Popular Article

SELF-REPLICATING RNA VIRUS VECTORS FOR VACCINATIONS

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ABSTRACT

Self-amplifying RNA viruses are characterized by a single-stranded RNA (ssRNA) genome that is enclosed in a protein capsid and envelope structure. RNA viruses may carry positive or negative sense genomes, as seen in the case of alphaviruses and flaviviruses, or negative sense genomes as seen in the case of rhabdoviruses and measles viruses. However, genomes of RNA viruses can function in the cytoplasm without transporting nucleic acids to the nucleus. If the infecting newly introduced ssRNA genome has positive polarity, translation can start right away. While the production of a positive-strand RNA template is necessary for negative-sense RNA molecules. All self-amplifying viruses with RNA as a genome initiate the replication process by expressing their non-structural genes, which results in the generation of the RNA replicon, an RNA replication complex. The robust RNA replication that occurs within cells that are infected is caused by this complex. Strong sub-genomic promoters have been found to enable a single RNA molecule to produce approximately 200,000 copies of its own. This unique property has been used to create expression vectors from self-amplifying RNA viruses that have been used in primary cells, in-vivo research, and a variety of mammalian and non-mammalian cell lines.

Keywords: Self-replication, single-stranded RNA virus, vectors, *in vivo* research

I. INTRODUCTION

Traditionally, live attenuated and inactivated vaccines were employed to combat infectious diseases. Nowadays, so many types of new-generation vaccines are being developed due to the increased knowledge and techniques in various fields of science. In recent years, a variety of self-amplifying RNA virus vectors have been used in attempts to produce vaccines, aiming to combat various kinds of infectious diseases. One of self-amplifying RNA's (RepRNA) most significant features is its ability to replicate multiple times, mimicking virus reproduction and providing an important advantage over inactivated or non-replicating vaccines. To prevent the formation of progeny viruses, RepRNA is extracted from virus genomes containing defects. RepRNA effectively duplicates and translates the antigens it has encoded, leading to the production of neutralizing antibodies that offer defense against a range of diseases.

Several RNA viral vectors based on alphaviruses, flaviviruses, and rhabdovirus, were already engineered to develop vaccines against various diseases by incorporating genes of surface viral proteins. The various expression systems for different RNA viruses were developed. For instance, the Semliki Forest virus (SFV) and alphavirus have three expression systems namely the replication-deficient system, replication-proficient system, and DNA layered system, each with

its mechanism and advantages. Vaccine development attempts were done using ss RNA viral vectors for various viral diseases that endanger the life of the host like human immunodeficiency virus (HIV), Influenza, Ebola, severe-acute-respiratory-syndrome coronavirus (SARS CoV), etc. These vaccines showed increased stimulation of the immune system generated neutralizing antibodies against targeted antigens and conferred different levels of protection in various animal models (Fig. 1). Specific target antigens like nanoparticles (NPs) for HIV, hemagglutinin (HA) for influenza, glycoprotein (GP) for Ebola, and S protein and GP for SARS CoV were used to be incorporated into the engineered RNA viral vectors. These ssRNA viral vectors are also employed to develop vaccines against non-viral disease-causing agents like *Mycobacterium tuberculosis*, *Bacillus anthracis*, *Clostridium botulinum*, *Brucella abortus*, *Listeria monocytogenes*, *Staphylococcus* sp., etc with promising results.

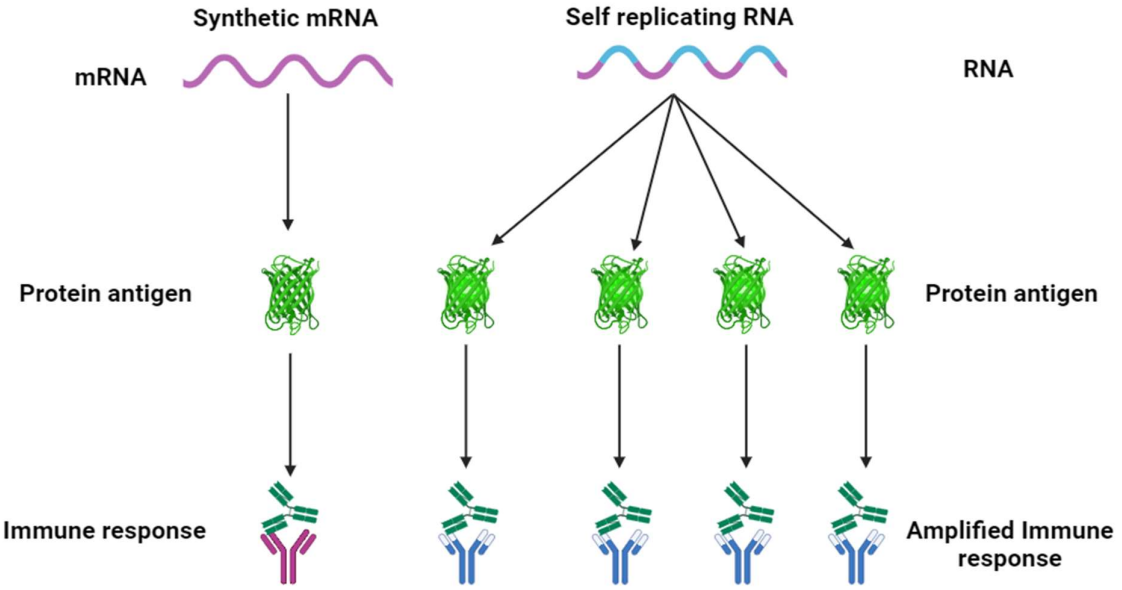

Fig. 1: Self-Replicating RNA Virus Vaccines Resulting in Amplified Immune Response with Similar Dose

II. DELIVERY OF SELF-AMPLIFYING RNA'S

Various cell types can absorb naked mRNA and rapidly express it. For vaccine administration to be effective, an understanding of cellular endocytic pathways is essential. When it comes to establishing and maintaining the balance of immunological defense, dendritic cells (DC) play an important role in determining the effectiveness of vaccination therapy. Because of this, DCs are crucial targets for the delivery of vaccines, especially RNA vaccines. Although the future potential of self-amplifying replicon RNA (RepRNA) vaccines encounters difficulties because of their susceptibility to RNase degradation. RepRNA vaccinations need to be delivered to the translation site via the proper cytosolic pathway, similar to mRNA vaccines. Endosomal or proteasomal processing is necessary for the transport of antigens, however, this processing cannot guarantee the survival of an RNA vaccine or its necessary delivery to the cellular translation machinery. Virus-like replicon particles (VRPs) have been used as a delivery system to address the issue. Nevertheless, this strategy needs specialized infrastructure and might be constrained by stability and cell tropism concerns.

The synthetic delivery of vaccine antigens has increased during the past two decades, especially when biocompatible and biodegradable nanoparticulate delivery

vehicles have been employed. The delivery carriers may consist of lipoproteins, lipids, polysaccharides, or combinations of them. Understanding DC requirements for interaction with delivery vehicles and subsequent intracellular distribution to RNA translation sites is essential for the successful delivery of RepRNA to DCs using nanoparticles. The composition of the delivery vehicle is designed to shield the RepRNA from RNases by encapsulating it, making it easier for it to reach DCs, and maintain a level of compaction that allows it to make contact with the ribosomal translation machinery. Formulations containing nanoparticles have demonstrated abilities to aid in the uptake of proteins by DCs, whether it is drugs or antigens. Gold microparticles have also been used to carry replicon RNA, however they don't have the same nanoparticle characteristics or biodegradability. Utilizing cationic delivery systems, including cationic liposomes, effectively encapsulates nucleic acids to create polyplexes and lipoplexes and transfers RNA for translation. In this respect, chitosan-based nanogels have also been employed. Techniques influencing the architectures of nanoparticles are being investigated to improve interaction with DCs.

III. CONCLUSION

Compared to traditional vaccines, the use of ssRNA viral vectors has many advantages that make them an appealing option for both therapeutic and prophylactic uses. Researchers have demonstrated that the use of ssRNA viral vectors results in the generation of neutralizing antibodies, protecting specific infectious agents. The findings suggest positive future potential for the use of ssRNA viral vectors. Since only the necessary antigen gene is engineered, researchers can avoid the burden of handling highly contagious agents in the lab. Furthermore, considering the viral RNA spontaneously degrades in 3–5 days, there is minimal concern about the incorporation of viral genes into the host genome. To ensure RNA stability, more research is necessary to optimize dosage, adjuvant composition, and delivery methods.

IV. REFERENCES

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