Molecular dynamics simulation of the RNA-dependent RNA polymerase of Hepatitis C Virus

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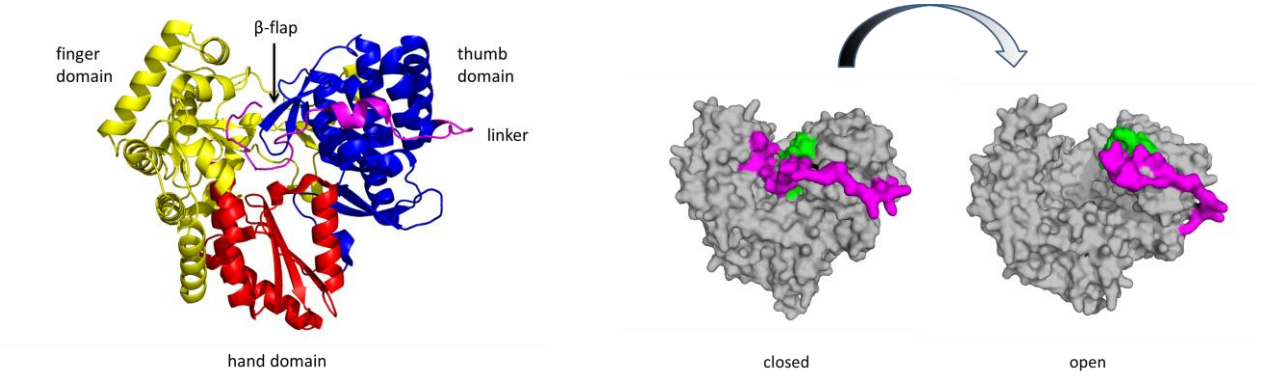
The Hepatitis C virus (HCV) causes severe damage to the liver and can lead to liver cirrhosis or liver cancer.[1] One common target in the pharmaceutical research against Hepatitis C is the non-structural Protein 5B (NS5B), which is the RNA-dependent RNA polymerase of the virus and therefore responsible for the replication of the viral genome. The three dimensional structure of NS5B has already been solved in more than 120 crystal structures as apoprotein or as complex with ligands. They all represent a closed conformation of the protein, which can bind NTP and RNA, but is structurally not able to perform the elongation process.[2] Mainly two regions of the protein are responsible for the closed conformation, the "linker" and the "β-flap" (Figure). They occlude the catalytic center and hinder the transition from the initiation to the processive RNA synthesis.[3]-[5]

We have investigated the conformational flexibility of the NS5B protein by means of molecular dynamics simulations in an implicit solvent environment. The starting crystal structures had been co-crystallized with GTP and the inhibitor HCV-796 (PDB-Codes 2XI3 and 3FQK). The resulting trajectories reveal the opening of the enzyme in the presence of GTP while the closed conformation was observed with bound HCV-796. The linker and β-flap segments mentioned above play indeed an important role during the alteration of conformation, in addition to the rotation of the thumb domain of the protein. Geometrical analysis of the trajectory also indicates a correlated movement of linker and β-flap.



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