An In Silico Design of Peptides Targeting the S1/S2 Cleavage Site of the SARS-CoV-2 Spike Protein

ABSTRACT

SARS-CoV-2, responsible for the COVID-19 pandemic, invades host cells via its spike protein, which includes critical binding regions, such as the receptor-binding domain (RBD), the S1/S2 cleavage site, the S2 cleavage site, and heptad-repeat (HR) sections. Peptides targeting the RBD and HR1 inhibit binding to host ACE2 receptors and the formation of the fusion core. Other peptides target proteases, such as TMPRSS2 and cathepsin L, to prevent the cleavage of the S protein. However, research has largely ignored peptides targeting the S1/S2 cleavage site. In this study, bioinformatics was used to investigate the binding of the S1/S2 cleavage site to host proteases, including furin, trypsin, TMPRSS2, matriptase, cathepsin B, and cathepsin L. Peptides targeting the S1/S2 site were designed by identifying binding residues. Peptides were docked to the S1/S2 site using HADDOCK (High-Ambiguity-Driven protein–protein DOCKing). Nine peptides with the lowest HADDOCK scores and strong binding affinities were selected, which was followed by molecular dynamics simulations (MDSs) for further investigation. Among these peptides, BR582 and BR599 stand out. They exhibited relatively high interaction energies with the S protein at −1004.769 ± 21.2 kJ/mol and −1040.334 ± 24.1 kJ/mol, respectively. It is noteworthy that the binding of these peptides to the S protein remained stable during the MDSs. In conclusion, this research highlights the potential of peptides targeting the S1/S2 cleavage site as a means to prevent SARS-CoV-2 from entering cells, and contributes to the development of therapeutic interventions against COVID-19.