Determinants of Binding Dynamics in the Effective Peptide Inhibitors

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The infection process of SARS-CoV-2 begins with the interaction between the receptor-binding domain (RBD) of the viral spike protein and the human angiotensin-converting enzyme 2 (ACE2). Blocking this interaction is a key strategy in combating the virus. Instead of relying on engineered ACE2 protein decoys which require complex and expensive techniques, researchers have turned their attention to developing peptide mimics of ACE2. These peptides are easier to synthesize and may exhibit stronger binding affinities. By mimicking the interaction between ACE2 and the spike protein, these peptides have been shown to successfully inhibit their binding. In 2021, Karoyan and colleagues used combinatorial chemistry to develop 10 peptide mimics of ACE2, including one peptide that achieved an impressive 95% inhibition of SARS-CoV-2 replication. In this study, we performed molecular dynamics (MD) simulations of these peptides in implicit solvent using the Amber program. We calculated their intrinsic dynamic physical properties and developed a consensus scoring function to predict the experimental percentage inhibition of SARS-CoV-2 replication. Our scoring function successfully captured the general activity trends of the peptides, with a few outliers that could be explained by specific underlying factors. We also examined the contribution of each calculated parameter to the predictive power of the model, providing valuable insights into how it can be further refined for greater accuracy. This approach highlights the potential of using cost-effective MD simulations for designing peptide inhibitors, making this strategy accessible to a broader range of researchers and offering new opportunities for future antiviral development.