The relationships between variability, architecture and mutation co-occurrence in the HIV-1 integrase: implications of Raltegravir treatment.

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Abstract

One of the primary drug targets in the therapy against immunodeficiency virus type 1 (HIV-1) is the integrase - the enzyme responsible for the integration of the viral DNA into the host genome. The integrase inhibitor Raltegravir has been widely used in antiretroviral therapy; however, Raltegravir-resistant HIV-1 strains have become a worldwide problem. Here, we compared the variability of each position of the HIV-1 integrase sequence in clinical isolates of Raltegravir-treated and drug-naïve patients by calculating their Shannon entropies. We also built tridimensional models of the HIV-1 integrase and a mutation co-occurrence network. The relationship between variability, architecture, and co-occurrence was investigated. To investigate the

It was observed that positions bearing major resistance-related mutations are highly conserved among non-treated patients and variable among the treated ones. The integrase structure showed that the highest-entropy residues are in the vicinity of the host DNA, and their variations may impact the protein-DNA interface. The co-occurrence network and structural analysis support the hypothesis that the resistance-related E138K mutation compensates for mutated DNA-anchoring lysine residues.

The study results reveal patterns by which the integrase adapts during the Raltegravir therapy; this information can be useful to rethink the drugs currently used or to guide the development of new ones.

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