Biomaterials 35 (2014) 7157–7171

Contents lists available at ScienceDirect

Biomaterials

journal homepage: www.elsevier.com/locate/biomaterials

Kidney-specific drug delivery system for renal fibrosis based on coordination-driven assembly of catechol-derived chitosan

Hongzhi Qiao [a,1], Minjie Sun [a,1], Zhigui Su [a], Ying Xie [a], Minglei Chen [a], Li Zong [a,*], Yahan Gao [a], Huipeng Li [a], Jianping Qi [b], Qun Zhao [c], Xiaochen Gu [d], Qineng Ping [a,*]

[a] Department of Pharmaceutics, State Key Laboratory of Natural Medicines, China Pharmaceutical University, 24 Tong Jia Xiang, Nanjing 210009, China
[b] Key Laboratory of Smart Drug Delivery (Fudan University), Ministry of Education, Shanghai 201203, China
[c] Department of Pharmaceutics, Nanjing University of Traditional Chinese Medicine, Nanjing 210029, China
[d] Faculty of Pharmacy, University of Manitoba, Winnipeg, MB R3E 0T5, Canada

ARTICLE INFO

Article history:
Received 6 March 2014
Accepted 28 April 2014
Available online 23 May 2014

Keywords:
Kidney targeting
Catechol-derived chitosan
Coordination nanocomplex
pH-sensitive
Renal fibrosis

ABSTRACT

Renal fibrosis is a common progressive kidney disease, and there is a lack of efficient treatment for the condition. In this study, we designed a kidney-specific nanocomplex by forming coordination-driven assembly from catechol-derived low molecular weight chitosan (HCA-Chi), metal ions and active drug molecules. The coordination activities of various metals and ligands, cytotoxicity, immunogenicity and biodistribution of HCA-Chi were investigated. Autofluorescent doxorubicin (DOX) was selected to fabricate HCA-Chi-Cu-DOX ternary nanocomplex for investigating cellular uptake behavior, transmembrane and targeting properties. The nanodevice demonstrated satisfactory stability under normal physiological conditions and pH-responsive drug release in acidic environments. Uptake of HCA-Chi-Cu-DOX by HK-2 cells was dependent on exposure time, concentration, and temperature, and was inhibited by blockers of megalin receptor. Tissue distribution showed that HCA-Chi-Cu-DOX nanocomplex was specifically accumulated in kidney with a renal relative uptake rate (r_e) of 25.6. When active anti-fibrosis compound emodin was installed in HCA-Chi-Zn-emodin and intravenously injected to the ureter obstructed mice, obvious attenuation of fibrotic progression was exhibited. It was concluded that HCA-Chi coordination-driven nanocomplex showed special renal targeting capacity and could be utilized to develop drug delivery systems for treating renal fibrosis.

1. Introduction

Renal fibrosis is a common consequence of virtually all progressive kidney diseases, and the number of patients suffering from renal fibrosis has remarkably increased for the past decade [1]. Inflammatory stimulation, epithelial–mesenchymal transition, and accumulation of extracellular matrix (ECM) have all contributed to kidney fibrosis [2–4]; failure to treat renal fibrosis can lead to end-stage renal failure, a devastating disorder that ultimately requires dialysis or kidney transplantation. There is no effective treatment method to directly halt or reverse renal fibrosis [3]. Cytostatic and immunosuppressant drugs used in clinical practice commonly result in significant adverse effects [5].

Several active ingredients from traditional Chinese herbs including triptolide, emodin and salvianolic acid B have recently been tested positive in treating kidney fibrosis [6–9]; these compounds generally contain multiple hydroxyl, carboxyl, amino and aromatic structures and possess versatile pharmacological activities to renal injury (Supplementary Data, Fig. S1). Nevertheless, they have also shown low aqueous solubility, short retention time, and non-specific biodistribution that may compromise clinical applications [10,11]. A clinically appropriate, water-dispersible drug delivery system with specific renal targeting capability is hence desirable in order to increase drug bioavailability and improve therapeutic efficacy *in vivo*.

Glomerular filtration barrier frequently excludes drug carriers like liposomes and antibodies from access to luminal surface of proximal tubular cells [12]. Certain macromolecular carriers with relatively low molecular weight, for example, protein-based, polymeric, and folate-conjugated carriers, were reported to be more appropriate for specific drug targeting to kidney [13–15]. An active ingredient is to be covalently bound to the vehicles in order

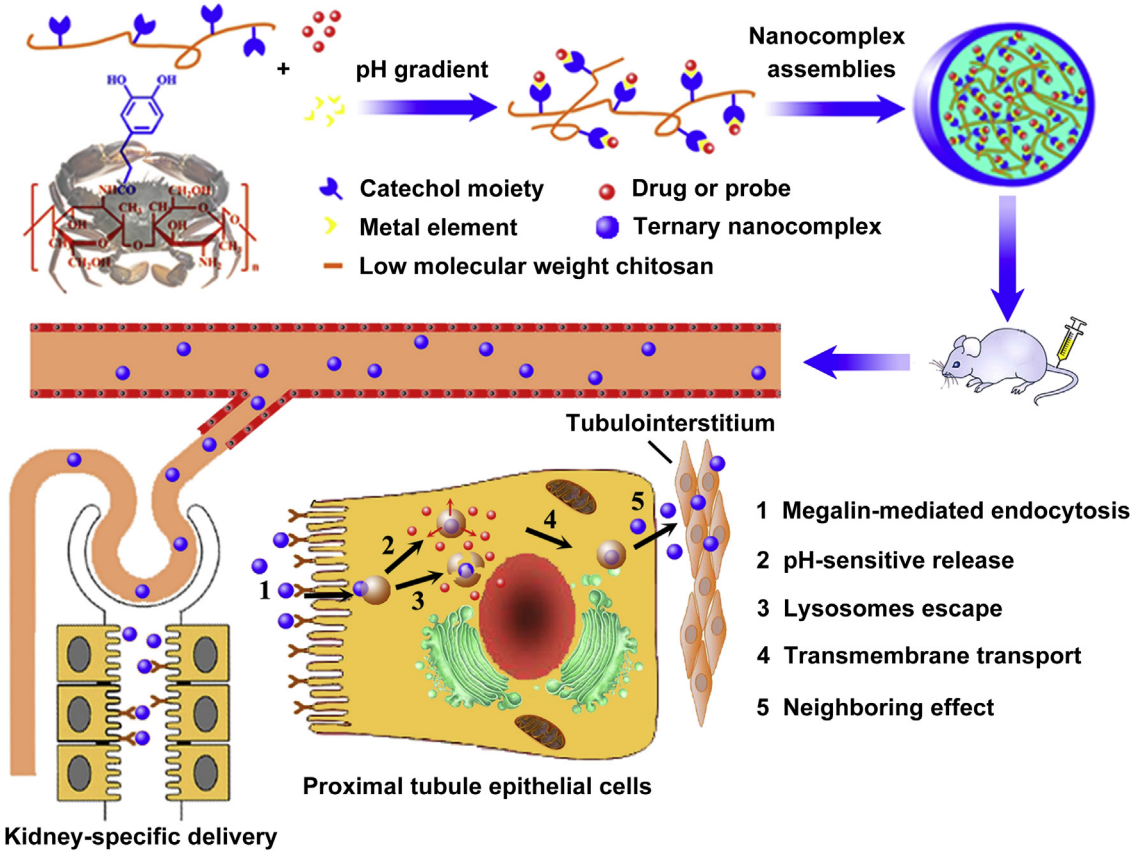
* Corresponding authors. Tel./fax: +86 25 83271092.
E-mail addresses: zong216@yahoo.com.cn (L. Zong), pingqn@cpu.edu.cn (Q. Ping).
[1] The two authors contribute equally to this work.

http://dx.doi.org/10.1016/j.biomaterials.2014.04.106
0142-9612/

to prolong systemic circulation and to increase renal accumulation. However, covalent binding may involve complex and bio-incompatible procedures, subsequently increasing manufacturing difficulty and cumulative toxicity risk [16]. In addition, inflammatory responses due to kidney injury often lead to extracellular acidosis [17], which provides an imperative acidic milieu for pH-triggered drug delivery systems and potentiates burst release of drug in renal nidus. These characteristics could be selectively utilized to design smart drug delivery strategies to target kidney locations and kidney diseases.

Coordination nanocomplexes have recently emerged as a novel family of nanodevices [18]. Their potentials in functionality and flexibility are based on metal-ligand bonding, which have created new perspectives in a variety of fields including smart drug delivery [19]. Compared to traditional nanoparticles, coordination-driven nanocomplex assemblies have multiple selections for metallic elements and tunable dimensionality; superior stability and intrinsic pH-sensitivity of coordination bonds would make them viable for specific drug delivery in physiological conditions and smart release [18]. Furthermore, coordination assemblies are both facile and versatile relative to macromolecular prodrugs, which are capable of minimizing incomplete drug release and reducing cumulative drug toxicity simultaneously. While technical breakthroughs have been made in the field, no application of coordination nanocomplex in kidney drug targeting and delivery has been explored. It is worth noting that assembly of coordination nanocomplex requires appropriate ligands for installing drugs, and many active compounds mentioned above for kidney fibrosis possess potential coordination sites with metals to form nanocomplex delivery systems [20,21].

In this study, we designed a kidney-specific drug nanocomplex primarily based on coordination bonding. Low molecular weight chitosan, which had demonstrated specific kidney targeting accompanied by coordination ability mainly from primary amine [22,23], was selected to prepare a multi-ligand polymeric carrier for drug delivery. In attempting to impart diversiform coordination zones to chitosan, catechol-derived hydrocaffeic acid based ligands inspired by mussels were introduced as high-affinity anchors for coordination and nanocomplex stabilization [24,25]. The coordination nanocomplex was fabricated through a two-step solvothermal method under pH gradient in the presence of catechol-derived chitosan (HCA-Chi), metal ion and the drug. Doxorubicin (DOX) was utilized as a probe for proof of concept because of its autofluorescence and representative coordination functional groups similar to some of the anti-fibrosis compounds. Scheme 1 depicts the proposed mechanism of kidney-specific delivery and intracellular transport of the prepared nanocomplex. The ternary nanocomplex would be stable in circulation system (pH 7.4), thus being specifically transferred to proximal tubule and uptaken into epithelial cells through megalin-mediated pathway. Once endocytosed into cells, the nanocomplex would partially release drug in lysosomes resulting from a pH-stimulated cleavage of coordination bond, while transmembrane transport and excretion at basolateral membrane continue to the tubulointerstitium, producing a neighboring effect [26]. To further verify the potential of this nanodevice in treating renal fibrosis, emodin was selected to fabricate emodin-installed coordination nanocomplex, and its therapeutic viability was further evaluated in unilateral ureter obstruction (UUO) mice.



Scheme 1. pH-response nanodevice based on coordination-driven assembly of HCA-Chi for sequential and kidney-specific drug delivery.