Role of a new termination complex in the control of HIV-1 transcriptional latency

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Despite the successful use of Anti-Retroviral Therapies (ART), HIV infection remains an incurable disease due to the persistence of viral reservoirs. These reservoirs are mainly composed of resting CD4+ T cells harboring silent but replication-competent integrated proviruses. In latently infected cells, HIV-1 expression is repressed by several transcriptional blocks among which Premature Transcription Termination (PTT) leads to the accumulation of short viral transcripts. As the HIV-1 integrated provirus contains duplicated Long Terminal Repeats (LTRs) at each side of its genome, HIV-1 5'LTR promoter harbors a proximal-polyadenylation signal (PAS) downstream of the Transcription Start Site (TSS). We thus hypothesized that HIV-1 proximal-PAS could favor the recruitment of the Cleavage and PolyAdenylation (CPA) complex to promote viral transcripts PTT in latently infected cells. We first evaluated the contribution of the CPA complex in the regulation of LTR-driven basal transcription in HeLa cells harboring an integrated LTR-reporter gene. Amongst the different CPA subunits, we found that only PCF11 represses HIV-1 for the most part independently of the PAS-motif and the other CPA factors. We further investigated whether PCF11 could associate with other non-canonical termination factors to repress HIV-1. Interestingly, we found that PCF11 strongly interacts with WDR82, a protein that was recently shown to enforce early termination of non-coding RNAs in human cells. Then, we addressed the role of this newly identified nuclear complex on HIV-1 repression in JLat latency models. Our chromatin immunoprecipitation (ChIP) experiments indicate that both factors are specifically recruited near the TSS on HIV-1 latent provirus. Using 4-thiouracil metabolic labelling of newly synthesized transcripts, we showed that depletions of PCF11 and WDR82 significantly reactivates HIV-1 latent provirus transcription. Moreover, we observed that HIV-1 latent provirus reactivation upon PCF11 knockdown is reduced in WDR82-depleted cells. Finally, in a population of Jurkat CD4+ T cells infected with HIV-GKO dual-fluorescence reporter virus, PCF11 and WDR82 knockdowns reactivate latent proviruses expression, suggesting that both factors are required for the maintenance of HIV-1 post-integration latency. Thus, our study highlights the key role of a new PCF11-associated complex is the regulation of HIV-1 transcriptional latency.