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Mini Review

Circular RNA: The Research Direction of future Virus Vaccines?

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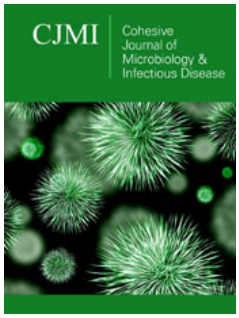

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Abstract

The SARS-CoV epidemic has been ongoing worldwide for three years since reported. During the epidemic, scientists worldwide have worked tirelessly to develop various vaccines and effective drugs. This short review focuses on the current state of vaccine research and discusses the future direction of vaccine development.

Introduction

With the spread of pandemics, the need for more effective protection is rising. Traditional inactivated vaccines and mRNA vaccines are coming into the limelight and becoming mainstream. This paper aims to discuss new directions and breakthroughs in vaccine protection in the face of infectious disease outbreaks and to provide ideas and possibilities for subsequent development.

Background

Since the new coronavirus pandemic in late 2019, the global death toll has reached millions, and the number of infected people has reached hundreds of millions. There are numerous ways to fight off the virus, from the short-term effectiveness of inactivated vaccines at the beginning to mRNA vaccines. However, in May this year, circ RNA vaccines came into the spotlight. Wei noted in his article that circ RNA induces many neutralizing antibodies and T cell replication in cellular immunity by expressing a trimeric RBD on the S protein. Compared to mRNA vaccines, circ RNA vaccines can induce a higher proportion of neutralizing antibodies and Th1-skewed T cell immune response through high levels of persistent antigen. More importantly, such neutralizing antibodies aimed to induce against Omicron, which means that this could be a new direction for future vaccine research [1].

Structure and Function

Due to the specific structure of the S protein surface and the possible existence of highly conserved and vulnerable regions within its RBD, a booster injection of a third shot led to a broad and effective enhancement of neutralizing antibody levels. More and more studies are beginning to confirm this idea. It also inspired us: can we achieve protection against the virus by continuously inducing antigen production and thus directing neutralizing antibodies to persist at high levels? Then Circular RNA comes in. Circular RNAs are a class of non-coding

RNAs with a circular structure and no terminal motifs, such as a cap at the 5' end and a poly-A tail at the 3' end. Circ RNAs were discovered in 1976 and proved highly conserved in species evolution during repeated sequencing and studies [2]. Based on its structural properties, circ RNA forms and expresses stably, to some extent even more stable than linear RNA, and is resistant to degradation by various RNA exonucleases. Also, circ RNA is more durable in protein expression than traditional linear RNA [3]. A significant advantage of circular RNAs over linear mRNAs is their stability. The circular RNA structure allows them to avoid recognition by the innate immune system and nucleic acid exonucleases, significantly reducing immunogenicity and providing higher stability.

Compared with Traditional Vaccines

Attenuated and inactivated vaccine

Traditional attenuated and inactivated vaccines are now successfully used to prevent various diseases. However, their drawback is also apparent: the potential virulence may become the causative factor for future disease outbreaks [4].

Protein vaccine

Protein vaccines are commonly used in emergency outbreaks of SARS-CoV-2 and have the advantage of being stable and easy to distribute. The rapid-onset robust immune response provides good and short-term protection from the virus. However, protein vaccines are weak in stimulating a T-cell response and require adjuvants. The S protein may have incorrect isomerization if not produced in mammalian cells [5].

DNA vaccine

DNA vaccines may sound like a viable option: low production costs and the ability to produce rapidly; induce B and T cell responses, and have a long shelf life; however, owing to their low safety profile and susceptibility to integration with recipient chromosomal DNA resulting in insertional mutations, DNA vaccines did not get widely applied [6].

mRNA vaccine

mRNA vaccines are vaccines that express antigens after delivery of mRNA to host cells. The cells use mRNA as a template to generate antigens using host cell translation mechanisms, build proteins through a translational process, and elicit B- and T-cell immune responses. Due to its high-yield in vitro transcriptional response, mRNA has the potential for rapid, inexpensive, and scalable manufacturing, significantly reducing development time and allowing for rapid response to epidemics. Compared to DNA vaccines, mRNA vaccines are superior because they do not interact with or integrate into the genome [7]. mRNA vaccines also have the advantages of not needing to deal with infectious viruses, causing fewer adverse reactions such as allergies, and being able to be produced quickly, making them a hot topic for vaccine research in recent years.

However, the unstable and inefficient delivery of mRNA in vivo has limited the application of this vaccine. Studies have extensively explored effective delivery systems for mRNA vaccines to prevent rapid degradation of mRNA and facilitate its entry into target cells. New delivery methods have been generated, such as the widespread use of Lipid Nanoparticle (LNP) carrier technology, which has solved the problem of mRNA delivery routes [8]. Nevertheless, there are still some questions about mRNA that still need people to address: for example, encoding only some fragments rather than the whole virus limits its immunogenicity; lack of interaction with RNA receptors in vivo may weaken immune stimulation; a Low-temperature environment is the ideal storage environment for mRNA vaccines, and in vivo administration and uptake of vaccines is challenging [9,10].

Circ RNA vaccine

Since cyclic RNA does not require the addition of a 5' cap and poly-adenylate tail (poly-A tail) at the 3' end, it may not be more complicated than synthesizing linear mRNA in the production process. Moreover, circular RNA folding produces a more compact conformation than linear RNA, and more circular RNA can be loaded using the same LNP, providing efficiency in the delivery of RNA therapeutics [11]. All in all, the development of circ RNA for vaccines seems to be full of rationale. First, circ RNA expression is stable and requires slight modification to express stably in eukaryotic cells [12]. Secondly, the unique loop structure of circ RNA (the poly-A tail at the 3' end connected to the 5' end of the cap at the upstream head) allows the connected covalent bond to confer the ability of circ RNA to resist decline. Also, researchers have viewed circ RNA as a method to regulate gene expression. Through stable expression and translation in rhesus monkeys and mice, circ RNA exerts a special protective effect in animals potentially infected with SARS-CoV-2. In addition, the team also demonstrated that synthetic circ RNA could play against SARS-CoV-2 pseudo virus by expressing neutralizing antibodies and hACE2 decoys [13]. These results above provide a bright prospect for further research on circ RNA vaccines against viral infections. circRNA vaccines have a tremendous upside and a broad market prospect in the future.

Future outlooks

As the research progressed, some researchers elucidated the mechanisms of circ RNA. Of course, we still need more studies to explain further questions:

A. How to effectively control the expression level of circ RNA to prevent its over-expression and cause unintended effects

B. Can we continue to reduce the immunogenicity of cyclic RNA itself and generated during the production process?

C. In the face of SARS-CoV-2, which has many mutation sites and is prone to mutation, will the circ RNA vaccine that has been synthesized and implanted in the body continue to work without adverse effects? Although circ RNA research has reached significant progress, unfortunately, most of the current research is still in the experimental or preclinical stage, and the action of circ RNA in humans has not been in clinical trials. However, considering the future direction of viral vaccine

development, the circ RNA vaccine has a relatively far-reaching prospect. We expect that with the help of capital, this innovative technology will enter the clinical development stage soon and show its potential to treat diseases.

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References

1. Qu L, Yi Z, Shen Y, Lin L, Chen F, et al. (2022) Circular RNA vaccines against SARS-CoV-2 and emerging variants. Cell 18(10): 1728-1744.
2. Kristensen LS, Andersen MS, Stagsted LW, Ebbesen KK, Hansen TB (2019) The biogenesis, biology and characterization of circular RNAs. Nat Rev Genet 20(11): 675-691.
3. Wesselhoeft RA, Kowalski PS, Anderson DG (2018) Engineering circular RNA for potent and stable translation in eukaryotic cells. Nat Commun 9: 2629.
4. Vetter V, Denizer G, Friedland LR, Krishnan J, Shapiro M (2018) Understanding modern-day vaccines: what you need to know. Ann Med 50(2): 110-120.
5. Keech C, Albert G, Cho I, Robertson A, Reed P, et al. (2020) Phase 1-2 trial of a SARS-CoV-2 recombinant spike protein nanoparticle vaccine. N Engl J Med 383: 2320-2332.
6. Chavda VP, Hossain MK, Beladiya J, Apostolopoulos V (2021) Nucleic acid vaccines for COVID-19: a paradigm shift in the vaccine development arena. Biologics 1(3): 337-356.
7. McIvor RS (2011) Therapeutic delivery of mRNA: the medium is the message. Mol Ther 19: 822-823.
8. Miao L, Li L, Huang Y, Delcassian D, Chahal J, et al. (2019) Delivery of mRNA vaccines with heterocyclic lipids increases anti-tumor efficacy by STING-mediated immune cell activation. Nat Biotechnol. 37: 1174-1185.
9. Polack FP, Thomas SJ, Kitchin N, Absalon J, Gurtman A, et al. (2020) Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine. N Engl J Med 383: 2603-2615.
10. Baden LR, El Sahly, Essink B, Kotloff K, Frey S, et al. (2021) Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. N Engl J Med 384: 403-416.
11. Chen X, Lu Y (2021) Circular RNA: Biosynthesis. Front Bioeng Biotechnol 9: 787881.
12. Wesselhoeft RA, Kowalski PS, Parker H, Huang Y, Bisaria N (2019) RNA circularization diminishes immunogenicity and can extend translation duration *In Vivo*. Mol Cell 74(3): 508-520.
13. Li C, Zhan W, Yang Z, Tu C, Hu G, et al. (2022) Broad neutralization of SARS-CoV-2 variants by an inhalable bispecific single-domain antibody. Cell 185(8):1389-1401.