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Editorial

Pharmacology: SARS-CoV-2 and its Therapeutics

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The whole world is facing a massive challenge with the SARS-CoV-2 pandemic. Although several vaccines have been developed, manufacturing them at a large scale and immunizing the vast population over the globe is a huge task. In addition to vaccine production and immunization challenges, the emergence of new viral variants is a new threat. Although it is recently reported that the current vaccine will protect people, with reduced efficacy, from different viral variants, it remains elusive how long these vaccines will protect human beings from the coronavirus and its variants.

Further study needs to be completed to investigate if there is an antibody-dependent enhancement (ADE) over time for approved vaccines. Therefore, antiviral therapy will be urgently needed for a rapid response to the SARS-CoV-2 pandemic. Some antiviral therapies have already shown promising results in clinical trials and were approved for broader use. However, no effective therapy has been identified yet. Therefore, no standard therapeutic protocol is available.

In a short time, drug screening for repurposing will provide a valuable and effective solution for identifying potential therapeutics against SARS-CoV-2. For example, remdesivir, which inhibits the RNA-dependent RNA polymerase and stops viral genome replication by incorporating into the nascent viral RNA, was originally developed for Ebola virus infections, has been approved by the US Food and Drug Administration as an emergency use for the treatment of COVID-19 [1]. However, the efficacy and toxicity of this drug need further improvements. The key advantage of this strategy is that these drugs are available in the market, and their safety and toxicity are already known.

Several studies are focused on identifying drug targets specific to the viral life cycle, which includes interactions between viral spike protein and human angiotensin-converting enzyme 2 (ACE2) receptor. For example, umifenovir (Arbidol), an antiviral molecule initially developed for the treatment of influenza infection, has shown promising results against SARS-CoV-2 [2]. Similarly, Tranexamic acid, which inhibits the conversion of plasminogen to plasmin and alters the endogenous protease plasmin, was also proposed to act as a SARS-CoV-2 entry inhibitor by inhibiting the cleavage of a newly inserted furin site in the S protein, abolishing infectivity [3,4]. A neutralizing antibody is another alternative for inhibiting virus entry to cells. However, it might also lead to ADE. However, the use of nanobodies as neutralizing antibodies can prevent the ADE effect. Recently, several nanobodies against SARS-CoV-2 have been identified, which have shown cross-neutralization activity. Therefore, they have excellent therapeutic potential against the SARS-CoV-2 virus. Several other nanobodies have been identified recently that act against the SARS-CoV-2 [5-7].

After cell entry, virus infection can be inhibited by the well-known FDA-approved antimalarial drug Chloroquine (CQ) or hydroxychloroquine (HCQ) in cell culture. It is reported that they inhibit virus infection by preventing endocytosis, rapid elevation of endosomal pH, and abrogation of virus-endosome fusion. Chloroquine was found to exert antiviral effects during pre-and post-coronavirus infections by interfering with glycosylation of human ACE2 and

blocking the fusion of these viruses to the host cell. Hydroxychloroquine is more soluble and has the same mechanism of action but a better safety profile than chloroquine. However, CQ and HCQ do not show benefits in clinical trial [8].

The next target for inhibiting virus growth is to modulate the polyprotein processing by viral proteases. 3CLpro and PLpro help to process viral polyproteins pp1a and pp1ab into 16non structural proteins (nsps). These cleavage activities are important for the virus life cycle because they generate most of the structure and non-structural proteins, including the RNA-dependent RNA polymerase (RdRp) necessary for viral RNA replication and transcription. Because of highly conserved protease structures and cleavage sites, viral protease is one of the most attractive targets for therapeutics development. It has been shown recently that SARS-CoV-2 3CLpro specific α-ketoamide is a potent inhibitor at lower than 10 μM concentration in Calu3 lung cells [9]. Protease inhibitors used in human immunodeficiency virus (HIV) therapy, such as lopinavir/ritonavir (a combination known as Kaletra), nelfinavir, also limit SARS-CoV-2 propagation in infected cells, but, unfortunately, the first clinical trial result shows that it does not have any significant effect on SARS-CoV-2 infection [10].

Historically, the most attractive antiviral compounds are those that block virus replication by inhibiting RNA-dependent RNA polymerase (RdRp) activity. Nucleotide and nucleoside analogs are among the most promising groups of RdRp inhibitors. While nucleoside analogs have been successfully used for the treatment of other viral diseases, but SARS-CoV-2 is different from other viruses. SARS-CoV-2 contains a viral exonuclease nsp14 ExoN with a proof-reading activity to remove the nucleotide analog and reduce the antiviral efficacy. It has been shown in *in vitro* studies that SARS-CoV-2 polymerase can incorporate ribavirin triphosphate during replication, but nsp14 ExoN detects this nucleotide analog and eliminate it by repairmechanism [10].

In conclusion, we have several possible mechanisms to counter the SARS-CoV-2 infection. Time will tell how fast we can develop the right combination of therapies to deal with SARS-CoV-2.

Bibliography

1. M G Santoro and E Carafoli. "Remdesivir: From Ebola to COVID-19". *Biochemical and Biophysical Research Communications* 538 (2021): 145-150.
2. M Nojomi., *et al*. "Effect of Arbidol (Umifenovir) on COVID-19: a randomized controlled trial". *BMC Infectious Diseases* 20.1 (2020): 954.
3. T N MD. "Antiviral Effects of Tranexamic Acid (TXA) as a Preventative Treatment Following COVID- 19 Exposure". clinicaltrials.gov, Clinical Trial Registration NCT04550338 (2021).
4. C B Keragala and R L Medcalf. "Plasminogen: an enigmatic zymogen". *Blood* 137.21 (2021): 2881-2889.
5. T Li., *et al*. "A synthetic nanobody targeting RBD protects hamsters from SARS-CoV-2 infection". *Nature Communication* 12.1 (2021): 4635.
6. P Pymm., *et al*. "Nanobody cocktails potently neutralize SARS-CoV-2 D614G N501Y variant and protect mice". *PNAS* 118.19 (2021).
7. J Xu., *et al*. "Nanobodies from camelid mice and llamas neutralize SARS-CoV-2 variants". *Nature* 595.7866 (2021): 278-282.
8. David R Boulware., *et al*. "A Randomized Trial of Hydroxychloroquine as Postexposure Prophylaxis for Covid -19". *The New England Journal of Medicine* 383 (2020): 517-525.
9. "Lopinavir/ritonavir: A rapid review of effectiveness in COVID-19". The Centre for Evidence-Based Medicine (2020).
10. F Robson., *et al*. "Coronavirus RNA Proofreading: Molecular Basis and Therapeutic Targeting". *Molecular Cell* 79.5 (2020): 710-727.

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