Identification of binding sites in nicastrin and binding modes of its inhibitors

Ngceboyakwethu P Zinyama, Upenyu Guyo, Grace Mugumbate

Abstract

Background: Nicastrin is a confirmed breast cancer target, but the lack of knowledge about its binding sites and the structural basis of interactions with known small molecules makes the development of small molecules against it challenging.
Methods: Molecular docking and molecular dynamics simulations were used in this work to identify binding sites in nicastrin, a gamma-secretase component that has been implicated in breast cancer and a potential drug target in cancer chemotherapy.
Results: Docking calculations identified three binding sites, however binding site analysis using druggability assessment identified a region that encompasses the DYIGS motif, the DYIGS site as the most favorable binding site. This site was validated by a 50 ns molecular dynamic simulation with a known inhibitor CID44433923 and free energy of binding was found to be -11.4 kcal/mol and mainly driven by hydrophobic interactions. Per residue decomposition analysis showed that Gln139, Val138 and Arg105 had a relatively high contribution towards the free energy of binding. These results suggest that these residues might be critical in nicastrin inhibition. Binding mode analysis by docking previously reported nicastrin inhibitors identified residues Gln139, Val138 and Asp143 as key in the interactions.
Conclusions: This work affords an insight into the binding mechanism of small molecules and might direct drug design efforts towards nicastrin.

Keywords: nicastrin, docking, molecular dynamic simulations, binding site, free energy of binding, druggability, breast cancer