The drug-induced interface that drives HIV-1 integrase hypermultimerization and loss of function

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Abstract

Allosteric HIV-1 integrase (IN) inhibitors (ALLINIs) are an emerging class of small molecules that disrupt viral maturation by inducing aberrant multimerization of IN. Here, we present co-crystal structures of HIV-1 IN with two potent ALLINIs, BI-D and the drug candidate STP0404. The structures reveal atomistic details of the ALLINI-induced interface of the IN catalytic core and carboxyl-terminal domains (CCD and CTD). Projecting from their principal binding pocket on the HIV-1 IN CCD dimer, the compounds harness a triad of invariant IN CTD residues, Tyr226, Trp235, and Lys266, to nucleate the CTD-CCD interaction. The ALLINI-induced interface primarily involves the CTD SH3-like fold and extends to the beginning of the IN carboxyl-terminal tail. We show that mutations of HIV-1 IN CTD residues that participate in the interface with the CCD greatly reduce the IN-aggregation properties of STP0404. Our results provide a reliable template for the rational development of this series of antiretrovirals through optimization of their key contacts with the viral target.