Structural Differences between B and F Subtypes of HIV PR

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One of the major problems facing the development of successful therapies against AIDS is the emergence of viral variants that exhibit drug resistance, as well as viral subtypes naturally more liable to development of therapeutic failure. In this work we solved by molecular replacement the crystal structures of four HIV-1 proteases complexed with the inhibitor TL-3: of the subtype B wild type (*Bwt*) at 2.1Å resolution, of the subtype F wild type (*Fwt*) at 2.1Å, and a mutant of each subtype (*Bmut* and *Fmut*) at 1.75Å and 2.80Å, respectively. All crystals were in space group $P6_1$

The mutation V82A in the proteases *Bmut* and *Fmut* causes repacking of the S1' pocket, which rearranges the inhibitor's side chain at the P1' subsite. Our analysis further indicates that some polymorphic substitutions between subtypes B and F could lead to stabilization of naturally flexible regions of subtype F proteases, resulting in an intrinsically less active and drug resistant enzyme. On subtype F proteases the polymorphic substitution M36I leads to the displacement of the loop between residues 35-41, which would cause loss of the flexibility of the flaps and of the loop 76-83 in the active site. Our comparisons further indicate that the polymorphic substitution L89M on non-B subtypes could be equivalent to the L90M resistance mutation on subtype B proteases.

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