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Background

Human Immunodeficiency Virus (HIV-1) persists in a latent state within resting CD4+ T cells of infected patients treated with highly active retroviral therapy (HAART). This latent reservoir should be eliminated for the clearance of infection. In these cells, silenced replication-competent viruses are integrated into the host genome and can be reactivated by T-cell stimuli. The establishment of this post-integration form of latency is a multifactorial process leading to transcriptional repression. The cellular and molecular mechanisms underlying HIV-1 promoter reactivation from latently infected cells are still poorly understood.

Materials and methods

We used a Jurkat CD4+T cell model of post-integration latency (J-lat cells) to assess the role of cellular factors in controlling gene silencing and Tat-mediated reactivation of silenced HIV proviruses. Our study focused on: (1) the Tat-associated-kinase complex P-TEFb (e.g. Cyclin T1 and CDK9), stimulating progressive elongation, (2) chromatin remodeler SWI/SNF complexes (e.g. Brm and Brg-1), (3) and potential regulators of gene silencing as Heterochromatin Protein 1-γ (HP1-γ and Argonaute 1 (Ago1). Upon transient shRNA knockdowns, viral reactivation by NFkB inducers (TNFα) and/or HDAC inhibitors (TSA) was analyzed by FACS and un-spliced and multi-spliced forms of HIV-1 transcripts were quantified by RT-qPCR.

Results

Our results showed that, as expected, P-TEFb factors inhibition impaired transcriptional reactivation of latent HIV-1. On the contrary, Brg-1 knockdown stimulated TNFα-induced HIV-1 expression, suggesting that the SWI/SNF complex could participate to transcriptional repression in this model. Furthermore, TNFα- and TSA-induced viral mRNA transcript abundance showed a 3 to 4 fold increase upon Ago1 knockdown.

Conclusion

HIV-1 viral clearance through reactivation would imply the regulation of cellular cofactors involved in the chromatin control of the LTR. Our data suggest that establishment and reactivation of viral latency is under the control of several cellular mechanisms involving factors controlling heterochromatin formation, as well as complexes mediating RNA silencing.