MEDS Clinical Medicine (2021) 2: 1-3
Clausius Scientific Press, Canada

DOI: 10.23977/medsc.2021.020201
ISSN 2616-1907

Explore the Future Direction of HIV-1 Latent Virus

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Keywords: BRD4, HIV-1, Latency, Tat, Reactivation

Abstract: Human immunodeficiency virus-1 (HIV-1) can be latent in quiescent CD4+ T cells, in which the viral DNA is silent in transcription and undetectable by the immune system. HIV-1 proviral DNA survives in the latent form primarily in quiescent CD4+ T cells. Although the current antiretroviral therapy (ART) can effectively inhibit the virus replication in HIV-1 infected people and suppress HIV to an undetectable level, ART does not work on latent HIV-1. Therefore, current ART cannot completely cure HIV-1 infected people, and HIV-1 infected people must use life-long ART to inhibit virus replication. Therefore, developing drugs that can act directly on latent HIV-1 is the biggest obstacle to the treatment of HIV-1 infection.

1. Introduction

Viruses use latency as a means of immune evasion and long-term survival so that they can remain in infected individuals leading to chronic infection. Many molecular factors have been shown to contribute to latency, and the importance of each pathway is still controversial. When the virus infects resting CD4+ T cells, the virus can establish latency in which integrated cDNA copies of the HIV-1 viral genome (the provirus) are inserted into host cell DNA. This proviral HIV-1 DNA is transcriptionally silent and hidden from immune mechanisms. [1]

2. Why is Tat So Important in HIV-1 Reactivation?

Tat, providing the first example of viral gene expression regulating viral. transcription through prolonged control, is an RNA polymerase (RNAP II). Brady et al. reported that Tat increased the density of RNAP II by 9-15 fold in the first 25 nucleotides downstream of the transcription initiation site, indicating that Tat stimulated the transcription of HIV-1. When HIV infects a cell, HIV depends on cytokines and viral factors to effectively transcribe its genome. After the integration of the HIV genome in the early stages of T cell infection, HIV depends on transcription of viral trans-activator Tat. The interaction between Tat and positive transcription elongation factor b (P-TEFb) is mediated by Cyclin T1 protein, which is determined by the Tat-P-TEFb complex's affinity with trans-activation response (TAR) element structure, loop-specific binding, and the formation of Tat, Cyclin T1, and TAR complexes. Tat increases more stable and active P-TEFb compounds function by inserting grooves at heterodimer interface. Tat amino acid sequence 1-48 is activation domain and also can bind to Cyclin T1, which can be change overall shape and surface of

P-TEFb. P-TEFb is an essential HIV-1 cofactor. The effective transcription of HIV-1 depends on the recruitment of P-TEFb. P-TEFb is a transcription factor composed of cyclin-dependent kinase 9, (CDK 9) Cyclin T1, Cyclin T2a, and Cyclin T2b, but only Cyclin T1 is a co-factor that activates Tat. Because Cyclin T1 does not change its CD4+ T cells activation states and macrophage differentiation. The CDK 9 subunit of P-TEFb catalyzes the phosphorylation of proteins, including the C-terminal domain (CTD) of the largest subunit of RNAP II. The phosphorylation of RNAP II binds to the HIV promoter which enhances HIV-1 viral transcriptional elongation. At the same time, the participation of Tat has a certain impact on the initiation of the viral long terminal repeat (LTR). Without the participation of Tat, the transcription of HIV-1 LTR will be stopped.

3. The Mechanism of Tat is Fascinating.

Tat interacts through the TAR element in. the LTR, which is a 59 residue RNA precursor. TAR is added at the 5'teminal end of all HIV transcripts. Tat must transactivate TAR near the transcription initiation site of HIV-1, and the complete stem-loop in TAR is necessary for the transactivation of Tat. Tat binds to the RNA binding structure in the middle of the C-terminal of the protein to initiate viral transcription.14 TAR is the RNA stem-loop structure existing in the 5'terminal end of all viruses and Tat may induce the replication of potential HIV-1 virus reservoir at the same time. In the absence of Tat, HIV-1 still transcribes but only produces short transcripts.

4. BRD4-P-Tefb Molecular Mechanism in HIV-1 Infected Individuals.

The formation of short and abortive viral transcripts may be due to the tight binding of 5 terminal ends of TAR RNA structure with negative transcriptional elongation and DRB sensitivity inducible factors.21 Not only that, in the presence of Tat, bromodomain-containing protein 4 (BRD4) is a competitive role to the P-TEFb factor recruited by Tat. Brd4 interacts with P-TEFb through the short CTD, an effect that occurs in the BRD4 C-terminal half, with each P-TEFb subunit and independently with BRD4. P-TEFb counteracts DSIF and negative elongation factor (NELF). Moreover, CDK 9 in the recruited P-TEFb can phosphorylates RD protein (a possesses the unique Arg-Asp which is RD dipeptide repeat sequence) form NELF. Resulting that NELF no longer inhibits the transcription of HIV-1 and regulates the interaction between DSIF and RNAP II. Therefore, the presence of Tat determines the transcription elongation factor.6 At the same time, any defect in HIV transcription will lead to the production of potential proviral. The inactivation or decreased expression of known key transcription factors, such as NF-κB and P-TEFb, can lead to the restriction of HIV transcription. Also, the binding of the restricted chromatin structure of HIV-LTR with limited P-TEFb results in transcriptional silencing, which leads to the HIV-1 latency of the primary CD4+ T cells. Thus, developing a drug for inhibit BRD4-P-TEFb will be a promising way to solve the latent state of CD4+ cells.

5. Tat is Important in the Reactivation of the HIV-1 Latency Mechanism.

Binding of the Tat to P-TEFb results in changes of the P-TEFb structure. However, the importance of relationship between Tat and BRD4 still need to be considered. Human Bromodomain and Extra-Terminal motif (BET) protein replace XEMIX 1/7SK snRNP by Cyclin T1 and CDK 9 compounds of P-TEFb to match chromatin acetylation state with transcriptional extension, which makes latter activate RNAP II through phosphorylation of serine 2. The salt sensitivity of BRD4 core and P-TEFb binding may affect the competition between BRD4 and Tat form BET family proteins. Ser175 is located at the interface of Cyclin T1, CDK9, and tat. Activation of T cell receptor (TCR) induces phosphorylation of ser175 residue, which can enhance

the binding efficiency of Tat to Cyclin T1 and decrease the binding efficiency of Brd4. But this phosphorylation is uncertain. Mutations at different sites in Tat and Brd4 can lead to changes in the binding efficiency of Tat between BRD4. However, in Mbonye et al. modeling, phosphorylation of S175 potentially stabilized the interaction between Tat and CDK9. Yang et al. reported that the Delta BD I and BD II mutants could not recognize BRD4 because of the lack of two bromodomains. Therefore, the changes of molecular factor structure of Tat-related reactivation mechanism may affect the overall appearance of HIV-1 latent virus reactivation. Thus, modulate Tat-related reactivation mechanism could be a possible way to solve latent HIV-1 reactivation in the future. Induction of transcriptional activation by HIV-1 by factors that inhibit mechanisms opposite to Tat. Not only BRD4 is associated with the HIV-1 latent reactivation, but increased expression of the related BET protein, BRD2, can increase the number of latently infected HIV-1 cells (REF). JQ1 is an inhibitor of BET family proteins that was used by Boehm et al. in an experiment testing HIV-1 latent reactivation. They found that JQ1 binding to Tat leads to more reactivation of HIV-1. In a separate study, a series of (+)-JQ1 analogues 16a-e containing an N-[z-amino phenyl] formamide moiety were tested as a potential dual HDAC/BRD4 inhibitor. In this study, they replaced t-butyloxycarbonyl moiety (+)-JQ1 with variable zinc-binding groups (ZBG) and linker might produce a new HDAC/BRD4 inhibitor. Inhibition of BRD4 may increase P-TEFb activity to promote Tat levels. Oral BET inhibitor OTX 015, a thienotriazolodiazepine can effectively activate HIV-1 in different latency models. The synergize of OTX 015 and prostratin did not increase the CD4, CCR5, and CXCR4 gene expression. In various subtypes of acute leukemia, such as OCI-AML3, Jurkat, and other model cells. Exposure to OTX 015 at a dosage decreases protein levels of BRD2 and BRD4 but does not affect BRD3. Therefore, the inhibition of BET has great potential in the activation of HIV-1 latency.

6. Conclusion

Based on the previous exploration of Tat-related molecular mechanism, BET family protein-related inhibitors could still have great potential to explore in the future. The relatively drug synergy is a crucial factor affecting the HIV-1 latency, but the future development may focus on more in-depth exploration and research towards simple and effective drugs.

References

[1] Dahabieh, Matthew S et al. "Understanding HIV latency: the road to an HIV cure." Annual review of medicine, vol.66, no.03, pp.407-421, 2015.