Comparative dynamics study of HIV-1 and HTLV-I proteases reveals a conserved structure stabilizing interaction network

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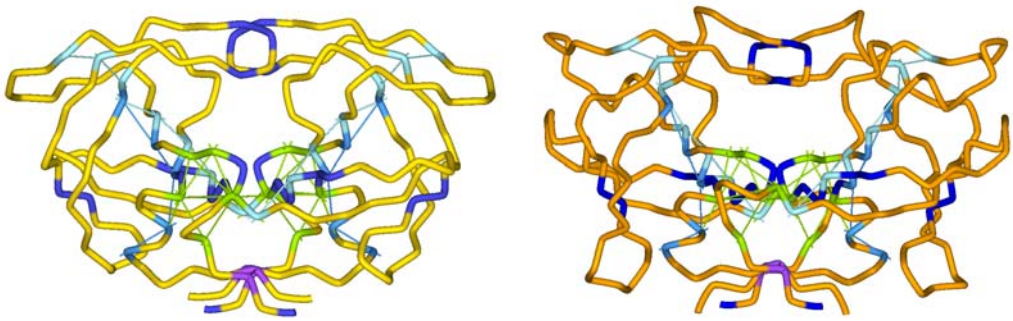
The two human retroviruses human T-lymphotropic virus type I (HTLV-I) and human immune deficiency virus type 1 (HIV-1) are the causing agents of severe and fatal diseases like adult T-cell leukemia (ATL), tropical spastic paraparesis (TSP/HAM) and acquired immune deficiency syndrome (AIDS). For both viruses processing of viral proteins by their protease enzymes is essential for replication [1]. A variety of HIV protease inhibitors have been developed and are in clinical use. The retroviral enzymes HIV-1 protease and HTLV-I protease share 31% sequence identity and high structural similarities. Yet, their substrate specificities and inhibition profiles differ substantially, and no effective inhibitors specifically targeting HTLV-I protease are available to date.



We performed all-atom molecular dynamics simulations for both proteases in their ligand-free state and in complex with model substrates [2,3] in order to compare their dynamic behavior and enhance our understanding of the factors, which determine the similarities and differences of the physiological properties of both proteins.
Despite their low level of sequence identity, both enzymes exhibit striking similarities in their local and global protein dynamics as evidenced for example by the flap motions. By combining the dynamical studies with a sequence conservation analysis we identified an interaction network of contacts between conserved residues that interconnects secondary structure elements and serves as a scaffold for the protein fold. This interaction network is stable over the simulation time of 50 ns and may provide an explanation for the highly similar dynamic behavior of the two retroviral proteases.

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