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OPINION

Probable Molecular Mechanism of Remdesivir for the Treatment of COVID-19: Need to Know More

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COVID-19 is now pandemic throughout the world. Scientist, doctors are searching for effective therapy of this diseases. The remdesivir, an antiviral drug, is appeared as 'molecule of hope' for the treatment of this disease. USFDA gave emergency approval to this drug for the treatment of COVID-19. The molecular mechanism is unknown. In this paper, we tried to describe the probable molecular mechanism of remdesivir to inhibit the RNA synthesis of SARS-CoV-2. However, more detail mechanism is needed to understand mechanism of action of remdesivir. © 2020 IMSS. Published by Elsevier Inc.

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The current pandemic COVID-19 is caused by a novel coronavirus, SARS-CoV-2. The disease is highly infectious like other coronaviral disease and causing already more than 2.3 lacs deaths worldwide, posing a serious threat to mankind (1,2). Scientists, doctors and other health professional are working very hard to combat this current situation, but still there is no drug or vaccine available to treat this morbid disease. But researchers are trying to develop new therapeutics (3). However this situation initiates a global effort to find out effective measures or discovery of new drugs or vaccines to stop the spreading of this deadly virus, but, since the development of a new vaccine or drug is a time-consuming process, repurposing of existing drug could be act as a brilliant alternative with potential to combat the disease effectively.

One of these drugs is remdesivir (RDV), which shows a broad spectrum of anti-viral activity against many viruses like Ebola (4,5), Nipah (6–8), respiratory syncytial virus (RSV) family (8) and a diverse category of coronaviruses including SARS CoV and MERS CoV (9). Remdesivir is a nucleotide analogue (4), and the triphosphate form of RDV, i.e., RDV-TP is being used as a substrate for many viral RNA-dependent RNA polymerase (RdRp) complexes and it has been reported to inhibit the viral RNA synthesis by a specific mechanism of delayed chain termination for all three coronaviruses (MERS-CoV, SARS-CoV and SARS-CoV-2) RdRp (10). It has been observed that RDV-TP resembles specifically Adenosine triphosphate (ATP) molecule and competes with the nucleotide during the viral RNA synthesis (Figure 1). It has been reported that 3′ hydroxyl group of RDV-TP forms a phosphodiester bond with the next nucleotide but it terminates the formation of viral RNA synthesis at 3 nucleotides downstream, precisely at i + 3 position, whereas the RDV-TP is the i-th position. Moreover, it has also been fascinating to note that the underlying mechanism of chain termination is more or less common in many viruses including all the recent coronaviruses, namely MERS-CoV, SARS-CoV and SARS-CoV-2, though the precise molecular mechanism remains elusive. Additionally, it has been reported very recently that the main reason of chain termination at i + 4 position is due to a steric clash between 1′-CN substituent of the incorporated RDV-TP and a specific residue S861 (10). It is consistent with the chain termination at i + 3 position due to the imposed inability of RdRp to translocate a single position downstream, so eventually it terminates the nascent viral RNA synthesis. Moreover, it has also been imperative to

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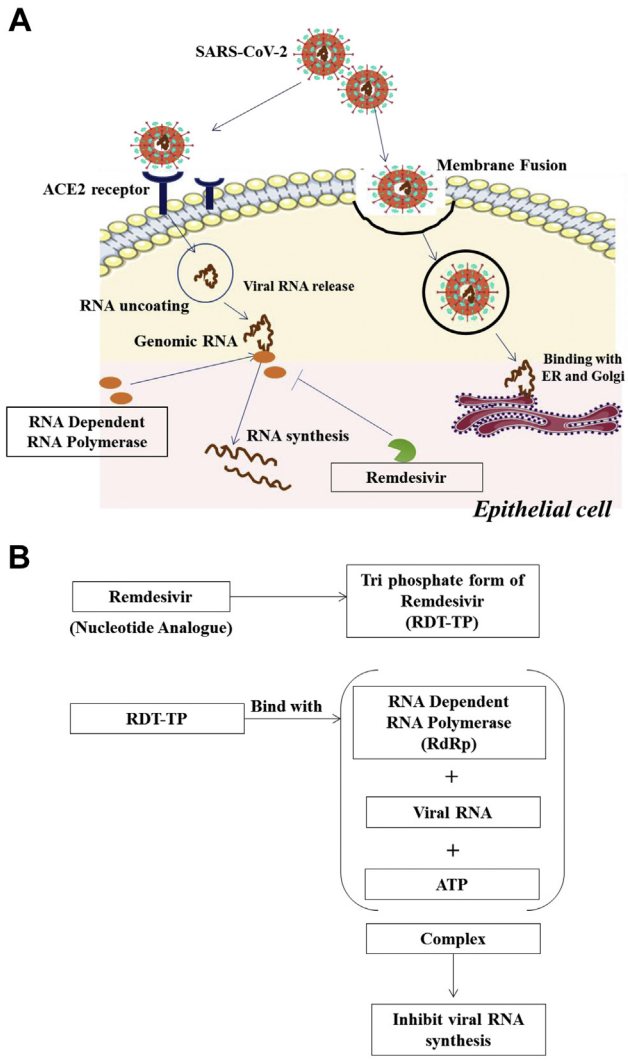

Figure 1. Probable molecular mechanism of Remdisivir against SARS-CoV- 2. (A) Thematic diagram shows the SARS-CoV-2 viral entry and its RNA synthesis which can be block by Remdisivir. (B) Detail molecular mechanism of Remdisivir to inhibit the synthesis of viral RNA.

note that this serine residue is conserved in all coronaviruses. Though, the actual molecular mechanism is still not very clear but this could be a plausible explanation of termination viral RNA synthesis. Recently, scientists also expressed RdRp of different viruses and measure kinetic parameters to infer its interaction with RDV-TP and also determined a score of 0.77 mmol half maximal concentration against SARS-CoV-2 (11).

It can be concluded that this chain termination method could be a general mechanism of anti-viral activity of this particular substrate to a broad spectrum of different viral infection, but still the availability of human trial and safety data is pending, and also a detailed anti-viral profiling of this compound in cell culture study is highly appreciated at this moment.

Conflict of Interest

No potential conflict of interest was declared by authors.

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