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Review

Host Methyltransferases and Demethylases: Potential New Epigenetic Targets for HIV Cure Strategies and Beyond

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Running title: Methylation Enzymes and HIV Infection

Abstract

A successful HIV cure strategy may require reversing HIV latency to purge hidden viral reservoirs or enhancing HIV latency to permanently silence HIV transcription. Epigenetic modifying agents show promise as anti-latency therapeutics *in vitro* and *ex vivo* but also affect other steps in the viral life cycle. In this review, we summarize what we know about cellular DNA and protein methyltransferases as well as demethylases involved in HIV infection. We describe the biology and function of DNA methyltransferases, and their controversial role in HIV infection. We further explain the biology of protein methyltransferases and their effects on lysine and arginine methylation of histone and non-histone proteins. We end with a focus on protein demethylases, their unique modes of action and their emerging influence on HIV infection. An outlook on the use of methylation-modifying agents in investigational HIV cure strategies is provided.

Keywords: methyltransferase, histone demethylase, methyltransferase inhibitors, demethylase inhibitors, HIV cure, latency reactivation

1. Introduction

Epigenetic modifications of nucleic acids, histones and non-histone proteins are important regulators of gene transcription and expression and are targets in clinical efforts to reverse HIV latency. One such modification is methylation, which involves the transfer of a methyl group with S-adenosyl-l-methionine (SAM) as a methyl donor[1]. This modification is a reversible process regulated by methyltransferases (MTs) and demethylases. Both methyltransferases and demethylases are highly specific for the position of their substrate and extent of methylation. Methylation of nucleic acids, histones and non-histone proteins regulates gene transcription and expression by altering chromatin packaging, promoting chromatin accessibility, creating DNA-protein interactions, and generating interaction interfaces for the assembly of macromolecular complexes[1, 2].

Epigenetic regulation of DNA, histone and non-histone proteins plays an important role in HIV transcription and is a target in preclinical efforts to reverse HIV latency, a major hurdle to curing HIV infection. HIV latency is established by integrating viral DNA into the host chromatin[3]. Once integrated, proviral cDNA is organized into higher-order chromatin and becomes subject to regulation by host chromatin-modifying enzymes, including deacetylases, methyltransferases and demethylases. Hypo-acetylation of histone proteins by histone deacetylases helps to maintain HIV-1 latency by repressing viral transcription[4]. Critical cofactors that further contribute to latency include the positive transcription elongation factor b (P-TEFb), NF-κB, and the virally encoded transactivator of transcription (Tat)[5-7]. Tat binds to an RNA stem-loop structure called TAR at the 5′ end of all nascent viral transcripts and recruits P-TEFb, which together with other elongation factors, forms a “super-elongation complex” at the

elongating RNA polymerase II[8-10]. Tat itself is subject to reversible methylation by SETD7/SET7/9/KMT7 at lysine 51 in its basic RNA-binding domain[11] (**Figure 1**). This methylation event positively supports the transcriptional activity of Tat[11] and is reversed by the demethylase activity of LSD1/KDM1A[12]. Tat is also methylated by the histone lysine methyltransferase SETDB1 at lysine 51[13], by SETD7 at lysine 71[14], and by arginine methyltransferase PRMT6 at R52 and R53[15] (**Figure 1**).

Latent HIV-1 proviruses are primarily found integrated into actively transcribed genes but characteristically display heterochromatic features[16, 17]. The long terminal repeat (LTR) of latent proviruses accumulates histone deacetylases (HDACs) that result in high levels of deacetylated histones[18, 19]. Besides histone deacetylation, a growing list of MTs and demethylases indicates that methylation of DNA, histones and non-histone proteins is essential for HIV-1 transcription. In this review, we summarize the DNA and protein methyltransferases and demethylases involved in HIV infection, and their implications for HIV cure strategies.

2. Methyltransferases

2.1 ***DNA methyltransferases***

DNA methylation is an epigenetic mark that mediates transcriptional activation or repression of genes[20]. DNA is methylated within cytosine-phosphate-guanine (CpG) and non-CpG dinucleotide sites by addition of a methyl group to the fifth carbon atom of the cytosine residues using SAM as a methyl donor[21]. This process is catalyzed by specific DNA methyltransferase (DNMT) enzymes. In mammals, five structurally and functionally distinct DNMTs have been characterized: DNMT1, DNMT2, DNMT3A, DNMT3B and DNMT3L[21]. DNMT3L does not

possess catalytic activity, and DNMT2 mainly methylates RNA. DNMT1, DNMT3A and DNMT3B mediate two different DNA methylation mechanisms: (1) *de novo* methylation which creates new marks on DNA and (2) maintenance of previously methylated genomic sites during DNA replication[21]. At gene promoters, the presence of DNA methylation is linked to chromatin silencing[22, 23]. The repressive effect of DNA methylation on gene expression is mediated by two mechanisms: (1) the interference of DNA methylation with the recognition of transcription factor binding sites which results in impairment of gene activation[24], and (2) the recognition of DNA methylation by specific Methyl-CpG binding proteins, that recruit co-repressor protein complexes and thereby mediate silencing[25].

The role of DNA methylation in HIV-1 infection is controversial. Kauder et al. identified methyl-CpG binding domain protein 2 as a regulator of HIV-1 latency and reported the hypermethylation of two CpG islands surrounding the HIV-1 transcriptional start site in latently infected Jurkat cells (J-Lat) and in primary $CD4^+$ T cells[26]. Furthermore, methyl-CpG binding domain protein 2, which is present at one of these CpG islands during latency and absent upon inhibition of cytosine methylation with 5-aza-2'deoxycytidine, possibly recruits transcriptional repressors to methylated DNA and thereby contributes to HIV-1 latency[26]. A separate study showed high levels of CpG methylation of the HIV-1 5' LTR in an *in vitro* model of latency and in latently infected T cells isolated from HIV-1-infected patients in a model in which CpG methylation acts as a late event during establishment of HIV-1 latency not required for initial provirus silencing[27]. Recently, Maricato et al. reported that HIV-1 infection increases the methylation level of cellular DNA in peripheral blood mononuclear cells (PBMC)[28]. A separate study found overall low levels of 5' LTR DNA methylation in resting $CD4^+$ T cells isolated from a group of HIV-infected individuals under antiretroviral treatment for up to 3 years[29]. However,

in some long-term-treated individuals, the authors detected proviral molecules with a high density of 5' LTR CpG methylation. They proposed that transient stimulation of cells harboring latent proviruses contributes, at least in part, to the methylation of the HIV-1 promoter over time[29]. Collectively, these four studies support a model in which DNA methylation contributes to HIV-1 transcriptional gene silencing, likely by inhibiting transcriptional initiation of the integrated provirus and inhibiting viral post-integration reactivation from latency. In contrast, Blazkova et al. reported very low levels of methylated CpG dinucleotides within the promoter/enhancer region of latent HIV proviruses found in resting $CD4^+$ T cells isolated from aviremic infected individuals[30]. The different results can possibly be explained by the use of different primers and the length of antiretroviral treatment of patients.

So far, only DNMT1, DNMT2 and DNMT3B have been implicated in HIV infection[31, 32]. DNMT1, which is the most abundant DNMT in the cell and transcribed mostly during the S phase of the cell cycle, is primarily responsible for maintaining methylation via transfer of methyl groups to the hemi-methylated DNA strands after DNA replication, but also has *de novo* DNMT activity[33]. In addition, DNMT1 influences transcriptional regulation by interacting with HDAC2 and novel co-repressors to form a complex at replication foci[34]. Further, DNMT1 represses transcription from E2F-responsive promoters by recruitment of transcription factors retinoblastoma protein Rb and E2F1, as well as histone deacetylase HDAC1[35]. Recently, DNMT2 was shown to re-localize from the nucleus to stress granules (SGs) and to methylate HIV-1 RNA in a sequence-independent manner, thereby providing post-transcriptional stability to the HIV-1 RNA[32].

DNMT3B, which is highly expressed in early embryonic stem cells, cannot differentiate between un-methylated and hemi-methylated CpG sites, and cannot copy or contribute to the

maintenance of a specific pattern of methylation[33]. However, DNMT3B has an important role in *de novo* methylation of unmodified cytosine residues[33].

Several groups reported that infection of $CD4^+$ T cells with HIV-1 increases expression and activity of DNMTs[31, 36-38]. One study showed that acute infection with wild-type and integration-defective HIV-1 increases cellular DNMT1 expression and activity, resulting in hypermethylation and reduced expression of the tumor suppressor gene $p16^{INK4A}$ in lymphoid cell lines[37]. Youngblood et al. reported that HIV-1 early gene expression caused DNMT1 induction, a process prevented by treatment with the phytoalexin resveratrol thought to interfere with transcription factor AP1 activity[38]. The HIV-1 responsive element was mapped to nt –1634 to –1214 in the DNMT1 promoter, which overlaps with AP1 sites[38]. An independent study evaluating the effect of HIV-1 infection on cellular vitamin D receptor (VDR) expression showed that infection enhanced expression of HDAC1, DNMT1 and DNMT3B[31]. Recently, Pion et al. reported that HIV-1 infection downregulates expression of master transcription factor Foxp3 in regulatory T cells, which was associated with an increase in the expression of DNMT3B and higher methylation of CpG sites in the FOXP3 locus[39].

Others linked the increase in DNMT expression to an overall increase in methylated genomic DNA in HIV-infected cells and the *de novo* methylation of a single CpG dinucleotide in the gamma interferon (IFN-γ) gene promoter to the down-regulation of IFN-γ production in HIV-infected $CD4^+$ T cells[36, 37]. In an attempt to exploit these findings therapeutically, Martinez-Colom et al. designed a chimeric protein (IN3b) that linked the N-terminal domain of the HIV integrase enzyme with the C-terminal domain of DNMT3B to induce long-term silencing of HIV gene expression in host cells[40]. However, reduced DNMT1 and DNMT3A activity was reported

in primary oral epithelial cells isolated from aviremic treated HIV^+ individuals[41], suggesting that DNA methylation is deregulated, yet not always up-regulated, in HIV infection.

A recent study aimed to investigate the influence of antiretroviral therapy on methylation markers found in PBMCs isolated from blood from a group of HIV infected, ART treated patients, that the percentage of 5-methylcytosine was inversely correlated with proviral DNA and active replication while DNMT1 and DNMT3A independently correlated with active viral replication[42]. Differential DNA methylation associated with HIV infection was also reported in a recent large-scale epigenome-wide study where HIV-infected and uninfected patients from the Veteran Aging Cohort Study (VACS) were profiled for CpG sites in DNA extracted from the blood[43]. The authors identified 20 epigenome-wide significant CpGs for HIV-1 infection, including 2 CpGs in the promoter of the NLR family, CARD domain containing gene 5 (NLRC5), a key regulator of major histocompatibility complex class I gene expression, which showed significantly lower methylation in HIV-infected subjects than in uninfected subjects and which was negatively correlated with viral load in the HIV-infected samples[43].

2.2 ***Protein methyltransferases***

Protein methyltransferases (PMTs) are enzymes that covalently transfer methyl groups from the cofactor SAM to specific amino acid residues within nuclear and cytoplasmic proteins. Based on their structure, SAM-dependent MTs are divided into three classes: PMTs with seven-strand twisted β-sheet structure[44], SET (SuVar3-9, enhancer of Zeste, Trithorax) domain lysine MTs[45], and membrane-associated MTs[46]. These enzymes mediate protein methylation via O-methylation or N-methylation. Methylations of glutamic acid and aspartic acid are a type of O-methylation,

and N-methylation involves methylation of lysine, arginine, histidine, alanine, proline, glutamine, phenylalanine, asparagine, and methionine. Among these, methylation of lysines and arginines is most common[47]. Lysines can be mono-, di-, or tri-methylated, but arginines can be mono-methylated or symmetrically or asymmetrically di-methylated. Protein lysine and arginine methylation results either in gene activation or repression, depending on the amino acid residue that becomes methylated and the state of methylation.

2.2.1 **Lysine methyltransferases (KMT)**

More than 50 human KMTs have been found that methylate histones and non-histone substrates. Based on their catalytic domain, KMTs are grouped into two different families: (1) DOT1-like (DOT1L) that does not possess a SET domain, and (2) the SET domain–containing MTs (reviewed in[48]). SET domain-containing MTs can be further divided into four families: SET1, SET2, SUV39, and RIZ[48]. Except for family members EZH1 and EZH2, the SET1 family is characterized by the SET domain, followed by a post-SET domain. SET2 class members are NSD1-3, SETD2 and the SMYD family, which all have a SET domain positioned between a post-SET and an AWS domain. The SUV39 family members SUV39H1, SUV39H2, G9a, GLP, SETDB1, and SETDB2 all contain a pre-SET domain. Finally, the RIZ family members BLIMP1, PFM1 and RIZ1 are characterized by a SET domain at the amino terminus. In addition, several SET domain–containing methyltransferases include SET7/9, SET8, SUV4-20H1, and SUV4-20H2, which do not belong to any of these families. Figure 2 shows the KMTs that have been implicated in HIV infection (**Figure 2**).

2.2.1.1 Enhancer of zeste homolog 2 (EZH2)

EZH2 belongs to the SET1 family of KMTs and tri-methylates histone H3 lysine 27 (H3K27me3)[49]. This subunit of the polycomb repressor complex 2 (PRC2) is an important regulator of chromatin state involved in the maintenance of transcriptional silencing[50]. EZH2 lacks enzymatic activity as an isolated protein and only methylates lysine residues when in complex with EED and SUZ12[51]. EZH2 is modified via O-GlcNAcylation by O-linked *N*-acetylglucosamine transferase, resulting in increased stability of EZH2 and higher cellular histone H3 lysine 27 tri-methylation levels[52].

EZH2 associates with the promoter/enhancer region of HIV-1 proviruses in latently infected Jurkat T-cell lines and is found with the corresponding H3K27me3 mark[53]. Knockdown of EZH2 with shRNA or treatment with the chemical inhibitor 3-deazaneplanocin A efficiently reactivates a significant portion of silenced proviruses. Further, knockdown of EZH2 sensitizes latent proviruses to external stimuli, such as T-cell receptor stimulation, and interferes with the reversion of reactivated proviruses back to latency, underscoring its restrictive role in HIV-1 latency[53]. In addition, Nguyen et al. showed that treatment with newer inhibitors of EZH2 (GSK-343, EPZ-6438) was sufficient to induce the reactivation of latent proviruses in a primary T-cell model using primarily latently infected Th17-polarized cells or in resting memory T cells isolated from aviremic HIV-1-infected patients[54]. In contrast, Tripathy et al. showed that GSK343 reduced tri-methylation of HIV provirus–associated histone H3K27 without increasing proviral expression in latently infected resting $CD4^+$ T cells[55]. However, after reduction of H3K27 methylation at the HIV-1 LTR, subsequent exposure to the HDAC inhibitors suberoylanilide hydroxamic acid (SAHA) or vorinostat resulted in increases in viral gag RNA

and p24 antigen production, pointing to the combination of HMT and HDAC inhibitors as a promising reversal strategy in HIV latency[55].

2.2.1.2 Euchromatin histone methyltransferases EHMT1 (GLP) and EHMT2 (G9a)

Euchromatin histone methyltransferases (EHMTs) are SUV39 family members. They are evolutionarily conserved proteins that mono- and di-methylate histone 3 at lysine 9 (H3K9me1 and H3K9me2) in euchromatic regions of the genome[56]. In mammals, there are two EHMT proteins: G9a-like protein GLP is encoded by *EHMT1*, and G9a is encoded by *EHMT2*[56]. EHMTs are characterized by an N-terminal SET and Pre-SET domain and a series of ankyrin repeats that are required for protein–protein interactions, particularly with H3K9me1 and H3K9me2, the marks that EHMT proteins generate[57]. G9a methylates itself and mediates the interaction with the epigenetic regulator heterochromatin protein 1 (HP1)[58]. G9a hetero-dimerizes with GLP via its carboxyl terminal SET domain to catalyze methylation[59, 60]. In addition to H3K9, both proteins, independently and in the complex, mono- and di-methylate histone H3 lysine 27 (H3K27)[61] and histone H1 isotype 4 (H1.4)[62, 63]. Additionally, during the G1 phase G9a mono-methylates histone H3 lysine 56 (H3K56me1) to regulate DNA replication[64]. Furthermore, G9a and GLP methylate a number of non-histone substrates, including CEBPβ, DNMT1, HDAC1, KLF12[65], and lysine 373 of p53[66].

In HIV-1 latency, both, G9a and GLP, are responsible for transcriptional repression of the HIV-LTR by promoting repressive di-methylation at H3K9[67]. Imai et al. reported that wild-type but not mutant, G9a lacking the SET domain significantly inhibited basal and TNFα- or Tat-induced HIV-1 gene expression in ACH-2 and OM10.1 T-cell lines. Treatment with BIX01294,

a chemical inhibitor of G9a, reactivated HIV-1 in latently infected cells. When G9a expression was knocked down by small interfering RNAs, HIV-1 replication was augmented from cells transiently transfected with a full-length HIV-1 clone. The authors also used chromatin immunoprecipitation assays to show G9a and H3K9me2 on histones in the vicinity of the HIV-1 LTR[67]. H3K9 di-methylation was also decreased after treatment with 5'-deoxy-5'-methylthioadenosine, a broad-spectrum histone methyltransferase inhibitor, causing reactivation of latent HIV-1 in C11 cells[67]. In addition, chemical inhibition of G9a by the compound UNC-0638 reactivated latent proviruses in the Th17 primary T-cell model of HIV latency, as well as in resting memory T cells isolated from aviremic HIV-1-infected individuals[54]. As Ding et al. showed that GLP knockdown also induces HIV-1 LTR expression[68], the two EHMT enzymes may be significant in maintaining HIV-1 latency by catalyzing di-methylation of H3K9[68].

2.2.1.3 SETD2

The histone-lysine N-methyltransferase SETD2, also referred to as HYPB, tri-methylates lysine 36 on histone 3 (H3K36me3), using di-methylated H3K36me2 as substrate[69]. H3K36me3 is a signature chromatin mark associated with active transcription implicated in coupling transcription with mRNA splicing[70]. Further, SETD2 has been linked to maintenance of genomic integrity through coordination of homologous recombination repair after double strand breaks, suggesting a role as tumor suppressor[71-73].

In HIV infection, SETD2 is recruited to the RNA polymerase II (RNAPII) elongation complex in HLM107 cells, a HeLa-derived cell line that contains a single integrated, Rev-defective, HIV-1 provirus[74]. Previously, Yoh et al. reported that Spt6, a transcription elongation

factor and histone H3 chaperone, binds serine 2 (Ser2P) of the C-terminal domain of RNAPII and recruits the "interacts-with-Spt6" (Iws1) transcription factor and the REF1/Aly mRNA export adaptor to facilitate mRNA export[75]. Subsequently, the same authors showed that Iws1 recruits SETD2 to the RNAPII elongation complex, which is required for H3K36 tri-methylation across the transcribed region of the HIV-1 gene in HLM107 cells[74]. Knockdown of Iws1 disrupts binding of SETD2, but not Spt6, to the coding region of the integrated HIV-1 provirus, whereas depletion of SETD2 did not affect binding of these factors. These data suggest a mechanism by which Iws1 connects SETD2-mediated H3K36me3 with Spt6-driven nucleosome reassembly. Both are thought to depend upon the histone H3 chaperone activity of Spt6, thereby affecting mRNA export and the histone modification state of actively transcribed HIV-1[74].

2.2.1.4 SET domain containing lysine methyltransferase SETD7 (SET7/9, KMT7)

SETD7 was first identified to specifically mono-methylate histone 3 lysine 4 (H3K4me1), a marker for transcriptional activation[76, 77]. In addition, SETD7 methylates several non-histone proteins, including p53[78], RB[79], NF-κB subunit p65[80], TAF10[81], ARTD1[82], ER[83], HIF-1α[84], STAT3[85], DNMT1[86], SOX2[87], SUV39H1[88], PGC-1α[89], β-catenin[90], IFITM3[91], FOXO3[92] and YY1[93]. Despite the large number of substrates, SETD7's exact *in vivo* function remains largely undetermined. SETD7 knockout mouse models have no obvious developmental defects and show no apparent deficiencies in DNA damage and p53 responses[94, 95].

SETD7 functions as a coactivator of HIV transcription[11]. The enzyme associates *in vivo* with the HIV promoter in reactivated J-Lat T cell models of HIV latency and mono-methylates lysines 51 and 71, two highly conserved residues in Tat[11, 14]. Knockdown of SETD7 suppresses Tat

transactivation of the HIV promoter, but does not affect the transcriptional activity of methylation-deficient Tat (K51A or K71R)[11, 14]. SETD7 itself binds TAR RNA and forms a complex with Tat and P-TEFb, suggesting a positive role of SETD7-mediated Tat methylation in early steps of the Tat transactivation cycle[11].

2.2.1.5 SET domain, bifurcated 1 (SETDB1)

SETDB1 regulates the tri-methylation of histone H3 on lysine 9 (H3K9me3), a specific mark for gene silencing and transcriptional repression[77-79]. In mouse embryonic stem (ES) cells, SETDB1 recruited to histone 3 by the Krüppel-associated box-associated protein 1 (KAP1/TRIM28/TIF1B), which results in H3K9 tri-methylation and subsequent silencing of endogenous and introduced retroviruses[80]. The human SETDB1 protein is organized into six domains: the tandem Tudor domains in the N-terminal region[96], the methyl-CpG-binding domain (MBD) in the middle region[78], and the pre-SET, SET, and post-SET domains in the C-terminus[77, 78]. Interestingly, to function as an H3K9 MT, SETDB1 needs to undergo posttranslational modifications[78]. The C-terminal region of SETDB1 is ubiquitinated at lysine 867, which is necessary for full H3K9 MT activity in mammalian cells[97].

SETDB1 associates with the HIV-Tat protein[13]. SiRNA knockdown of SETDB1 in cell systems with both transient and integrated LTR reporter genes results in increased transcription of the HIV-LTR in the presence of suboptimal levels of Tat, indicating a repressive role for SETDB1 in HIV transcription[13]. *In vitro* methylation assays with Tat peptides and SETDB1 show increased incorporation of methyl groups on lysine 51; however, lysine 50 was also susceptible for methylation[13]. The association of Tat with histone methyltransferases and the

ability for Tat to be differentially methylated at K51 suggest a very sophisticated mechanism of transcriptional regulation of the HIV-1 promoter as monomethylation by SETD7 acts as an activator and trimethylation by SETDB1 presumably as an inhibitory mark in Tat.

2.2.1.6 SET domain, bifurcated 2 (SETDB2)

SETDB2, also referred to as CLLD8/KMT1F, belongs to the SUV39 subfamily of histone 3 lysine 9 MTs. SETDB2 specifically tri-methylates H3K9me3. The H3K9 histone methylation mark is associated with gene silencing, and recent work has linked SETDB2 to antiviral and anti-inflammatory responses through negative regulation of lipopolysaccharide (LPS) and IFNβ-induced genes in macrophages[98, 99]. Further, SETDB2 has been associated with embryonic development and cell division[100-102].

SETDB2 co-immunoprecipitates with the HIV-Tat protein, but the function of this *in vitro* association remains to be determined[13]. A separate study evaluating epigenetic modifications in primary blood cells after HIV-1 infection found SETDB2 transcripts highly upregulated in activated as well as resting cells, indicating that HIV-1 infection could be linked to the expression of this gene[28].

2.2.1.7 SET and MYND domain-containing protein 2 (SMYD2)

SMYD2 is a member of the SMYD family of five methyltransferases. SMYD1–5 contain a catalytic SET domain that is split by a zinc finger that contains the myeloid translocation protein-8, Nervy, and DEAF-1 (MYND) motif, followed by a cysteine-rich post-SET domain[103].

SMYD2 regulates transcription by methylating H3K36 and H3K4, functioning as a repressor or activator, respectively, depending on the presence of heat shock protein 90 (HSP90)[103, 104]. SMYD2 itself methylates HSP90 and, in muscle cells, controls protein complex formation in the cytoplasm[105]. Further, SMYD2 inhibits p53 function by methylating lysine 370 (K370)[106] as well as K810 and K860 within the retinoblastoma (RB) tumor suppressor (citation). Other non-histone substrates of SMYD2 include estrogen receptor α (ERα), poly-(ADP-ribose) polymerase 1 (PARP1), BTF3, PDAP1, AHNAK, and AHNAK2[107].

In latently infected T-cell lines and in primary $CD4^+$ T cells knockdown of SMYD2 or its pharmacological inhibition reactivates latent HIV-1, identifying SMYD2 as a repressor of HIV transcription[108]. This repressive function is associated with the enrichment of mono-methylated lysine 20 at histone H4 (H4K20me1) at the latent promoter, a modification catalyzed by SMYD2 *in vitro* and in cells. The H4K20me1 "reader protein" lethal 3 malignant brain tumor 1 (L3MBTL1), which has chromatin-compacting properties, is recruited to the latent HIV-1 promoter in a SMYD2-dependent manner, supporting the model that the SMYD2-H4K20me1-L3MBTL1 axis promotes latency in HIV infection[108].

2.2.1.8 Suppressor of variegation 3–9 homolog 1 (SUV39H1)

SUV39H1, also known as KMT1A, was the first identified human lysine MT[109]. It specifically catalyzes tri-methylation on histone H3 lysine 9 (H3K9me3) using mono-methylated H3K9 as substrate[109]. H3K9me3 is a hallmark of facultative and constitutive heterochromatin and is enriched in silenced genes[110]. SUV39H1 exerts its function in complexes with other H3K9 MTs, such as G9a, GLP, and SETDB1, by creating a binding site for heterochromatic protein 1α

(HP1α), which binds H3K9me2/3 through its chromodomain[111]. HP1α further recruits SUV4−20H enzymes to heterochromatic regions, which generate H4K20me3, another heterochromatic histone modification[112]. SUV39H1 consists of a catalytic SET domain and a chromodomain, a reader domain for tri-methylated H3K9[113-115]. The catalytic activity of SUV39H1 is reduced by tri-methylated H3K4 confirming an observation in *Drosophila* that H3K9 methylation dependent heterochromatin formation is initiated through active removal of H3K4 methylation[116, 117]. So far only histones have been identified as substrates for SUV39H1.

Several studies link SUV39H1 to HIV-1 latency. Marban et al. reported that, in microglial cells, DNA-bound CTIP2 associates with SUV39H1, which increases local H3K9 methylation[118]. This results in recruitment of HP1 proteins to the viral promoter and formation of local heterochromatin, leading to HIV-1 silencing[118]. Similarly, du Chéné et al. showed that SUV39H1, HP1γ and H3K9me3 are associated with chromatin-mediated repression of integrated HIV-1 gene expression in several cell systems, including HeLa cells containing a single integrated copy of an HIV-1 LTR reporter gene and peripheral blood mononucleated cells (PBMCs) isolated from infected individuals[119]. The importance of H3K9 tri-methylation has also been shown in recent work using chaetocin, an SUV39H1/ G9a histone MT inhibitor (HMTI)[120]. Chaetocin treatment caused a 25-fold induction of latent HIV-1 expression in Jurkat cells containing a pTY-LAI-luciferase reporter virus, while exhibiting minimal toxicity and T-cell activation. Induction of HIV-1 gene expression is associated with loss of H3K9 tri-methylation at the viral LTR, and a corresponding increase in H3K9 acetylation, a marker for gene activation[1, 120]. A separate study evaluating the therapeutic potential of MT inhibitors in HIV infection found that chaetocin induced HIV-1 transcription in 50% of $CD8^+$-depleted PBMCs and in 86% of resting $CD4^+$ T-cell cultures isolated from aviremic HIV-1-infected individuals[121]. Besides

chaetocin, multiple short chain fatty acids (SCFAs) from periodontal pathogens and also therapeutic doses of irradiation reactivate HIV-1 and reduce the presence of SUV39H1 at the HIV-1 promoter[122, 123].

2.2.1.9 B Lymphocyte-induced maturation protein-1 (Blimp-1)

The RIZ family member BLIMP-1, also referred to as PR domain zinc finger protein 1 (PRDM1), is a transcription factor that contains five Krüppel-like zinc-fingers that mediate DNA binding, nuclear import and recruitment of histone-modifying enzymes as well as a PR/SET domain at the amino terminus (reviewed in[124]). BLIMP-1 is critical for the differentiation of mature B cells into immunoglobulin-secreting cells and is also expressed in dendritic cells, macrophages, keratinocytes, and T cells[125-129]. In T cells, BLIMP-1 regulates the activation and generation of $CD4^+$ and $CD8^+$ T-cell effector populations[129-131]. BLIMP-1 represses the transcription of several regulatory factors, including Bcl-6, T-bet, IL-2, IFN-γ and IFN-β, while enhancing the transcription of IL-10[132-135].

Several studies address the role of BLIMP-1 in HIV-1 infection in different cell populations[136-139]. De Masson et al. showed that BLIMP-1 overexpression is associated with low viral transcription levels in central memory $CD4^+$ T cells from HIV-1 elite controllers, a rare group of HIV-positive individuals who maintain undetectable viral loads in the absence of any treatment, suggesting that induction of BLIMP-1 may reduce the size of the HIV-1 reservoirs[139]. Other studies showed that BLIMP-1 expression is increased in chronically infected HIV-1 patients and correlates with enhanced expression of negative regulators of T-cell activation, including PD-1, LAG3 and CTLA-4, as well as with T-cell exhaustion and apoptosis[136, 137].

Seddiki et al. reported higher BLIMP-1 levels in total $CD4^+$ T cells from HIV-1 progressors than long-term non-progressors or healthy controls, implying a positive role in HIV infection[138]. In support of this, the HIV-1 transactivator Tat was shown to induce BLIMP-1 expression in activated, but not in resting, $CD8^+$ T cells[140]. Further, Tat up-regulates, in both activated $CD4^+$ and $CD8^+$ T cells, the release of IL-2[140], which is an inducer of BLIMP-1[141], supporting a model that in activated T cells BLIMP1 could support HIV infection.

At the molecular level, the HIV-1 LTR includes binding sites for BLIMP-1, suggesting that this factor directly binds proviral DNA[142]. BLIMP-1 was found highly expressed in memory, as compared to naive $CD4^+$ T cells, where it represses basal and Tat-mediated HIV-1 transcription[143]. To do this, BLIMP-1 binds an interferon-stimulated response element (ISRE) within the HIV-1 provirus under latent conditions and is displaced after T-cell activation. Reduction of BLIMP-1 in infected primary T cells increases RNA polymerase II processivity, histone acetylation and basal HIV-1 transcription[143]. It remains unknown whether and how the SET domain of BLIMP1 is involved. However, it is intriguing that BLIMP1 has these strong repressive activities and we speculate that high BLIMP-1 levels in memory T cells contribute to the establishment and maintenance of latent HIV-1.

2.2.2 Protein-arginine N-methyltransferases

In mammals, nine protein arginine methyltransferases (PRMT1-9) transfer methyl groups from SAM to the terminal guanidino nitrogens of arginine residues in target proteins[44] (**Figure 3**). PRMT family members are characterized by four different motifs (I, post-I, II, and III) and a conserved THW loop important for the formation of the AdoMet-binding pocket[144]. Type I

PRMTs form asymmetric (ω-N^G,ω-N^G) dimethyl-arginine, whereas type II enzymes give rise to symmetric (ω-N^G,ω-N'^G) dimethyl-arginine[145]. Type III PRMTs generate monomethyl arginine at terminal nitrogen atoms (ω-NG-methylarginine), which is an intermediate of PRMT type I and II reactions[146]. Methylation of an arginine does not alter the positive charge of the guanidinium side chain, but changes its structure and the affinity between the substrate and its binding partners, resulting in promotion or inhibition of interactions[147]. So far, CARM1, PRMT1, and PRMT6 have been implicated in HIV infection (**Figure 3**).

2.2.2.1 Coactivator-associated arginine methyltransferase 1 (CARM1)

CARM1, also called PRMT4, produces mainly asymmetric di-methylated arginines (Rme2a) and methylates histone H3 primarily on two sites, R17 and R26 with an additional methylation site R42 recently identified[148-151]. CARM1 is recruited to promoters upon gene activation and methylates multiple non-histone proteins involved in gene transcription, including transcriptional coactivators CBP/p300 and SRCs, mediator Med12, RNA pol II, RNA-binding proteins PABP1, HuR, and HuD, as well as the splicing factors CA150, SAP49, and SmB[152-159].

A recent study, investigating how H3K27 acetylation (H3K27ac) regulates HIV-1 transcription, found that acetylation at H3K27 (H3K27ac) increases H3R26 methylation (H3K26me2a) catalyzed by CARM1[160]. H3K27ac is a key epigenetic mark that correlates with gene transcriptional activation[161, 162]. It recruits the super elongation complex (SEC), which is essential for HIV-1 LTR-mediated transcription[160]. As H3K27ac stimulates H3R26 methylation, this methylation mark interferes with SEC recruitment, initiating a negative regulatory feedback loop[160]. In line with CARM1's negative effect on SEC recruitment, its inhibition resulted in

reactivation of HIV-1 transcription in several HIV latency cell models, including in primary resting CD4+ T cells, and acted synergistically with other latency reversing agents, such as the BET inhibitor JQ1 and HDAC inhibitor SAHA[160].

2.2.2.2 PRMT1

PRMT1 is a type I protein arginine methyltransferase that is primarily responsible for asymmetric di-methylation of H4R3me2a, a mark of transcriptional activation[163]. In addition, PRMT1 modifies a large number of other proteins including histone H2, H3, hnRNPs, RNA helicase A, ERα, PIAS1, CITED2, FOXO1 and TAF15 (reviewed in[44]).

In HIV-1 transcription, PRMT1 participates in NF-κB-dependent gene expression[164]. Hassa et al. showed that, under TNFα stimulation, PRMT1 synergistically co-activates the HIV-1 LTR together with p300/CREB binding protein, coactivator-associated arginine methyltransferase 1 (CARM1), and poly (ADP-ribose) polymerase 1(PARP1). PRMT1 forms a nuclear aggregate with p65 and PARP1 and is recruited to p65-containing complexes at the HIV promoter[164]. However, the exact mechanism of cross-talk between these coactivators is still unclear. PRMT1 might directly methylate NF-κB, p300, CARM1, or PARP1 or exert its function via di-methylation of H4R3me2a, which has been shown to be essential to maintain "active" chromatin[163].

2.2.2.3 PRMT6

The type I protein arginine methyltransferase PRMT6 catalyzes asymmetric di-methylation of H3R2me2a, using mono-methylated arginine as a substrate[165]. Di-methylation of H3R2 results in transcriptional repression and is also a negative regulator of H3K4 tri-methylation (H3K4me3), as it inhibits the activity of the H3K4 methyltransferase MLL1 and blocks recruitment of the MLL-complex subunit WDR5 to histone H3[165-167]. In addition, PRMT6 di-methylates H3R42me2a[151], and H2AR292a[168], leading to either transcriptional repression or activation. Similar to other PRMTs, PRMT6 typically targets glycine-arginine rich (GAR) motifs in substrates[169, 170]. However, PRMT6 methylates also non-GAR motifs, such as in the HIV-1 Tat protein leading to restriction of viral transcription and replication[171]. Interestingly, PRMT6 was also reported to auto-methylate itself in a non-GAR motif, which results in increased protein stability and activity[172]. In agreement with its primary nuclear localization, PRMT6 methylates HMGA1a, a high-mobility group protein involved in transcriptional regulation of genes[169, 173]. In addition, PRMT6 controls gene expression by directly interacting with transcription factors, including NF-κB and G-protein pathway suppressor 2[174, 175]. Because those two molecules are directly involved in inflammatory responses, it is possible that PRMT6 also plays a role in inflammation responses.

PRMT6 restricts HIV infection by methylating and impairing the function of various HIV-1 proteins, such as Tat, Rev and nucleocapsid protein p7 (NC). In the context of HIV-1, PRMT6 was first identified to associate and methylate Tat within cells[171]. Overexpression of wild-type PRMT6 decreases Tat transactivation of an HIV-1 LTR reporter plasmid in a dose-dependent manner, and knockdown of PRMT6 increases HIV-1 production in HEK293T cells, indicating that PRMT6 acts as restriction factor for HIV replication[171]. Subsequently, Xie et al. reported that PRMT6 targets R52 and R53 in Tat, which leads to decreased interaction with the Tat

transactivation region (TAR) in viral RNAs and also negatively affects complex formation of Tat-TAR with the critical cofactor cyclin T1[15]. Interestingly, PRMT6 increases Tat half-life, which could play a critical role in Tat persisting within the infected cell and the extracellular environment[176]. Further, overexpression of PRMT6 leads to exclusion of R52/53-methylated Tat from the nucleolus[177]. Experiments using fluorescence recovery after photo-bleaching indicate that Tat's nucleolar accumulation is largely mediated through binding to nucleolar components, which is prevented by methylation of Tat by PRMT6[177]. PRMT6 also di-methylates Rev at a single arginine in the N-terminal portion of its arginine-rich motif and associates with Rev *in vivo*[178]. This study also showed that PRMT6 significantly decreases Rev-mediated viral RNA export from the nucleus to the cytoplasm in a dose-dependent manner[178]. Beyond that, PRMT6 di-methylates HIV NC in each of its two basic regions at positions R10 and R32, leading to decreased RNA annealing and diminished initiation of reverse transcription[179]. Thus, PRMT6 is an HIV restriction factor that acts at multiple steps of the viral lifecycle. Recently, inhibitors of PRMT6 have been developed for cancer therapy and could also have potential for treatment of HIV infection[180, 181].

2.2.3 Other methyltransferases

2.2.3.1 Protein-L-isoaspartate (D-aspartate) O-methyltransferase (PCMT1)

PCMT1, also referred to as PIMT1, is an enzyme that catalyzes methyl esterification of L-isoaspartyl (L-isoAsp) and D-isoaspartyl (D-isoAsp) residues to L-aspartic acid (L-Asp)[182]. During stress-related conditions, oxidative environmental conditions, and with age, L-Asp and L-

Asn residues are non-enzymatically modified via dehydration (L-Asp) or deamidation (L-Asn), resulting in formation and accumulation of L-isoAsp, D-isoAsp, and D-aspartic acid (D-Asp) residues[182]. These changes result in structurally nonfunctional proteins[183]. In this context, PCMT1 functions as a chaperone or repair enzyme of aged or damaged proteins and facilitates the restoration to aspartate residues[184]. PCMT1 is ubiquitously expressed in all living organisms. Since its expression decreases with age, it has been associated with age-related diseases such as Alzheimer's dementia[185]. Further, PCMT1-deficient mice show acceleration of aging characterized by induced accumulation of L-isoAsp, D-isoAsp, and D-Asp residues in proteins and dysfunction of proteins[186].

PCMT1 methylates histone H4 at aspartic acid 24 (H4D24me)[187]. This histone mark is recognized by VprBP (HIV-1 viral protein R (Vpr)-binding protein), also known as DCAF1 (DDB1- and CUL4-associated factor 1), which is a chromodomain-containing protein[187]. In HIV-infection, VprBP is recruited by HIV-1 Vpr in order to hijack the CUL4A-RBX1-DDB1-DCAF1/VprBP complex leading to cell-cycle arrest in G2 phase, and also to protect the viral protein from proteasomal degradation[188].

2.2.3.2 Trimethylguanosine synthase (TGS1)

Human TGS1 was originally identified as an interaction partner of PRIP (PPAR-interacting protein) and, therefore, named PIMT (PRIP-interacting protein with methyltransferase domain)[189]. TGS1 is specific for guanine and catalyzes two successive methyl-transfer reactions from AdoMet to the N2 position of 7-methylguanosine[190, 191]. The enzyme adds two methyl groups to RNAPII-transcribed small nuclear RNA (snRNA), small nucleolar RNA (snoRNA),

and telomerase RNA, for the conversion of 7-monomethylguanosine caps to 2,2,7-trimethylguanosine caps[190, 191]. 5'-mRNA capping affects pre-mRNA synthesis and splicing, RNA transport to the cytoplasm, and mRNA translation and turnover.

Yedavalli et al. showed that, like snRNAs and snoRNAs, some Rev/RRE-dependent HIV-1 RNAs are TMG-capped by TGS1 and proposed a new regulatory mechanism for selective expression[192]. The study showed that TGS1 enhances HIV-1 gene expression and that intracellular HIV-1 RNAs are 7-methylguanosine - and trimethylguanosine-capped. Furthermore, TGS1 selectively modulates the expression p55 and p24 HIV-1 proteins encoded by Rev/RRE-dependent RNAs. Activation of PBMCs or purified $CD4^+$ T cells significantly increased the expression of TGS1, indicating that TGS1 might be a limiting factor in quiescent cells[192].

3. **Demethylases**

Up to date, two classes of lysine-specific KDMs are known: 1) the amine-oxidase type lysine-specific demethylases 1 and 2 (LSD1 and 2; also known as KDM1A and B, respectively), which are both dependent on flavin adenine dinucleotide (FAD) as a co-factor; and 2) the JumonjiC (JMJC) domain–containing histone demethylases, in which the demethylase activity is dependent on Fe(II) and α-ketoglutarate (2-oxoglutarate (2-OG)) (reviewed in[48]). The latter consists of a group with over 30 members and can be divided, based on the JMJC-domain homology, into seven subfamilies (KDM2–8)[48, 193-195]. The LSD-family members generate an imine intermediate that is hydrolysed to the demethylated lysine and formaldehyde[193]. Upon recycling of the cofactor FAD, hydrogen peroxide is formed as a byproduct of demethylation. As these enzymes require a free electron pair on the lysine ε-nitrogen atom to initiate demethylation,

LSD1 and 2 demethylate only mono- and di-methylated, but not tri-methylated, lysines[193]. In contrast, the JMJC domain-containing demethylases are able to remove methyl groups from all three methyl lysine states, with concomitant production of succinate, carbon dioxide, the demethylated lysine and formaldehyde[196, 197]. The target specificity of KDMs is regulated by their participation in different complexes[48]. So far, only LSD1 and the JMJC protein UTX have been implicated in HIV infection (**Figure 4**). No reports link HIV to ten-eleven-translocation (TET) enzymes involved in active DNA demethylation[198]. A subset of JMJC proteins also act as arginine demethylases[199].

3.1 Lysine demethylases

3.1.1 Lysine-specific histone demethylase 1A (KDM1A, LSD1)

LSD1 is the first discovered histone demethylase and belongs to the family of FAD-dependent amine oxidases[193]. LSD1 contains an N-terminal SWIRM domain, a Tower domain and an amine oxidase domain at the C-terminus[200-202]. In the presence of the RCOR1/CoREST complex, LSD1 catalyzes demethylation of mono- and di-methylated H3K4[193]. In addition, LSD1 interacts with JMJD2C, a histone tri-demethylase, and cooperatively removes methyl groups from mono-, di- and tri-methylated H3K9[203, 204]. LSD1 also demethylates several non-histone proteins, including K370 in p53, K185 of E2F1, and K1096, in the DNA methylase DNMT1[205-207].

LSD1 is an HIV-Tat K51-specific demethylase, which is required for the activation of HIV-1 transcription in latently infected $CD4^+$ T cells[12]. LSD1 and its cofactor CoREST associate with

the HIV promoter *in vivo* and activate Tat transcriptional activity in a K51-dependent manner in T cells[12]. In addition, small hairpin RNAs directed against LSD1 or inhibition of its activity with the monoamine oxidase inhibitor phenelzine suppresses the activation of HIV transcription in latently infected T cells, indicating that the LSD1/CoREST complex, normally known as a transcriptional repressor, acts as a coactivator of HIV transcription in infected T cells by demethylating K51 in Tat[12]. In contrast, in microglial cells, an important HIV-1 target in the central nervous system, LSD1 represses HIV-1 transcription and viral expression in a synergistic manner with the COUP-TF interacting protein 2 (CTIP2)[208]. CTIP2 forces heterochromatin formation and HIV-1 gene silencing by recruiting HDAC and HMT activities at the integrated viral promoter[118]. Le Douce et al. further showed that recruitment of LSD1 at the HIV-1 proximal promoter is associated with H3K4me3 and H3K9me3 epigenetic marks and that LSD1-induced H3K4 tri-methylation is linked to SETD1A recruitment at the integrated provirus[208]. The cell-type specific role of LSD1 in HIV-1 infection remains an interesting subject of investigation. However, in latently infected T cells LSD1 inhibitors function to suppress reactivation of HIV transcription, in accordance with a proposed co-activator role of LSD1 in this cell type. Interestingly, they also suppress reactivation of latent infections of α-herpesvirus[209], suggesting a broader role of LSD1 in activating viral gene expression.

3.1.2 Lysine-specific demethylase 6A (KDM6A, UTX)

KDM6A, also referred to as UTX, specifically demethylates lysine 27 of histone 3 (H3K27)[210, 211]. UTX demethylates di- and tri-methylated, but not mono-methylated, H3K27[212]. Since H3K27me2 and H3K27me3 are highly correlated with genomic silencing and repression of

transcription, removal of these marks by UTX results in gene activation[213]. In addition, UTX interacts with protein complexes that are associated with H3K4 methylation, a mark of active transcription[214, 215]. Further, UTX binds the SWI/SNF chromatin-remodeling complex by engaging the BRG1 catalytic subdomain, resulting in nucleosome remodeling and gene activation of T-box factors[216].

At the HIV-1 LTR, the removal of the H3K27me3 mark by UTX is important for the robust induction of many specific genes during Tat-mediated HIV-1 transactivation[217]. Zhang et al. reported that Tat upregulates the expression of UTX and downregulates the H3K27me3 mark in TZM-bl cells[217]. Using chromatin immunoprecipitation assays, the authors found that UTX associates with nucleosomes at the 0 and +1 position relative to the start of transcription and downregulates the H3K27me2 and H3K27me3 states[217]. Also, UTX promoted HIV-1 gene expression by enhancing NF-κB p65 nuclear translocation, suggesting a novel function of UTX in the timely transition from poised to active chromatin in HIV-1 infection[217].

4. Concluding remarks

Current antiretroviral therapy suppresses HIV viral replication, requiring life-long adherence to continuously limit viral loads, but does not typically eradicate virus from the host. Successful sterilizing cure of HIV will require elimination of persistent viral reservoirs. One approach is to reactivate proviral genomes in latently infected cells in order to “purge” viral reservoirs[218]. Another is to find ways to permanently silence HIV in latent reservoirs so that likelihood of reactivation is diminished. Several “epigenetic modifying agents” including inhibitors of HDAC, HMT, and DNMT show great promise as anti-latency therapeutics *in vitro* and *ex vivo* and some, including valproic acid and SAHA/vorinostat, are currently being examined in clinical trials. Although the role of DNA methylation in HIV-1 infection is controversial, DNA

methyltransferase (DNMT) inhibitors are considered as reactivating agents. For example, the DNMT inhibitors Decitabine (5-aza-2' deoxycytidine, aza-CdR) and its analog azacitidine (5-azacytidine, Vidaza®), which are approved by the FDA for the treatment of myelodysplastic syndrome, are inducers of latent HIV-1[219]. In addition, decitabine synergizes with TNF-α and prostratin to significantly increase viral gene expression in several J-Lat cell lines[26].

Similarly, protein methyltransferases and demethylases are regulators with emerging impacts on HIV infection. Both groups harbor repressors (EZH2[53], G9a[67], SETDB1[13], SMYD2[108], SUV39H1[118, 119], CARM1[160] and PRMT6[15, 171]) and coactivators (SETD7[11, 14], LSD1[12, 208], UTX[217]) for HIV infection through histone and non-histone protein modification, most importantly Tat and NF-κB. Several inhibitors such as BIX01294[67], Chaetocin[120], UNC-0638[54], 3-deazaneplanocin[53], AZ391[108], GSK-343[54, 55], and EPZ-6438[54] have been tested in preclinical model cell lines for latency reactivation as well as in cells derived from patients[67]. Interestingly, some HMT inhibitors as discussed above can enhance proviral reactivation in combination with bromodomain inhibitors such as JQ1[108], or PKC agonists (prostratin), or HDAC inhibitors (such as vorinostat/SAHA)[55], making this class of compounds possible candidates for combinatorial treatments. Although research into HMT inhibitors and HIV latency reversal is less advanced than HDAC inhibitors, some methyltransferase inhibitors are now in clinical trials for the treatment of malignancies, making future clinical use in HIV infection more feasible. For example, the EZH2 inhibitors GSK126, tazemetosta, and CPI-1205, are currently in phase I clinical trials for the treatment of B cell lymphomas bearing EZH2-activating mutations (reviewed in[48]). Similarly, LSD1 inhibitors TCP, ORY-1001, GSK2879552, and 4SC-202 are in current trials for treatment of acute myeloid leukemia (AML), acute leukemia (phase I/IIA), for

AML and small cell lung cancer (SCLC) (phase I), and hematological malignancies (phase I), respectively (reviewed in[48]).

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Author Disclosure Statement

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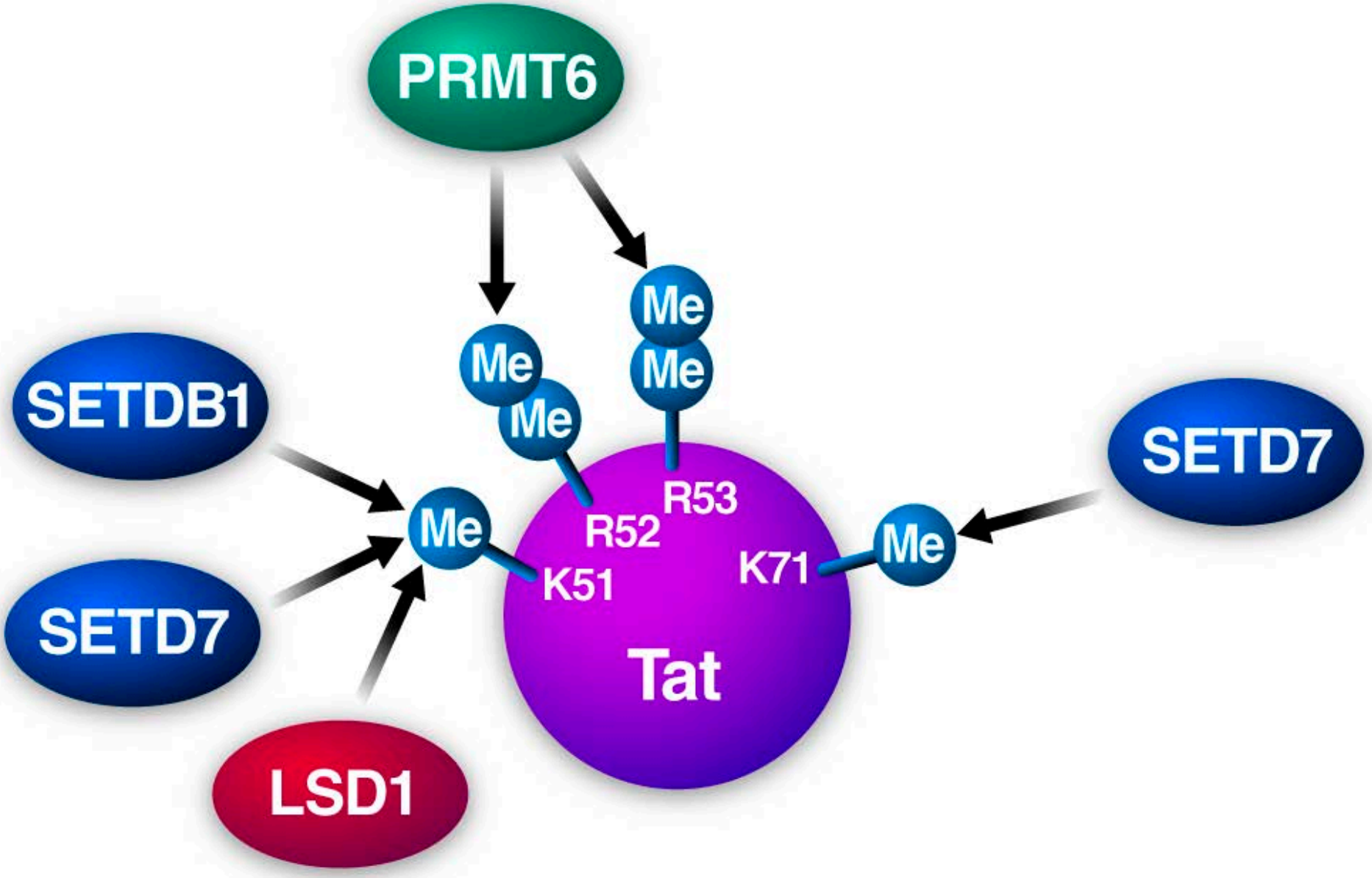
Figure Legends

Figure 1. Specificity of protein methyltransferases and demethylase LSD1 that target HIV-1-Tat at K51, R52, R53, and K71.

Figure 2. Histone lysine methyltransferases (KMT) and histone methyl marks implicated in HIV infection, showing residue-specific KMTs for H3K4/9/27/36 and H4K20. The majority of KMTs are highly specific for a single histone residue, whereas a few enzymes target multiple residues, as indicated.

Figure 3. Histone arginine methyltransferases (PRMT) and histone methyl marks implicated in HIV infection, showing residue-specific PRMTs for H3 and H4.

Figure 4. Histone demethylases and histone methyl marks implicated in HIV infection, showing residue-specific KMTs for H3K4, H3K9 and H3K27.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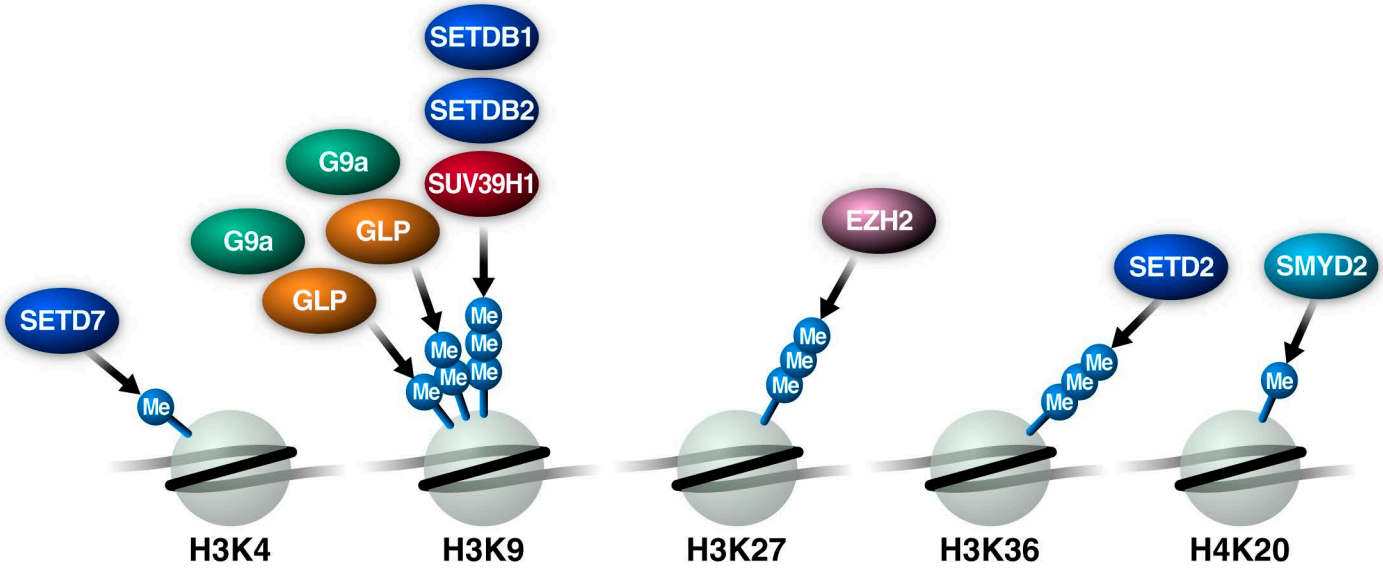
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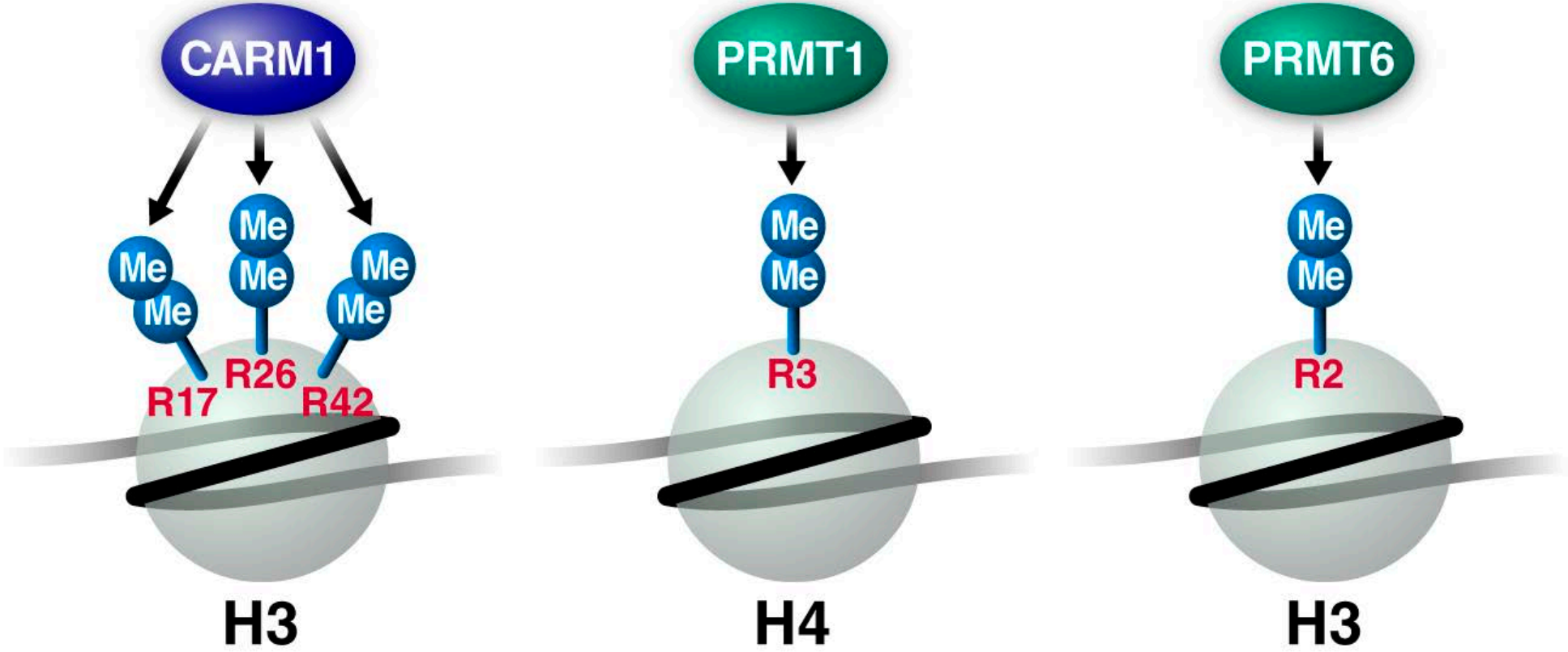
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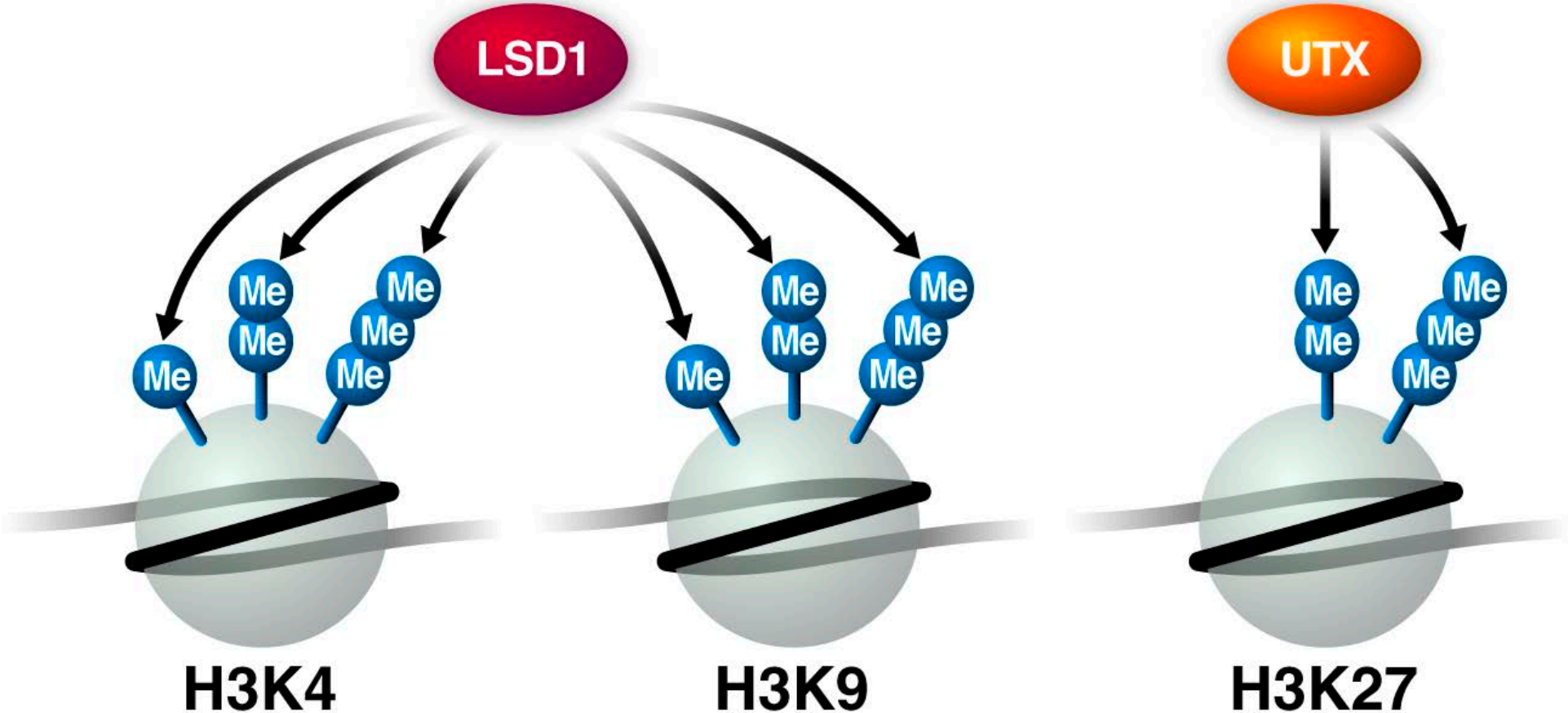
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