EDITORIAL FOCUS

Hitching a ride to renal repair

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IN THE UNITED STATES, it has been estimated that more than 30 million people have chronic kidney disease (CKD), with the figure projected to rise significantly over the next 10 yr (4). CKD imposes substantial economic burden, accounting for an important proportion of the Medicare budget. Furthermore, patients with CKD have increased risk of death from cardiovascular disease and end-stage renal disease (5). Alas, it is critical to develop therapeutic interventions to prevent, attenuate, or decelerate renal functional decline.

Drug therapy in patients with renal disease remains a major challenge for several reasons. These patients often require high drug concentrations in the kidney, which are frequently associated with important side effects (1). In addition, changes in glomerular filtration and tubular function may compromise the distribution of drugs to the kidney. Therefore, high renal drug concentrations do not always translate into high concentration of the therapeutic agent in the target cell type. Accordingly, therapeutic approaches that selectively target drugs to the kidney would overcome these limitations and enhance drug efficacy, providing functional recovery from renal disease.

Kidney-specific drug targeting is a promising, but underdeveloped, area (9). Current candidates for kidney-targeted drug delivery include macromolecular carriers such as endogenous low-molecular-weight proteins and glycoconjugates, as well as nanoparticles and liposomes (6, 7, 10). However, these delivery vectors are limited to certain regions of the nephron or associated with cytotoxicity. Therefore, of greater impact would be targeting therapeutics to the appropriate renal cell type, as different cell types play distinct roles in the pathogenesis of renal disease.

The study by Bidwell et. al. (2) in a recent issue of the American Journal of Physiology-Renal Physiology sheds new light on this evolving field by developing and characterizing a unique biopolymer-stabilized, elastin-like polypeptide (ELP) modified with a seven-amino-acid, kidney-targeting peptide (KTP) and a cysteine residue, a combination that confers very high renal specificity. In these elegant studies, authors evaluated in vivo pharmacokinetics, biodistribution, and intrarenal localization of KTP-ELP in rats and swine, whereas in vitro renal cell-type binding and cytotoxicity were assessed in three different human renal cell types. They found that KTP-ELP had longer plasma half-life and higher renal selectivity than untargeted ELP, reaching renal levels to over 150-fold higher than in other major organs. KTP-ELP particularly accumulated in proximal tubules and vascular endothelium and showed higher binding to human podocytes and proximal tubular epithelial and glomerular microvascular endothelial cells than untargeted ELP. Importantly, even high doses of KTP-ELP had no adverse effects on renal function nor induced renal parenchymal damage, underscoring the safety in the treatment of renal diseases. Therefore, these observations strongly suggest unique and novel therapeutic potential for KTP-ELP as a promising candidate for kidney-targeted drug delivery.

ELPs are large, biodegradable, nonimmunogenic, and highly manipulable biopolymers that act as carriers to improve drug pharmacokinetics and targeting (8). Interestingly, ELPs accumulate at high levels in the kidneys, and their protein-based nature facilitates their modification for fusion with peptides. Indeed, stabilization and kidney accumulation achieved by fusing ELP with the pro-angiogenic vascular endothelial growth factor ameliorates microvascular rarefaction and improves renal function in swine renovascular disease, underscoring the potential of ELPs as drug delivery vectors for renal repair (3). The present study extends these observations, demonstrating that their combination with KTPs enhances ELP intrarenal distribution and binding to human renal cells.

An important strength of this study is the use of a large animal model to confirm the potential of KTP-ELP to direct protein therapeutics to the kidney. The anatomy and physiology of the swine kidney is very similar to that of humans. Therefore, this strategy opens up the possibility of developing future targeted therapeutic interventions for patients with renal disease. Additional applications of this technology include demonstrating that their combination with KTPs enhances ELP labeling with tracers for imaging studies, which may serve as markers of renal function.

In summary, advances in drug development have propelled translational and clinical studies testing the efficacy of novel compounds to attenuate renal injury and prevent progressive functional decline. Such approaches target important pathogenic mechanisms of CKD, including inflammation, apoptosis, oxidative stress, and fibrosis, which compromise the integrity and function of several renal cell types. The study by Bidwell et. al. (2) supports the potential of a novel drug delivery vector to direct protein therapeutics to human podocytes and proximal tubule epithelial and glomerular microvascular endothelial cells. Only the future will tell us whether renoprotective drugs would benefit from the KTP-ELP construct to take a ride to renal repair.

DISCLOSURES
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AUTHOR CONTRIBUTIONS
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REFERENCES