HIV-1 Rev Regulates Host Transcription and RNA Processing Factor Tat-SF1 to Promote HIV-1 Infectivity

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Understanding HIV-1 gene regulation is significant for efforts to cure AIDS through the elimination of latent viral reservoirs. Alternative splicing of HIV-1 RNAs is strictly regulated throughout the viral life cycle and is essential for HIV-1 replication and infectivity. However, the molecular details of viral control over host splicing machinery remain elusive. The HIV-1 Rev protein binds a Rev Response Element (RRE) to direct nuclear export of unspliced HIV-1 RNA. Rev also plays a less well-defined role in HIV RNA splicing. A well-characterized host factor, U2AF2 is essential for the splicing of human gene transcripts. Recently, the HIV Rev protein was observed to bind a domain of U2AF2 called a "U2AF Homology Motif" (UHM) (PMID: 30892606). The UHM-containing, transcription and splicing factor Tat-SF1 is critical for HIV-1 Tat-dependent transactivation and HIV-1 RNA splicing, yet its interplay with HIV Rev was unknown. Here, we investigated a potential role for host Tat-SF1 with HIV Rev in comparison with U2AF2. First, we determined crystal structures of the Tat-SF1 and U2AF2 UHM complexes with HIV Rev ligands. Tat-SF1 binds Rev in a canonical fashion of UHM – ligand complexes, with a T-type aromatic interaction between a UHM phenylalanine and a Rev tryptophan. The conformation of U2AF2-bound Rev was dramatically distorted and showed a rotated orientation of the tryptophan. We next compared the association of the host factors with HIV Rev in cells, and we found that Tat-SF1 strongly co-immunoprecipitated with the Rev protein. Likewise, isothermal titration calorimetry showed high-affinity interactions between the Tat-SF1 UHM and Rev ligand. To resolve the functional consequences of Tat-SF1 compared to U2AF2 for HIV replication, we compared HIV infectivity following knockdown of each factor and found significant sensitivity to Tat-SF1 levels. Altogether, these results suggest that HIV-1 Rev recruits host Tat-SF1 for HIV-1 transactivation and splicing. As such, the HIV-1 Rev – host Tat-SF1 complex may offer a new target for first-in-class drugs that impair HIV-1 splicing and offer a potential innovative means to modulate Tat-transactivation of HIV-1 expression and hence latent viral reservoirs for HIV-1 "cure".