. Currently, more than 130 distinct types of histone modifications (i.e., different histones, different amino acids, and different modifications) have been identified (see Table 1). These modifications serve to alter the packing state of the DNA. Tightly packed DNA lies in a closed state inaccessible to RNA transcription repressing its expression or creating protein-protein interactions that further regulate transcription. For example, recent analyses of histone modifications in the ENCODE project found that the presence of H3K4me1 is associated with distal enhancers and probably mediates enhancer priming, whereas H3K4me3 is present at active promoters and H3K4me2 is present at both enhancers and promoters [10, 11]. High ratios of H3K4me1 to H3K4me3 are broadly used to distinguish enhancers from promoters [10, 12].

In this review, we provide our present understanding of the epigenetic regulation of T cell development, differentiation, and function, focusing on the effects of DNMTs, DNA demethylation enzymes, and diverse histone modification enzymes (see Fig. 1).

DNMTs

In mammals, DNA methylation is regulated by a family of DNMTs, which include three members: DNMT1, DNMT3a, and DNMT3b [13, 14]. While DNMT1 mediates the methylation of the daughter DNA strand during S phase to maintain the parental DNA methylation pattern, DNMT3a and DNMT3b generate de novo methylation [13]. DNA methylation is essential for embryonic development [13]. Both DNMT1 and DNMT3a have been shown to regulate T cell differentiation and function [15–21], while the role of DNMT3b in T cell biology is less understood.

DNMT1

DNMT1 regulates T cell development and proliferation in different T cell development stages and differentiation into Treg cells. Deletion of *Dnmt1* in early double-negative (DN) thymocytes with a *lck*-Cre transgenic mouse line leads to significantly reduced numbers of double-positive (DP) and single-positive (SP) thymocytes despite similar numbers of DN thymocytes [15]. *Dnmt1* deficiency impairs survival but not proliferation of DP TCR$\alpha\beta^+$ cells and *Dnmt1*$^{-/-}$ mice have enhanced presence of atypical CD8$^+$ TCR$\gamma\delta^+$ cells [15]. In contrast, deletion of *Dnmt1* in DP thymocytes with *Cd4*-Cre does not affect the T cell development but impairs activation-induced proliferation; deletion of *Dnmt1* with *Cd4*-Cre enhances cytokine mRNA expression (IFN-γ, IL-2, IL-3, and IL-4) by naive peripheral CD8$^+$ T cells [16]. Furthermore, DNMT1, but not DNMT3a, is required for the generation and function of Treg cells as mice with deletion of *Dnmt1* in the Treg compartment die of autoimmunity by 3 to 4 weeks of age, which resembles the phenotype of scurfy mice [17]. However, DNMT1 does not directly regulate the methylation of CpG sites within *Foxp3* [17]. Instead, deletion of *Dnmt1* leads to the reduction of global DNA methylation and methylation of several hundred pro-inflammatory and other genes that regulate *Foxp3* expression [17].

DNMT3a

DNMT3a is required for the suppression of anti-viral Th1-related gene expression [18]. Th1 cell development is dependent on STAT4 activation, the effect of which is limited by DNMT3a [18]. *Stat4*-deficient mice are protected from EAE development, but mice with deficiency of both *Stat4 and Dnmt3a* are susceptible to EAE induction again [18]. Similarly, DNMT3a, but not DNMT3b, limits the expression of the Th2 cytokines *Il13*, which is linked with asthma. Loss of *Dnmt3a* in T cells results in increased severity of asthma and a decrease of DNA methylation and alterations of histone modifications including lysine 27 on the histone H3 (H3K27) acetylation/methylation in the *Il13* locus [19]. The role of DNMT3a in CD8$^+$ memory generation is controversial. It has been shown that DNMT3a regulates the generation of CD8$^+$ memory T cells as deletion of *Dnmt3a* leads to more memory precursor cells and fewer terminal effector cells due to impaired suppression of *Tcf7* expression in effector T cells [20]. However, a recent study shows that memory precursor cells also acquire DNMT3a-mediated methylation programs that are later erased to allow the re-expression of naïve related genes as they dedifferentiate into memory T cells [21].

Ten-eleven translocation proteins

Ten-eleven translocations (TETs) are a family of proteins that play a major role in maintaining the fidelity of cellular DNA methylation patterns through mediating demethylation [22]. TET1, the founding member of the TET family, is identified as an enzyme processing the activity to catalyze the oxidation of methyl cytosine (5mC) to hydroxymethyl cytosine (5hmC), which leads to the final removal of the methyl group of the cytosine through further hydroxylation and oxidation [23].

Table 1 Histone modification enzymes

Family	Members	Residues modified
Histone acetyltransferases		
GNAF	Gcn5	H3K9, H3K14, H3K18
	PCAF	H3K9, H3K14, H3K18
	Hat1	H4k5, H4K12
	Elp3	H3
MYST	Esa1	H4K16
	Hbo1	H4K5, H5K8, H5K23
	MOF	H4K16
	MORF	H3K14
	Sas2	H4K16
	Sas3	H3K14, H3K23
	Tip60	H3K14, H4K5, H4K8, H4K12, H4K16
p300/CBP	p300	H2AK5, H2BK12, H2BK15, H3K14, H3K18, H4K5, H4K8
	CBP	H2AK5, H2BK12, H2BK15, H3K14, H3K18, H4K5, H4K8
Histone deacetylases		
HDAC I	HDAC1	H3K14
	HDAC2	H2A, H2B, H3, H4
	HDAC3	H3K14
	HDAC8	H3K14
HDAC II	HDAC4	H3K14
	HDAC5	H3K14
	HDAC6	H3K14
	HDAC7	H3K14
	HDAC9	H3K14
	HDAC10	H3k14
HDAC III	SIRT1	H3K9
	SIRT2	H4K16
	SIRT6	H3K9
	SIRT7	H3K18, H3K122
HDAC IV	HDAC11	H3K14
Histone methyltransferase		
SUV39	SUV39H1	H3K9
	SUV39H2	H3K9
	G9a	H3K9, H3K27
	GLP	H3K9, H3K27
	SETDB1	H3K9
	SETDB2	H3K9
EZH	Ezh1	H3K27
	Ezh2	H3K27
SET2	ASH1 and ASH1L	H3K4
	NSD1	H4K20, H3K36
	NSD2	H3K9, H3K27, H3K36, H4K20
	NSD3	H3K9, H3K27
MLL	MLL1	H3K4
	MLL2	H3K4
	MLL3	H3K4
	MLL4	H3K4
	MLL5	H3K4
SETD	SETD1A	H3K4
	SETD1B	H3K4
	SETD2	H3K36
	SETD3	H3K4, H3K36
	SETD7	H3K4, H3K9
	SETD8	H4K20
RIZ1	RIZ1	H3K9
SYMD2	SYMD2	H3K36
PRMT	PRMT1	H4R3
	CARM1	H3R2, H3R17, H3R26
	PRMT5	H3R8, H4R3
	PRMT6	H2AR3, H3R2, H4R3
	PRMT7	H3R2, H4R3
Histone demethylase		
KDM	KDM1A	H3K4, H3K9
	KDM1B	H3K4
	KDM4A	H3K9, H3K36
	KDM4B	H3K9, H3K36
	KDM5A	H3K4, H3K9
	KDM5B	H3K4
	KDM6A	H3K4, H3K27
	KDM6B	H3K27

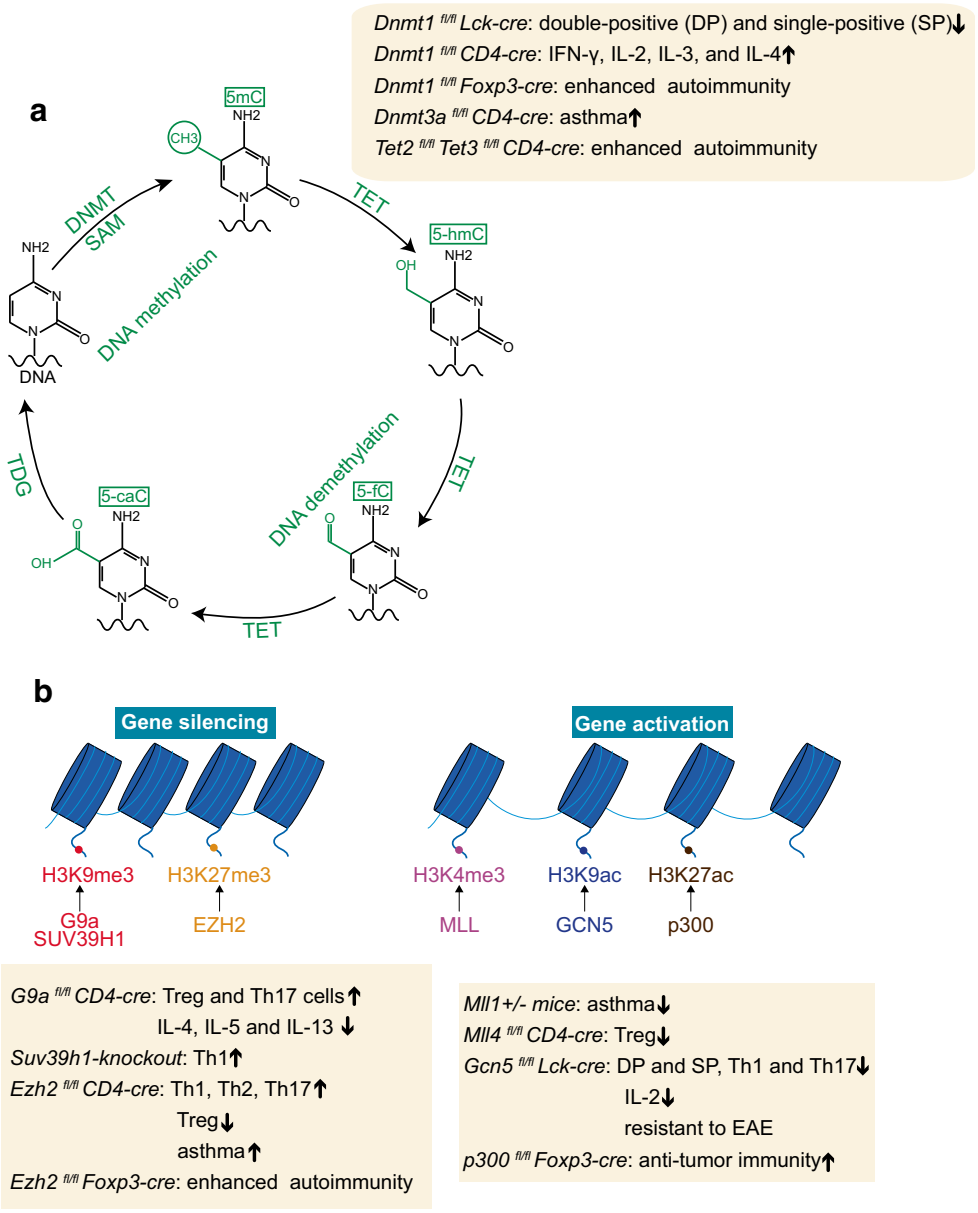

Fig. 1 Epigenetic modification enzymes and their functions in T cells. **a** DNMTs catalyze the transfer of a methyl group from *S*-adenyl methionine (SAM) to the fifth carbon of cytosine residue to form 5-methylcytosine (5mC). TET family proteins catalyze the oxidation of methyl cytosine (5mC) to form hydroxymethyl cytosine (5-hmC) and subsequent hydroxylation of 5hmC to form 5-formylcytosine (5-fC) and 5-carboxylcytosine (5-caC). 5-caC can be recognized by thymine-DNA glycosylase (TDG) that removes methyl group of the cytosine. **b** The tails of histone 3 (H3) are subjected to multiple types of post-translational modifications by a wide range of enzymes. While some marks are preferentially associated with euchromatin conformation and gene activation (H3K4me3, H3K9ac, H3K27ac) or with heterochromatin conformation and gene silencing (H3K9me3 and H3K27me3). Phenotypes of T cell-specific deletion of individual histone modification enzymes are indicated

5hmC distribution often correlates with chromatin accessibility and levels of 5hmC are positively associated with gene expression [24].

There are three members of this family, TET1, TET2, and TET3 [25]. The expressions of all three proteins are closely associated with and regulated during embryonic development [26]. While TET1 and TET3 both possess an N-terminal CXXC DNA-binding domain, TET2 lacks its CXXC domain due to chromosome inversion [27].

Currently, most studies of TET functions in T cells are focused on Treg differentiation, stability, and functions [28–30]. Upstream of the first coding exon of *Foxp3* gene, there are three conserved non-coding sequence (CNS) elements conserved non-coding sequence 1 (CNS1), 2, and 3 [31]. Conserved non-coding sequence 2 (CNS2), also known as Treg cell-specific demethylated region (TSDR), is essential for the stability of *Foxp3* transcription [32]. During Treg differentiation, 5mC is progressively lost at the CNS1 and CNS2 regions [28].

Nair et al. reported that deletion of TET2 leads to enhanced levels of 5mC+5hmC/total C at CNS2 in Treg cells [29]. However, other studies showed that deletion of individual TET1, 2, or 3 does not significantly change the DNA methylation pattern of *Foxp3* gene [30, 33, 34]. Double deletion of TET2/3 or TET1/2 increases the 5mC+5hmC/total C, indicating redundancy and addictive functions of the three TETs on regulation of Treg stability and functions [28, 30]. Mice bearing TET2/3 deletion in T cells develop autoimmunity by 8 weeks, which resembles the scurfy mice [28, 33], indicating critical roles of these two proteins in regulation of Treg cells. TET1/2 double knockout mice also have enhanced inflammation and

autoantibody production, although the phenotype is milder compared to TET2/3 double knockout animals [30]. TET expression and activity have been shown to be regulated by nutrient and metabolite concentrations [30, 35]. H_2S can enhance TET1 and TET2 expression and vitamin C regulates TET2 activity, thus regulating Treg generation and function [30, 35].

Histone acetyltransferases

Histone acetyltransferases (HATs) are a diverse set of enzymes and evolutionarily conserved from yeast to humans [36]. They often contain multiple subunits and catalyze the acetylation of histones at lysine residues [36]. Acetylation of histone lysines can regulate the chromatin conformation and acetylated lysines interact with proteins containing bromodomain, YEAST domains, or double plant homeodomain (PHD) finger domains [36, 37]. Typically lysine acetylation of histones is correlated to transcriptional activation. The 17 human HATs are grouped into three major families based on their similarity of the catalytic domains: the GCN5-related *N*-acetyltransferase (GNAT) family, the CREB-binding protein (CBP) co-activator family, and the MYST family (named after its four founding members MOZ, Ybf2, Sas2, and Tip60). In T cells, CBP/p300 and Gcn5 are currently the most investigated HATs.

p300

p300 was initially identified as a transcriptional co-factor for the adenovirus E1A-associated 300-kDa protein (p300) [38]. p300 and its close homolog CBP are large molecules containing multiple domains including CREB-binding domain, bromodomain, HAT domain, and other domains [9]. p300 is required for the activities of more than 50 critical transcriptional regulators in T cells [39] and regulates various aspects in T cell biology, including development, differentiation, and function.

p300 functions both as a chromatin-modification enzyme to regulate chromatin accessibility and gene expression and can form complexes with other transcriptional factors to regulate their transcriptional activities [40]. For example, CBP/p300 binds to and controls the transcriptional activity of nuclear factor of activated T cells (NFAT), a critical transcriptional factor for T cell activation [40]. The NFAT-dependent transcription is independent of the HAT activity of CBP/p300 [40]. During T cell differentiation, p300 forms different complexes under different T cell differentiation conditions to regulate T cell differentiation [41]. Under Th2 differentiation condition, p300, GATA binding protein 3 (GATA3), and chromodomain helicase DNA-binding protein 4 (Chd4) form a transcriptional complex at the Th2 cytokine loci and activate Th2 cytokine expression and repress the secretion of the Th1 cytokine IFN-γ [41]. Under Th17 differentiation conditions, RORγt and p300 are recruited to the *Il17* promoter to regulate the expression of Th17 signature genes [42] and pharmacologic inhibition (CBP30) of p300 can suppress human Th17 response [43]. In $CD8^+$ T cells, p300, the intracellular domain of Notch2 and the transcription factor CREB1 form a complex on the promoter of the gene encoding Granzyme B and regulate its expression, which is essential for the cytotoxic functions of $CD8^+$ T cells [44].

In addition to histones, non-histone proteins can also be subjected to p300-mediated acetylation and regulation. For example, Foxp3 has a short half-life and that acetylation of Foxp3 by p300 prevents its proteasomal degradation [45]. Conditional deletion or pharmacologic inhibition (CBP30) of p300 in Treg cells increased T cell receptor (TCR) -induced apoptosis and impaired the suppressive function of Treg cells [46].

Recently, the binding intensities of p300 and H3K27Ac have been used to identify the presence of enhancers [47]. In turn, this has led to the discovery of a subset of genes that are regulated by a group of enhancers called super-enhancers (SEs) [47]. With this approach, dominant SE architectures in T cells are identified in the loci of cytokines and cytokine receptors [47]. However, the locus encoding *Bach2*, a negative regulator of effector differentiation, is also highly enriched with p300 and H3K27Ac binding sites indicating the presence of a SE, highlighting the important and complex regulation of T cell differentiation by p300 and Bach2 [47].

GCN5

General control non-derepressible 5 (GCN5) is highly conserved and mammals contain two highly homologous GCN5-like paralogues, GCN5 and p300/CBP-associated factor (PCAF) [48]. GCN5 has been shown to regulate gene transcription by catalyzing the acetylation of lysine residues on multiple histones including H2B, H3, and H4 [36].

GCN5 is required for T cell development and activation as the numbers of DP and SP are significantly reduced in the thymus of *Gcn5*-deficient mice [49]. Upon TCR stimulation, GCN5 is recruited onto the *Il-2* promoter by NFAT, and it catalyzes the acetylation of lysine residue 9 of histone H3 (H3K9) but not NFAT to regulate IL-2 production [49]. Similarly, PU.1 recruits GCN5 and PCAF, but not p300, to *Il-9* promoter to enhance IL-9 production and promote Th9 induction [50]. Inhibition of GCN5 activity results in reduced IL-9 production but not IL-10 and IL-21, two other cytokines produced by Th9 cells, indicating that PU.1-dependent recruitment of GCN5 is promoter specific [50].

GCN5 promotes Th1 and Th17 differentiation by modulating the expression of their lineage-specific transcription factors T-bet and RORγt and the loss of *Gcn5* impairs the differentiation of Th1/Th17 but not Th2 and Treg [49]. Mice with T cell-specific deletion of *Gcn5* were resistant to EAE induction [49].

Histone deacetylases

Histone deacetylases are key regulators of T cell-mediated immunity in mice and humans that reverse the effects of HATs [37]. Mammalian histone deacetylase (HDAC) proteins are a group of 18 enzymes that are subdivided into four different classes (see Table 1). Classes I (HDAC1, 2, 3, and 8), II (IIa: HDAC4, 5, 6, and 7; IIb: HDAC9 and 10), and IV (HDAC11) are considered classical HDACs whose activities are inhibited by trichostatin A (TSA) and have a zinc-dependent active site, whereas class III enzymes are a family of NAD^+-dependent proteins known as sirtuins (SIRT 1–7) and are not affected by TSA [51]. HDACs are often resided within large co-repressor complexes, and proteomic approaches have shown that HDACs interact with dozens to hundreds of proteins that affect their activities [52].

HDAC functions in T cell biology have been extensively reviewed in a recent article by Ellmeier et al. [37]. T cell-specific deletion of single members of HDACs often does not change the gross T cell development and homeostasis probably owing to the compensatory or redundant functions among HDACs [53]. However, simultaneous deletion of *Hdac1* and *Hdac2* with a *Cd4*-Cre transgenic mouse line leads to spontaneous expression of CD8 linage genes such as *Cd8a*, *Cd8b*, and *eomesodermin* (*Eomes*) in MHC class II-selected $CD4^+$ help cells [54]. Activation of the HDAC1/2 double deficient $CD4^+$ T cells results in upregulation of $CD8^+$ cytotoxic effector molecules such as Eomes, IFN-γ, Runx3, T-bet, Granzyme B, and perforin [54]. *Hdac1*-deficient T cells have enhanced Th1 and Th2 differentiation [55, 56]; mice bearing specific deletion of *Hdac1* in the T cell compartments have elevated Th2 cell-type allergic inflammation [56]. It is of note that under Th1 conditions, deletion of HDAC1 only enhanced IFN-γ expression but not Th2 cytokines and vice versa [55], suggesting that HDAC1 only represses the expression of poised genes but not silent genes. HDAC11 has also been reported to inhibit T effector function by suppressing Eomes and T-bet [57]. In contrast, HDAC9 positively regulates the extent of $CD4^+$ T cell-mediated immunity in MRL/lpr lupus model and specific inhibition of HDAC9 activity may represent a novel strategy to suppress autoimmunity [58].

HDACs are involved in the regulation of Th17 cells and Th17 cell-associated autoimmunity both through their effects on histones and direct post-translational modification of transcription factors [59]. *Sirt1*$^{-/-}$ T cells have reduced potential to differentiate into Th17 cells and are less potent in inducing EAE [59], in contrast to a previous study showing that *Sirt1*$^{-/-}$ mice are more susceptible to EAE [60]. It has been shown that RORγt is highly acetylated in the absence of SIRT1, reducing its transcriptional activity [59]. HDAC1 does not affect Th17 differentiation but mice bearing T cell-specific deletion of *Hdac1* are completely resistant to EAE induction [55]. This is probably due to enhanced phosphorylation of STAT1 in the absence of HDAC1, which suppresses the expression of *Ccr4* and *Ccr6*, key regulators of T cell migration into the CNS [55].

Treg cells are the most studied T cell subtype in the context of regulation by HDACs [45]. FoxP3 is subjected to post-translational modifications, which affects its stability, transcriptional activity, and suppressive function [61]. There are several lysine residues within FoxP3 that can be acetylated and deacetylated by HDACs [62]. Several members of the HDAC family, including HDAC1, HDAC2, HDAC3, HDAC6, HDAC7, HDAC9, HDAC11, and SIRT1, have been shown to interact with FoxP3 and regulate FoxP3 activity both positively and negatively [37]. A pan-HDAC inhibitor trichostatin A leads to increases in the proportion and absolute numbers of Tregs in mice and addition of HDAC inhibitors enhances in vitro human Treg differentiation [63], arguing a general inhibitory role of HDACs on Treg differentiation and function. However, Treg cell-specific deletion of *Hdac3*, *Hdac5*, or *Sirt3* indicates a positive role of these HDACs in Treg function [37]. These HDAC individual deficient mice spontaneously develop autoimmunity due to impaired Treg function [64], although the molecular mechanisms underlying are less clear. These data indicate that HDACs have redundant and complex roles in regulation of Treg generation and functions.

Histone methyltransferase

Histones can be methylated at lysine and arginine residues, which are catalyzed by lysine methyltransferases (KMTs) and arginine methyltransferases (PRMTs), respectively, with *S*-adenosyl-L-methionine (SAM) as the methyl donor [65]. Histone methylation involves the transfer of up to three methyl groups, thus resulting in mono-, di-, or tri-methylated lysine, respectively, and in mono- or di- (asymmetric or symmetric) methylated arginine [65].

The most extensively studied histone lysine methylation sites are histone 3 lysine 4 (H3K4), H3K9, H3K27, histone 3 lysine 36 (H3K36), histone 3 lysine 79 (H3K79), and histone 4 lysine 20 (H4K20) (Table 1), although many methylated lysine residues have been found also in H1, H2A, H2B, and in further positions within H3 and H4 [66]. While some lysine methylation marks are preferentially associated with euchromatin conformation and hence gene activation (H3K4, H3K36, and H3K79) or with heterochromatin conformation and gene silencing (H3K9, H3K27, and H4K20) probably due to the recruitment of different effector proteins by the readers [66]. The final effects on chromatin are determined by the interplays of several histone modifications together. In T cells, G9a, TRIM28, EZH2, Suv39h1, and MLL are the most investigated histone methyltransferases (HMTs).

G9a

G9a is euchromatic histone lysine *N*-methyltransferase 2 (EHMT2) and is encoded by the *Ehmt2* gene. G9a can catalyze the mono- and di-methylation of histone H3K9

(H3K9me1 and H3K9me2) and K27 (H3K27me1 and H3K27me2), which are generally associated with gene silencing and *G9a*-deficient cells have a drastic reduction in these modifications [67].

G9a is required for $CD8^+$ T cell development and identity by interacting with Runx3 to Runx1 and is necessary for continued silencing of helper lineage genes in dividing CD8 T cells in lymphopenia environment or in response to tumor antigens [68]. Deletion of *G9a* in T cells results in derepression of several genes, which are otherwise expressed only in $CD4^+$ T cells [68]. Blimp-1 regulates the differentiation of short-lived effector cells while suppressing the development of memory precursor $CD8^+$ T cells [69]. Blimp1 recruits G9a to the *Il2ra* locus and *Cd27* locus to suppress their expression, although the direct histone substrates of G9a remain unclear [69]. cAMP responsive element modulator (CREM) α has been reported to recruit DNMT3a and G9a to *Cd8* gene cluster, which leads to the silence of *Cd8a* and *Cd8b* gene and expansion of double negative T cells in SLE patients and MRL/lpr mice [70].

T cell-specific deletion of *G9a* or pharmacological inhibition of G9a methyltransferase activity results in increased frequencies of both Treg and Th17 cells during intestinal inflammation, suggesting that G9a-mediated majorly di-methylation of histone H3 lysine 9 (H3K9me2) negatively regulates the differentiation of these cell lineages in vivo [71]. However, G9a seems to play a positive role in Th2 differentiation as *G9a*-deficient T cells have specifically impaired induction of Th2 lineage-specific cytokines IL-4, IL-5, and IL-13 and fail to amount a Th2 immune response to intestinal *Trichuris muris* [72]. The mechanism for the positive regulatory of G9a on Th2 differentiation is not well understood. In addition to regulating the chromatin structure, it has been reported that G9a is recruited to the nuclear envelope and interacts with lamin B1 during T cell adhesion; depletion or inhibition of G9a blocks T cell migration in both 2D and 3D environments [73].

Suv39h1

Suv39h1, a histone methyltransferase, is a member of the suppressor of variegation 3–9 homolog family with a chromodomain and a C-terminal SET domain. Suv39h1 contributes to the generation of di- and tri-methylation of lysine 9 of histone H3 (H3K9me3) [65]. H3K9me2/me3 are bound by the chromodomain of heterochromatin protein 1 (HP1), which can self-oligomerize and further recruit repressive histone modifiers, forming compacted heterochromatin conformation [74]. TGF-β is a multifaceted cytokine in immune regulation and can suppress TCR-mediated *Il2* production [75]. One mechanism involves Smad2/3-dependent recruitment of Suv39h1 to the *Il2* promoter, thus suppressing the IL-2 production [75].

In Th2 cells, a high ratio of H3K9me3/H3K9ac is found at the silent key Th1 gene such as *Ifng* promoter, which is Suv39h1 dependent [76]. Suv39h1-deficient Th2 cells are more prone to be reprogrammed to Th1 cells and Suv39h1-deficient mice have reduced pathology in an allergic asthma model [76]. Recently, the same group shows that Suv39h1 regulates $CD8^+$ T effector versus memory differentiation [77]. In a *Listeria monocytogenes* infection model, *Suv39h1*-deficient mice have significantly reduced antigen-specific effector $CD8^+$ T cells and these cells have reduced H3K9me3 depositions in the loci of genes associated with stemness and memory phenotype such as *Il7r* (CD127), *Sell* (CD62L), *Ccr7*, and *Cxcr4* [77]. As a result, *Suv39h1*-deficient $CD8^+$ T cells show sustained survival and increased reprogramming capacity into long-term memory cells [77].

Ezh2

Polycomb-repressive complex 2 (PRC2), a multiple protein complex including enhancer of zeste homolog 1/2, EED, Suz12, and RbAp48, mediates the compaction of chromatin, through the methylation of H3K27. Ezh1 and Ezh2 are the enzymatic subunits of PRC2 and catalyze the di- and tri-methylation of H3K27 [78]. Compared to the less understood role of Ezh1 in T cell biology, the functions of Ezh2 have been intensively studied in recent years [78].

Ezh2-deficient T cells have enhanced Th1, Th2, and Th17 differentiation but reduced Treg differentiation [79]. Tumes et al. found that *Ezh2*-deficient T cells spontaneously secrete Th1 and Th2 cytokines and deletion of *Ezh2* in T cells with *Cd4*-Cre renders the mice susceptible to allergic asthma [80]. The levels of H3K27me3 occupancies in the loci of both T helper linage-specific cytokines (*Ifng*, *Il4*, and *Il17*) and transcriptional factors, i.e., *Tbx21* and *Gata3*, are reduced in the absence of Ezh2 [79, 80]. Neutralization of IFN-γ or IL-4 can partially rescue the defective Treg differentiation of *Ezh2*-deficient CD4 T cells, and combination of blockade of IFN-γ and IL-4 almost completely reverses the impaired Treg differentiation [79]. These data, together with the absence of changes to H3K27me3 status in the *Foxp3* locus in the absence of Ezh2 [79], argue an indirect role of Ezh2 on the regulation of Treg differentiation. However, mice bearing deletion of *Ezh2* in the Treg compartment using *Foxp3*-Cre result in spontaneous autoimmunity with reduced $FoxP3^+$ T cells in non-lymphoid tissues and enhanced disease severity of EAE [81]. The authors propose that Ezh2 is required for the maintenance of the Treg cell identity [81]. It is of note that mice bearing deletion of *Ezh2* in the T cell compartment using *Cd4*-Cre do not show grossly elevated inflammation, despite enhanced percentages of T effector cells and reduced Treg cells in these mice [79]. These data indicate that Ezh2 may be required for both T effector and Treg survival. Consistent with

this, Zhang et al. reported that deletion of *Ezh2* in T cells activates multiple death pathways in differentiated T effector cells [82]. In addition to its effects of H3K27, Ezh2 is known to regulate actin polymerization through methylation and its absence results in impairment of the immune synapse and T cell activation in response to antigen presentation [83]. Together, these findings suggest that the regulation of cell survival by Ezh2 probably is dominant over the regulation of T cell differentiation by Ezh2 in vivo.

The functions of Ezh2 in regulation of memory $CD8^+$ T cells are complex. Recently, Ezh2 has been shown to be required for cytotoxic T effector cell expansion and differentiation [84]. Both no role and suppressive role of Ezh2 on the formation of memory precursor $CD8^+$ cells have been reported [84, 85]. Ezh2-mediated H3K27me3 marks at pro-memory genes occurred rather later during T effector generation in a LCMV infection model [84], suggesting a temporal model of loss of memory potential through selective epigenetic-silencing of pro-memory genes in effector T cells [84]. Pharmacological inhibition of Ezh2 or ablation of *Ezh2* in Treg can enhance the antitumor immunity by enhancing expression of Th1 type chemokines CXCL9 and CXCL10 by ovarian cancer cells and by driving the tumor-infiltrating Tregs into a pro-inflammatory phenotype, remodeling the tumor microenvironment, and improving the recruitment and function of $CD4^+$ and $CD8^+$ effector T cells that eliminate tumors [86]. Similarly, Goswami et al. show inhibition of Ezh2 in human T cell-elicited phenotypic functional alterations of Tregs and enhanced cytotoxic activity of T effector cells [87]. In addition, modulating *Ezh2* expression in T cells can further improve antitumor responses elicited by anti-CTLA-4 therapy [87].

Mixed-lineage leukemia

Mixed-lineage leukemia (MLL) (also known as lysine methyltransferase 2, KMT2) family proteins methylate H3K4 to promote chromatin accessibility and gene transcription [88]. MLL proteins reside in large, multi-subunit complexes including WD repeat protein 5 (WDR5), retinoblastoma binding protein 5 (RbBP5), ASH2L, and DPY30 [88].

MLL1 is required in the maintenance of H3K4me2 and H3K9ac in *Gata3* locus and $Mll1^{+/-}$ mice have reduced Th2-induced allergic asthma [89]. It has been shown that IL-12 induces MLL1 expression, which is required for the proliferation of Th1 cells [90]. MLL4 deficiency impairs the development of Treg cells by regulating H3K4 monomethylation of *Foxp3* at direct binding sites and catalyzing H3K4 methylation at distant unbound enhancers *in trans* via long-distance chromatin looping [91].

Histone demethylases

Histone methylation has long been regarded as irreversible because of the high thermodynamics of the N-CH_3 bond. The identification of the amine oxidase lysine-specific demethylase 1A (LSD1; also known as KDM1A) as a histone demethylase of histone H3 lysine 4 (H3K4) changed this perception. Subsequently, a large family of Jmjc domain-containing histone lysine demethylases have been identified, which remove methyl marks on K4, K9, K36, and K27 of histone 3 (H3K4, H3K9, H3K36, and H3K27) with distinct mechanisms from LSD1. Among them, ubiquitously transcribed tetratricopeptide repeat, X chromosome (Utx) and Jmjd3, a homologous form of Utx, specifically demethylate H3K27 [92].

Utx and Jmjd3

Utx (also known as KDM6A) and Jmjd3 (also known as KDM6B) are required for embryonic development as deletion of either gene is embryonically lethal [93]. The regulation of these two proteins on development relies on their demethylase activity, as well demethylase activity-independent functions [93]. Deletion of neither *Utx* nor *Jmjd3* does not significantly affect T cell development; however, $Utx^{-/-}Jmjd3^{-/-}$ double KO mice have significantly reduced numbers of naïve peripheral $CD4^+$ T cells, suggesting Utx and Jmjd3 play redundant roles in regulation of proper T cell development and maturation in the thymus beyond the DP stage [94]. The expression of a key gene required for thymus egress, *S1pr1*, is significantly reduced in the absence of Utx and Jmjd3 [94]. Opposite roles of Utx and Jmjd3 have also been documented in acute lymphoblastic leukemia [95]. Jmjd3 seems to play complex and multifaceted roles in regulation T cell differentiation in vivo and in vitro [96, 97]. Jmjd3 regulates the methylation status of H3K27 and/or H3K4 in the promoter and body regions of target genes [96, 98]. These loci-specific effects of Jmjd3 on target gene expression are mediated through interaction with a specific transcription factor T-bet [96]. Smad3 interacts with Ash2L in the presence of Jmjd3 but fails to interact in *Jmjd3*-deficient Treg cells, suggesting that Jmjd3 is required for Smad3-Ash2L interaction during Treg cell differentiation [96]. Jmjd3 can be recruited to the CNS2 of *Il17* loci to mediate *Il17a* and *Il17f* expression and deletion of CNS2 led to significantly reduced IL-17 expression under Th17 differentiation conditions [98].

Conclusions and perspective

Over last decade, we have witnessed an ever-growing interest and knowledge of epigenetic regulation in many aspects of

cellular processes and functions. The functions and mechanisms underlying regulation of T cell biology such as T cell development, differentiation, effector versus memory generation, and functions by epigenetic modifications mediated by multiple histone modification enzymes, DNA methyltransferases, and DNA demethylases are starting to be elucidated. It is of note that many of the genes for these enzymes are mutated in leukemia highlighting their importance in hematopoietic cell development and function as well as encouraging the invention of pharmaceutical grade specific inhibitors and their use in oncology. Furthermore, targeting different histone and DNA modification enzymes may have tremendous potential for the treatment of cancers and autoimmune diseases. Although much knowledge has been gained in these aspects, there are still many unanswered questions: (1) how the specificity of regulation of specified genes under different conditions by these enzymes is achieved and (2) how to target the histone and DNA modification enzymes and minimize the side effects. Full understanding of the mechanisms of regulation of T cell biology by the histone and DNA modification enzymes requires further investigations.

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Compliance with ethical standards

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