

The dual role of integrase in HIV-1 replication

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Introduction:

A key HIV-1 enzyme integrase catalyzes irreversible insertion of a viral DNA copy of its RNA genome into human chromosome, which is essential for viral replication. Therefore, integrase is an important therapeutic target. Productive integration into host chromatin results in the formation of the strand transfer complex (STC) containing catalytically joined viral and target DNAs. We have used cryo-EM coupled with biochemistry and virology experiments to obtain high-resolution structures for STCs and to characterize the integrase multi-subunit assemblies into large, nucleoprotein complexes. We are currently extending these studies to elucidate structural basis for the mode of action of clinically used integrase strand transfer inhibitors (INSTIs), which bind to the enzyme active site in the context of the integrase-viral DNA complex and block the strand transfer reaction. Our parallel efforts are focused on studying allosteric HIV-1 integrase inhibitors (ALLINIs), which are currently undergoing clinical trials (2-5). Unlike INSTIs, ALLINIs bind at the integrase dimer interface and induce aberrant protein multimerization. Unexpectedly, in infected cells ALLINIs were significantly more potent during virion maturation rather than during integration. ALLINIs markedly altered virus particle morphogenesis by misplacing the ribonucleoprotein complexes outside the protective viral capsid shell and yielded inactive virions. In turn, these findings have suggested that integrase has a second function in HIV-1 biology. Our follow up studies have revealed that integrase directly binds the viral RNA genome in virions. These interactions have specificity, as integrase exhibits distinct preference for select viral RNA structural elements. ALLINIs impair integrase binding to viral RNA in virions of wild-type, but not escape mutant, virus. These results reveal an unexpected biological role of integrase binding to the viral RNA genome during virion morphogenesis and elucidate the mode of action of ALLINIs. Collectively our findings indicate that viral integrase plays a dual role during HIV-1 replication. Recent Publications 1. Passos D O, Li M, Yang R, Rebenburg S V, Ghirlando R (2017) Cryo-EM structures and atomic model of the HIV-1 strand transfer complex

intasome. *Science*. 355(6320):89-92. 2. Kessl J J, Kutluay S B, Townsend D, Rebenburg S, Slaughter A et al. (2016) HIV-1 integrase binds the viral RNA genome and is essential during virion morphogenesis. *Cell*. 166(5):1257-1268. 3. Sharma A, Slaughter A, Jena N, Feng L, Kessl J J (2014) A new class of multimerization selective inhibitors of HIV-1 integrase. *PLoS Pathog*. 10(5):e1004171. 4. Jurado K A, Wang H, Slaughter A, Feng L, Kessl J J et al. (2013) Allosteric integrase potency is determined through the inhibition of HIV-1 particle maturation. *Proc. Natl. Acad. Sci. USA*. 110(21):8690-8695. 5. Hoyte A C, Jamin A V, Koneru P C, Kobe M J, Larue R C (2017) Resistance to pyridine-based inhibitor KF116 reveals an unexpected role of integrase in HIV-1 Gag-Pol polyprotein proteolytic processing. *J Biol Chem*. 292(48):19814-19825.