A promising strategy against SARS-CoV-2: pyrimidine inhibitors synergize with nucleoside analogues

Long Min1 and Qiu Sun

Signal Transduction and Targeted Therapy (2022)7:88; https://doi.org/10.1038/s41392-022-00956-6

In a recent study published in Nature, David C. Schultz et al. demonstrated a new high-efficient therapy to fight against SARS-CoV-2, that is, combining pyrimidine biosynthetic inhibitors with antiviral nucleoside analogues.1

By February 10, 2022, SARS-CoV-2 has infected more than 400 million people, including more than 5.79 million deaths. Patients infected with SARS-CoV-2 usually develop mild to severe symptoms, and several patients lead to severe clinical outcomes. Although some vaccines or drugs have entered clinical practice, there is still a lack of effective antiviral therapy against the constantly changing virus.

SARS-CoV-2 is a family of single-stranded positive-sense RNA viruses. It replicates RNA by using RNA-dependent RNA polymerase (RdRp). Nucleoside analogues can interfere with this step by incorporating into the growing viral RNA chain through RdRp, then the RNA replication process will be forced to terminate or mutate, ultimately inhibiting viral replication.2

Nucleoside analogues have now become a large class of approved drugs that act directly as antivirals. Due to the conservative structures of RdRp in different viruses, some of the nucleoside analogues are believed to be used to inhibit SARS-CoV-2.

The respiratory epithelial cell is the main cellular target of SARS-CoV-2 in vivo. The authors used the human respiratory epithelial cell line Calu-3 to screen the small molecule compound library that included approved drugs, drugs in clinical trials, and drugs with antiviral activity with known targets.3 After the comprehensive evaluation of the potency and toxicity of each compound, 122 compounds of which about 13% belong to nucleoside analogues, including remdesivir and molnupiravir, which are approved to use in the treatment of SARS-CoV-2 had screened out.4,5

To determine the breadth of antiviral activities of these nucleoside analogues, they tested a group of cell lines which are permissive to infect with SARS-CoV-2. It was found that different nucleoside analogues showed their cell-type-specific antiviral activities. For example, tuberculin showed antiviral activities in Calu-3, Caco-2 and Huh7.5, but was toxic in A549-Ace2 and Vero cells. On the contrary, thiouanine and 6-mercaptopurine were active in Calu-3 and A549-Ace2 cells, but not active in Caco-2 or Vero cells. Among them, remdesivir and molnupiravir exhibited the highest antiviral activities. Since remdesivir is an adenosine analogue and molupiravir is a cytosine analogue, it is speculated that the combination of remdesivir and molnupiravir could show antiviral synergy, however, further studies prove that it was just an additive effect.

Nucleoside analogues can act as synthetic analogues in the replication of DNA or RNA; in addition, a subset of nucleoside analogues also works as an anti-metabolite to consume the supply of deoxynucleotides required for DNA replication or inhibit nucleoside biosynthesis enzymes by binding to metabolic enzymes and competing with natural ligands to inhibit RNA synthesis; therefore, anti-metabolite is thought to work as a broad-spectrum antiviral strategy.

There are two pathways for nucleoside biogenesis in cells, de novo synthesis and salvage pathway. The de novo synthesis can supply sufficient energy for viral replication while the salvage pathways cannot. Based on this, the researchers screened a series of compounds that inhibit nucleoside biosynthetic enzymes and found two DHODH inhibitors in de novo pyrimidine synthesis, BAY-2402234 and Brequinar, as well as the UMPs inhibitor pyrazofurin.

Surprisingly, the DHODH inhibitors co-administrated with remdesivir and molnupiravir showed striking synergy. The combining therapy, DHODH inhibitors combined with remdesivir and molnupiravir, also showed positive results in diverse strains of SARS-CoV-2 (alpha, beta, gamma and delta). Undoubtedly, this result brings hope to novel drug development in the treatment of SARS-CoV-2 (Fig 1).

Since late 2019, this disaster has influenced the world, even though some vaccines and drugs have been in clinical, it is urgent to develop effective drugs or therapies to combat SARS-CoV-2 due to the constant mutating that makes the virus more infective, easier to transmit, even evade vaccines and ineffective existing treatment drugs. After screening 18,000 drugs for antiviral activity by live SARS-CoV-2 infection in human respiratory epithelial cells, the David C. Schultz group found remdesivir and molnupiravir to have shown antiviral activity and selectivity against SARS-CoV-2, and further proved that the combination of remdesivir and molnupiravir with DHODH inhibitors would be effective in reducing virus replication and inflammation after SARS-CoV-2 infection. This combination therapy offers a new direction for the treatment of SARS-CoV-2 and the emerging strains. Researchers also found Paxlovid, a SARS-CoV-2 protease inhibitor, combined with molnupiravir or remdesivir against SARS-CoV-2 beta or delta strains shown an additive effect. Thus, there may be many potential combinations that need to be tested in the clinical setting, which can alter the trajectory of this terrible pandemic. It is urgent to overcome the terrible pandemic since 2019 as soon as possible, and combination therapy may be the new start point to winning the war.
ADDITIONAL INFORMATION

Competing interests: Q.S. is the editorial board member of Signal Transduction and Targeted Therapy, but she has not been involved in the process of the manuscript handling.

REFERENCES

1. Schultz, D. C. et al. Pyrimidine inhibitors synergize with nucleoside analogues to block SARS-CoV-2. Nature (2022). https://doi.org/10.1038/s41586-022-04482-x.
2. Geraghty, R. J., Aliota, M. T. & Bonnac, L. F. Broad-spectrum antiviral strategies and nucleoside analogues. Viruses 13, 667 (2021).
3. Janes, J. et al. The ReFRAME library as a comprehensive drug repurposing library and its application to the treatment of cryptosporidiosis. Proc. Natl. Acad. Sci. USA 115, 10750–10755 (2018).
4. Jayk Bernal, A. et al. Molnupiravir for oral treatment of Covid-19 in nonhospitalized patients. N. Engl. J. Med. 386, 509–520 (2022).
5. Wiersinga, W. J. et al. Pathophysiology, transmission, diagnosis, and treatment of coronavirus disease 2019 (COVID-19): a review. J. Am. Med. Assoc. 324, 782–793 (2020).

Open Access This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made. The images or other third party material in this article are included in the article’s Creative Commons license, unless indicated otherwise in a credit line to the material. If material is not included in the article’s Creative Commons license and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this license, visit http://creativecommons.org/licenses/by/4.0/.

© The Author(s) 2022