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CRISPR/Cas9 delivery via lipid nanoparticle for targeted PLVAP gene editing in kidney endothelial cells

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Objectives : The kidney presents biological barriers to targeted treatments due to its intricate vasculature and filtration system, making the efficient and precise delivery of CRISPR/Cas9-based gene therapy a significant challenge, despite its promise for treating genetic disorders. To overcome these challenges, we developed a lipid nanoparticle (LNP) platform conjugated with vascular endothelial growth factor receptor (VEGFR)-specific peptides to facilitate the targeted delivery of the CRISPR/Cas9 system into kidney endothelial cells.
Methods : To selectively target kidney endothelial cells, we modified the surface of LNPs with VEGFR-targeting peptides. These nanoparticles encapsulated the CRISPR/Cas9 system, which is designed to downregulate plasmalemma vesicle-associated protein (PLVAP). The efficiency of cellular uptake and gene silencing was evaluated in human kidney endothelial cells using molecular and functional assays
Results : The engineered LNPs demonstrated high affinity for kidney endothelial cells through VEGFR targeting. PLVAP is abnormally elevated in diabetic kidney disease (DKD) and contributes to increased vascular permeability. The CRISPR/Cas9 system successfully downregulated PLVAP expression, resulting in stabilized endothelial function and reduced vascular permeability. These findings showed the potential of this approach for precision gene therapy targeting endothelial dysfunction.
Conclusions : Our study demonstrates an optimized LNP-based system for the targeted delivery of the CRISPR/Cas9 system to kidney endothelial cells. This platform enables efficient gene editing and holds potential therapeutic applications for DKD and other renal pathologies. Future studies will focus on in vivo validation, long-term efficacy, and safety assessment of this delivery strategy in preclinical disease models.