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Mechanism and factors that control HIV-1 transcription and latency activation

Key words: HIV-1; transcriptional elongation; RNA polymerase II; Tat; P-TEFb

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- The HIV-1 provirus depends on the host RNA Polymerase II (Pol II) for transcription. The widespread evidence suggests that transcription elongation plays a prominent role in regulating gene expression.
- The human Positive Transcription Elongation Factor b (P-TEFb) is a key host factor for Tat-dependent HIV-1 transcription. Without P-TEFb, HIV-1 can generate only short abortive transcripts.
- P-TEFb is maintained in a functional equilibrium. P-TEFb is reversibly sequestered in the inhibitory 7SK snRNP, which serve as a cellular reservoir of unused P-TEFb activity. Under certain conditions, P-TEFb can be released from 7SK snRNP and activate transcription.
- Tat assembles the Super Elongation Complex (SEC) to promote HIV-1 transcription. Two different elongation factors, P-TEFb and ELL1/2, along with other factors are involved in the same SEC complex, which is then recruited by Tat to the viral LTR, where they can work synergistically to release the paused Pol II to stimulate elongation.

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- Brd4-P-TEFb interaction and its effect on HIV-1 transcription and latency. Brd4 serves as the cellular equivalent of Tat to recruit P-TEFb to the chromatin loci of many genes and plays a positive role in releasing Pol II from pausing. However, Brd4 competes with Tat for binding to P-TEFb and thus is a potent inhibitor of Tat-transactivation.

- Identification of small molecule drugs that can antagonize Brd4's inhibition of Tat-transactivation and thereby activating latent HIV-1 proviruses may, in the presence of Highly Active Antiretroviral Therapy (HAART), permit clearance of infected cells by the immune system. The BET bromodomain inhibitor JQ1 has been shown to efficiently reactivate latent HIV-1 in various models.

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