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MRNA VACCINES APPLICATION IN CANCER IMMUNOTHERAPY: A COMPREHENSIVE REVIEW

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ABSTRACT

mRNA therapy is a novel anticancer strategy based on in vitro transcription (IVT), showing potential for treating malignant tumors, which remain the second leading cause of mortality worldwide. Cancer immunotherapies aim to activate host anti-tumor immunity and modify the suppressive tumor microenvironment, reducing tumors and increasing patient survival rates. Cancer vaccines, acting on tumor-associated or tumor-specific antigens (TAA or TSA), offer effective prophylactic and therapeutic options due to immunologic memory, providing specific, safe, and well-tolerated therapy. However, challenges exist, such as allergic reactions to PEG components in LNP-encapsulated mRNA, which can induce severe allergic reactions due to IgE-mediated responses. Repeated vaccine administration may also cause liver toxicity due to slow degradation of delivery materials. In conclusion, mRNA vaccines significantly advance cancer immunotherapy by inducing antitumor adaptive immune responses and suppressing tumor cells. Personalized mRNA vaccines, produced using next-generation sequencing (NGS) technology, represent a new direction in precision cancer therapy. Future studies should focus on overcoming existing challenges and combining mRNA cancer immunotherapy with other treatments to enhance clinical outcomes andpersonalized cancer care.

KEYWORDS: *mRNA vaccines, Immunotherapy, LNP, IVT.*

INTRODUCTION

Cancer immunotherapies have shown therapeutic efficiency, especially after the approval of six checkpoint inhibitors and two CAR-T cell therapies by the FDA. Their aim is to activate host anti-tumor immunity and modify the suppressive tumor microenvironment, reducing tumors and increasing patient survival rates. Cancer vaccines, targeting tumor-associated or tumor-specific antigens (TAA or TSA), offer effective prophylactic and therapeutic options by inhibiting malignant cells and achieving chronic therapeutic responses due to immunologic memory.[1,2]

Currently, there are four main types of cancer vaccines: those based on tumor or immune cells, peptides, viral vectors, and nucleic acids. Messenger RNA (mRNA) vaccines have emerged as a promising alternative to DNA vaccines for preventing infectious diseases and treating cancer.

Compared to traditional treatments, mRNA cancer vaccines offer increased specificity, efficacy, and fewer adverse effects, making them a promising new approach in cancer immunotherapy.[3]

Exciting early-phase results are emerging from preclinical and clinical trials evaluating various therapeutic mRNA cancer vaccines. These vaccines are designed to encode crucial components of the immune response, including tumor-specific antigens (TSAs), tumor-associated antigens (TAAs), and immune modulatory factors. This targeted approach aims to activate the immune system to exert antitumor effects. Currently, multiple therapeutic mRNA vaccines are undergoingphase 1/2 trials, showing promising early results in advancing cancer immunotherapy.[4,5]

This review evaluates the therapeutic efficiency of mRNA vaccines by providing an overview of their pharmacological action and optimization mechanisms. It discusses current challenges in vaccine implementation and proposes strategies to overcome these challenges to enhance therapeutic efficiency and immune responses.

PHARMACOLOGICAL ACTION OF mRNA VACCINES

mRNA is a single-stranded macromolecule that carries genetic information from DNA in the cell nucleus and is regulated by ribosomes in the cytoplasm, where it is translated into proteins. When an mRNA cancer vaccine

is injected, the enclosed mRNA is translated by ribosomes to produce proteins. These proteins undergo post-translational modifications to become correctly folded functional proteins that regulate the immune system. Exogenous mRNA entering the cytoplasm triggers reactions similar to those of endogenous mRNA. After translation, the proteins are further modified and transported into subcellular compartments.[6]

INDUCTION OF INNATE IMMUNE RESPONSE
IMMUNE CELL RECOGNITION[7]

Upon injection, mRNA and its associated delivery components within the vaccine are recognized as foreign substances by various Pattern Recognition Receptors (PRRs) located on the cytoplasm, cell membranes, and endosomes. These PRRs, such as Toll-like receptors (TLRs) including TLR3, TLR7, and TLR8, are predominantly expressed on Antigen Presenting Cells (APCs). Upon activation by the mRNA components, TLRs initiate a cascade of events by detecting Pathogen-Associated Molecular Patterns (PAMPs), triggering an innate immune response. This response leads to the production of proinflammatory cytokines and co-stimulatory molecules on APCs. Ultimately, these molecular signals facilitate the generation of adaptive immune responses involving B cells and T cells, which are critical for effective cancer immunotherapy.

The immunogenicity of in vitro transcribed (IVT) mRNA vaccines primarily hinges on the activation of TLR7 and TLR8, which are expressed on B cells, macrophages, and dendritic cells. Activation occurs through the myeloid differentiation primary response 88 (MYD88)/TLR7-dependent signaling pathway, which enhances the adaptive immune responses induced by mRNA vaccines. This pathway plays a pivotal role in stimulating B cells to mount robust adaptive immune responses against tumor-specific antigens encoded by the mRNA vaccines, thus bolstering their therapeutic potential in cancer treatment.

NON-IMMUNE CELL RECOGNITION

Upon administration, exogenous mRNA is recognized by Cytoplasmic Retinoic acid- inducible gene-like receptor (RLR) and Melanoma differentiation-associated gene 5 (MDA5). These receptors initiate the expression of cytokines and chemokines, leading to recruitment of innate immune cells to the site of mRNA injection.

Early induction of cytokines is critical for vaccine efficacy but can also induce adverse effects such as autoimmune reactions or weaken immune responses to mRNA vaccines. To mitigate these issues, techniques like incorporating unsaturated lipid tails, dihydroimidazole junctions, and cyclic amine heads can activate antigen-presenting cells (APCs) through the Intracellular Interferon gene pathway instead of the Toll-like receptor (TLR) pathway. This method of APC activation helps reduce cytokine-induced autoimmune responses while enhancing the antitumor effects of mRNA vaccines.

INDUCTION OF ACQUIRED IMMUNITY RESPONSE

Upon administration, mRNA encoded proteins are taken up by antigen-presenting cells (APCs) such as macrophages via endocytosis or phagocytosis. Within APCs, these proteins are processed into antigenic phagocytic vesicles or endosomes, which are then presented on the cell surface through Major Histocompatibility Complex (MHC) I and II molecules on dendritic cells. APCs present exogenous antigens to CD4+ T cells via MHC II and cross-present them to CD8+ T cells via MHC I, known as cross-priming. This process activates cytotoxic T lymphocytes (CTLs), crucial for the antitumor immune response. CD4+ T cells further support B cells and CD8+ T cells by secreting cytokines that amplify their antitumor effects.

Effective antigen presentation is essential for inducing acquired immunity. mRNA vaccines encode tumor-associated antigens (TAAs) expressed on cancer cells, including tissue differentiation antigens like human carcinoembryonic antigens and MART-1, tumor germline antigens such as NY-ESO-1 or MAGE-3, tumor-specific mutational antigens like EGFR and MUC1, tumor cell overexpressed proteins such as MUM-1 and β-catenin, and viral proteins like EBV and HPV. mRNA vaccines encoding neoantigens resulting from genetic abnormalities leading to tumor development are particularly potent, as these antigens are recognized by T cells due to somatic mutations, enhancing the vaccine's therapeutic effectiveness.

RATIONAL DESIGN AND OPTIMIZATION OF mRNA CANCER VACCINES

A typical mRNA consists of mainly 4 regions.

- A cap flanked by 5’ untranslated region (UTR)
- 3’UTR
- An open reading frame (ORF) encoding cancer antigens in mRNA cancer vaccines.
- Poly A tail

Modification can be applied to the components which can lead to increase in stability, translationalefficiency, and immunostimulatory properties. Design and optimization can be applied in 3 ways.

Design and optimization of[12]

- Coding Region
- Noncoding region
- Delivery Formats.

DESIGN AND OPTIMISATION OF CODING REGION: Codon composition of a mRNA affects the translational efficiency. Substituting the rare codons with regular synonym codons that contain similar tRNA in the cytosol accelerates translation and increase yield. However rare codon optimization for nucleic acid therapies may have potentially serious consequences which should be monitored. Another strategy which can

be applied is the enrichment of GC content which translates at a rate of 100 times than with low GC content. Chemical modification of nucleosides has also been applied which increases the translational efficiency but decreases the immunogenicity.[13]

DESIGN AND OPTIMISATION OF NON-CODING REGION: The 5' and 3' untranslated regions (UTRs) adjacent to the coding region play crucial roles in mRNA stability. Optimization of these components enhances mRNA efficiency and half-life by avoiding START codons in the 5' UTR that disrupt ORF translation and minimizing stable secondary structures that impede ribosome recruitment and codon recognition. Shorter 5' UTRs can improve translation efficiency,while incorporating the 3' UTR from alpha and beta globulin mRNAs enhances mRNA stability and translation. The 5' cap structure is vital for mRNA vaccines, facilitating effective protein synthesis by regulating pre-mRNA splicing, nuclear export, and protecting RNA from exonuclease cleavage. 5' capping is achieved using a vaccinia virus capping enzyme or by incorporating synthetic cap or anti-reverse cap analogs during or after transcription process.[14]

The POLY A TAIL has a significant role in maintaining the stability of mRNA by reducing the degradation of RNA. The length of Poly A tail is directly proportional to the translational efficiency of mRNA. There are two ways to add a poly(A) tail to in vitro transcribed (IVT) mRNA i.e.

(i) Extending the IVTmRNA after transcription by using recombinant poly(A)polymerase

(ii) Including poly(A) tail encoding DNA template from which IVT mRNA is transcribed. mRNA transcribed from a DNA template yields transcripts with a defined poly(A) tail length, whereas the enzymatic polyadenylation process yieldsmRNA transcripts with variable length poly(A) tails. In addition, deadenylating by poly(A)-specific nucleases can be inhibited by the incorporation of modified nucleotides into the PolyA tail.

OPTIMISATION OF mRNA DELIVER SYSTEM: Generation of IV mRNA transcript is followed by process of delivery into cytoplasm of the target cells. Due to negatively charged naked structure of RNA and large molecular size mRNA is prone to degradation by nucleases and cannot cross cell membrane. To overcome this following delivery strategies has been employed

i. Ex vivo loading of mRNA in to Dendritic cells.
ii. Direct injection of mRNA with or without a carrier.

Ex vivo loading of mRNA in to Dendritic cells: Dendritic cells (DCs) are key antigen-presenting cells in the immune system, crucial for initiating immune responses against specific tumor antigens encoded by mRNA. DCs can internalize naked mRNA via various endocytic pathways, and in ex vivo settings, this process is often enhanced using electroporation to achieve high transfection efficiency without the need for carrier molecules. Ex vivo transfection of mRNA has been shown to predominantly induce cell-mediated immune responses. In this approach, DCs are transfected with mRNA encoding tumor-associated antigens (TAAs) or total tumor RNA, and after loading, these cells are reinfused into the patient to trigger an immune response against the tumor. While ex vivo loading offers efficient and targeted transfection into cellular targets, it is costly and labor-intensive for vaccination purposes.[15]

Direct injection of mRNA with or without a carrier: In this method, native mRNA is directly injected, inducing antigen-specific antibodies and a T cell response. This approach offers precise and inexpensive loading. However, the vaccine platform suffers from a short extracellular half-life due to rapid degradation of naked mRNA by ubiquitous RNA. Viral vector technologies used for mRNA loading face significant drawbacks, such as preexisting or anti-vector immunity, which can affect vaccine efficacy. To overcome these limitations, various physical and synthetic methods have been developed. These include the gene gun method, electroporation, virus-like particles produced in yeast, and synthetic delivery vehicles like liposomes, lipoplexes, and cationic polymers. These methods protect mRNA from degradation, enhance cellular uptake, and improve vaccine delivery.[16]

Lipid nanoparticles: One of the advanced and widely used mRNA delivery vector which is widely accepted after the implementation of vaccine against SARS CoV-2. Formulated with Nano sized lipid particles which can efficiently deliver mRNA intracellular by fusing with the lipid bilayer of early endosomes thereby transporting into cytosol. Lipid nanoparticles typically 100nm size which typically consists of four components.[17]

- Ionizable lipids
- Lipid linked polyethylene glycol (PEG)
- Cholesterol
- Phospholipids.

Ionizable lipids: A major component determining the potency of LNPs is their hydrophilic head group, hydrocarbon chains for self-assembly, and linkers connecting the head groups to the chains. These components are unionized within LNPs, forming electrostatically stable lipoplexes with mRNA. They maintain a neutral pH (7.4) in systemic circulation but get protonated in the early endosomal region (pH 6.5), facilitating endosomal fusion and cytosolic release. The lack of substantial positive charge at physiological pH improves pharmacokinetics, increasing the half- life in the bloodstream and enhancing accumulation in target tissues like solid tumors. However, some components may induce inflammation and cell toxicity by activating the TLR pathway.[18]

Polyethylene glycol (PEG) Lipid: Generally, PEG comprises less than 2.5% of the total formulation in lipid

nanoparticles (LNPs). Its structure includes a hydrophilic PEG polymer conjugated with a hydrophobic lipid anchor. PEG is located on the surface of the LNP, with the lipid domain hidden and the PEG domain protruding. It plays a crucial role in balancing circulation time and cellular uptake, preventing particle aggregation, determining particle size, and improving storage stability. However, balancing PEG quantity is essential, as high concentrations can hinder RNA delivery into cells. Additionally, the development of anti-PEG antibodies raises concerns about potential allergic reactions.[19]

Phospholipids and Cholesterol: Both are involved in the regulation of structural integrity and phase transition behavior of the LNPs. Both components are unlikely to elicit significant innate immune recognition and inflammatory responses as they have been present naturally in mammalian cell membranes.[20] The main advantage of mRNA- vaccine is the modularity and versatility of the platform. LNP compartments and their ratios, targeting moieties and overall lipid mRNA ratios can be tailored and optimized for different targets and applicants.[21]

mRNA vaccine administration routes: Administration rout of vaccine in a therapy has a Variousroutes of mRNA administration offer unique advantages and challenges for cancer therapy. Intramuscular administration stands out for its ease, tolerance, and flexibility in dosing, making it a common choice in clinical settings. Intravenous administration is preferred for its ability to reach multiple lymphoid organs and facilitate repeated dosing, ensuring sustained immunity. Intranasal delivery effectively targets peripheral antigen-presenting cells, despite limitations in nasal cavity volume. Intranodal injection provides direct access to lymphatic cells but requires specialized equipment and skilled handling. Intratumoral administration induces local immune responses but faces challenges in uniformly distributing the vaccine in large tumors. Intradermal and subcutaneous routes target regional antigen-presenting cells but may cause severe local reactions and require careful management. Evaluating the kinetics of vaccine distribution through clinical trials is crucial for optimizing treatment strategies and understanding immune responses, thereby enhancing the efficacy of mRNA vaccines in cancer immunotherapy.

BIOMARKERS

The mechanism of mRNA vaccines diverges from traditional cancer therapies like chemotherapy or radiation by focusing on immune system activation for immunotherapy. Assessing mRNA vaccine efficacy relies on novel biomarker approaches. These include monitoring immune response indicators such as cytokines, chemokines, and immune cell populations. Flow cytometry analyzes cell phenotypes, functionalities, and activation statuses, while ELISPOT assays measure cytokine responses. Immunological assays like peripheral cytokine profiles and tetramer analysis assess antigen-specific CD8 T cells. T cell receptor sequencing and PCR evaluate immune repertoire diversity, and single-cell RNA sequencing identifies immune cell subsets and gene expressions. Circulating tumor DNA levels serve as crucial biomarkers for treatment response monitoring, correlating reductions with prolonged survival. Integrating these evaluations and standardizing protocols for immunologic and radiologic endpoints are crucial for enhancing the effectiveness of immunotherapy in cancer patients.[27]

Challenges: Adverse drug reactions related to mRNA vaccines

Clinical research has shown that allergic reactions to mRNA vaccines are rare, though some severe cases occur. All current mRNA delivery systems in clinical trials use lipid nanoparticles (LNPs). The exact compositions of the LNPs for the authorized SARS-CoV-2 mRNA vaccines (mRNA-1273 and BNT162b2) have been disclosed. One LNP encapsulated with polyethylene glycol (PEG) components has a higher risk of allergic reactions, as PEG can trigger IgE-mediated responses and recurrent allergies due to its high molecular weight, increasing drug sensitivity and severe reactions.[28] Recently severe allergic reactions after bowel preparation with drug containing PEG3350 were observed. In addition, doxorubicin liposomes containing PEG were also reported to produce allergic reactions.[29]

Repeated administration of vaccines in tumor treatment can potentially induce liver toxicity due to the slow degradation of delivery materials, such as MC3 with a dilinoleic alkyl tail. Ongoing research aims to develop safer delivery systems and stimulate natural biological delivery methods to mitigate adverse drug reactions. These efforts have led to the development of new delivery systems like MNPs, nanohydrogels, self-assembling polymeric micelles, and bio-inspired nanovehicles.[30]

CONCLUSIONS

In conclusion, mRNA vaccines have significantly advanced cancer immunotherapy by inducing antitumor immune responses. Personalized mRNA vaccines, enabled by next-generation sequencing (NGS), offer new precision cancer therapy avenues. Computational approaches predict neoantigens and their HLA presentation. However, instability and in vivo delivery challenges hinder clinical application. Continuous clinical trials have mitigated some limitations, but challenges remain. Future studies should focus on overcoming these hurdles with technological innovations and combining mRNA cancer vaccines with other immunotherapies to improve clinical outcomes and personalized cancer treatment.

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