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CHANGES IN ACTIVE SITE GEOMETRY THROUGH NON ACTIVE SITE C95A MUTATION IN TETHERED HIV-1 PROTEASE HETERODIMER

MV. Hosur K. Kannan M. Kumar
Solid State Physics Division, Bhabha Atomic Research Center, Mumbai, India-400085

The emergence of drug-resistance through mutations in the HIV-1 protease enzyme is reducing the effectiveness of the designed inhibitors as drugs against AIDS. These mutations occur both within and away from the active site. To explore structural effects, we have mutated CYS95, which besides being a non active site residue is also highly conserved among various isolates of the virus. We report here X-ray structure of C95M/C1095A double mutant of tethered HIV-1 protease refined to 2.1 Å resolution (R-work = 19.5% and R-free = 26.1%). The unliganded structure shows closed flap conformations contradicting the belief that the flap is closed only in presence of an inhibitor. Comparison of the present structure with that of C95M single mutant reveals a shift of about 0.6 Å in the positions of the catalytic aspartates Asp25 and Asp1025 and the bound nucleophillic water. There is no repacking of residues around the site of mutation, leading to creation of an internal cavity and consequent destabilisation of the dimer. These changes in the active site geometry and stability are proposed to be the reason for the observed higher activity of this double mutant compared to the single mutant. We thus conclude that non active site mutations can exert influence by causing subtle changes in the active site geometry. This observation also provides a rationale for non active site drug resistance mutations.

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