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Lipid Nanoparticle Delivery Systems for Pulmonary RNA Therapeutics: Overcoming the Mucosal Barrier

Ptaszek Sahay*

Department of Pulmonology, The University of Texas at Austin, Austin, TX 78712, USA

Introduction

The field of RNA therapeutics has witnessed a transformative evolution over the past two decades, culminating in the widespread success of mRNA-based vaccines and therapeutics. Among the many promising applications, pulmonary RNA delivery stands out for its potential in treating a variety of respiratory disorders including genetic diseases (e.g., cystic fibrosis), viral infections (e.g., COVID-19) and cancers (e.g., lung carcinoma). However, the lung's unique environment, particularly the presence of the mucosal barrier, presents significant challenges to the efficient and targeted delivery of RNA molecules [1]. Lipid Nanoparticles (LNPs) have emerged as a leading delivery platform for RNA due to their biocompatibility, ability to encapsulate nucleic acids and potential for modification to enhance target specificity and overcome physiological barriers. This article explores the role of LNPs in pulmonary RNA delivery, with a particular focus on strategies to overcome the mucosal barrier. It reviews the biological and physicochemical aspects of lung delivery, LNP design considerations, current advancements and future perspectives [2].

Description

The respiratory tract offers a direct and non-invasive route for drug administration. It provides a vast surface area (~100 m^2 in humans), rich vascularization and rapid absorption kinetics. Pulmonary RNA therapeutics hold the promise of local delivery for lung-specific diseases and even systemic effects via alveolar absorption. A viscoelastic gel composed of mucins, proteins, salts and lipids that traps foreign particles and impairs nanoparticle penetration. Coordinated ciliary motion propels mucus (and entrapped particles) towards the oropharynx for removal. RNases in the lung lining fluid rapidly degrade naked RNA. Resident macrophages and dendritic cells may recognize and eliminate foreign particles. Crossing the cell membrane and endosomal escape are critical challenges post-delivery. LNPs are nanoscale delivery systems composed of ionizable lipids, phospholipids, cholesterol and Polyethylene Glycol (PEG)-lipids. Their structural design facilitates RNA encapsulation, protection from degradation and efficient intracellular delivery. Facilitate RNA encapsulation and endosomal escape by becoming protonated in acidic endosomes. Enhance membrane fusion and structural integrity. Modulates membrane fluidity and stability. Improve circulation time and reduce aggregation [3].

The mucus barrier is the most formidable obstacle in pulmonary RNA delivery. Several strategies have been employed to enhance LNP transport through mucus. PEG chains reduce mucoadhesion by shielding LNP surface charge and hydrophobicity. Improve diffusion through mucus without significantly impairing cellular uptake. Neutral surface charge minimizes interaction with mucus components. Nanoparticles <200 nm demonstrate enhanced diffusion through the mucus mesh. Uniform size distribution reduces aggregation and improves penetration. Co-administration of agents like N-acetylcysteine or dornase alfa can thin mucus and improve LNP transport. Novel lipid compositions that inherently avoid mucin binding can be used. Use of synthetic lipids with reduced hydrophobic interactions with mucins. LNPs that degrade or change conformation in response to mucosal enzymes can release RNA closer to target cells. Designing LNPs for pulmonary use requires attention to both formulation and delivery parameters. Ionizable lipids with low pKa values favor endosomal escape but must also maintain mucus compatibility. LNP formulations must withstand aerosolization stress and maintain stability during nebulization. Ensuring consistent dosing with nebulizers or inhalers is critical. Lung-specific formulations should avoid long-term accumulation and toxicity. Avoiding immune activation by selecting non-immunogenic lipids or shielding ligands [4].

Several preclinical and early-phase clinical studies have demonstrated the feasibility of LNP-mediated RNA delivery to the lungs. Intranasal or aerosolized mRNA vaccines in LNPs have shown robust mucosal immunity in animal models. Delivery of CFTR mRNA via LNPs has restored chloride transport in preclinical models. siRNA-loaded LNPs targeting oncogenes have shown tumor suppression in murine lung cancer models. mRNA encoding viral antigens has been successfully delivered to lung tissues for immunization. mRNA therapeutics are short-lived, requiring repeated dosing. Repeated inhalation can provoke local immune responses. Producing stable, aerosolizable LNPs at large scale remains a technical hurdle. Inhaled RNA therapies face stringent regulatory scrutiny due to novelty and delivery complexities. Rationally designed lipids with enhanced biodegradability and reduced toxicity. Combining targeting ligands, stimuli-responsive elements and immunomodulators. Inspired by exosomes, these nanoparticles may offer improved mucus penetration and cell specificity. Combining polymers, peptides and lipids to leverage complementary advantages. Utilizing machine learning to predict optimal LNP compositions for lung delivery [5].

Conclusion

Lipid nanoparticle delivery systems represent a cornerstone in the advancement of pulmonary RNA therapeutics. The lung, with its accessible surface and immunological landscape, is a promising target for local RNA delivery, yet the mucosal barrier presents substantial challenges. Innovations in nanoparticle design, particularly surface engineering and lipid chemistry, are key to overcoming these obstacles. As our understanding deepens and technologies mature, LNP-mediated RNA therapeutics hold the potential to revolutionize treatment paradigms for respiratory diseases—from genetic disorders and infections to cancers. Strategic collaborations across disciplines, regulatory frameworks and translational studies will be pivotal in realizing this promise for clinical application.

***Address for Correspondence:** Ptaszek Sahay, Department of Pulmonology, The University of Texas at Austin, Austin, TX 78712, USA, E-mail: ptaszekahay.sah@etr.edu*

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Conflict of Interest

None.

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