RESEARCH HIGHLIGHT

Lipid nanoparticle-mRNA: another step in the fight against COVID-19

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One of the most important therapies useful in preventing progression of COVID-19 in high-risk patients are monoclonal antibodies targeting the surface glycoprotein. In a recent work in Cell Research, Deng et al. use lipid nanoparticles encapsulating mRNA encoding SARS-CoV-2-specific antibody chains to protect animals from lethal infection.

The COVID-19 global pandemic poses immense challenges to global health. Rapid spread of the disease has prompted intense research to identify therapeutics and vaccines. Currently, vaccines are the most effective approach to preventing COVID-19 but the emergence of variants of concern (VOC) has compromised vaccine efficacy. Also, vaccines cannot be used as treatment so are not useful in critically ill patients. Considering these limitations, there is an urgent need for the development of therapeutic approaches. In August 2020, Food and Drug Administration (FDA) issued an Emergency Use Authorization (EUA) for convalescent plasma for the treatment of hospitalized patients with COVID-19, but later clinical trials showed that this intervention was generally not effective.[1] Subsequently, several potent monoclonal antibodies (mAbs) with anti-viral activity in vitro and in preclinical studies were identified and shown to be effective in clinical trials. These antibodies are most effective when delivered prophylactically, or more feasibly, to patients in the early stages of the disease.[2] There are two major challenges to the use of mAb-based therapy: the cost of large-scale production of these antibodies is high and mAbs are generally delivered intravenously, which is problematic in low resource and overburdened clinical settings.

In a recent work in *Cell Research*, Deng et al. show that the same technology that was useful in COVID-19 vaccine development could be used to deliver antibody prophylactically to SARS-CoV-2-infected mice and hamsters.[3] Delivery of mRNA encoding proteins has evolved as a powerful technology over the past few years. Multiple studies have described methods to encapsulate the RNA in lipid nanoparticles (LNPs) to protect the RNA from degradation by ubiquitous RNases and to use modified nucleosides to make the RNA less immunogenic.[4] The greatest success of this approach was in the rapid development of SARS-CoV-2-specific vaccines, which have proven highly efficacious.[5] Deng et al. used this method to encapsulate mRNA encoding the two chains of an antibody that they previously showed exhibited good protective efficacy against SARS-CoV-2. In this report, mice and hamsters were immunized with the LNP-mRNA construct. The authors observed strikingly lower viral loads and diminished lung pathology in mRNA-HB27-LNP-treated mice after infection with a lethal strain of mouse-adapted virus, as compared to mice receiving placebo (Fig. 1).[6] Similar results were observed in mice infected with a VOC, the Beta variant of SARS-CoV-2, and in infected hamsters. Hamsters are very useful for transmission studies and it will be important to assess the effect of these antibodies on virus loads in both donor and recipient animals.

mRNA-LNP constructs have been used previously in preclinical studies in the context of viral diseases such as human immunodeficiency virus (HIV), rabies virus, influenza virus, Zika virus, respiratory syncytial virus, and chikungunya virus (CHIKV).[7] LNP-mRNA constructs have several advantages. First, in pharmacokinetics studies, Deng et al. showed that serum levels of antibody are greater than those observed after treatment with the original mAb. The data also indicate that the LNP-mRNA encoded antibody has a greater half-life than directly administered protein. Thus, the antibody partially protected mice up to 63 days after immunization. Second, once the sequence of the mRNA encoding the heavy and light chains of an antibody of interest is determined, it is relatively simple and rapid to engineer cells expressing the antibody. Thus, both the speed and cost of development of LNP-mRNA particles are favorable compared to those of mAbs.

There are a few issues that still need to be considered. Probably most important is that the antibodies generated from LNP-mRNA are only as effective as the original antibody. Many of the mAbs used clinically, which were useful against the original strain of SARS-CoV-2, lost activity against the Beta, Delta and Omicron variants, with greatest loss of activity against the Omicron variant. Of approved antibodies, only sotrovimab, bebtelovimab and Evusheld (a mixture of modified AZD8895 and AZD1061) retained efficacy against the Omicron variant.[8] In the context of predominant Omicron infection, these would be the only ones of the presently approved antibodies that might be considered for development as LNP-mRNA-based therapy. The Fc and complement binding components of the antibodies formulated as Evusheld have been modified to have a longer half-life than other mAbs and therefore, Evusheld may be useful for prophylaxis in high-risk populations.[9] Evusheld formulated as an LNP-mRNA construct may be especially useful in clinical settings, if half-life is even further prolonged. A second issue is the LNP-mRNA molecules are generally delivered intravenously, which will limit its use to specific healthcare settings.[10] Additional studies to examine other routes of administration may enhance its widespread utility and should be considered.

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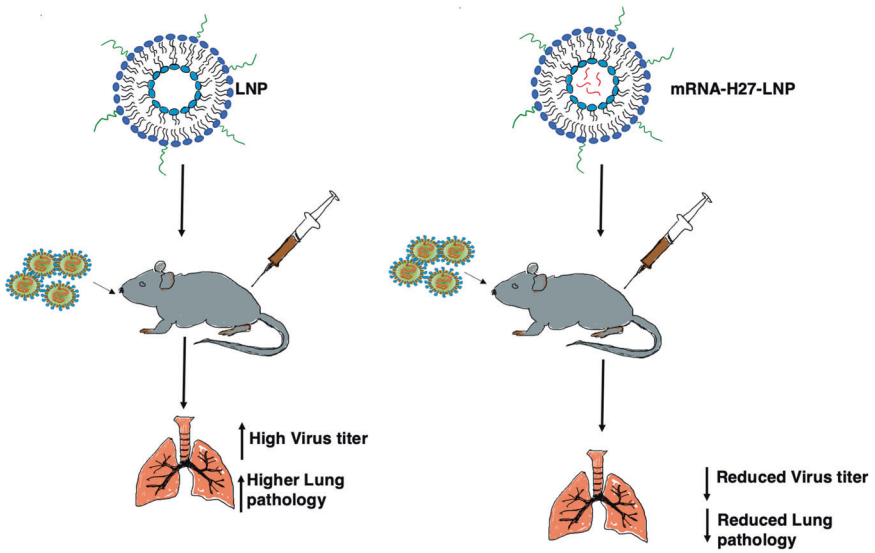

Fig. 1 LNP-mRNAs encoding SARS-CoV-2 antibody are protective after virus challenge. Mice were immunized with empty mRNA-LNP or mRNA-H27-LNP before infection with SARS-CoV-2. Mice receiving mRNA-HB27-LNP showed lower virus titers and reduced pathological changes in the lungs.

In summary, Deng et al. describe a novel approach to engineering virus-specific antibodies using LNP-mRNA technology. LNP-mRNA constructs are rapidly produced and by using host cells to express proteins, their generation is highly efficient. Because engineering these constructs is rapid, it will be possible to respond rapidly to the need for new antibodies for the prophylaxis and treatment of SARS-CoV-2 variants. The approach described by Deng et al. is cost effective and may be especially useful in settings with limited resources.

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COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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