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Abstract

Insights into the Activity of Second-Generation Maturation Inhibitors against HIV Clade C †

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Abstract: Maturation inhibitors represent a new underdeveloped class of antiretroviral agents that block virus maturation by binding to the target of protease (PR)-Gag precursor ($Pr55^{Gag}$). Development of a maturation inhibitor is based on a number of small molecules that are capable of blocking the cleavage event between p24-CA and spacer peptide 1. The bulk of the literature on HIV antiretroviral therapy and drug resistance has primarily been derived from HIV-1B, and relatively less is known about the context of HIV-1C that is responsible for more than 95% of HIV infections of India and half of these infections globally. We and others have shown that the presence of maturation inhibitor resistance mutations would make HIV-1B particles either less fit or dependent on these drugs to replicate. By contrast, it is unclear how HIV-1C would naturally acquire these mutations yet remain replication competent in the absence of the selective pressure of maturation inhibitors. Bevirimat, the first-in-class MI, was found to be inactive against HIV-C due to polymorphisms in the SP1 region. We have identified novel second generation of HIV maturation inhibitors with high potency against HIV clade C (IC_{50} values in the low nM range). The mutations identified during selection experiments revealed the putative binding pocket of these compounds on HIV-1 subtype C Gag. While working on the role of CA-C terminal domain (CA-CTD) domain in HIV-1 Gag assembly and release, we have found that core glycine-rich residues of the β-turn motif are crucial in Gag-membrane binding, multimerization, and assembly. Furthermore, we have identified a novel mutation in CA-CTD that is dependent on both classes of MIs. In conclusion, our studies provide insights into the mechanistic action of MIs on HIV-1 Gag processing and stabilization.

Keywords: HIV-1; subtype C; Gag; antiviral; maturation