Cryo-EM structures of the deltaretroviral intasome in complex with the host factor Protein Phosphatase 2A subunit B56γ and HIV integrase inhibitors

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Background: Human T-cell lymphotropic virus type 1 (HTLV-1) is one of the most oncogenic human viruses. Despite the potential for HIV integrase strand transfer inhibitors (INSTIs) to present a treatment option for HTLV-1, the structural understanding of HTLV-1 integrase (IN) and INSTI binding is, like HTLV-1 therapy itself, non-existent.

Methods: Using biochemical assays we screened a small chemical library for activity to block HTLV-1 integration *in vitro*. To identify potent INSTIs and determine EC_{50} values, we infected Jurkat T-cells by co-culture with MT-2 cells. We used X-ray crystallography and cryo-electron (cryo-EM) microscopy to determine the structures of the integration-competent assembly of simian deltaretroviral IN and its nascent viral DNA (vDNA) (the intasome), in complex with its host factor Protein Phosphatase 2A (PP2A) B56g and three different INSTIs.

Results: The cryo-EM structure of the intasome is a tetrameric assembly of IN bound to a pair of vDNA mimics. Two molecules of B56g are bound by the intasome. Employing molecular mimicry, HTLV-1 IN has a conserved Short Linear Motif (SLiM) located on the linker connecting the IN catalytic core domain and CTD, which binds at two unique sites on B56g. We identified a novel naphthyridine compound, XZ450, which potently blocks HTLV-1 infection. Cryo-EM structures of INSTIs raltegravir, bictegravir, and XZ450 bound to the intasome active site show that, despite marked variation in the residues in the active site, HTLV-1 IN remains susceptible to inhibition by HIV INSTIs.

Conclusion: Whilst PP2A hijacking through the B56-binding SLiM has been described for viruses like Ebola and HIV, we show here for the first time the atomic details of the interaction. This insight is crucial for understanding the distribution of integrated proviruses in infected individuals. Our findings elucidate the binding of INSTIs to the HTLV-1 intasome and support their use for pre-exposure prophylaxis of HTLV-1 infection.

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