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Editorial

Deciphering the HIV reservoir: From epigenetic regulators to RNA-mediated regulation

The human immunodeficiency virus 1 (HIV-1) latent reservoir constitutes the central barrier to a functional cure of HIV infection. This reservoir primarily resides within resting memory $CD4^+$ T cells, wherein the integrated proviral DNA persists in a transcriptionally silent state within host chromatin. This latent state allows the virus to evade both combination antiretroviral therapy (cART) and immune-mediated clearance. Upon treatment interruption, latent viruses can be reactivated, leading to rapid viral rebound. Current cure strategies targeting the HIV reservoir focus mainly on "Shock and Kill" and "Block and Lock" approaches. However, existing latency-reversing or promoting agents fail to achieve either complete viral reservoir eradication or sustained transcriptional silencing. Therefore, further research into mechanisms regulating HIV latency is critical to discover effective strategies eradicating or silencing the latent reservoir.

Recent advances in HIV latency research have yielded new mechanistic insight, particularly with respect to the roles of epigenetic modulators, non-coding RNAs, and host transcriptional complexes. This review summarizes six recent studies that clarify the molecular mechanisms underlying persistence HIV-1 and other retroviruses. Together, these findings identify new targetable host and viral factors that support the development of a functional cure of HIV infection.

The epigenetic reader bromodomain-containing protein 4 (BRD4) [1] suppresses HIV-1 transcription by competitively binding the host positive transcription elongation factor b (P-TEFb), hindering recruitment of P-TEFb by the viral transactivator Tat to the HIV long terminal repeat (LTR). In 2019, Niu *et al.* discovered that ZL0580 induces epigenetic silencing of HIV by modulating BRD4, although its mechanism was not fully clear.

Pellaers *et al.* [2] further studied ZL0580 and recently confirmed its role in suppressing HIV-1 transcription. Luciferase assays showed that ZL0580 inhibited transcription with the half-maximal inhibitory concentration (IC_{50}) values of 6.43 μmol/L in non-reactivated and 4.14 μmol/L in tumor necrosis factor-α reactivated SupT1 cells. Branched-DNA imaging, a single-cell FISH technique for simultaneous detection of viral DNA and RNA, showed a reduction in viral RNA without affecting viral DNA after ZL0580 treatment, indicating inhibition of transcription. Unlike JQ1, which binds the KAc pocket (To recognize the acetylated lysine sites on histones), ZL0580 targets a non-KAc site on BRD4, strengthening BRD4-histone interactions, as evidenced by colocalization analysis of BRD4 with acetylated histones in the presence of JQ1 and ZL0580. In Tat-transfected HeLa-TZMbl cells, ZL0580 inhibited Tat-dependent transcription, confirming its action through the Tat-P-TEFb pathway. The LEDGIN CX014442 inhibits the interaction between LEDGF/p75 (The lens epithelium-derived growth factor, main determinant of integration site selection) and the HIV integrase, resulting in an inhibition of integration combined with a retargeting of the residual integrants to silent chomatin regions. When combined with the integrase inhibitor CX014442, ZL0580 achieved near-complete silencing at high doses, both in latency cell line models and primary cells infected *in vitro*. Altogether, this study identifies BRD4 as a promising target for the "Block and Lock" cure strategy and shows that ZL0580 enhances transcriptional repression *via* a unique binding mode to BRD4. Combined with LEDGF/p75-integrase inhibitors, it offers a dual-locking approach for HIV functional cure.

BRD9 recruits proteins including GLTSCR1, BRG1, and SS18 to form the non-canonical BAF (ncBAF) complex, thereby exerting transcriptional regulatory functions. BRD9 is known to play pivotal roles in diverse biological processes such as cell proliferation, differentiation, and inflammatory responses. Nevertheless, its role in the regulation of HIV-1 latency remains to be elucidated.

In this context, Luk *et al.* [3] used phenotypic screening of an epigenetic compound library *via* enzyme-linked immunosorbent assays and found that the BRD9-specific inhibitor I-BRD9 effectively reverses HIV-1 latency. Further tests across multiple cell models showed that I-BRD9 dose-dependently activates HIV-1 LTR transcription and Gag gene expression, reactivating latent HIV-1. Additional approaches, such as BRD9 knockdown (siRNA), knockout (CRISPR/Cas9), and protein degradation (VZ185), also promoted reactivation. Notably, combining VZ185 with the BRD4 inhibitor JQ1 enhanced reservoir activation, suggesting complementary regulatory mechanisms.

ChIP-qPCR assays confirmed that BRD9 binds to both the LTR promoter and Gag gene regions of HIV-1. An optimized CUT and RUN assay further showed that BRD9 suppresses viral transcription by blocking Tat binding to the viral genome. Combined analysis of CUT and RUN-seq and RNA sequencing also identified BRD9-regulated genes, such as ATAD2 and MTHFD2, as key contributors to HIV-1 latency.

In conclusion, this study confirms that BRD9, a member of the BET family, plays a key role in maintaining HIV-1 latency, highlighting its potential as a therapeutic target for next-generation latency-reversing agents.

Protein arginine methyltransferase 3 (PRMT3) regulates gene expression through histone modifications and plays roles in various

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biological processes, including cancer development, liver fat accumulation, and antiviral immunity. However, its function in HIV-1 transcriptional reactivation and latency remains poorly understood.

Wang *et al*. [4] used a dCas9-based screen to identify PRMT3 as a protein that strongly binds to the HIV-1 LTR. This interaction enhanced by Tat. Functional studies showed that knocking out or inhibiting PRMT3 significantly reduced Tat-dependent HIV-1 transcription and latency reversal, indicating that PRMT3 promotes HIV-1 latency reversal. Mechanistically, PRMT3 collaborates with the transcription factor TEAD4 to bind the TEAD4 motif (GGAAT) in the HIV-1 LTR. PRMT3 catalyzes H4R3Me2a, a histone modification that increases chromatin accessibility in the LTR region. This facilitates the recruitment of P-TEFb, which enhances Tat-dependent HIV-1 transcription and latency activation.

This study identified PRMT3 as a key host factor in HIV-1 transcription and latency reversal and outlines a regulatory pathway involving PRMT3-TEAD4 complex formation, chromatin modification (H4R3Me2a), increased chromatin accessibility, and P-TEFb recruitment. These findings suggest that PRMT3 is a promising target for therapies aimed at eliminating latent HIV-1 reservoirs.

The HIV-1 antisense transcript (AST) induces histone modifications that promote a closed chromatin structure at the viral 5′ LTR, suppressing viral transcription. However, the role of AST in maintaining latency and its potential as a latency-inducing agent need further investigation.

To explore the functional domains of AST, Li *et al*. [5] divided its sequence into five domains (U3, A, B, C, and D), and created deletion and substitution mutants. ChIP-qPCR showed that the U3 domain (positions 1–376) binds to the 5′-LTR through two pyrimidine-rich motifs (Y1/Y2). The B domain (positions 927–1476) enhances AST binding to PRC2 *via* two overlapping G-rich sequences capable of forming quadruplexes, promoting PRC2 recruitment to the LTR and establishing latency. Mass spectrometry also identified interactions between AST and host factors involved in HIV-1 silencing, including components of the BAF/PBAF complex (SMARCD1–3), YY1, HDAC2, and Polycomb complex members (RBBP4 and RNF2). In $CD4^+$ T cells from individuals on suppressive ART, AST overexpression blocked viral transcriptional reactivation by latency-reversing agents.

In conclusion, this study clarified how AST suppresses HIV-1 transcription and stabilizes latency, suggesting that AST-based strategies could help to block viral transcription as part of a functional HIV cure approach.

Human T-cell leukemia virus type 1 (HTLV-1), like HIV-1, is a retrovirus that integrates into the host genome. However, the infection dynamics differ: whereas HIV-1 replicates rapidly, leading to immune collapse, HTLV-1 typically establishes latent infections, allowing long-term survival of infected cells and potentially causing leukemia. Previously, the molecular mechanisms behind HTLV-1′s spontaneous latency were unclear.

Sugata *et al*. [6] identified an open chromatin region (OCR) within the HTLV-1 provirus using ATAC-seq. This region, absent in HIV-1 and other delta retroviruses, strongly suppresses the 5′-LTR promoter. ChIP-seq showed that the host transcription factor RUNX1 and its associated complex (CBFβ, GATA3, and ETS1) bind to the OCR, repressing viral expression and inducing latency. Disrupting RUNX binding sites or inhibiting RUNX1 with Ro5-3335 reactivated latent HTLV-1 in both cell lines and primary cells from infected individuals. Remarkably, inserting the HTLV-1 OCR into the nef region of HIV-1 significantly reduced HIV-1′s 5′-LTR activity and viral replication.

This study revealed that HTLV-1 achieves reversible latency through the OCR, which recruits the RUNX complex to suppress viral activity. It also explains the molecular basis for the differing infection dynamics between HTLV-1 and HIV-1. Importantly, the OCR functions as a broad-spectrum silencer, offering new insights for developing "Block and Lock" therapies to target HIV-1 latency.

A recent study published in *Cell* [7] investigated preventive and treatment strategies for HTLV-1 subtype-C (HTLV-1c) infection. Researchers developed and characterized a humanized mouse model of HTLV-1c infection. They found that HTLV-1c-related diseases are more aggressive than the more common HTLV-1a, which may explain the higher risk of pulmonary complications in HTLV-1c cases. Treatment with tenofovir and dolutegravir significantly reduced HTLV-1c transmission and slowed disease progression *in vivo*. Using scRNA-seq and intracellular flow cytometry, the team found that HTLV-1c disrupts intrinsic apoptotic pathways in infected cells. Pharmacological inhibition studies showed that BH3 mimetics targeting MCL-1, but not BCL-2, BCL-XL, or BCL-w, effectively eliminated HTLV-1c-infected cells *in vitro* and *in vivo*. Combining MCL-1 inhibition with tenofovir and dolutegravir further delayed disease progression in mice. These findings suggest that combining antiretroviral therapy with MCL-1 inhibition could be a promising, clinically viable, and potentially curative strategy for treating HTLV-1c infection.

Recent studies have uncovered key mechanisms of HIV-1 latency, identifying new targets like BRD9 (inhibited by I-BRD9) and PRMT3, and strategies like the "Block and Lock" compound ZL0580 and AST-based regulation. Cross-viral elements such as HTLV-1 OCR also show silencing potential. However, clinical translation faces hurdles, including off-target effects, immunogenicity risks, and limitations of cell-based models. Future directions include: (1) Optimizing combo therapies (*e.g.*, BRD9/BRD4 inhibitors + PRMT3 modulators, ZL0580 + LEDGINs); (2) RNA-targeted tools (siRNA/CRISPR against AST networks); (3) refining OCR/RUNX1 interactions for safe silencing; and (4) deploying degradation strategies to erase latency components.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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