Exploring the Mechanisms of Antiviral Therapeutics: A 3D Model of SARS-CoV-2 RdRp in Complex with Remdesivir

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Abstract

The recently discovered severe acute respiratory syndrome coronavirus 2 (SARS-Cov-2) causes coronavirus disease 2019 (COVID-19), a respiratory disease affecting the human population worldwide. SARS-CoV-2 replication requires the RNA dependent RNA polymerase (RdRp) complex, composed of non-structural proteins (nsp) 7, 8, and 12. Nsp 7 and 8 function as a primase, whereas nsp12 functions as RdRp for replication and transcription. This polymerase is the target of the antiviral drug remdesivir, an adenosine monophosphate analog. During RNA replication catalyzed by RdRp, remdesivir is covalently attached to the growing RNA strand, resulting in chain termination. Here, we designed a 3-dimensional (3D) model of the SARS-COV-2 nsp12-nsp7-nsp8 RdRp complex bound to template-primer double-stranded (ds)RNA and remdesivir using Jmol and PDB 7BV2 cryo-EM structure (Yin et al., 2020). The 3D model shows the nsp12 subunit bound to dsRNA template and growing RNA strand that forms a corkscrew-like structure within the center channel. The model highlights specific residues aspartic acid 760, valine557, and serine861 within the active site and the interactions of the template-primer RNA strands with remdesivir. An additional 3D model illustrates the structural similarity of remdesivir to adenosine monophosphate. These 3D models enable students to visualize complex biomolecules and understand mechanisms of therapeutics.