Trends in Molecular Medicine | Strategy of the Month

Lipid Nanoparticle-Mediated Delivery of mRNA Therapeutics and Vaccines

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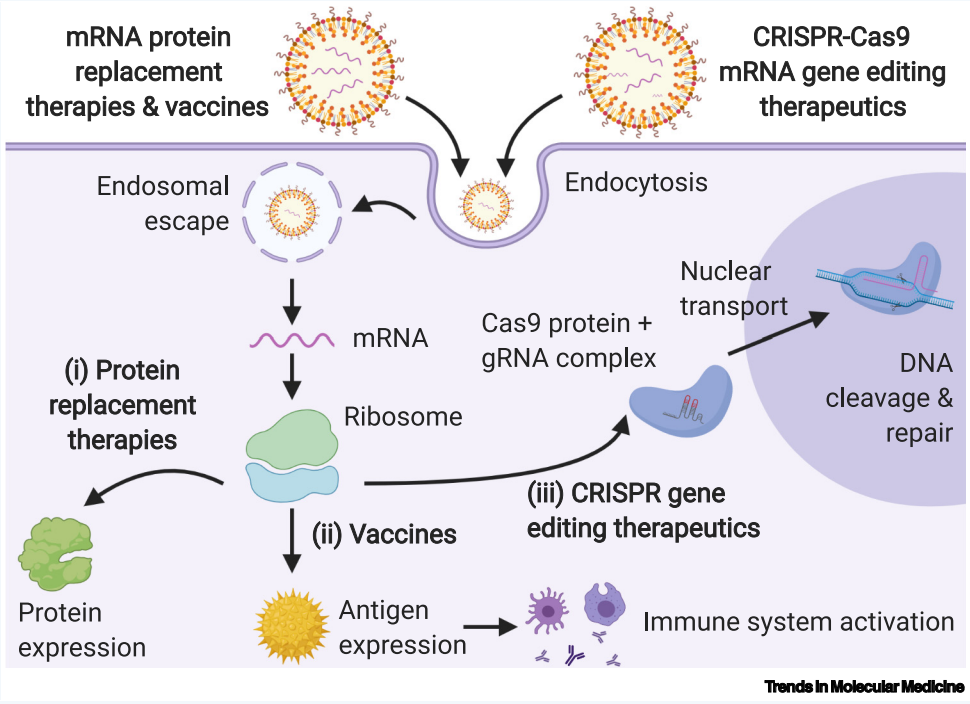
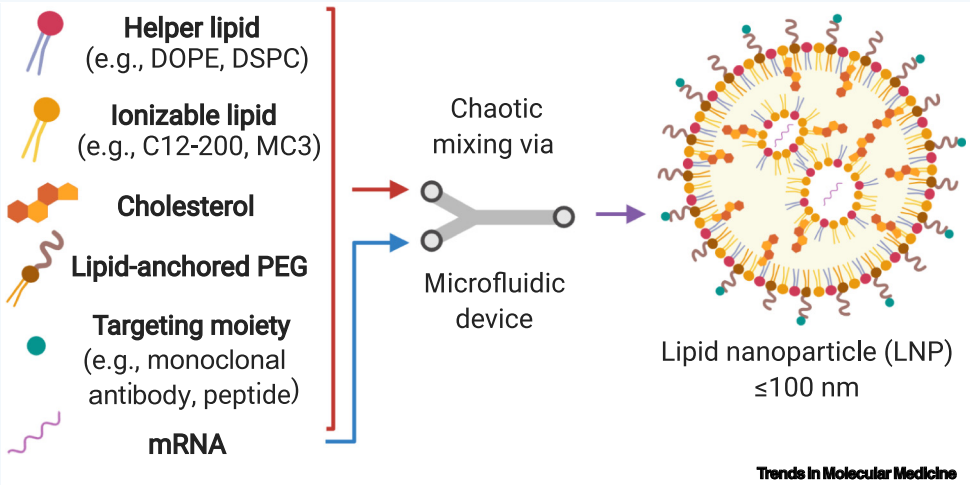


As mRNA is degraded by nucleases and cannot easily cross the cell membrane due to its large size and negative charge, delivery requires encapsulation in vehicles, such as lipid nanoparticles (LNPs). Cellular uptake of LNPs begins with endocytosis followed by endosomal escape, LNP degradation, and mRNA release into the cytosol. mRNA is then translated into protein for therapeutic applications, including (i) protein replacement therapies, (ii) vaccines, and (iii) gene editing.



LNPs are often formulated with the following four lipid components: (i) helper lipid to encapsulate cargo, (ii) ionizable lipid to enhance endosomal escape and delivery, (iii) cholesterol to promote stability, and (iv) lipid-anchored poly(ethylene glycol) (PEG) to reduce immune system recognition and improve biodistribution. Other targeting moieties, such as antibodies or peptides, may be added to further direct localization. Lipid components are often combined with mRNA via microfluidic mixing to form LNPs.

ADVANTAGES:
LNPs for gene therapy are advantageous over viral vectors as they have lower immunogenicity, can deliver larger cargos, and are easier to synthesize and manufacture at a large scale.

Unlike DNA, mRNA poses no risk of genome integration.

Ionizable LNPs mitigate the toxicity associated with cationic lipid and polymer nanoparticle systems while enabling potent endosomal escape.

LNP design is modular and versatile because components and their molar ratios, targeting moieties, and overall lipid-to-mRNA ratios can be optimized for different cell targets and disease applications.

CHALLENGES:
LNPs face several delivery barriers, including nonspecific serum protein interactions, rapid clearance, off-target localization, and degradation in the endosome.

mRNA delivery induces transient protein production, requiring repeated administration for sustained expression.

The development of anti-PEG antibodies raises concerns about potential allergic responses to LNPs.

APPLICATIONS:
Onpattro, an RNA interference drug, was the first FDA-approved LNP–nucleic acid therapeutic for the treatment of polyneuropathy caused by transthyretin amyloidosis.

Pfizer-BioNTech and Moderna mRNA–LNP coronavirus disease 2019 (COVID-19) vaccines were given FDA emergency use authorization in 2020.

Phase I/II clinical trials are ongoing for inhalation of LNPs for the treatment of cystic fibrosis via the protein target CFTR.

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  https://doi.org/10.1016/j.molmed.2021.03.003

Declaration of Interests

No interests are declared.

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