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The structural basis for the interdependence of drug resistance: HIV-1 protease

Debra Ragland
University of Massachusetts Medical School, USA

HIV-1 protease is responsible for the cleavage of 12 non-homologous sites within the Gag and Gag-Pro-Pol polyproteins in the viral genome. Under the selective pressure of protease inhibition, the virus evolves mutations within (primary) and outside of (secondary) the active site, allowing the protease to process substrates while simultaneously countering inhibition. The primary protease mutations impede inhibitor binding directly, while the secondary mutations are considered accessory mutations that compensate for a loss in fitness. However, the role of secondary mutations in conferring drug resistance remains a largely unresolved topic. We have shown previously that mutations distal to the active site are able to perturb binding of darunavir (DRV) via the protein's internal hydrogen-bonding network. In this study, we show that mutations distal to the active site, regardless of context, can play an interdependent role in drug resistance. Applying eigenvalue decomposition to collections of hydrogen bonding and van der Waals interactions from a series of molecular dynamics simulations of 15 diverse HIV-1 protease variants, we identify sites in the protease where amino acid substitutions lead to perturbations in nonbonded interactions with DRV and/or the hydrogen-bonding network of the protease itself. While primary mutations are known to drive resistance in HIV-1 protease, these findings delineate the significant contributions of accessory mutations to resistance. Identifying the variable positions in the protease that have the greatest impact on drug resistance may aid in the future structure-based design of inhibitors.

draglan@clemson.edu

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