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Research Article

mRNA based vaccines as an alternative to conventional vaccine approaches

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Abstract

In recent years, vaccines based on mRNA are providing protection against infectious diseases and treatment for cancer. These vaccines offer many advantages as compared to traditional vaccines. They can be rapidly and easily manufactured at a low cost and are reliable for administration. These vaccines can generate both cell-mediated and humoral immunity. Their administration is still limited because of the risk of quick degradation and ineffectiveness after delivery. Technological advancements are recently being made to overcome these issues. This review summarizes current mRNA vaccine development, safety concerns, advances in delivery systems, clinical trials, and various therapeutic applications of mRNA vaccines.

Introduction

Vaccination is one of the most efficacious medical techniques for the prevention and control of the infectious disease. Thousands of deaths worldwide can be prevented by the use of vaccines [1]. Due to the excessive use of vaccines, the prevention of several contagious diseases such as smallpox, polio, measles, mumps, rubella, and other infant diseases has been achieved [2]. Traditional vaccines comprise live attenuated, inactivated pathogens and subunit vaccines [3]. The adaptive immune response is generated by inoculating the individual with the inactivated or attenuated form of the pathogen or its component [4]. Although these vaccines are effective against numerous ailments, they cannot eradicate pathogens like malaria parasite Plasmodium falciparum, Hepatitis C, HIV (human immunodeficiency virus), and cannot prevent non-infectious disorders like cancer [3]. The attenuated virus vaccine manufacturing process is slowly followed by complex purification and testing which demand considerable investment. These vaccines have different growth conditions for different viruses in cell culture and purification procedures also vary.[5] Live attenuated vaccine administration can also cause diseases in immunocompromised patients and there is a probability of reversion into active pathogen as a result of back mutation [2].

Non-viral vaccines

Non-viral nucleic acid vaccines based on mRNA generate an immune response as immunization with the live microbe and provide a better alternative to conventional vaccines. The foremost successful in-vivo administration of mRNA was carried out in a mice model in 1990 and the expression of the protein was observed [6]. The preliminary analysis of mRNA did not induce any progress in the development of mRNA vaccines because of the obstacles such as instability of mRNA, strong innate immunity, and strenuous in-vivo delivery of mRNA [7].

Safety and efficacy of mRNA vaccines

Ever since researchers have used advanced techniques for the industrial production of safe and effective mRNA vaccines for tumor and viral disease therapeutics. The safety and efficacy and production of mRNA-based vaccines made them more advantageous than conventional vaccines [1]. Referring to

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safety, infectious agents are not involved in the production and these vaccines do not induce innate responses while generating both humoral and cell-mediated immune responses. Moreover, after protein production, mRNA vaccine strands are degraded. In relation to efficacy, through structural alterations, mRNA with more stability and high translational ability is produced. mRNAs are formulated into carrier molecules for efficient delivery and expression into the cell [1,8] mRNA vaccine production is established in the laboratory and can be produced speedily at a low cost making them suitable for fighting against pandemics such as SARS-CoV-2 (Severe acute respiratory syndrome coronavirus 2) [3]. In 1997, mRNA-based drug organization was inaugurated for the first time [8]. Over the last few years, the mRNA vaccine field is emerging with the accumulation of preclinical date and the initiation of human clinical trials [1].

Classification of mRNA-based vaccines

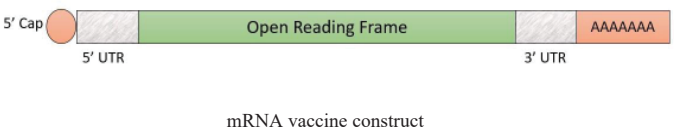
There are two categories in which mRNA vaccines are classified: conventional non-replicating mRNA and virally derived, self-amplifying RNA. Non-replicating mRNA vaccine constructs are of small size, simple design, and contain vaccine antigen encoded by its open reading frame, preventing undesirable immune responses. Self-replicating (Self-amplifying) RNA encodes additional replicate components in addition to the desired antigen. The replicase complex is derived from another virus such as alphavirus that permits the replication generating many copies of target mRNA resulting in increased gene expression [1,9]. Low doses of self-amplifying mRNA showed greater antigen expression in comparison with conventional mRNA against Influenza, Rabies, and Ebola [10].

Synthesis of mRNA

mRNA is composed of a 5' cap, 5' UTRs (untranslated regions), an ORF (open reading frame)which begins with a start codon and ends with a stop codon, 3' UTRs, and a poly(A) sequence as shown in Figure 1. [11,12] mRNA is manufactured in vitro by transcribing a synthetic DNA template with the help of DNA-dependent RNA polymerase [13]. The DNA construct that encodes immunogen can be synthesized once the genetic sequence of the pathogen and the target antigen is known [14]. The efficient translation of mRNA is ensured by cap and polyadenylate tail structures. 5′ caps which is 7-methylguanosine triphosphate prevent exonuclease degradation of mRNA and poly-A tail and provide stability [3].

Modifications in mRNA vaccine structure

The structural components of the mRNA vaccine can be modified to improve stability and translational efficiency. 3' and 5' UTR on the sides of the open reading frame are responsible for increasing the half-life and expression level of the mRNA vaccine [15]. These untranslated regions contain regulatory sequences which regulate mRNA stability [15]. The size of the poly-A tail can be increased for improving mRNA stability and translation [16]. Codon optimization such as uridine depletion and increased GC content can be done for increasing protein translation [17]. Also, the secondary structure of mRNA can also be changed by codon optimization for protecting it against endonuclease degradation [15]. Intracellular mRNA delivery can be increased by using lipids and proteins as delivery vehicles [18].



mRNA vaccine construct

Figure 1: The structure of mRNA vaccine template transcribed from DNA construct in vitro. This mRNA consists of 5'cap, 3' and 5' UTR regions on the sides of nucleotide sequence encoding target immunogen and poly-A tail.

Another approach for improving mRNA stability and translation efficiency is the use of modified nucleosides in the mRNA construct. e.g., using pseudouridine instead of uridine prevents innate immune responses and increases translation [19]. Throughout the process of in vitro mRNA transcription, several immature mRNAs are produced which can activate the innate immune system and reduce mRNA translation. These contaminants can be removed by performing HPLC (high-pressure liquid chromatography) and FPLC (fast protein liquid chromatography) and pure mRNA is obtained [17,20]. The purification of in-vitro transcribed mRNA is done by performing gel electrophoresis and then chromatography which excludes nucleosides triphosphates that are not incorporated [21].

Delivery systems

Up to the present time, the major hurdle in the development of mRNA vaccines was the unavailability of an efficient delivery system [3]. mRNA vaccine delivery into the cell is really challenging as naked RNA is readily degraded by extracellular nucleases upon recognition by the immune system [22,23]. Moreover, mRNA cannot proceed through the cell membrane because of its large size and negative charge [23]. It can also induce serious inflammatory and immunogenic reactions [3]. Thus for the efficient mRNA vaccination, specific systems must be established for the delivery of mRNA into the targeted cell [24].

Naked mRNA delivery

Naked mRNA is delivered into the body by injecting mRNA solution intramuscularly. mRNA can also be injected intradermally or subcutaneously. Another way of mRNA vaccine administration is through microneedles which are soluble [25]. Instant translation of mRNA occurs by combining with the ribosomes present in the cytosol [26]. However, for avoiding mRNA degradation by ribonucleases some chemical modifications should be done. Also, for the progress of mRNA across the cell membrane, neutralization of the negative charge on it should be done [25].

Lipid nanoparticles based delivery

The most usual vectors for the delivery of non-viral vaccines are lipids or lipid-like compounds.

Uptake and expression of mRNA vaccines in cells increase many times in contrast to naked RNA upon fusion with

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lipid nanoparticles because it provides protection against degradation [27-28]. Lipid nanoparticles also contain phospholipids, polyethylene glycol, and cholesterol [29]. In 2018 the first therapeutic RNA delivered by lipid nanoparticles was authorized by the FDA [7]. Metabolism of components of lipid nanoparticles is also necessary to prevent the accumulation in tissues [30].

Delivery through polymer-based vectors

Different cationic dendrimers which are polymeric macromolecules are used as vectors for the delivery of mRNA. Some of the polymers used are PEI (polyethyleneimine), PBAEs (poly beta-amino esters), and PAMAM (polyamidoamine) dendrimer. Out of these, PEI the water-soluble polymer is commonly used for mRNA delivery [8]. These polymers can efficiently pass through the cell membrane, because of their spherical 3-dimensional structure. However, their use is limited as they result in toxicity [31].

Peptide-based delivery

Peptides also have been used widely for efficient cellular transport of mRNA. mRNA Complex with nuclear protein protamine also stabilizes it against degradation [32].

Target cells for delivery

Dendritic cells which act as antigen-presenting cells and generate adaptive immune responses are an ideal target for mRNA delivery. Dendritic cells present antigens to both helper T cells and cytotoxic T cells as well as B cells [25]. Administration of mRNA vaccines is commonly done by injections but needle-free techniques can also be used [3]. mRNA is administered by intramuscular injection and after translation, antigenic proteins are presented by dendritic cells. mRNA antigens can be loaded into the dendritic cells obtained from the patient and then these engineered dendritic cells are again transferred into the patient's blood. For the loading of mRNA, the electroporation technique is used for cancer therapy [26].

Dendritic cells present the antigen to CD4+ T cells and CD8+ T cells [33]. CD4+ T cells result in the activation of humoral immune response and help CD8+ T cells [34]. B cell activation results in antibody production which is necessary for the neutralization of foreign antigens [19].

Administration routes

Several administration routes are used for mRNA vaccines e.g., intravenous, intraperitoneal, intradermal (ID), and intramuscular [35]. Intravenous injections are responsible for quick delivery through the circulation of blood [36]. High doses of mRNA can be administered by intramuscular injections but intravenous is more efficient [36].

mRNA vaccines for infectious diseases

mRNA vaccines are being developed for both therapeutic and prophylactic use against infectious diseases [3]. Clinical trials are conducted for different infectious disorders such as HIV, Influenza, Rabies virus, Zika virus, and COVID 19 as shown in Tables 1,2 [8]. Pandemics such as COVID 19 indicate the critical requirement for the quick and large-scale production of vaccines for which mRNA vaccines prove to be useful [3]. mRNA vaccine can also be designed for various pathogens and its production is cost-effective [29].

Conventional vaccines for influenza virus are less effective in elder people and can cause death because of back mutation [33]. Moreover, influenza viruses evolve quickly making them difficult to eliminate. For combating influenza viruses, mRNA vaccines are produced which encode the conserved regions of viral proteins [8].

HIV which causes a life-threatening syndrome AIDS (acquired immunodeficiency syndrome) has remained incurable for many years [8]. This is because of enveloping protein of HIV which shows incredible antigenic variation [23]. Currently, mRNA vaccines are being developed encoding HIV proteins but specific target antigens and proper delivery systems are required for an effective vaccine against HIV [23].

The mRNA vaccine for zika virus is under clinical trials and there is no licensed vaccine for this virus [41].

The effectiveness of mRNA vaccines was first demonstrated in mice against tuberculosis in 2004 [42]. BioNTech with the Bill & Melinda Gates Foundation announced to initiate the clinical trials for tuberculosis mRNA vaccine this year [43].

SARS-CoV-2 infection caused a global pandemic by affecting several thousands of people worldwide [44]. For SARS-CoV-2 the mRNA vaccine translates for the spike protein of COVID 19 [45]. The effectiveness of the mRNA vaccine against SRS-CoV-2 is 95% [46]. Recently two vaccines are approved for COVID 19 by US FDA [47]. These are BNT162b2

Table 1: mRNA vaccines clinical trials for infectious diseases.

Disease Type	Vaccine Name	NCT Number	Antigen	Phase	Status	Ref.
Zika Virus	mRNA- 1325	NCT03014089	-	I	Completed	[26]
Rabies	CV7201	NCT02241135	Rabies virus glycoprotein	I	Completed	[7]
	CV7202	NCT03713086	RABV-G protein	I	Active, Not recruiting	[7,8]
HIV Infection	iHIVARNA-01	NCT02413645	HTI	I	Completed	[8]
	iHIVARNA-01	NCT02888756	HTI	II	Terminated	[8,26]
Influenza	VAL-506440	NCT03076385	H10N8 HA	I	Completed	[8,7,37]
COVID-19	BNT162b2	NCT04368728	Spike Protein	I/II	Recruiting	[8,26]
	mRNA-1273	NCT04470427	Spike Protein	III	Recruiting	[26,38]
	CVnCoV	NCT04674189	S-2P	II	Recruiting	[39,40]

Table 2: Clinical trials of mRNA vaccines against Cancer.

Cancer Type	Antigen	NCT Number	Phase	Status	Ref.
Colorectal cancer	CEA	NCT00228189	I/II	Completed	[1,8]
Acute myeloid leukemia (AML)	WTI	NCT00834002	I	Completed	[26]
	Leukemia associated antigens	NCT00514189	I	Terminated	[8]
	WTI	NCT01686334	II	Recruiting	[8]
Melanoma	Melan-A, Mage-A1	NCT00204516	I/II	Completed	[1]
	gp100, tyrosinase	NCT00243529	I/II	Completed	[1,8]
Metastatic Prostate cancer	PSA, PAP, survivin	NCT01446731	II	Completed	[11]

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and mRNA-1273. BNT162b2 vaccine was generated by Pfizer and BioNTech which is now injected intramuscularly in two doses. an mRNA-1273 vaccine that encodes spike protein was developed by Moderna, NIAID, and BARDA [25]. Their success was made possible with the help of nanoparticle encapsulation for efficient delivery [48].

mRNA vaccines for cancer therapy

The objective of cancer immunotherapy is to generate anti-cancer immunity in the host and alter the tumor microenvironment resulting in tumor reductio [17]. The target of mRNA vaccine in cancer immunotherapy is tumor-associated antigens (TAAs) or tumor-specific antigens (TSA) which are expressed in cancerous cells [8,11]. This anticancer vaccine can be directly injected or tumor antigens can be loaded on dendritic cells for delivery [11]. RNActive® vaccines which contain TAAs are in phase I and II clinical trials for the treatment of multiple solid tumors. These vaccines are safe to use in patients and generate an immune response [17]. FDA has designated BNT111 as a fast track for clinical translation as it generate strong antigen-specific response in patients of melanoma [49]. mRNA vaccines can provide immunity against cancers as different neoantigens can be designed for each patient [50].

Conclusion

The mRNA vaccine technology possesses great potential than conventional vaccines for the treatment of emerging infectious diseases.

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