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Flap Conformations in HIV-1 Protease are Altered by Mutations
GAIL FANUCCI, MANDY BLACKBURN, ANGELO VELORO, LUIS GALIANO, University of Florida, DING FANGU, CARLOS SIMMERLING, Stony Brook —
HIV-1 protease (PR) is an enzyme that is a major drug target in the treatment of AIDS. Although the structure and function of HIV-1 PR have been studied for over 20 years, questions remain regarding the conformations and dynamics of the β-hairpin turns (flaps) that cover the active site cavity. Distance measurements with pulsed EPR spectroscopy of spin labeled constructs of HIV-1 PR have been used to characterize the flap conformations in the apo and inhibitor bound states. From the most probably distances and the breadth of the distance distribution profiles from analysis of the EPR data, insights regarding the flap conformations and flexibility are gained. The EPR results clearly show how drug pressure selected mutations alter the average conformation of the flaps and the degree of opening of the flaps. Molecular dynamics simulations successfully regenerate the experimentally determined distance distribution profiles, and more importantly, provide structural models for full interpretation of the EPR results. By combining experiment and theory to understand the role that altered flap flexibility/conformations play in the mechanism of drug resistance, key insights are gained toward the rational development of new inhibitors of this important enzyme.

Gail Fanucci

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