Mesoscale Nanoparticles

An Unexpected Means for Selective Therapeutic Targeting of Kidney Diseases!

May Lin Yap, Xiaowei Wang, Geoffrey A. Pietersz, Karlheinz Peter

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Nanoparticles have attracted major interests for biomedical applications mainly as imaging contrast agents and effective drug carriers as well as the combination of both, as theranostic nanoparticles. Based on substantial advances in multiple disciplines especially in biotechnology and chemistry, a broad variety of purpose-built nanoparticles with diverse characteristics can be generated. Chemical and physical alterations of the basic structure of nanoparticles, such as size, zeta potential (effective electrostatic charge), and surface functionalization for the coupling of various targeting moieties make nanoparticles highly adaptable engendering favorable characteristics for specific disease targeting, increased blood circulation half-life, solubility, and diffusivity.[1] We are currently witnessing the emergence of the first clinical applications particularly in cancer, but there are also concerns in regards to toxicity and environmental impact.

A previous article by Williams et al[2] systematically investigated the influence of various nanoparticle characteristics on organ targeting, particularly of size. Small nanoparticles of <10 nm tend to be rapidly cleared from the body and those between 10 and 250 nm tend to undergo enhanced permeability retention or are phagocytosed by the reticuloendothelial system and are taken up in the liver or spleen, illustrated in the Figure. Microparticles (>1000 nm) on the other hand exhibit nonspecific deposition in the lungs. The authors made the intriguing observation that mesoscale nanoparticles of 350 to 400 nm accumulated in the kidney with a broad distribution throughout the whole organ.

In a follow-up study in this edition of *Hypertension*, Williams et al[3] investigated the suitability of a poly (lactic-co-glycolic acid) polymer based nanoparticles of ≈350 nm for kidney targeting. The authors observed kidney deposition with a 28×-efficiency compared with the heart and almost 100× compared with the lungs. Similarly, the kidney to spleen and liver uptake ranges around 40× and 60×, respectively. The nanoparticles used in this study exhibited anionic properties, as earlier studies by the same group[2] concluded that the surface charge of these nanoparticles did not alter the distribution of the mesoscale nanoparticles in vivo. A recent study by Yang et al[4] described the development of a positively charged theranostic nanoparticle of around 280 nm built from poly (lactic-co-glycolic acid) incorporating an iron oxide core. Interestingly, the primary site of nanoparticle distribution was the liver, and only on the presence of kidney injury renal uptake was observed.[4] A main difference between the nanoparticles described by Williams et al[3] in comparison to Yang et al[4] was the addition of polyethylene glycol moieties, implying the importance of pegylation to prevent opsonization of nanoparticles for phagocytic uptake by circulating monocytes. This is not surprising as studies have shown that pegylation is commonly used to improve the pharmacokinetics of particles to avoid uptake by the mesoscale nanoparticles, thereby enhancing the half-life of nanoparticles.[1] Importantly, the building blocks of the generated mesoscale nanoparticles, poly (lactic-co-glycolic acid) and polyethylene glycol, are both US Food and Drug Administration approved[5] and the authors have also performed preliminary safety studies with these mesoscale nanoparticles, however, systematic toxicology studies have yet to be performed.

Williams et al[3] determined the exact localization of the generated mesoscale nanoparticles to be the renal proximal tubular epithelial cells. This finding unlocks the unique opportunity of therapeutic targeting strategies in chronic kidney disease, kidney post-transplant rejection, and most importantly for kidney cancer, because renal tubules are usually affected in these diseases. The proximal tubule has in particular been shown to be the site of origin of renal cell carcinoma, a cancer which affects around 300 000 individuals worldwide, and accounts for 80% to 90% of all kidney tumors.[6,7] Diagnosis at advanced stages usually correlates to poor prognosis; in part because of the lack of effective treatments with tolerable/acceptable side effects.[7] The same limitation holds true for various therapeutic approaches in the treatment of chronic kidney diseases. The generated mesoscale nanoparticles, especially as they show long-term deposition in the kidney (up to 28 days) and potentially slow drug release, would address a strong unmet medical need of kidney-targeted therapy.[3]

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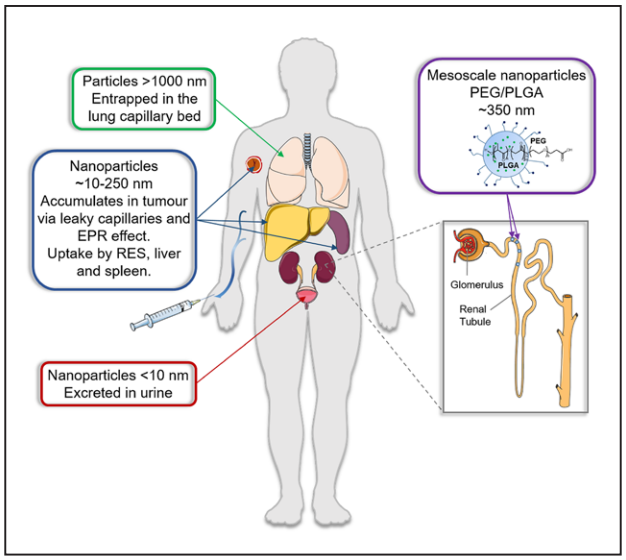

Figure. Specific targeting of mesoscale nanoparticles to the kidney proximal tubules within the size-dependant spectrum of nanoparticle organ biodistribution. EPR indicates enhanced permeability and retention; PEG, polyethylene glycol; PLGA, poly (lactic-co-glycolic acid); and RES, reticuloendothelial system. This figure was generated using Servier Medical Art.

The development of a drug-targeting tool for the kidneys is timely. Major advances have been achieved in developing new therapeutic approaches for kidney diseases, which will benefit substantially from an effective kidney targeting approach. For example, kinase inhibitors such as transforming growth factor-β, kinase inhibitors, p38 mitogen-activated protein kinase inhibitors, and platelet-derived growth factor receptor kinase inhibitors have been established as promising therapeutic approaches for renal fibrosis.[8] Additionally, small interference RNAs disrupting growth factors or profibrotic pathways have also been introduced in preclinical studies for treatment of renal fibrosis.[8] Furthermore, targeted drug delivery may also be useful as a preventative therapeutic approach for ischemia/reperfusion injury post-kidney transplantation, which can lead to inflammation and graft rejection. Ectonucleoside triphosphate diphosphohydrolase-1, CD39 (Cluster of Differentiation 39) is one such anti-inflammatory agent that has recently been described as an attractive therapy for kidney ischemia/reperfusion injury.[9] However, excessive bleeding presents as a main side effect of this approach and as such, selective kidney targeting as well as slow release of drugs such as CD39 in the tubules may bring forth a promising approach for prevention of ischemia/reperfusion injury and organ rejection.[10]

Despite this enthusiastic perspective there are 2 main caveats in relation to the study of Williams et al.[3] First, the study did not elucidate the mechanism by which selective targeting/uptake in the tubular cells is achieved. To avoid unexpected side effects, the mechanism should be clarified before potential clinical applications are contemplated. Second, there is a lack of investigation in an actual preclinical disease model. Would the presence of a disease, which usually involves a change in tissue architecture and permeability as well as the influx of inflammatory cells improve or decrease the targeting of the mesoscale nanoparticles to the kidney? While various animal models of kidney diseases have been established previously,[11] an animal study of targeted therapy in renal cell carcinoma would be of particular interest. Very recently, such a mouse model was introduced by Harlander et al,[12] in which a Vhl, Trp53, and Rb1 gene inactivation in the renal epithelial cell created a mouse model of renal cell carcinoma. Such a preclinical model would seem to be the next logical step toward further proof of concept of a successful therapeutic application of the newly described mesoscale nanoparticles. Furthermore, demonstrating efficacy in a mouse model does not automatically guarantee successful translation in the human disease setting. Moreover, the optimal size and dosing requirement for kidney accumulation will entail careful preclinical toxicology and eventual dose optimization for human clinical studies.

The development of therapeutic nanoparticles is a complex multidisciplinary process, and requires optimal choices in material, size, format, and surface charge. The study by Williams et al[3] demonstrates a pivotal novel development of a carefully tuned poly (lactic-co-glycolic acid)-polyethylene glycol based mesoscale nanoparticle with superior targeting toward the proximal kidney tubules. This study paves the way for further investigations on the development of novel pharmaceutic agents for targeted treatment of multiple kidney diseases including cancers such as renal cell carcinoma.

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Disclosures

None.

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