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Characterization of a new viral Biomolecular Condensate associated with PRC2 complex in HIV-1-infected cells.

The human immunodeficiency virus 1 (HIV-1) is a retrovirus that has infected over 75 million individuals worldwide. This virus primarily infects CD4+ T-cells but can also infect other immune cells, such as myeloid cells. Many people living with HIV-1 (PLWH) take combination antiretroviral therapy (cART) to reduce HIV-1 viral load. However, these drugs do not eradicate HIV-1 viral reservoirs. Thus, another means of treatment is needed to control viral transcription within immune cells and fully eradicate the infection. The Tat peptide mimetic, F07#13, has been demonstrated to inhibit viral transcription in HIV-1-infected T-cells and myeloid cells. F07#13 binds to CDK9 and inhibits the CDK9/Tat/cyclin T1 complex. This process leads to Tat degradation and the production of the non-coding TAR-gag RNA. TAR-gag has been demonstrated to bind to Tat suppressive proteins, including PRC2, Cul4B, and Sin3A, and regulate HIV-1 gene expression. A previous paper published by our lab demonstrated the presence of PRC2 binding spots on TAR-gag RNAs. Therefore, we believe PRC2 may be a major player in transcription inhibition by F07#13 in infected cells. To assess F07#13's mechanism of inhibition in T-cells and myeloid cells, we performed western blot analysis to identify changes in EZH2 and H3K27me3 protein levels in cells treated and untreated with F07#13. First, we identified that F07#13 decreases cell viability over time. We then discovered greater efficacy of transcription inhibition in infected myeloid cells (U1) compared to T-cells (J1.1) by F07#13. We also identified that PRC2 plays a greater role in transcription inhibition in infected T-cells compared to myeloid cells. Collectively, our data indicate that F07#13 can inhibit long processive transcription by assembly of a new viral "biomolecular condensate" that includes TAR-gag RNA as well as PRC2, Cul4B, and Sin3A suppressive proteins.

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