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Contributed Mini Review

Diverse nanoparticles deliver mRNA to enhance tumor immunotherapy

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Limited efficacy and severe side effects often result in suboptimal outcomes to solid tumor therapies. In contrast, the reduced side effects and potential long-term benefits of tumor immunotherapy offer promise, notwithstanding the challenges of variable patient responses and immune-related adverse events hindering its widespread application. Recent advances in mRNA technology have revolutionized cancer immunotherapy. The versatility of mRNA as a vaccine and therapeutic agent is evident in it overcoming the limitations of traditional approaches by reducing *in vivo* toxicity and enhancing immune response activation. The synergy between mRNA technology and immunotherapy is increasingly being utilized to improve cancer treatment efficacy. One critical aspect of maximizing the therapeutic impact of mRNA-based treatments is the selection of an effective delivery system. Due to their size properties and material characteristics, nanoparticles offer a transformative solution, enabling the targeted and efficient delivery of mRNA to tumor tissues or immune cells. This precision delivery mechanism significantly enhances the effectiveness of immunotherapy, and represents a significant advance in cancer treatment. This review aims to explore how mRNA delivery via nanoparticles enhances tumor immunotherapy. Examination of its applications and challenges provides insights and strategic perspectives to advance this innovative therapeutic approach. [BMB Reports 2025; 58(3): 124-132]

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INTRODUCTION

The development of clinical research in tumor immunotherapy faces challenges, such as low overall responsiveness and immune-related adverse reactions (1). Enhancing the efficacy of tumor immunotherapy and reducing toxic side effects are key issues that urgently need to be addressed, necessitating further research to explore and optimize immunotherapy strategies (2, 3). mRNA technology offers the advantage of simultaneously reducing *in vivo* toxicity and activating both humoral and cellular immunity, overcoming the limitations of traditional tumor immunotherapy (4, 5). Therefore, mRNA technology is expected to play a significant role in treating various diseases, with tumor immunotherapy being a primary focus (6).

In tumor immunotherapy, the activation and enhancement of immune cells are crucial, and different types of immune cells, such as dendritic cells (DCs), T-cells, and natural killer (NK)-cells, the stars of the immune cell family, play pivotal roles in tumor immunotherapy. However, the influence of multiple factors often hinders their optimal anti-tumor effect, limiting their efficacy in tumor immunotherapy. mRNA drugs, as potential drugs with good application prospects, can encode tumor-associated antigens, specific antigens, antibodies, or receptors. mRNA enters the cytoplasm and is translated into proteins, thereby inducing specific immune responses to prevent disease and provide treatment. A particularly important advantage of mRNA technology is that it can reduce *in vivo* toxicity while simultaneously activating humoral and cellular immunity, making up for the shortcomings of tumor immunotherapy. The effective delivery of mRNA to specific cells and its effects are expected to enhance the immune response of immune cells. Based on this technique, mRNA technology will inevitably participate in the treatment of various diseases, with tumor immunotherapy likely being the first key battlefield. More and more studies are combining mRNA therapy with tumor immunotherapy to achieve significant therapeutic effects.

However, mRNA therapy also faces certain limitations. First, as mRNA molecules are easily degraded *in vivo*, the instability of mRNA results in a shorter duration of action within cells, and requires frequent administration to maintain therapeutic

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efficacy. Second, from immunogenicity, mRNA may trigger strong immune responses, which may affect treatment efficacy, and lead to adverse reactions. Third, the delivery efficiency is low, and mRNA molecules cannot actively cross the cell membrane barrier, which seriously hinders the cytoplasmic delivery efficiency of mRNA. To overcome these difficulties, appropriate mRNA delivery systems are crucial to ensure the effectiveness and safety of mRNA drugs in treatment strategies. Currently, nanoparticle delivery of mRNA drugs is one of the most mature delivery methods, and has been widely used in immunotherapy for tumors.

Different types of nanoparticles applied to mRNA delivery display individual characteristics. For example, lipid nanoparticles offer good biocompatibility and stability, and can effectively deliver mRNA into cells. By adjusting their chemical composition and structure, polymer nanoparticles can efficiently encapsulate and release mRNA. The application of different types of nanoparticles in mRNA delivery provides multiple strategies for tumor immunotherapy. The selection of appropriate types of nanoparticles and the design of a reasonable delivery system can effectively improve the stability and delivery efficiency of mRNA, thereby enhancing the effectiveness of tumor immunotherapy while providing new ideas and strategies for tumor treatment, with excellent prospects for application.

USE OF mRNA VACCINES DELIVERED BY NANOPARTICLES FOR TUMOR IMMUNOTHERAPY

Nanoparticles in drug delivery systems

The urgent need to develop efficient targeted delivery systems for mRNA is driven by the limitations of mRNA stability and delivery efficiency (7). Leveraging their permeability and retention properties has demonstrated the superior efficacy of nanodrug delivery systems over conventional chemotherapy in targeting malignant tumors while minimizing toxic side effects (8, 9). Fig. 1, and Supplementary Table 1 of the Supplementary Information (SI), show a diverse array of nanoparticles and delivery strategies that research into mRNA delivery has designed to enhance tumor immunotherapy (10). Nano delivery systems that are based on nonviral vectors are highlighted for their ease of preparation and low immunogenicity, offering a promising method for mRNA delivery (11).

Lipid nanoparticles as leaders in the field of cancer immunotherapy

The cell membrane is mainly composed of lipids, and lipid vesicles can pass through the cell membrane. RNA that is encapsulated in them can thereby be released into the cytoplasm (12). Thus, the vesicle should first be a positively charged lipid that is capable of binding negatively charged RNA. Lipid nanoparticles (LNPs) are spherical vesicles that are formed of one or more phospholipid bilayers, and are composed of ionizable cationic lipids, phospholipids, cholesterol, polyethylene glycol (PEG) lipids, and mRNA (13). The preparation of LNP is well known to depend on its ability to self-assemble, as lipid components through intermolecular interactions are spontaneously organized into nanostructured entities. First, the negatively charged nucleic acid and positively charged lipid are bound by electrostatic binding; the assembly is then carried out by hydrophobic interaction and van der Waals interaction between the lipid components, to form the LNP (14). In the lipid bilayer, hydrophobic drugs can be embedded in the hydrophobic region, while hydrophilic drugs can be contained in the aqueous internal region of the liposome (15). Their stable nanostructures in physiological fluids together with their ability to fuse with negatively charged endosomal membranes have resulted in lipid-based nucleic acid delivery systems enjoying wide use as nonviral vectors (16). Naked mRNA is easily degraded by nucleases in body fluids, making it difficult to accumulate in target tissues. Additionally, the immune system can recognize and degrade exogenous nucleic acids, triggering an immune response (17, 18). To address these challenges, lipid nanoparticles (LNPs) are used to encapsulate mRNA drugs to provide protection against degradation, enhance delivery to target cells, reduce toxicity to normal tissues, prolong drug residence time, and improve drug effectiveness. mRNA-LNP therapy holds great promise for the treatment of malignant tumors (19). Recent developments in LNPs for mRNA delivery involve intradermal, subcutaneous, or intramuscular injection to present antigens to T-cells, expose antigens to B-cells, and activate immune responses (20). Once LNPs enter target cells, their mRNA escapes the cell membrane to be translated into target proteins in the cytoplasm, thereby playing a crucial role in tumor immunotherapy.

Compared to other types of nanoparticle-polymer nanoparticles, lipid nanoparticles have their individual advantages. Firstly, they can maintain a high concentration of drugs on the skin surface and tissues for a long time, improve drug stability, and reduce drug irritation to the skin. Secondly, lipid nanoparticles offer good biocompatibility and degradability, which allows them to circulate in the body for a longer period of time, and reduces the risk of non-specific binding with plasma proteins and other substances. Last, but not least, lipid nanoparticles display the ability to cross the blood-brain barrier and target various drug delivery pathways, which many polymer nanoparticles are unable to match. These advantages mean lipid nanoparticles present broad application prospects in the field of drug delivery.

Despite these advantages, the LNPs system is limited. Its limitations include low drug loading and biodistribution, leading to high uptake in the liver and spleen (21). As well, most mRNA is transported from endosomes to lysosomes to be degraded, with only a small fraction escaping into the cytoplasm, which poses a significant challenge in LNPs applications. But as nanotechnology continues to advance, lipid nanoparticles will enable more efficient drug delivery, making mRNA-LNP-based therapies increasingly popular in tumor immunotherapy (22).

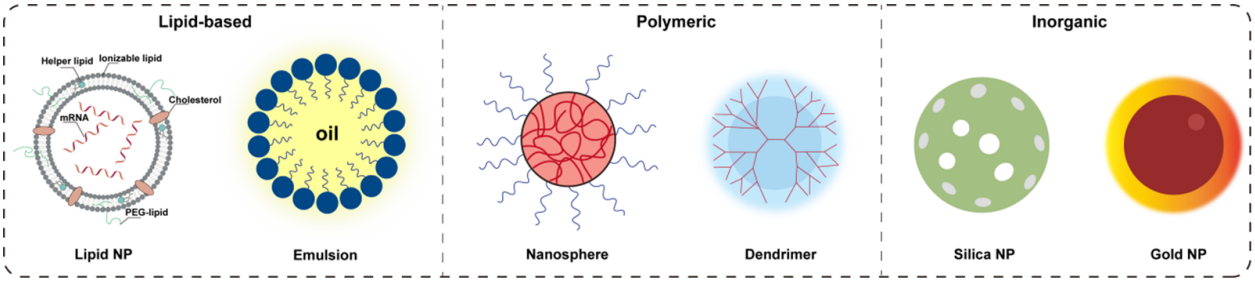

Fig. 1. Schematic of different types of nanoparticles. The following types of nanoparticles are shown: lipid-based nanoparticles (Lipid NP and Emulsion nanoparticles), Polymeric nanoparticles (Nanosphere and Dendrimer nanoparticles) and Inorganic nanoparticles (Silica NP and Gold NP) (31).

Polymeric nanoparticles for drug delivery-the rising star of cancer immunotherapy

Polymeric nanoparticles (PNP) are another important member of nanoparticle carriers. They are prepared from biocompatible and biodegradable polymers ranging (10 to 1,000) nm, and drugs are dissolved, embedded, encapsulated, or attached to nanoparticle matrices (23). However, lipid nanoparticles and polymer nanoparticles offer better performance in terms of biocompatibility, drug loading ability, and stability, while polymer nanoparticles offer unique advantages when special materials or designs are required. For example, chemical or physical modification of their surface can achieve targeted delivery to specific tissues. To improve the efficacy of drugs and reduce side effects, they have received extensive attention in the field of nanomedicine (24). The unique properties of polymeric nanoparticles (PNPs), such as small size, high surface area, and tunable pores, have resulted in PNPs showing great promise in the field of drug delivery (25). Such nanoparticles can encapsulate drugs within their core, embed them in a polymer matrix, chemically couple them to the polymer, or bind them to the nanoparticle surface (26). This versatility allows the efficient protection of drugs from enzymatic degradation, control of release rates, biodegradability, biocompatibility, and specific targeting (27). One recent advance in the field is the development of a polymeric nanoparticle platform to deliver mRNA-based drugs (28). Researchers have combined mPEG-PLGA copolymers with a cationic lipid-like material to create nanoparticles that are capable of delivering PTEN mRNA to tumor sites. This innovative nanodrug has been shown to effectively restore tumor suppressor function and induce immunogenic cell death in tumor cells, thus offering new possibilities for cancer immunotherapy (29).

Compared to lipid nanoparticles, the advantage of polymer nanoparticles lies in their ability to improve drug stability, while reducing drug degradation and denaturation, and decreasing drug irritation. Secondly, as many polymer nanoparticles are constituted of biodegradable polymers, they can be biodegraded after completing their drug delivery tasks, so reducing their impact on the environment. Finally, polymers can be synthesized from monomers with different properties, allowing the engineering of polymer nanoparticles to produce products of various shapes, sizes, and surface properties, such as porosity, thus providing more options and possibilities for drug delivery. The biocompatibility, stability, biodegradability, high customizability, and surface modification potential of polymer nanoparticles have revealed their numerous advantages in the field of drug delivery.

While polymeric nanoparticles have shown excellent potential, they also face limitations, such as low drug concentrations at target sites, unclear targeting mechanisms, and safety concerns *in vivo* (29). Further optimization and development are needed to address these challenges, and maximize the potential of polymeric nanoparticles for drug delivery. Overall, the development of polymeric nanoparticles for nucleic acid drug delivery holds great promise to advance tumor immunotherapy (30). With continued research and optimization, these nanoparticles have the potential to significantly improve the delivery of nucleic acid drugs, and enhance the efficacy of cancer treatments (31).

Overall, different types of nanoparticles offer individual strengths and advantages. In practical applications, the choice of nanoparticle depends on specific application requirements and drug properties to select the most suitable nanoparticle, and achieve the best therapeutic effect.

NANOPARTICLE DELIVERY OF mRNA ENHANCES THE IMMUNE RESPONSE OF IMMUNE CELLS, THEREBY IMPROVING TUMOR IMMUNOTHERAPY

mRNA vaccines are designed to activate the immune system by introducing RNA sequences that encode tumor antigens, effectively targeting and destroying cancer cells (32, 33). LNPs, a widely utilized non-viral vector for mRNA vaccine delivery, have emerged as a promising solution. LNPs protect mRNA from enzymatic degradation, facilitate uptake by antigen-presenting cells (APCs), and enhance the immunogenicity of mRNA-encoded proteins (34). LNPs offer high loading efficiency, large surface area, and excellent biocompatibility, facilitating

the cellular uptake of mRNA and escape from endosomes (35). Fig. 2 shows that furthermore, nanoparticle carriers shield mRNA from enzymatic degradation during *in vivo* delivery, extend its circulation time, and enhance delivery efficiency. These properties collectively contribute to the potential of mRNA vaccines in cancer therapy, and highlight the critical role of nanoparticle-based delivery systems in advancing the field of precision medicine for cancer treatment.

Nanoparticle delivery of mRNA enhances DC antigen presentation to elicit potent anti-tumor immune responses and improve cancer immunotherapy

Dendritic cells (DCs) play a crucial role in the immune response against tumors by presenting tumor antigens to T-cells, and activating an anti-tumor immune response (36). However, the efficiency of DC maturation and antigen presentation can be limited, which impacts the overall effectiveness of tumor immunotherapy (37, 38). To address this challenge, Qi and colleagues (39) have developed supramolecular lipid nanoparticles (SMLNPs) that are able to co-deliver nucleic acids and small-molecule drugs for targeted drug release. Their study utilized β-cyclodextrin (β-CD)-modified ionizable lipid (Lip-CD) to co-deliver mRNA and R848 to DCs. By activating the Toll-like receptor 7/8 (TLR7/8) pathway, they were able to enhance antigen presentation and promote antitumor activity. The incorporation of the R848 adjuvant into the mRNA vaccine through non-covalent host-guest complexation significantly improved DC maturation and antigen presentation post-vaccination, leading to more robust anti-tumor immune response, and the inhibition of tumor growth. This innovative approach of integrating immunomodulatory molecules into nano-delivery platforms based on a supramolecular strategy represents a promising new avenue to enhance the efficacy of mRNA vaccines in tumor immunotherapy. By leveraging the unique properties of SMLNPs to co-deliver multiple therapeutic agents and precisely target DCs, researchers can potentially improve the overall outcome of cancer immunotherapy, while paving the way for more effective treatment strategies in the future. Overall, their study provides new insights into mRNA-based cancer vaccine delivery systems and potential strategies for personalized cancer therapy.

Nanoparticle delivery of mRNA enhances tumor immunotherapy by enhancing strong and effective T-cell immune responses

The immune system is an important system for the human body to defend against the invasion of external pathogens, and T-cells are the main force of the immune system to kill tumor cells, which is one of the key points in the research of immunotherapy (40). As is well known, the efficacy of immunotherapy relies on a sustained and potent T-cell immune response. Traditional tumor therapies delivering mRNA-encoded antigens have shown limited effect, due to insufficient immune responses against these antigens (41). Oberli and colleagues (42) used Lipid Nanoparticle (LNP)-assisted mRNA vaccine delivery systems to deliver mRNA vaccines to induce strong cytotoxic T-cell responses. Their results showed that LNP was able to effectively deliver mRNA vaccines to antigen-presenting cells and induce strong $CD8^+$ T-cell responses *in vivo*. In addition, remarkable results were obtained in inducing

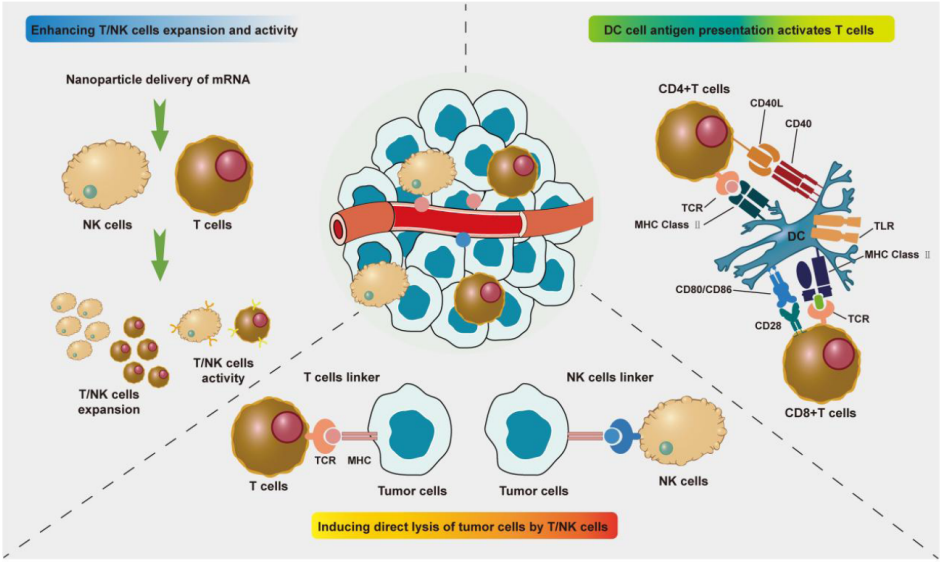

Fig. 2. Schematics of T/NK/DC cell enhanced tumor immunotherapy. Nanoparticles: left, enhance the proliferation and activity of T/NK cells by delivering mRNA; right, present DC-cells to activate T-cells; below: improve the ability of T/NK cells to directly kill tumor cells (47-49).

strong cytotoxic T-cell responses in mice and prolonging the survival of tumor-bearing mice, indicating that this approach can effectively deliver mRNA vaccines, showing the potential of anti-tumor immunity. Their study demonstrates that LNP provides a mRNA vaccine delivery vector that offers the promising ability to induce potent cytotoxic T-cell responses, providing a new strategy for cancer immunotherapy. In summary, the use of nanoparticles to deliver mRNA can induce potent T-cell killing. and offers excellent potential in cancer immunotherapy (43).

Nanoparticle delivery of mRNA enhances NK-cell killing and improves cancer immunotherapy

Natural killer (NK)-cells are key cells in the innate immune system that can directly recognize and kill tumor cells and virus-infected cells, without prior antigen recognition by antigen-presenting cells. NK-cells do not depend on the presence of MHC molecules, which allows them to attack tumor cells with low or absent MHC expression. To give full play to the advantages of NK cell-based immunotherapy strategy and improve the efficiency of immunotherapy, researchers have used lipid nanoparticles (LNPs) to deliver CAR mRNA to NK-cells expanded from peripheral blood mononuclear cells (PBMCs), and successfully generated CAR-NK cells with high anti-tumor activity (44). This technique demonsrates significant antitumor activity *in vitro* and *in vivo*, can effectively kill a variety of myeloid tumor and leukemia cell lines, and releases high levels of IFN-γ and Granzyme B. BCMA-CAR-NK and CD19-CAR-NK cells showed significantly higher cytotoxicity and IFN-gamma and Granzyme B secretion, compared to normal NK-cells. In addition, CD19-CAR-NK cells could significantly inhibit the growth of Nalm-6 tumor *in vivo*. Therefore, NK-cell immunotherapy offers a promising cancer treatment with rapid, broad-spectrum antitumor activity. With further research and optimization, NK-cell immunotherapy is expected to provide more treatment options for cancer patients.

In summary, as an innovative delivery platform, nanoparticles can improve the stability and intracellular delivery efficiency of mRNA, demonstrating the potential of nanoparticle delivery strategy for tumor immunotherapy, while opening up a new path to achieve more precise cancer treatment (45). In combination with diversified therapeutic strategies, mRNA vaccines offer great potential in the field of tumor immunotherapy, and are expected to provide patients with more accurate and effective treatment options (46-49).

APPLICATION OF NANOPARTICLE DELIVERY OF mRNA IN CANCER IMMUNOTHERAPY

The advances of drug delivery systems have made nanoparticles a promising tool to extend the plasma half-life of nucleic acids and improve their stability in systemic circulation (50). Nanoparticles can prolong the plasma half-life of nucleic acids in systemic circulation, increase stability, and improve accumulation in tumor tissues through enhanced permeability and retention (EPR) effects (51). The design and modification of

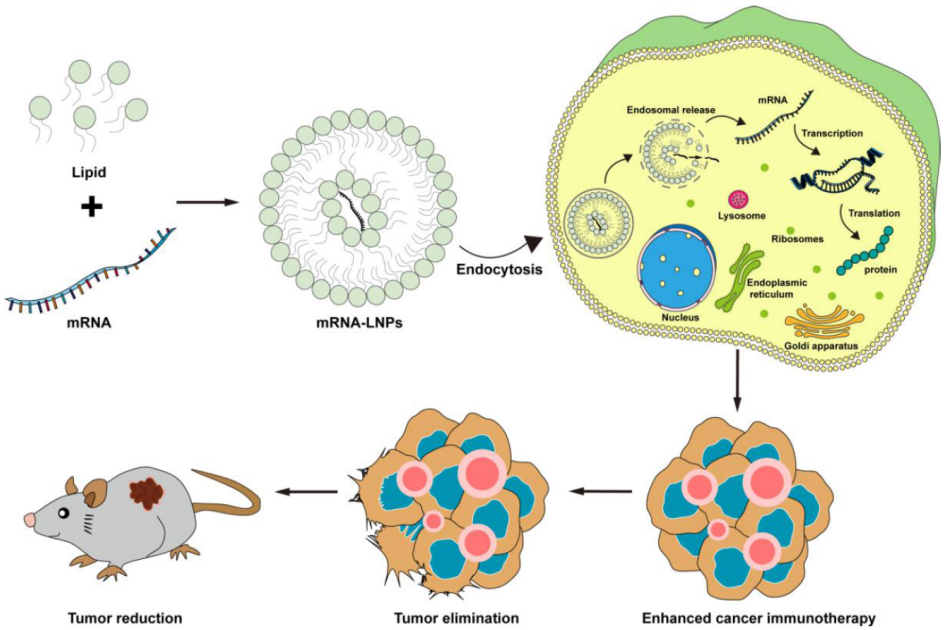

Fig. 3. Nanoparticle delivery of mRNA enhances tumor immunotherapy. Schematic of nanoparticle-encapsulated mRNA entering cells to enhance tumor immunotherapy and inhibit tumor growth.

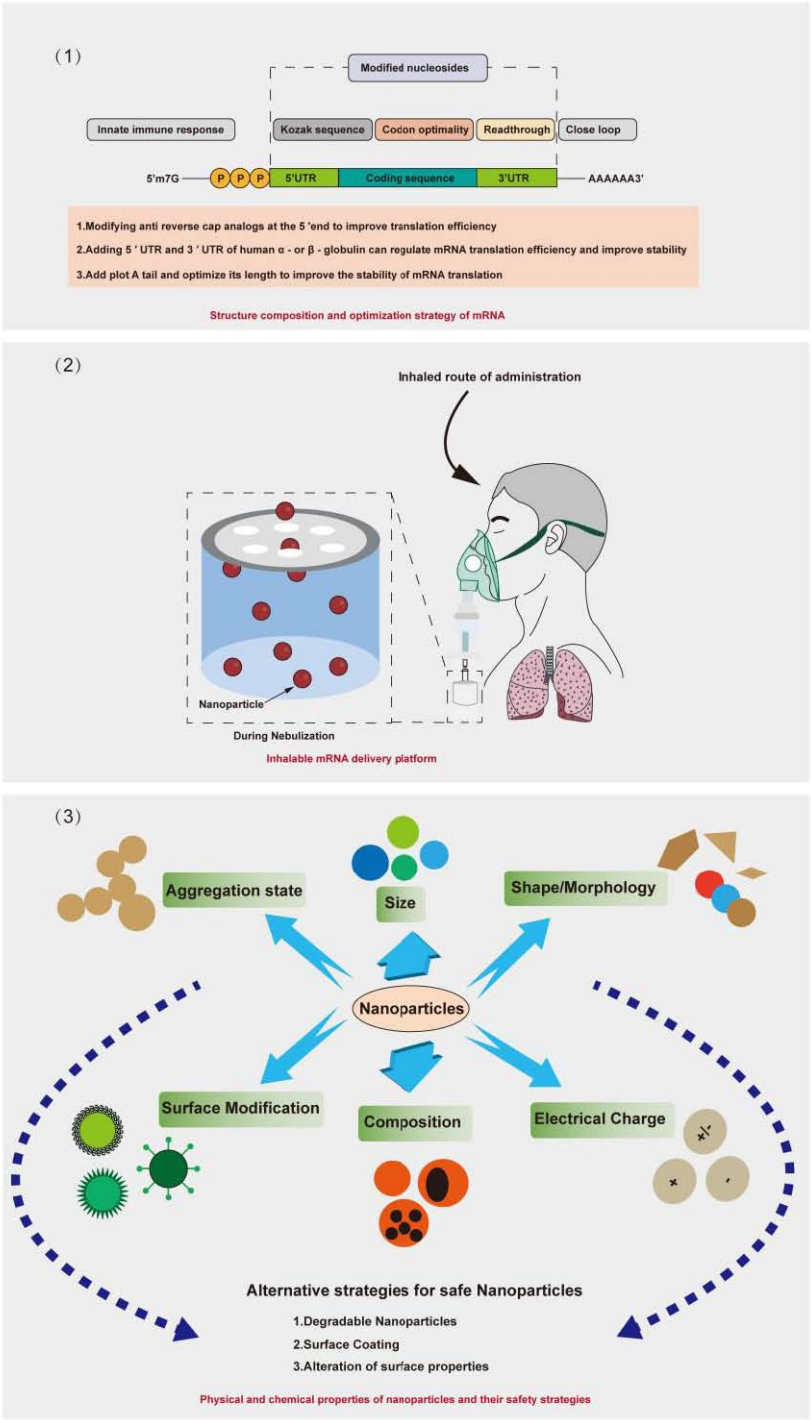

Fig. 4. Different strategies to enhance tumor immunity. The structural composition and optimization strategies of mRNA are shown, which improve the stability and translation efficiency of synthesized mRNA. Schematic of the inhalation delivery process of lipid nanoparticles used for mRNA inhalation delivery; the physical and chemical properties of nanoparticles include the size, surface modification, surface charge, composition, shape, and aggregation state of NPs, together with safer nanoparticle strategies.

nanomaterials have further diversified the modes of mRNA delivery, enabling effective delivery into cells, while enhancing melanoma immunotherapy in various ways. One of the key advantages to using nanoparticles for mRNA delivery is to reduce adverse side effects, as seen in Liu *et al*. (52). Using lipid nanoparticles to deliver immune-stimulated mRNA to the tumor microenvironment, they were able to inhibit melanoma tumor growth with minimal systemic toxicity. Intratumoral injection of lipid nanoparticles loaded with IL-12 mRNA showed significant efficacy in inhibiting tumor growth, while the combination of IL-12 and IL-27 mRNA produced a synergistic effect without systemic toxicity. The ability of nanoparticles to induce infiltration of immune effector cells into the tumor, including IFN-γ and TNF-α producing NK- and $CD8^+$ T-cells, highlights their potential to enhance anti- tumor immunity. This novel approach of intratumoral delivery of mRNA-loaded nanoparticles offers a promising strategy for cancer therapy, with the potential to treat a variety of malignant tumors (53).

Fig. 3, and Supplementary Table 2 of the I, show that the biocompatible and biodegradable nature of nanoparticle delivery systems for mRNA holds great promise for the development of mRNA-based therapies (54). By expanding the use of mRNA therapies to treat a wide range of diseases, nanoparticles are poised to revolutionize the field of nucleic acid therapeutics. The future of mRNA delivery through nanoparticles looks bright, with the potential to significantly impact the landscape of cancer treatment and beyond (55-59).

CONCLUSIONS

Nanobiotechnology and gene therapy have shown great promise in the treatment of tumors, particularly in the development of gene drugs for clinical applications (60-62). Due to their nano-size advantage, biocompatibility, and biodegradability, nanoparticles have emerged as effective carriers to deliver nucleic acids into cells (63). This technique has overcome many obstacles in the application of gene drugs, while significantly improving the effectiveness of mRNA drugs in tumor immunotherapy (64). Researchers have been designing and developing various types of nanoparticles, optimizing their structure, and modifying their surface to enhance mRNA loading capacity and delivery (65). These advances have reduced immunogenicity, while also improving the overall therapeutic effect of mRNA drugs in tumor immunotherapy. However, there remain challenges to be addressed in achieving tissue- or cell-specific delivery, and ensuring the complexity and safety of nanocarrier materials. The ideal delivery system should offer high transfection efficiency, safety, protection of mRNA from degradation, and targeted delivery capabilities. Future research will optimize three aspects: first, design of the sequence and structure of mRNA can effectively increase the expression of tumor-associated specific antigens in antigen-presenting cells or T-cells, to thereby achieve better anti-tumor effects. Secondly, design and optimization of the composition of the nano delivery system, can more effectively protect mRNA from degradation to improve its stability and delivery efficiency *in vivo*. Finally, in injection methods, an alternative method to the two main methods of intratumoral and intravenous injection is to use nebulizers for inhalation, which provides an efficient, non-invasive, precise, and patient-friendly method that can directly deliver drugs to the lungs, and exert their effects. As the field of nano-delivery systems continues to advance and immunotherapy regimens are further optimized, more innovative therapeutic strategies for tumor immunotherapy are expected to emerge. Fig. 4 shows that ongoing research and development offer great potential for nanobiotechnology and gene therapy to advance in the treatment of tumors, providing new hope for patients with cancer (66-69).

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CONFLICTS OF INTEREST

The authors have no conflicting interests.

AUTHOR CONTRIBUTIONS

Wei He, Meng Zhang, Yuexia Zhong, and Yuan Gao wrote and revised the article. Xiyan Lu and Dong Fan conceived the idea of the article.

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