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Commentary

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Recent Advances in the Noninvasive Delivery of mRNA

Mark Twain*

Department of Pharmacy, United Arab Emirates University, Al Ain, United Arab Emirates

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DESCRIPTION

mRNA-based therapeutics have gained significant attention due to their potential to treat various diseases, including genetic disorders, cancers, and infectious diseases. However, delivering mRNA molecules to target cells poses several challenges, such as their susceptibility to degradation, inefficient cellular uptake, and potential immunogenicity. Recent advancements in noninvasive delivery methods have addressed many of these challenges, making mRNA-based therapies more feasible and effective. One of the most significant recent breakthroughs in noninvasive mRNA delivery is the development of Lipid Nano Particles (LNPs). LNPs are lipid-based carriers that encapsulate mRNA molecules, protecting them from degradation and facilitating their delivery into cells. LNPs have shown remarkable success in delivering mRNA vaccines, as demonstrated by the rapid development and authorization of mRNA-based COVID-19 vaccines.

The success of mRNA vaccines against COVID-19 has been a major milestone in the field, highlighting the potential of mRNA therapeutics. These vaccines, such as the Pfizer-BioNTech and Moderna vaccines, utilize LNPs to deliver mRNA encoding the spike protein of the SARS-CoV-2 virus. The LNPs effectively deliver the mRNA into cells, triggering the production of the spike protein, which stimulates an immune response. The success of these vaccines has spurred further research and investment in mRNA-based therapies. Advancements in LNP technology have focused on improving their stability, delivery efficiency, and safety. Researchers have explored various lipid formulations and modifications to enhance LNP-mediated mRNA delivery. For example, the incorporation of ionizable lipids has significantly improved the endosomal escape of LNPs, allowing the mRNA to reach the cytoplasm and be translated into the desired protein. Additionally, surface modifications with Poly Ethylene Glycol (PEG) and other molecules have helped prolong the circulation time of LNPs and reduce their immunogenicity.

In addition to LNPs, other noninvasive delivery methods for mRNA have been investigated. One notable approach is the use of Cell-Penetrating Peptides (CPPs) and peptide-based carriers. CPPs possess the ability to penetrate cell membranes and facilitate the internalization of mRNA into cells. Researchers have developed CPP-mRNA complexes that can effectively deliver mRNA to a variety of cell types, including immune cells and cancer cells. These peptide-based delivery systems offer versatility and potential for targeted delivery by modifying the peptide sequence or adding targeting ligands.

Electroporation has also emerged as a powerful noninvasive delivery method for mRNA. Electroporation involves applying brief electric pulses to cells, creating temporary pores in the cell membrane that allow the entry of mRNA molecules. This technique has been successfully used in preclinical and clinical studies for the delivery of mRNA vaccines and gene therapies. Electroporation can achieve high transfection efficiency, making it particularly useful for *in vivo* applications. Another recent advance in noninvasive mRNA delivery is the utilization of Extracellular Vesicles (EVs). EVs are naturally occurring membrane-bound vesicles that can be isolated from various cell types, including mesenchymal stem cells and immune cells. These EVs can encapsulate and protect mRNA, allowing for its delivery to target cells. EVs offer several advantages, such as their natural biocompatibility, ability to cross biological barriers, and potential for targeted delivery by modifying their surface proteins. EV-mediated mRNA delivery has various applications, including regenerative medicine and cancer immunotherapy.

Furthermore, physical methods, such as ultrasound and laser-mediated techniques, have shown potential for noninvasive mRNA delivery. Ultrasound can enhance cellular uptake by inducing transient disruptions in the cell membrane, allowing mRNA to enter cells. Laser-mediated techniques utilize laser energy to create micropores in the cell membrane, facilitating the uptake of mRNA. These physical methods offer precise control and spatial targeting, making them attractive for localized delivery applications. Overall, recent advances in the noninvasive delivery of mRNA have directed for the development of novel therapeutics and vaccines. The use of LNPs, CPPs, electroporation, EVs, and physical methods has significantly improved the efficiency and safety of mRNA delivery. These advancements have the potential to revolutionize the treatment of diseases, including genetic disorders, cancers, and infectious diseases, by enabling precise and customizable protein production within target cells. Continued research and development in this field will likely lead to further refinements and innovations, bringing mRNA-based therapies closer to clinical reality.