Dynamical FMO Interaction Analysis of SARS-CoV-2 RNA dependent RNA polymerase and Remdesivir

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Remdesivir (Rem), one of the COVID-19 therapeutic agents, inhibits RNA elongation when it is located at the -3 position on the RNA recognized by RNA-dependent RNA polymerase (RdRp) of SARS-CoV-2 virus. In this study, we aim to elucidate the effect of different positions of Rem in the RNA sequence on the RNA strand elongation process.

Based on the cryo-electron microscopy structure of the RdRp-RNA-Rem complex (PDBID:7BV2), five structures were prepared by replacing the bases at positions +1 to -3 on the RNA with Rem/Adenine, and molecular dynamics (MD) calculations using the Amber program were performed for 50 ns each. Then Fragment Molecular Orbital (FMO) calculations were performed on the 50 extracted structures using the ABINIT-MP program to analyze the interaction around Rem.

MD calculations revealed that the structure at the end of the elongated strand (+1 position) is disordered when Rem is located at the position -3, and FMO calculations suggested reduction of its interaction energy by about 10%. On the other hand, the interaction of Rem at the -3 position with the surrounding residues were more unstable than that of Adenine. Although a local cation-π interaction was formed between the cyano-substituted sugar and LYS563, which is characteristic of the Rem structure, the interaction energy between Rem and whole complex was weakened. These results suggest that the dynamic behavior and stability of Rem at the -3 position may affect the arrest of RNA elongation.

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