Unveiling a Hidden Pocket in HIV-1 Protease: New Insights into Retroviral Protease Cantilever-Tip Region Characteristics

Dean Sherry¹ and Yasien Sayed¹

¹University of the Witwatersrand Johannesburg School of Molecular and Cell Biology

May 20, 2024

Abstract

The HIV-1 protease is critical for the process of viral maturation, making it an attractive target for antiretroviral therapy. As such it is one of the most well characterised proteins in the Protein Data Bank. There is some evidence to suggest that the HIV-1 protease is capable of accommodating small molecule fragments at several locations on its surface outside of the active site; namely, the Exo site, flap-top pocket, face site, and Eye site. However, some pockets on the surface of proteins remain unformed in the apo structure and these “cryptic sites” have also been known to accommodate small molecule ligands. To date, no cryptic sites have been identified in the structure of the HIV-1 protease. Here, we characterise a novel cryptic cantilever pocket on the surface of the HIV-1 protease through mixed-solvent molecular dynamics simulations using several probes: acetone, benzene, imidazole, isopropanol, and phenol. Structure-based analysis of the cryptic cantilever pocket suggest that the pocket may be amenable to ligand binding. Interestingly, we note that several homologous retroviral proteases exhibit evolutionarily conserved dynamics in the cantilever region and possess a conserved pocket in the cantilever region. Immobilisation of the cantilever region of the HIV-1 protease via disulphide cross-linking resulted in curling-in of the flap tips and the propensity for the protease to adopt a semi-open flap conformation. Together these results suggest that the mobility of the cantilever region plays a key role in the global dynamics of retroviral proteases. Moreover, the cryptic cantilever pocket of the HIV protease may represent an interesting target for future fragment-based ligand screening campaigns.

Hosted file