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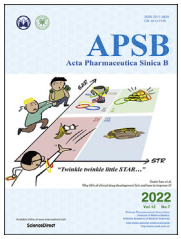

COMMENTARY

Viral miRNA-mediated activation of hyaluronan production as a drug target against COVID-19

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The global coronavirus disease 2019 (COVID-19) pandemic has caused more than 6.1 million deaths until March 24, 2022, as reported by the World Health Organization (WHO). Recently, breakthrough infections have appeared in individuals fully vaccinated against SARS-CoV-2[1], which could be attributed to the rapid mutation of the RNA virus[2]. Currently, following the Delta variant, the Omicron variant of SARS-CoV-2 is increasingly becoming the dominant epidemic strain in the world. It has been demonstrated that the Omicron variant could evade from the most of antibody-mediated neutralization, indicating a need to develop vaccines that can specifically target the Omicron variant. While the speed of vaccine development has been comparatively quick due to the admirable efforts made by researchers around the world, tremendous challenge remains in developing vaccines that are effective even against newly occurring variants of SARS-CoV-2. In addition, vaccine expenditures have posed a significant financial burden on most countries. As such, it is urgent to identify the therapeutic targets of COVID-19 and thereby develop drugs.

Previously, we discovered that miRNAs located in nucleus could activate gene transcription by targeting the enhancer[3], and these miRNAs were termed "nuclear activating miRNAs (NamiRNAs)". Growing research has revealed that both RNA and DNA viruses could produce small RNAs or miRNA-like non-coding RNAs. We recently discovered that SARS-CoV-2 RNA elements share human sequence identity[4], which could activate the expression of inflammation-related genes and promote the progression of COVID-19. The related research has been published as an article entitled "SARS-CoV-2 RNA elements share human sequence identity and upregulate hyaluronan *via* NamiRNA-enhancer network" in the journal of *EBioMedicine*[4]. We explored the underlying mechanism of COVID-19 caused by SARS-CoV-2 infection and highlighted some potential therapeutic strategies for COVID-19, especially in repurposing oral hymecromone.

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1. Human Identical Sequences serve as the key pathogenic factors for COVID-19

It is known that SARS-CoV-2 replicates in the cytoplasm, and recently, some reports suggested that unknown transcripts of SARS-CoV-2 also exist in the mitochondria and nucleoli of host cells[5,6]. A neglected yet valuable question is whether these transcripts in nuclei could interact with nuclear chromatin to induce clinical symptoms of COVID-19. We identified five fully identical sequences (24−27 nt length) between SARS-CoV-2 and human genomes, and termed them as "Human Identical Sequences (HIS)"[4]. We found that HIS could be the miRNA derived from SARS-CoV-2 and overlapped with the enhancer sites of the human genome. Further studies showed that HIS of SARS-CoV-2 could activate the expression of inflammation-related genes in human embryonic kidney cells HEK293T, human embryonic lung fibroblasts MRC5, and human umbilical vein endothelial cells HUVEC. This suggests that SARS-CoV-2 may activate the expression of inflammation-related genes in non-immune cells, especially in human fibroblasts. In particular, HIS activates the expression of ACE2, a known receptor that facilitates SARS-CoV-2's entry into cells. Therefore, HIS of SARS-CoV-2 not only induces cytokine storms by activating inflammation-related genes, but also activates the expression of viral receptor ACE2 to promote its infection.

Additionally, more than 100 pathogenic RNA viruses have short sequences identical to the human genome, including six other human coronaviruses (such as SARS-CoV and MERS-CoV), Avian influenza virus, Ebola, Zika virus, and so on. These findings highlight the importance of HIS for the pathogenicity of RNA viruses. Hence, HIS could be a promising drug target for RNA virus-associated diseases.

2. Hyaluronan is a promising biomarker for the progression of COVID-19

As an acidic mucopolysaccharide, hyaluronan regulates numerous physiological processes involved in water homeostasis and inflammation. We revealed that HIS could activate hyaluronan synthase *HAS2* and promote hyaluronan synthesis, which illustrated the potential mechanism of the accumulation of hyaluronan in severe COVID-19 patients[7]. Notably, the increased hyaluronan is closely associated with clinical symptoms of COVID-19, such as lymphocytopenia and pulmonary ground-glass opacity (GGO) lesions[4]. Notably, the binding of hyaluronan to its receptor CD44 on the surface of T lymphocytes can cause the apoptosis of activated T cells[8], which underlies lymphopenia observed in COVID-19 patients. Moreover, hyaluronan treatment alone can cause pulmonary lesions in mice[4], which are similar to pulmonary lesions found in COVID-19 patients based on CT results, which may be due to the strong water absorption capacity of hyaluronan. Thus, the accumulation of hyaluronan mediated by HIS is an important material basis behind clinical symptoms such as cytokine storm, lymphocytopenia, and pulmonary lesions in COVID-19 patients (Fig. 1).

Furthermore, since hyaluronan is closely associated with currently known indicators (such as C-reactive protein, and lymphocytes) of COVID-19 progression[9], it may also be used to distinguish different stages of COVID-19. The recent appearance of the Omicron variant has resulted in many asymptomatic infections of SARS-CoV-2 worldwide. However, some of the asymptomatic patients later developed symptomatic manifestations. In these cases, hyaluronan may serve as a promising biomarker for monitoring COVID-19 progression and assist physicians in identifying patients who will need additional medical care.

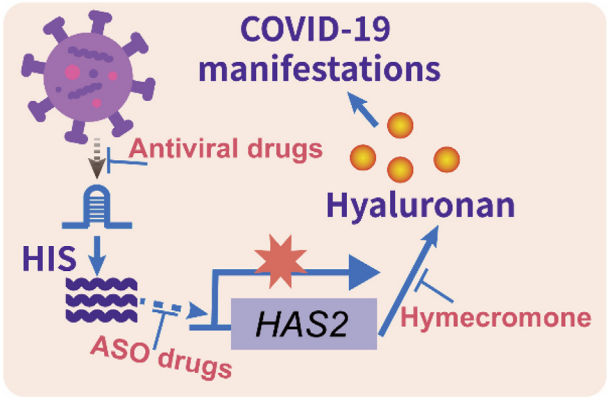

Figure 1 Promising therapeutic strategies for COVID-19 treatment. There are mainly two approaches to fighting SARS-CoV-2 infection. One approach is to reduce the viral load of SARS-CoV-2 using antiviral drugs (such as Paxlovid and Molnupiravir). Another approach is to prevent COVID-19 clinical manifestations by blocking the interaction between SARS-CoV-2 and human through ASO drugs or hymecromone. Combining hymecromone with antiviral drugs could be more effective for treating COVID-19.

3. Prescription hymecromone could be an effective oral drug to fight against COVID-19

The development of new drugs typically requires considerable costs, both in terms of time and money. Given the urgency of COVID-19, repurposing old drugs could be a quick and effective way to combat the pandemic. As mentioned above, hyaluronan is a potential target for blocking the clinical symptoms of COVID-19. An inhibitor of hyaluronan synthesis, hymecromone has been approved to treat cholecystitis and biliary tract spasms as an oral prescription medicine in China. In some other countries, hymecromone is used to prevent prostate cancer as a health product. We have confirmed that hymecromone could inhibit hyaluronan production in HEK293T and MRC5 cells[4], thereby demonstrating its potential to treat COVID-19 by reducing hyaluronan. Through a subsequent clinical trial, we also found that hymecromone could improve clinical manifestations (such as lymphopenia and pulmonary lesions)[9]. Assuredly, many lives could be saved if the efficacy of hymecromone against COVID-19 is confirmed in a larger sample. To this end, repurposing oral hymecromone is a promising strategy for COVID-19 treatment (Fig. 1).

The combination of hymecromone with antiviral drugs (such as Paxlovid and Molnupiravir) could be another effective approach in treating COVID-19. On one hand, antiviral drugs can inhibit the replication of SARS-CoV-2 and decrease HIS production (Fig. 1), resulting in a reduction of hyaluronan. On the other hand, hymecromone can inhibit hyaluronan production directly to prevent clinical manifestations of COVID-19. On these grounds, the therapeutic effects of hymecromone combined with antiviral drugs on COVID-19 deserve further investigation.

4. Antisense oligonucleotides targeting HIS are a novel direction for COVID-19 treatment

Antisense oligonucleotides (ASO) are single-strand oligonucleotide molecules (18−30 nt) that can form a hybrid with a single-stranded DNA or RNA to further regulate gene expression through various mechanisms. Already, certain ASO drugs have been approved to treat particular diseases. For example, Nusinersen (SPINRAZA™) is used to treat spinal muscular atrophy (SMA)[10]. Similarly, HIS of SARS-CoV-2 could be a potential target for designing a novel ASO drug due to their ability to upregulate genes (such as HAS2, and ACE2) that affect COVID-19 progression. Mechanically, the hybrids formed between ASO and HIS would prevent the binding of HIS to the human enhancer and block the activation of gene transcription associated with COVID-19 (Fig. 1). In other words, ASO drugs could intercept the interaction between SARS-CoV-2 and human by binding to HIS and thereby facilitate the recovery of COVID-19 patients.

5. Future perspectives

In the short term, the combination of hymecromone with antiviral drugs could be a fast and effective defense against SARS-CoV-2. In the long term, it may be necessary for us to develop specific ASO drugs that target HIS of SARS-CoV-2 to confirm its therapeutic effect. Moreover, considering that HIS could be a key pathogenic factor for RNA viruses, ASO drugs targeting HIS could be a novel direction for treating RNA virus-associated diseases broadly. In the same vein, blocking HIS production with gene editing technology could be yet another innovative strategy for tackling pathogenic RNA viruses. Finally, removing key pathogenic factors (such as HIS) from the genomes of pathogenic RNA viruses could also serve to weaken the virulence of these viruses for vaccine development.

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