Computational Design of Stapled Peptide Inhibitor against SARS-CoV-2 Receptor Binding Domain

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Abstract

Since its first detection in 2019, the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) has been the cause of millions of deaths worldwide. Despite the development and administration of different vaccines, the situation is still worrisome as the virus is constantly mutating to produce newer variants some of which are highly infectious. This raises an urgent requirement to understand the infection mechanism and thereby design therapeutic-based treatment for COVID-19. The gateway of the virus to the host cell is mediated by the binding of the Receptor Binding Domain (RBD) of the virus spike protein to the Angiotensin-Converting Enzyme 2 (ACE2) of the human cell. Therefore, the RBD of SARS-CoV-2 can be used as a target to design therapeutics. The α1 helix of ACE2 which forms direct contact with the RBD surface has been used as a template in the current study to design stapled peptide therapeutics. Using computer simulation, the mechanism and thermodynamics of the binding of six stapled peptides with RBD have been estimated. Among these, the one with two lactam stapling agents has shown binding affinity, sufficient to overcome RBD-ACE2 binding. Analyses of the mechanistic detail reveal that a reorganization of amino acids at the RBD-ACE2 interface produces favorable enthalpy of binding whereas conformational restriction of the free peptide reduces the loss in entropy to result in higher binding affinity. The understanding of the relation of the nature of the stapling agent with their binding affinity opens up the avenue to explore stapled peptides as therapeutic against SARS-CoV-2.

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