Kidney-targeting multimodal micelles towards polycystic kidney disease therapy

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INTRODUCTION

Drugs such as tolvaptan and pioglitazone have been repurposed for ADPKD. However, these drugs suffer from short half-life, poor bioavailability, and adverse side effects. To mitigate these limitations, nanoparticles, such as multimodal micelles (MMMs), have been proven to act as protective drug carriers. To that end, we describe the development of kidney-targeting MMMs (KM^3) that are small enough to pass through the glomerular filtration barrier, and actively target renal epithelial cells through megalin-binding peptides.

METHODS

The kidney-targeting peptide, $KKEEE_3K$, and cy7 were conjugated to DSPE-PEG2000 and coassembled. Micelles were characterized by dynamic light scattering at varying pH correlating to regions of the nephron (pH 4.5, 5.5, 6.5, 7.4), transmission electron microscopy, and zeta potential. Human proximal tubule epithelial cells were incubated with KM^3 or non-targeting (NT) micelles and binding assessed under confocal microscopy. To test in vivo targeting, biodistribution, and safety, KM^3, non-targeting micelles, or PBS were injected into C57BL/6 mice via tail vein injection. After 24 hours, mice were euthanized, blood drawn, and organs excised and imaged. Organs were sectioned and stained with H and E, megalin antibodies, or WGA, PHA-L, or PNA. Serum blood urea nitrogen (BUN) and urine creatinine were measured with commercial kits.

RESULTS

The diameter remained stable across pH, and KM^3 had a diameter between 13.9–14.9 nm and NT micelles 11.0–12.8 nm. When KM^3 were cultured with proximal tubule cells, confocal microscopy showed a 35% higher binding of KM^3 compared to NT micelles. *Ex vivo* optical imaging demonstrated accumulation of KM^3 mostly in the kidney (34.6% vs. 25.8%). In addition, KM^3 colocalized to a greater extent than NT micelles to megalin, and were present on tubule cells but not retained within the glomerulus. Upon H and E staining, no sign of cellular or tissue damage was found for all organs. Serum BUN and urine creatinine were within the reported values for healthy mice (25.0–75.0 mg/dL, 4.7 ± 3.1 mg/dL) confirming safety of micelles.

CONCLUSION

We present the first kidney-targeting nanoparticle strategy for ADPKD. Future studies will test KM^3 in CKD mouse models and incorporate drug candidates to enhance therapeutic efficacy while limiting off-target side effects.