Molecular dynamics simulation study of the drug resistance mechanism of hepatitis C virus NS3/4A to Paritaprevir due to D168N/Y mutations

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Abstract:

Hepatitis C virus (HCV) NS3/4A protease is an attractive target for the development of antiviral therapy. However, drug resistance is a major problem since this can limit drug efficacy. Understanding of drug-resistance mechanism is therefore very important for the guidance of further design high efficiency and specificity antiviral drug. Paritaprevir is an attractive inhibitor with IC_{50} value of 1.0 nM against HCV NS3/4A protease genotype 1a [1]. Although it shows good potency towards the wild-type strain, the D168Y variant was found to confer the highest level of resistance (219). In this work, molecular dynamics simulations of paritaprevir complexed with wild-type and two mutated (D168N and D168Y) strains were carried out. Strong hydrogen bonding interactions between protein and ligand were observed in the wild-type complex while the mutant systems show relatively weak interaction. Moreover, the salt-bridges between residues 168 and 155 were observed in only the wild-type system. This should be responsible for the large conformation changes of the binding pocket in D168N/Y mutants. The per-residue free energy decomposition suggests that the key residues involved in inhibitor binding were residues Q41, H57, V132, K136, S139, R155, A156 in the NS3 domain. Detailed information could be useful for the further design of high potent anti HCV NS3/4A inhibitors.

References

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