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Viewpoint

Using Clustered Regularly Interspaced Short Palindromic Repeats for Recombinant Biosynthesis of Antimicrobial Peptides as Anti-COVID-19 Agents

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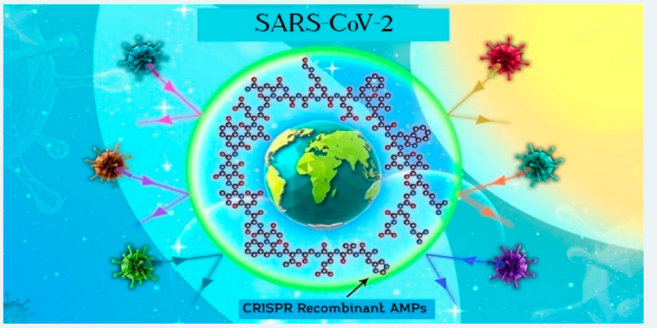
ABSTRACT: The SARS-CoV-2 pandemic has caused the death of 5.5 million people and the infection of more than 323 million people as of January 2022. The remarkable increase in pathogenicity and virulence might have occurred as a result of viral RNA mutations. To date, few antiviral drugs have been authorized for emergency use, but not yet approved, to treat mild to moderate COVID-19, with serious drawbacks and side effects. Antimicrobial peptides (AMPs) play an important role in the host's innate and adaptive immune system against a wide range of microbial infections. Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR) is thought to be used to increase the recombinant biosynthesis of AMPs. There have been studies that reported the production of AMPs using CRISPR. Therefore, CRISPR is expected to play an important role in the production of AMPs as next-generation, safe, affordable, and efficient antiviral drugs in general and for the treatment of COVID-19 in particular, in addition to AMPs being efficient immunomodulators.



KEYWORDS: *antimicrobial peptides, antiviral, COVID-19, CRISPR, immunomodulator*

The SARS-CoV-2 pandemic has caused the death of 5.5 million people and the infection of more than 323 million people as of January 2022.[1] The remarkable increase in pathogenicity and virulence might have occurred as a result of the mutations of the viral RNA.[2]

To date, few antiviral drugs were authorized for emergency use by the U.S. Food and Drug Administration (FDA), but not yet approved, to treat mild to moderate COVID-19 in adults with a high risk for development of severe symptoms, including hospitalization or death. A significant percentage of patient recovery was reported, compared to placebo, by the administration of those drugs within 5 days of treatment. However, serious drawbacks were reported, among which that they are not authorized to be administrated for more than 5 days, for pre- or postexposure prevention to COVID-19, for patients who suffer from severe symptoms and need hospitalization, or as a substitute for vaccination. In addition, possible side effects of those drugs may occur, including (but not limited to) diarrhea, high blood pressure, and muscle aches. Furthermore, it was reported that potentially significant drug interactions occurred that may cause life-threatening reactions.[3,4]

Antimicrobial peptides (AMPs) are versatile molecules, composed of 10−50 amino acids (2−9 kDa). They play an important role in the host's innate immune system against a wide range of microbial infections.[5] More than 3100 AMPs have been identified, where approximately 180 were reported to be antiviral.[6] AMPs have been known for their antimicrobial (virus, bacteria, and fungi) activity as well as their immunomodulatory response enhancement.[7]

Previous reports confirmed the antiviral activity of AMPs on enveloped RNA and DNA and most nonenveloped viruses, particularly the SARS coronavirus.[8,9] Their route of antiviral action may take place by first blocking viral entry by the interaction with heparan sulfate on the host cell surface or the interaction with specific cellular receptors and, second, blocking of cell-to-cell spread, thus preventing the virus movement outside the cell; and third, AMPs may interact with the lipid membrane of the viral envelope, causing its translocation or lysis.[10] It was also reported that AMPs may cause viral gene silencing, thus blocking its protein expression.[11]

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Recently, there have been several reports studying AMP immunomodulatory activity. They act as chemoattractants to several immune cells, such as monocytes, neutrophils, dendritic cells (DCs), and T-lymphocytes. They also play an important role in activating macrophages, mast cells, and chemokine production. Therefore, pro- and anti-inflammatory responses are enhanced in combination with innate and adaptive immunity activation.[12]

Despite the high stability and specificity of the naturally produced AMPs, they are still produced in low amounts and are susceptible to proteolysis.[13] As a result, there is a need for the development of new technologies to enhance the biosynthesis of AMPs at the quality and quantity levels.[14] Although microbial cassettes and genetically modified plants were used to enhance the production of AMPs, the quality of their production was poor.

The most recent approach to enhance the biosynthesis of AMPs is using the Clustered Regularly Interspaced Short Palindromic Repeats-associated protein (CRISPR-Cas) system. CRISPR is thought to be used to increase the recombinant biosynthesis of AMPs in nearly all organisms. It takes place through the integration of target genes of a specific AMP within the CRISPR-edited host genome at specific sites to induce high production levels of the targeted AMP.[15] Specific sites at the target coding gene sequence of the AMP are spliced to be introduced to CRISPR RNA with the help of the associated protein (Cas9) which is later inserted into the host, thus enabling the expression of the modified AMP.[13]

Park et al.[16] reported the production of AMPs (lysozyme, moricin, and lebocin) using CRISPR-Cas9. They produced a guide RNA-Cas9 complex that was inserted into *Bombyx mori* cells, thus allowing the analysis of the mutation of the *Cactus* gene that produces the antibacterial molecules. The activity of the lysozyme produced using CRISPR-Cas9 was 10 times higher than that naturally produced.

Therefore, CRISPR is expected to play an important role in the production of AMPs as next-generation antiviral drugs in general and for the treatment of COVID-19 in particular, in addition to AMPs being efficient immunomodulators.[17] Being safe, affordable, and efficient, AMPs may be superior to all other control strategies, making it worthwhile to conduct more research in the future to improve their antimicrobial activity.

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Author Contributions

S.E. and M.A. conceived the idea, drafted the manuscript, revised the first draft, and read and approved the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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