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Renal targeting delivery systems

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“Despite much progress achieved in the SPs design, unexpectedly low targeting efficiency, retention and poor cell permeability are still the major obstacles in the development of SPs candidates”

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In the last few decades, renal diseases have received increasing attention throughout the world [1,2]. Encouraging progress has been achieved through revealing the specific anatomical architecture, pathogenesis of diseases and therapeutic advances, which offers ample opportunities for renal targeting therapy. Specific drug delivery to lesion sites can generate high intrarenal concentrations as well as avoiding systemic side effects or therapeutic resistance. Various renoprotective targeting delivery strategies have emerged since Haas *et al.* first comprehensively raised the significance and possibility of renal-targeting drug delivery [3,4]. In this editorial, we outline the potential delivery systems for targeting drugs to the kidneys using nanotechnology and prodrug technology and highlight the prospects and future challenges in this research field.

Nanoparticles for renal-targeting delivery

Nanotechnology involving the creation and manipulation of materials at nanoscale levels to yield products that behave differently from their macroscale counterparts has already shown a potential to revolutionize disease prevention, diagnosis and treatment. Nanotechnology-based targeting delivery systems directed to livers or tumors which are characterized by abundant blood flow have now been successfully developed, which are one of the key-driving forces behind the development of nanotechnology-based renal-targeting delivery systems. Because the kidney also receives abundant blood flow, the established design principles can be used to fabricate smart nanoparticles (NPs) that can be taken up and retained exclusively by renal cells. Substances such as inorganic or organic nanosized particles, multifunctional liposomes and micelles, collectively referred to as NPs herein, can be designed to specifically deliver drugs with unique characteristics to the kidneys.

NPs with diameters between 70 and 130 nm are able to extravasate through the glomerular vasculature but cannot further traverse through the glomerular basement membrane (GBM), and thus, have to be deposited and retained in the glomerular mesangium by passing through endothelial fenestrations [5], which is described as enhanced permeability and retention effect of glomerular mesangium. The well-defined nanosized gold NPs [6] and albumin NPs [7] have shown a passive accumulation in glomerular mesangium of healthy mice after iv. injection. Apart from passive targeting via the enhanced permeability and retention effect, active targeting could be pursued with the employment of specific ligands or antibodies in liposomes [8,9]. Underlying the fact that sufficiently small NPs are capable of permeating the GBM and crossing through the filtration slits (pore sizes of 10–70 nm) to reach renal tubules, the ultrasmall colloidal nanocarriers (5–30 nm) [10] and multimodal micelles (10–15 nm) [11] were adopted to fabricate targeting delivery systems for podocytes and renal tubular cells. Besides, other physicochemical properties of NPs, including surface charge, shape, flexibility and deformability could have impacts on their ability to overcome the glomerular filtration barrier and enter renal tubules. The better understanding of renal ultrastructure

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and the smart designing of NPs based on nanotechnology will be of great benefit to the development of novel renal delivery strategies focusing on different lesions of nephropathy.

Macromolecular prodrugs for renal-targeting delivery

Macromolecular prodrugs (MPs), typically consisting of a small molecular therapeutic agent bound to a macromolecular carrier via covalent bond, have been exploited in the development of site-specific drug delivery systems. Since its advent several decades ago, there have been numerous studies reporting the success of renal-targeting delivery by using MPs. Due to the renal clearance and disposition of MPs circulating in the vasculature after iv. injection, MPs less than 5–7 nm in size (or a molecular weight of less than 50 kDa [12]) are susceptible to glomerular filtration and reach proximal tubules, then accumulate in tubular cells via endocytosis. The electric charge and hydrophilic/lipophilic balance are also the factors that may influence the targeting profile.

Almost all the reported macromolecular carriers forming MPs with a relatively low molecular weight for renal-targeting delivery are directly accumulated at proximal tubular cells, where multiple enzymes, transport proteins and active receptors are highly expressed for the facilitation of the reabsorption of endogenous compounds as well as the specific uptake of MPs and the release of free drug from MPs. These macromolecular molecules include low molecular weight proteins (LMWPs, molecular weight <30 kDa) [13], low molecular weight chitosans (LMWCs, molecular weight <31 kDa) [14], L-serine (Ser)-modified polyamidoamine dendrimer (PAMAM, molecular weight: 7.0–9.7 kDa) [15], and poly (vinylpyrrolidone-co-dimethyl maleic acid) (PVD, molecular weight: 6–8 kDa) [16]. Indeed, many more promising MPs for renal targeting to proximal tubules can be envisioned with the consideration of the common denominators of the macromolecular carriers mentioned above. However, there are few reports available to investigate the possibility of MPs for targeting treatment of renal glomerular diseases. The reason for this may be the high permeability and low retention of MPs in glomeruli. If many efforts are made to keep MPs above the glomerular filtration threshold (~50 kDa [17]) for the reduction of permeability by increasing the molecular weight, the unwanted distribution in other organs may be also obtained.

Despite promising results obtained in animal models, MPs as renal-targeting delivery systems also face appreciable limitations that may obstruct their further transfer into application in clinical trials and subsequently to the market: uncertain immunogenicity and compatibility; high batch-to-batch variability and wide molecular weight distribution; poor solubility and insufficient drug loading. Especially, the repeated administration of MPs for the treatment of kidney diseases may cause undesired interactions with the GMB and subsequently increase the risk of inflammation and secondary glomerular injury. Hence, considering that the design and safety evaluation of MPs for renal targeting delivery are far from complete, more progress should be made in resolving the challenges issues of MPs and further exploration is needed to ascertain whether there is a possibility for the specific treatment of podocyte-associated diseases by using MPs.

Small-molecule prodrugs for renal targeting delivery

Small-molecule prodrugs (SPs), as an effective way of delivering active compounds to the kidneys, have been developed for several years. Drieman *et al.* successfully synthesized a number of structurally different N-acetyl-L-γ-glutamyl prodrugs and some of them showed a selective accumulation in the kidneys resulting from active transport by tubular cells [18]. Due to the high affinity of folate binding to protein expressed in the proximal tubular epithelium, a diethylene triamine pentaacetic acid (DTPA)-folate conjugate showed a rapid accumulation in the kidney [19]. In addition, a prednisolone carbamate–glucosamine conjugate has been designed as a kidney selective prodrug showing an excellent kidney targeting property without any glucocorticoid-like adverse effect on bone density [20]. The design principles of SPs for renal targeting delivery are mainly based on the site-specific cleavage of enzymes, active transport or reabsorption in renal tubules, which makes it possible to target drugs to renal tubules for the treatment of renal ischemia–reperfusion injury or tubulointerstitial fibrosis. Unlike MPs, SPs commonly have the homogeneous and well-defined molecular weights, structures and confirmed biocompatibilities, which may benefit their further translation to clinical applications. Therefore, specific structure modification of parent drugs is the key to the development of kidney-targeted prodrugs.

Future perspective

NPs, MPs and SPs as the mainstream strategies for renal targeting delivery have been fabricated over 30 years, which shows amelioration of various nephropathies including inflammation, fibrosis and cancer. The conventional

immunosuppressants, kinase inhibitors, microRNAs (miRNA) and small interfering RNA (siRNA) are involved as model drugs to exert therapeutic effects.

As the field of nanotechnology rapidly expands, previous studies on NPs have reported important discoveries in kidney targeting. Refining the developed NPs with tunable biophysical properties and multiple functions (dual therapy or dual targeting) could yield a new generation of NPs with better biocompatibility for renal targeting and retention. One example of such new NPs, already in development recently by our group, is based on dual regulations of anti-inflammatory and antifibrotic effects for the targeting therapy against chronic glomerulonephritis by functional core-shell structural nanocells, with the aim to realize combination targeting therapy.

Regarding MPs, especially the ones with new backbones, current knowledge about the safety is insufficient. More detailed investigation should be performed to identify the risks associated with MPs after repeated iv. administration, with particular attention paid to interactions with the GBM, which may induce the secondary renal inflammation and glomerular injury. In addition, there is an urgent requirement for the establishment of a database on human health risks and hazards associated with different macromolecular carriers.

Despite much progress achieved in the SPs design, unexpectedly low targeting efficiency, retention and poor cell permeability are still the major obstacles in the development of SPs candidates. These may be the reasons why there are few reports on SPs for renal targeting delivery in recent years. In our opinion, the design of self-assembling SPs might be a way out of the dilemma and realize the specific targeting to other types of cells, such as podocytes or mesangial cells.

Looking to the future, NPs are the most promising candidates for future clinical translation, as the accumulated experience and the clinical success in anticancer NP formulations to date provides a reference framework for a better generation of renal-targeting NP designs in order to meet the clinical use.

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