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OPINION

Should We Try SARS-CoV-2 Helicase Inhibitors for COVID-19 Therapy?

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The discovery of new drugs for treating the new coronavirus (SARS-CoV-2) or repurposing those already in use for other viral infections is possible through understanding of the viral replication cycle and pathogenicity. This article highlights the advantage of targeting one of the non-structural proteins, helicase (nsp13), over other SARS-CoV-2 proteins. Highlighting the experience gained from targeting Nsp13 in similar coronaviruses (SARS-CoV and MERS) and known inhibitors, the article calls for research on helicase inhibitors as potential COVID-19 therapy. © 2020 IMSS. Published by Elsevier Inc.

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The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) viral pandemic that causes coronavirus disease 2019 (COVID-19) is the worst respiratory disease outbreak of the generation, if not a century, and currently crippling the entire global fabric of the human socioeconomic life. As with other coronaviruses, SARS-CoV-2 is believed to jump species barriers and the first known human infection appeared in the Wuhan province of China in December 2019. With no known efficacious therapy for COVID-19, repurposing other known antiviral drugs and pathologies related to the lethal episode of COVID-19 are our best approach for rigorous experimental (*in vitro* and *in vivo*) tests and clinical trials. In this regard, the closely related coronaviruses such as severe acute respiratory syndrome (SARS-CoV) and Middle East respiratory syndrome (MERS-CoV) gave us good level of understanding in the replication cycle of the virus; the host reaction to infection leading to pneumonia and organ failure (or death); and potential therapeutic targets (Figure 1). The close genomic relationship of SARS-CoV-2 with SARS-CoV, for example, with 80% nucleotide identity has been a good playground for putting forward similar therapeutic insights. Although their infectivity was not as severe as the above-mentioned three coronaviruses, other human coronavirus that gave us clue on potential coronavirus therapeutics are 229E, HKU1, NL63 and OC43. One of the most attractive therapeutic approaches that we learnt from these coronaviruses is based on targeting key enzymes such as proteases, polymerases, and helicases, which are all involved in the replication cycle of the virus. Good examples of antiviral drugs with protease and polymerase mechanism of action are indinavir, saquinavir, lopinavir/ritonavir and remdesivir, which gained attention in recent weeks for clinical trial of COVID-19 infection (1). Our present perspective is to present the potential application of helicase inhibitors.

Unlike the structural proteins of coronaviruses such as spike (S) proteins, which showed a great deal of variability among coronavirus species, the key non-structural proteins (NSP) such as helicase (nsp13) have been shown to be

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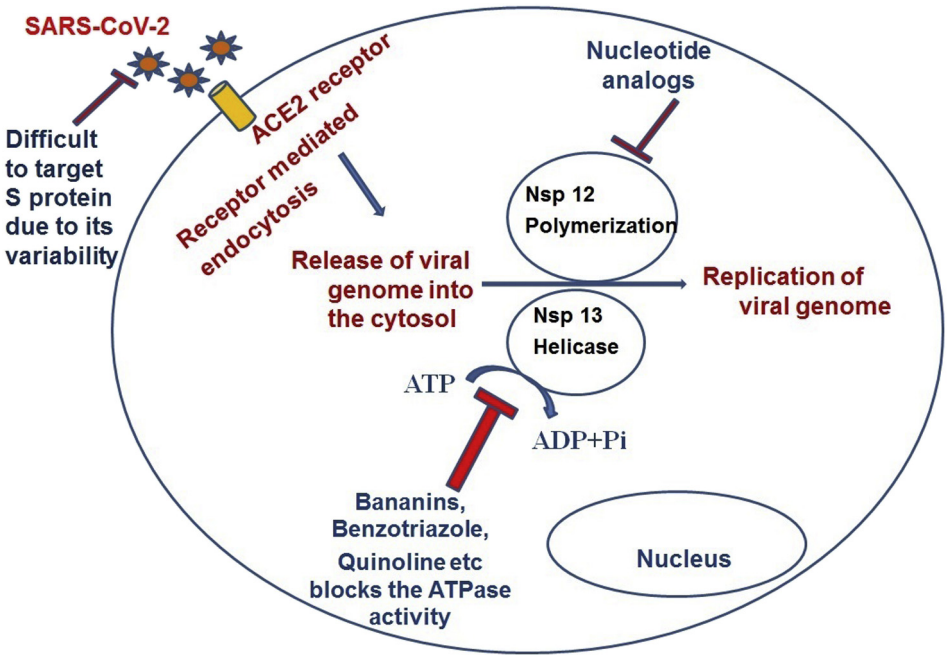

Figure 1. Plausible targets for drug development against CoV2.

conserved. This means that known therapeutics that targets these enzymes even in closely related coronavirus species could have application to SARS-CoV-2 infection. Given that, most laboratories globally are now closed due to the COVID-19 crisis and we are unable to confirm the structural details of SARS-CoV-2 helicases, therapeutic insights could be made based on what is already known in the literature.

Studies on SARS-CoV nsp13 have shown that the enzyme catalyses an NTP-dependent 5′−3′ direction unwinding reaction to covert duplex oligonucleotides (either RNA or DNA) into single strands (2,3). The various binding domains of the enzyme including the zinc-binding domain, stalk domain, 1B domain, 1A domain and 2A domain have been established. Of these, the direct effect of domain 1A in unwinding has been postulated (3). The study by Mirza and Froeyen (4) based on in silico modelling and virtual screening included SARS-CoV-2 nsp13, with its predicted similarity in amino acids/protein profile with SARS- and MERS-Nsp13. They have shown that small molecular weight compounds with potential to inhibit the putative ATP binding site associated with the NTPase activity have promise. Moreover, the NTPase active site residues of SARS-CoV-2 including Lys288, Ser289, Asp374, Glu375, Gln404 and Arg567 are conserved and predicted to be similar with SARS-Nsp13. An interesting insight into the putative role of ATP hydrolysis site of the SARS-CoV nsp13 has also been presented by Jia et al. (3) They have shown that SARS-nsp12 (RNA polymerase) can also play a role by enhancing the helicase activity of SARS-Nsp13 through direct interaction: data that appears to be in agreement with other studies (5). Noting the differential characteristics of nsp13 in unwinding duplex RNA and duplex DNA, Jang et al. (6) also highlighted the requirement of ATP for the enzymatic activity. Other interesting data on the subject came from MERS-CoV helicase nsp13 study by Zaher et al. (7) who identified some potential inhibitors based on in silico molecular docking experiment.

Taking all these data together, it is now apparent that inhibitors of the nsp13 activity offer potential therapeutic option for coronavirus including SAR-CoV-2. Among the various approaches of nsp13 activity inhibition are targeting ATP binding or direct NTPase activity, nucleic acids binding to the helicase, blocking helicase translocation, etc. The class of compounds identified with a promise through such mechanisms include benzotriazole, imidazole, imidazodiazepine, phenothiazine, quinoline, anthracycline, triphenylmethane, tropolone, pyrrole, acridone, small peptide, and bananin derivatives (8). For example, bananins have been shown to inhibit SARS-CoV ATPase activity leading to inhibition of viral replication *in vitro* with IC_{50} values far less than 10 mM (9). On these bases, studies on the potential of viral helicase inhibitors in SARS-CoV-2 infection or COVID-19 is well justified.

Competing Interests

All authors have declared no conflict on interest in the writing of this manuscript.

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