Genetics Day Poster Submission

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Title: LONGEVITY-ASSOCIATED REGULATION OF SIRT6 BY AMPK TILTS THE BALANCE OF GROWTH VS STRESS RESPONSE

Abstract: 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 TatSF1 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 TatSF1 with HIV Rev in comparison with U2AF2. First, we determined crystal structures of the TatSF1 and U2AF2 UHM complexes with HIV Rev ligands. TatSF1 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 TatSF1 strongly co-immunoprecipitated with the Rev protein. Likewise, isothermal titration calorimetry showed high-affinity interactions between the TatSF1 UHM and Rev ligand. To resolve the functional consequences of TatSF1 compared to U2AF2 for HIV replication, we compared both HIV infectivity and viral minigene expression following knockdown of each factor and found significant sensitivity to TatSF1 levels. Altogether, these results suggest that HIV-1 Rev binds host TatSF1 for HIV-1 transactivation and/or splicing. As such, the HIV-1 Rev - host TatSF1 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".