Development of Lipid Nanoparticles for mRNA Delivery: From COVID-19 Vaccines to Cancer Immunotherapies

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Abstract

Successful implementation of mRNA COVID-19 vaccines is greatly credited to the development of lipid nanoparticles (LNPs) that protect mRNA from degradation and ensure effective cellular uptake and mRNA endosome escape. The goal of our work is to develop low-immunogenic and targeted mRNA-LNPs for mRNA therapeutics, which are a promising strategy to combat diverse diseases beyond COVID-19 vaccines. Systemic RNA delivery to the secondary lymphoid organs (SLOs) for immunotherapy offers distinct advantages over traditional intramuscular methods employed in COVID-19 vaccines, including an increased amount of antigen administration and direct access to most immune cells and lymphoid organs in the circulatory system. We propose a LNP system incorporating phosphatidylserine (PS) for the efficient systemic delivery of mRNA to SLOs. PS is known to bind endocytosis receptors on macrophages and is used by many viruses for enhanced cellular uptake. Our result demonstrated that the PS-LNP performed efficient mRNA expression in the spleen and lymph nodes. Furthermore, traditional LNP formulations for mRNA delivery contain poly(ethylene) glycol (PEG), a polymer widely used in drug delivery carriers but recently associated with efficacy and immunogenicity concerns. We propose poly(carboxybetaine)-lipids (PCB-lipids) as surrogates for PEG-lipids used mRNA formulations. In vitro studies with immortalized and primary cells show that PCB-containing LNPs have higher mRNA transfection efficiency than PEG-containing LNPs across different formulations. Primary cell engineering and in vivo immunization studies in mice further demonstrate greater therapeutic efficacy of PCB-containing LNPs over PEG counterparts. These formulations exhibit a safe immunotoxicity profile and effectively mitigate the accelerated blood clearance effect that has been observed for PEG-containing LNPs, enabling repeated administrations without efficacy loss.