Homology models and molecular dynamics simulations of main proteinase from coronavirus associated with severe acute respiratory syndrome (SARS)

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Abstract

In this study, two homology models (denoted as MproST and MproSH) of main proteinase (Mpro) from the novel coronavirus associated with severe acute respiratory syndrome (SARS-CoV) were constructed based on the crystal structures of Mpro from transmissible gastroenteritis coronavirus (TGEV) (MproT) and human coronavirus HcoV-229E (MproH), respectively. Both MproST and MproSH exhibit similar folds as their respective template proteins. These homology models reveal three distinct functional domains as well as an intervening loop connecting domains II and III as found in both template proteins. A catalytic cleft containing the substrate binding sites S1 and S2 between domains I and II are also observed. S2 undergoes more significant structural fluctuation than S1 during the 400 ps molecular dynamics simulations because it is located at the open mouth of the catalytic cleft, while S1 is situated in the very bottom of this cleft. The thermal unfolding of these proteins begins at domain III, where the structure is least conserved among these proteins. Mpro may still maintain its proteolytic activity while it is partially unfolded. The electrostatic interaction between Arg40 and Asp186 plays an important role in maintaining the structural integrity of both S1 and S2.