Lipid nanoparticles as efficient therapy vectors for skeletal muscle pathologies

Eva Lipkow*[1]

[1]IGBMC – Université de Strasbourg, CNRS, INSERM, Pathophysiology of neuromuscular diseases, IGBMC, CNRS UMR 7104, 1 rue Laurent Fries, 67404 Illkirch, France. – France

Résumé

Research area: Translational research
Jacqueline Ji1, Eva Lipkow1, Corine Crucifix1, Nicolas Anton[2], Jocelyn Laporte1

1 Institut de Génétique et de Biologie Moléculaire et Cellulaire (IGBMC), Illkirch-Graffenstaden, France, [2] Laboratoire de Conception et Application de Molécules Bioactives, Strasbourg, France

Rare muscle disorders, such as congenital myopathies, are life-threatening diseases for which no treatment is currently available. The most utilised gene therapy vectors for treating these genetic muscle disorders are adeno-associated viruses (AAVs). However, recombinant adeno-associated vectors (rAAV) face several limitations, including restricted transgene capacity (below 2.5 kb), immunogenic responses due to preexisting immunity, and particularly liver toxicity resulting from the accumulation of rAAV in the liver, which triggers a strong immune response. To date, gene therapy vectors that achieve high efficiency, muscle specificity, and safety have not yet been developed.

To overcome these challenges, we developed a novel lipid nanoparticle (LNP)-based delivery system specifically designed to target skeletal muscle. Since the success of the COVID-19 mRNA (messenger RNA) vaccine, LNPs hold substantial promise for expanding the landscape of mRNA-based therapy to gene therapy applications. LNPs have demonstrated a higher payload capacity, compatibility with repeated administration, and reduced immunogenicity compared to viral vectors. Moreover, we rationally designed LNPs to be muscle-specific by conjugating MyomP1, a peptide from the muscle-fusogenic protein Myomerger, onto the nanoparticle's surface. We encapsulated either pADN or mRNA encoding luciferase reporter genes. In vitro studies in murine C2C12 myoblasts, myotubes, and human myoblasts demonstrated that MyomP1-modified LNPs achieved a 10-fold increase in transduction efficiency compared to unmodified LNPs. In vivo, studies further demonstrated that MyomP1-functionalized LNPs significantly enhanced muscle transduction when delivering DNA cargo, whereas the same modification induced a liver-detargeting effect in mRNA delivery.

These findings highlight the versatility and safety of LNP-based gene delivery and suggest that MyomP1-engineered LNPs possess significant potential to enhance therapeutic outcomes for patients with rare muscle diseases, providing a promising alternative to traditional viral gene therapy platforms.

*Intervenant

Mots-Clés: gene therapy, lipid nanoparticle, peptide, muscle, nucleic acid delivery