Review Article

Lessons to Learn from the COVID-19 Pandemic: Recent Advances in mRNA Vaccines Against Viral Diseases

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Abstract | The most effective way to prevent infectious viral diseases is through vaccination. The use of mRNA technology in vaccine development has proven to be a highly effective approach that can be utilized to rapidly develop vaccines against infectious viral pathogens. This technology has the potential to revolutionize vaccine development, offering a more efficient and cost-effective approach that can be tailored to specific viral strains. Moreover, mRNA-based vaccines offer several advantages over conventional or molecular-based vaccine types. The mRNA vaccine only encodes the target viral protein, with no infection hazard or even nucleic acid integration. Furthermore, mRNA vaccines can stimulate both specific cellular and humoral immunity in a short time scale to combat a life-threatening or emerging viral disease. This review will comprehensively cover the recent advances in mRNA vaccine production, the delivery methods, and the essential compositions added to the mRNA vaccines to enhance efficacy and stability. This information ultimately would pave the way to better thinking to combat viral infectious diseases.

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Introduction

Vaccines are highly effective in preventing the spread of infectious diseases, saving countless lives each year (Pollard and Bijker, 2021). Moreover, vaccines have been extensively implemented in recent decades, eliminating life-threatening viral diseases, including smallpox, and significantly reducing the incidence of polio, measles, and other infectious diseases. The World Health Organization reported that vaccination annually prevents at least 2 million deaths from measles, influenza, and pertussis (Sahin *et al*., 2014; Chaudhary *et al*., 2021). However, conventional vaccines have limitations for disease prevention and treatment, including time-consuming and complex processes (i.e., live, inactivated, dendritic cell vaccines), the risk of escape mutants and limited T-cell response (i.e., peptide vaccines), risk of integration and anti-DNA autoantibodies formation (i.e., DNA vaccines), which limit their usage for human vaccinations. All these drawbacks necessitate to think better for the next generation of vaccines with suitable format that shows promise in preventing and treating infectious diseases (Wang *et al*., 2021).

Since the emergence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), messenger RNA (mRNA) vaccination has surged and has been found to provide outstanding immune responses for curbing the contemporary COVID-19 (Sahin *et al.*, 2020; Baden *et al.*, 2021). The mRNA vaccines are single nucleotide sequences that serve as a template for efficient protein translation without the fear of possible integration (Pardi *et al.*, 2018). mRNA vaccines typically utilize the body's cells to naturally induce innate and adaptive immunity. This vaccine production technology allows for proper post-translational modifications and full functionality of protein products, ensuring proper translation folding and assembly of multimeric and versatile proteins that cannot be produced in common bioreactors. mRNA also permits the transfer of the produced products into both intracellular and transmembrane trafficking pathways to their suitable cellular locations to enhance the target immune response accordingly (Heil *et al.*, 2013; Kowalski *et al.*, 2019; Jackson *et al.*, 2020). From a commercial perspective, mRNA vaccines offer rapid development and large-scale production through a cell-free process. This advantage is due to the highly productive transcription reaction in vitro, which is also extremely cost-effective (Karikó *et al.*, 2008; Thess *et al.*, 2015; Guan and Rosenecker, 2017).

It is important to note that while mRNA vaccines have shown great promise, they are still in their infancy compared to conventional vaccines due to their poor stability and immunogenicity, which limit their usage *in vivo* (Kauffman *et al.*, 2016; Maruggi *et al.*, 2019; Pollard and Bijker, 2021; Wang *et al.*, 2021). Therefore, further research and development on the delivery and immunogenicity of mRNA vaccines would allow for their widespread use in vivo, especially in life-threatening diseases.

It is evident that mRNA vaccines hold great promise in preventing viral diseases caused by agents such as SARS-CoV-2, influenza viruses, and other life-threatening viral models. This review will discuss the main modifications made to mRNA vaccines to improve their efficiency and delivery methods and the recent progress of mRNA vaccination to viral diseases. Modifications to the methylated cap, the mRNA's coding and non-coding parts, the poly(A)-tail, and the advanced delivery methods to increase stability will be described. These data could ultimately pave the way to curb viral infectious diseases.

Key components for maximum mRNA vaccine production

Cap structure

Once the mRNA is transcribed, a cap structure is attached to the 5′ end. The cap structure plays a crucial role in the mRNA stability of the transcripts, which supports further RNA regulatory steps, including mRNA translation, splicing, and transportation in the cell (Roundtree *et al.*, 2017). The typical eukaryotic cap structure (commonly named as cap0) is composed of a modified nucleobase (i.e., methylated guanosine at N7 position; m7G cap); this modified nucleobase attached to the adjacent nucleobases (1+) with 5′-5′ triphosphate linkage (Ogino and Green, 2019). It is important to note that modified nucleobases, especially m7G cap structure in the mRNA, support differentiation between self and nonself RNA (exogenous RNAs, including viral RNA). Innate immune sensors, including Pattern Recognition Receptors (PRRs) such as RIG-I (not identified in chickens) and MDA5, usually sense the 5′ diphosphorylated and triphosphorylated transcripts (uncapped transcripts), which support RNA degradation in type I interferon pathway (Ivashkiv and Donlin, 2014; Santhakumar *et al.*, 2017). Therefore, the presence of a cap structure is pivotal to be included in the mRNA vaccine.

From the commercial perspective, mRNA vaccine capping can be generated using either recombinant vaccinia to generate the wild-type eukaryotic cap structure (Kyrieleis *et al.*, 2015) or through the introduction of an artificially synthesized cap (i.e., chemically synthesized cap analogue structures), including Anti-Reverse Cap Analog (ARCA) and Clean-Cap®, which provide enhanced half-lifetime and translation efficiency (Sahin *et al.*, 2014; Chaudhary *et al.*, 2021). Interestingly, the advantage of using the cap analogues was leveraged in the major mRNA vaccines used to compact COVID-19, including BNT162b1 and BNT162b2 (BioNTech/Pfizer) (Sahin *et al.*, 2020).

5′ and 3′ untranslated regions

Although the upstream and downstream sequences of coding regions are non-coding sequences (i.e., are not translated into proteins), the 5′ and 3′ untranslated regions (UTR) have pivotal roles for efficient translation and stability, respectively (Mignone *et al.*, 2002). The most common mRNA vaccines are designed with 5′ UTR to contain the eukaryotic Kozak (CA/GCCAUGG, the underlined sequence

is the start codon), which is usually associated with enhanced translation initiation (Simonetti *et al.*, 2020). Similarly, the 3′ UTR is usually designed to contain a long half-lifetime eukaryotic β-globulin mRNA that increases the stability of the in-vitro transcribed-mRNA (IVT-mRNA) (Linares-Fernández *et al.*, 2021).

Coding region

From the facts described earlier, there is no doubt that the coding sequence of the designated ORF itself significantly impacts the translation efficiency. Using the most common (i.e., do not use rare) codons has the privilege of a maximum translation resulting from optimal RNA structure and folding. The most likely strategy is using the codon of highly expressing mammalian genes (Mauro and Chappell, 2014). Learning for the lesson of COVID-19 vaccination, incorporating N1- methyl pseudouridine or pseudouridine instead of uracil has been noticed to enhance translation capacity and stability (Karikó *et al.*, 2008), which will be described later in this review.

Poly (A) tail

Adding poly A tail is one of the most common modifications added co-transcriptionally in the nucleus. The poly-A tail size ranges from 20-250 nucleotides in the mammalian transcriptome. The primary function is to protect the mRNA from the degradation processes, and the length of the poly-A tail acts as a timer for mRNA stability; the lengthy tail is associated with improved stability (Eckmann *et al.*, 2011). Typically, the poly-A tail is added to IVT-mRNA by linking the A string using poly-A polymerase or by adding poly T sequence to the template DNA backbone (Eckmann *et al.*, 2011).

mRNA vaccine delivery approaches in vivo

For mRNA to function appropriately, it is essential to avoid degradation by nucleases outside the cell, remain intact, and enter it. However, since individual nucleic acid molecules are not efficiently taken up by cells, different techniques have been proposed for mRNA delivery using viral and non-viral delivery systems. Non-viral delivery systems for mRNA can be divided into mRNA delivery encapsulated in liposomes (the most common method of delivery of mRNA vaccines so far) or various polycationic polymers and mechanical mRNA delivery across the cell membrane using electroporation, gene guns, ultrasound, or high-pressure injection, which can be used both *in vivo* and *in vitro* (Pardi *et al.*, 2018).

Lipid nanoparticles (LNPs, Liposomes)

The lipid nanoparticles are usually comprised of four main components; the ionizable cationic lipid, lipid-conjugated poly-ethylene glycol (PEGylated lipid), cholesterol, and phospholipids that compose the two lipid bilayers (Hou *et al.*, 2021). The primary way mRNA delivery systems enter the cell is through endocytosis. This involves intricate processes that determine the intracellular location of mRNA. When the cell membrane invaginates, mRNAs get inside the endosomes. These endosomes then mature and fuse with lysosomes, which contain hydrolytic enzymes and create an acidic environment that may destroy the delivery system and liberate nucleic acid. Therefore, the delivery system components should provide an optimal time interval between the mRNA exit from the endosomes and the nucleic acid degradation (Sahin *et al.*, 2014). It is essential to mention that the approved vaccines against COVID-19 that deliver the mRNA encoding the SARS-CoV-2 Spike -protein (and others, see Table 1) usually use LNPs, including BNT162b2 (BioN-Tech/Pfizer) and mRNA-1273 (Moderna) vaccines (Sahin *et al.*, 2020; Baden *et al.*, 2021); however, the ratio between each component of the LNPs differ between different vaccines and the producing company.

Polymers

Although polymeric materials are an excellent method of delivering nucleic acid into the cells, they are not as widely used for nucleic acid delivery as lipids because they are hard to degrade *in vivo*. Therefore, scientists strive to find an alternate example of polymers for vaccine delivery; chief among those is chitosan. Chitosan is a versatile biopolymer derived from chitin. It contains chemical groups that can be modified for a wide range of potential applications. Chitosan nanoparticles have a positive surface charge and mucoadhesive properties, allowing them to attach to mucous membranes, release drugs, and support further biodegradation (Mohammed *et al.*, 2017).

Physical/mechanical delivery methods

Various physical manipulations are also adopted to deliver nucleic acids into cells, such as electroporation, ultrasound, and gene guns. Electroporation is the most effective mRNA delivery method, preventing unwanted immune responses and reducing cellular toxicity (Hashimoto and Takemoto, 2015).

Table 1: *Preclinical and clinical trials for mRNA vaccines against viral diseases.*

S. No.	Virus model	mRNA	Antigen	Delivery method	Preclinical and clinical phases	Reference
1	SARS-CoV-2	mRNA-1273	Full-length Prefusion S protein	Lipid Nanoparticle (LNP)	Phase III/ complete	(Baden *et al.*, 2021)
		BNT162b1, BNT162b2	PBD of S protein	LNP	Phase III/ complete	(Mulligan *et al.*, 2020)
2	Zika virus	mRNA-1325	Glycoproteins of ZIKV	-(unknown)	Phase I	(Richner *et al.*, 2017)
		mRNA-1893	Glycoproteins of ZIKV	LNP	Phase II	
3	HIV	AGS-004	HIV-1 Surface antigen	Dendritic cell	Phase II	(Pardi *et al.*, 2019)
4	Influenza viruses	VAL-506440	Membrane-bound form of the hemagglutinin glycoprotein	LNP	Phase I	(Chaudhary *et al.*, 2021)
		VAL-339851	HA	LNP	Phase I	(Chaudhary *et al.*, 2021)
		mRNA-1010-1020-1030	-	-	Phase I	(Chaudhary *et al.*, 2021)
5	Cytomegalovirus	mRNA-1647, mRNA-1443	gB	LNP	Phase I	(Nelson *et al.*, 2020)
6	Respiratory syncytial virus	mRNA-1345	F protein	-	Phase II/III	(Espeseth *et al.*, 2020)
7	Rabies	CV7202	Glycoproteins of Rabies virus	LNP	Phase I	(Schnee *et al.*, 2016)
8	Human metapneumovirus and parainfluenza virus type 3	mRNA-1653	Full-length membrane-bound fusion proteins of hMPV and PIV3	LNP	Phase I	(Chaudhary *et al.*, 2021)
9	Pseudorabies virus		gD	LNP	Mice	(Jiang *et al.*, 2020)
10	Chikungunya virus		Structural proteins (C-E3-E2-6K-E1)	LNP	Mice	(Chaudhary *et al.*, 2021)
11	Hepatitis C virus		E1 and modified E2	LNP	Mice	(Jiang *et al.*, 2020)
12	Nipah virus		Hendra virus glycoproteins	LNP	Syrian Hamsters	(Lo *et al.*, 2020)
13	Powassan virus		prM and E	LNP	Mice	(VanBlargan *et al.*, 2018)
14	Herpes simplex type 1		gC2, gD2, gE2	LNP	Mice	(LaTourette *et al.*, 2020)
15	Varicella-zoster		gE	LNP	Non-human primates	(Monslow *et al.*, 2020)
16	Dengue Virus		NS	LNP	Mice	(Roth *et al.*, 2019)

Although the recent progress in mRNA delivery is slow, the contemporary pandemic would be a good chance for innovation of further vaccine delivery methods. Moreover, combining different mRNA delivery systems may be the most efficient approach. Further research is needed to optimize mRNA delivery.

Recent progress of mRNA vaccines against viral diseases

mRNA therapeutics are currently being developed for various applications, and vaccines for infectious diseases represent one of the most advanced uses. In preclinical trials and clinical use, most mRNA vaccines are administered by injecting the skin, muscle, or subcutaneous tissue. Once administered, various immune or non-immune cells take up the mRNA and translate it into antigens that are then displayed to T and B cells. The mRNA and delivery vehicle used together enhances the immunogenicity and efficacy of mRNA vaccines. Fifteen mRNA vaccine candidates against infectious diseases had entered clinical trials by the start of 2020 (Chaudhary *et al.*, 2021); the recent progress in the mRNA vaccination has been summarized in Table 1.

Conclusions and Recommendations

mRNA vaccines are a safe and promising platform for preventing infectious diseases. They offer significant advantages over other vaccines, such as low

reactogenicity, efficient immune response activation, and rapid, inexpensive, and scalable production. The mRNA vaccine platform also allows easy target gene replacement, reducing the time lag between epidemic outbreaks and vaccine release. However, mRNA vaccination is still in its infancy, and further investigations are needed to improve efficacy and in vivo delivery methods. As stated above, using modified nucleobases such as pseudouridine and methylated pseudouridine are promising tools to enhance immunogenicity and stability. Moreover, using other methylated nucleobases could be beneficial for enhancing immunogenicity. Chief among those using the methylated adenosines at N6-position (m6A), N1-position (m1A), methylated ribose to any nucleotide (Nm) which has been reported to have enhanced immunogenicity and reduced innate immune recognition as exogenous/nonself RNA in various viral models as we and others reported earlier (Bayoumi *et al*., 2020; Tsai and Cullen, 2020; Bayoumi and Munir, 2021a, 2021b). Therefore, using these modified bases would be promising to be incorporated in the potential mRNA vaccines.

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Novelty Statement

Combating infectious diseases is an urgent need. Therefore, there is a pressing need to conduct further research and development of more stable and immunogenic mRNA vaccines. Such vaccines would serve as a "magic bullet" to enable their widespread use, especially in the fight against emerging life-threatening diseases. For the first time, this review provides comprehensive information required for mRNA vaccination.

Author's Contribution

MMB contributed to the conceptualization, formal analysis, writing of the original draft, and revised version. The author contributed to the article and approved the submitted version.

Conflict of interest

The authors have declared no conflict of interest.

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