Histone deacetylase 2 enzymatic activity modulated by its active site loop configuration: an in silico dynamics investigation
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Abstract: Histone deacetylases (HDACs) are hydrolases involved in cellular epigenetic regulation, and have been implicated in several diseases including cancers, Alzheimer’s disease and HIV-1 latent infection. HDACs regulate protein acetylation, which has been linked to several pathophysiologic states of HIV-1 infection. Crystal structures of the human histone deacetylase 2 have been reported, by which describes their bindings to either known or potential drug candidates for HDACs. However, after superimposing several different reported structures of HDAC2, an unstructured loop adjacent to the active site displayed various conformations, shaping the overall ligand fit and accessibility of the active site. Hence, in this study, behaviour and dynamics of the loop were investigated, especially in its fast-to-slow motion time scales using molecular dynamics (MD) simulations. Additionally, in combination with longer time scale all-atom molecular dynamics simulations, a ligand recognition mechanism was devised, showing several key interactions of important residues lining the loop (Tyr206-Gly220) that dynamically alter its overall configuration. Molecular mechanics (MM) calculations were also performed subsequently in order to predict the per-residue free energy decomposition. The contribution energy profile was then derived, yielding the proposed role of the loop in regulating ligand specificity and its highly influential function in the differentiation of specificity among HDAC isoforms.

Keywords: Histone deacetylase; Molecular dynamics simulations; Loop interactions; Enzyme activity