Nephrology and Renal Diseases

Review Article

A mini review highlights on the application of nano-materials for Kidney disease: A key development in Medicinal therapy

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Abstract

Nanoparticles have been one of the emerging tools in medical field as a technology well-suited for the diagnosis and treatment of various diseases. They have been heralded as efficacious owing to both in terms of improved therapeutic efficacy as well as reduction of treatment side effects in some cases. Various nanomaterials have been developed which can be tagged with targeting moieties, and with drug delivery and imaging capability or combination of both as theranostic agent.

Biotechnology to a large extent relies greatly on biomolecules such as proteins and DNA. Research in the field of bio technology will undeniably profit with the initiation of chemical and materials synthesis (e.g. multifunctional nanoparticle systems) that allows fusion of these biomolecules to nanostructured inorganic and organic materials. These nanomaterials have been thoroughly investigated for treatment and detection of various pathological conditions. This mini review highlights, the shape, size of nanoparticles to demonstrate the current research and applications of nanoparticles in the treatment of kidney diseases.

Introduction

Chronic kidney disease (CKD) is characterized by progressive loss of kidney function which decreases the ability of the body to eliminate soluble waste resulting in the gathering of "uremictoxins" [1]. It is now well documented that CKD is an inflammatory disorder and uremic toxins playa major role in creating the inflammatory milieu [1,2]. CKD is defined by either a reduction inglomerular filtration rate (GFR) and/or the presence of abnormalities in the urine such as protein, redblood cells or white blood cells.

Nano particles play a substantial role in one of the most promising technologies, known as nanotechnology. Nano carbon provides huge possibilities to human civilization. Activated carbons have been used since the prehistoric ageand have been playing major roles in many applications [2-4]. In the last decade, nano carbon, consisting of polymeric matrix materials and nano fillers, have held scientific, industrial and academic significance due to their improved properties.At low filler contents as compared with the conventional micro and macro or neat counterparts, theyexhibit superior property enhancements. They willconstitute 20% of demand in 2025. Thermoplastic composites are superior to conventional microscalecomposites and can be synthesized using simpleand inexpensive techniques [4].

Nano material have huge applications in electronics, medical technology, aviation, aeronautics, polymer, engineering fields, and natural products etc. Which plays important role in our daily lifes [5].

Its well documented about the significance of Kidney organ for the survivial of human being. With the technology available for decades there is still need for developing new nano technology. In addition to the technology being somewhat stagnant over the past two and half decades, there is increasing demand for renal replacement therapy or as it's increasingly being called renal substitution therapy because none of these artificial techniques really replace kidney function entirely [3-4]. Itswell known that the epidemic of chronic kidney disease, which is now affecting more than 26 million people in the United States with a very high mortality from cardiovascular disease, and the continued growth of the dialysis population projected to be over 500,000 in this country just by 2010, and we were trying to look for a way to really leapfrog from a technology point of view how patients are treated.

There are 2 general ways to produce nano-materials. The first is to start with a bulk material and then breakdownit into smaller pieces by mechanical, chemical or other form of energy -- this is termed top-down. Additional way is to synthesize the material from atomic or molecular species via chemical reactions, allowing for the precursor particles to grow in size -- this is called bottom-up. Nanotechnology, the ability to work at the atomic and molecular levels, is encouraging research and development investments in pharmaceutical discovery, diagnostics, and drug delivery and is coming to the forefront in the field of Kidney-renal substitution therapy. The novel aspect of bottom-up nanotechnology to engineer ion-selective membranes and how this aids in the management of patients with end-stage kidney-renal disease [4-6].

Since few decades, abundant nanoparticle platforms have been studied for their use in therapeutic applications. Various systems have been applied in the construction of technical systems that

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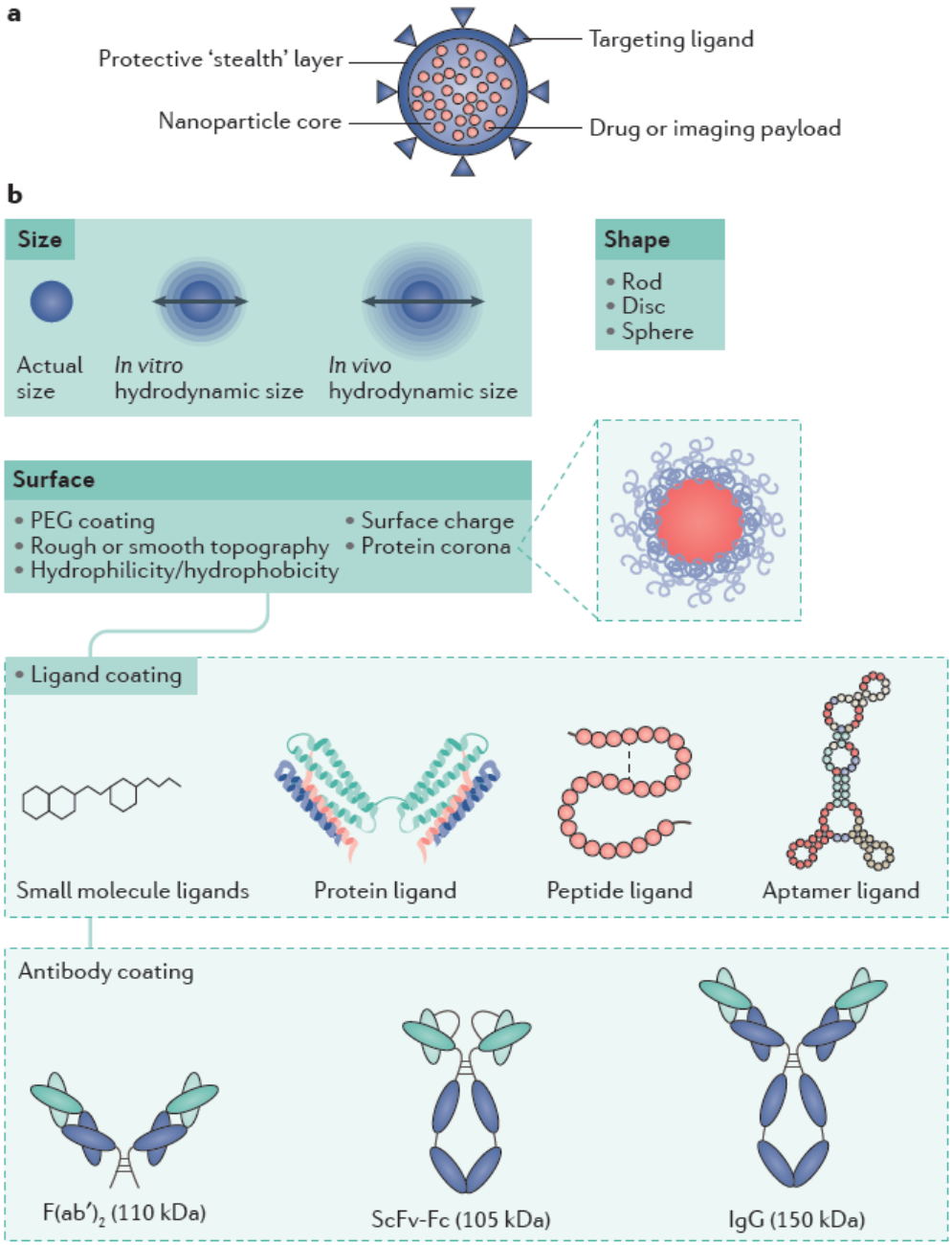

Figure 1. Nanoparticle composition and features. **a.** Nanoparticles are composed ofa core (payload) encapsulated in a protective layer. The surface can be modified to limitthe interactions of the particle with its environment. **b.** Several parameters such as size,shape and surface modification contribute to the biological and physicochemicalproperties of nanoparticles. The investigation of such properties is crucial to achieve thetranslational application of nanomedicines for kidney disease therapy. PEG, polyethyleneglycol; ScFv-Fc, single-chain variable fragment-constant fragment [8-11].

combines different functionalities which bring liposomes, polymer-drug conjugates, polymer-protein conjugates, dendrimers, polymeric micelles, polymerosomes and other nanoparticles into the realm of nanotechnology proper, as opposed to traditional pharmacology or supramolecular chemistry.Therefore, the development of polymeric nanomedicines as therapeutic agents has generated great enthusiasm both in academia and industry. The contribution of polymeric nanomedicines in the treatment of several categories of diseases including Kidney, renal,cancer, inflammatory, immunological diseases, and brain disorders is also presented [6-7].

Abundant studies in tumour therapy demonstrate that NPs can enhance drug delivery, and improve drug Cmax, pharmacokinetics and plasma area under the curve (AUC; ameasure of total drug introduction over time), comparedto the standard dose and formulation [8-11]. Hence forth, NPversus drug pharmacokinetics; encapsulated versus freecirculating drugs; drug versus NP Cmax; drug versus NPAUC; and parameters that can further affect plasma versus kidney pharmacokinetics and AUC are important. drug is generally broad and flat, whereas that of thefree drug peaks and has a tail64. These discoveries implythat NPs might reduce Cmax-associated toxicity, but

not AUC-related toxicity, as the total dose of the drug is stillreleased by NPs, albeit at a reduced rate [11].

Nano Particle size: Nano Particle size has been broadly discovered to design effective nanomedicines. Most therapeutic NPs are 30-150 nm and are not subject to kidney filtration into the urine,unless they are tarnished into particles <10 nm, or theglomerular filtration barrier is damaged by disease (Figure 2). In healthy states, colloids and particles with a hydrodynamic diameter up to 5-7 nm fall below the kidney filtration threshold, pass through the glomerulus and are excreted 188. NPs below 5.5 nm can be excreted via renal clearance, with an efficiency of >50% of the injected dose4 h after administration [12,13].

The transport of NPs in the circulation is subjective to a greater degree by the applied convective forces in blood than by Brownian motion. Therefore, shape has animportant effect on in vivo performance and bio distribution of NPs, which exist in a wide range of geometries [14]. For example, a top-down fabrication method termed particle replication in non-wetting templates (PRINT) utilizes slithography techniques to create polymeric NPs of awide variety of geometries, shapes, and aspect ratios [15,16]. Cylindrical and discoidal shapes are uniquely subject toblood flow (they have high aspect ratios and minimal regions of curvature), which touches their interactionwith macrophages and cell membranes as particles withreduced curvature undergo faster internalization uponincubation with macrophages [17,18]. Similarly, nanowormornanorod (elongated cylindrical) structures showgreater tumour accumulation than other shapes [19,20].

Non-spherical NPs marginate to vessel walls more efficientlythan spherical NPs, although they are also more rapidly cleared depending on their aspect ratio anddimension [18,21-22]. In general, shapes that can sheltercellular membrane wrapping processes are optimalfor cellular internalization [23-24].

Major diseases leading to Kidney failure

There are major disease which leads to kidney failure which has been well studied, these are more Prevalent in developing countries, and since few decades in developed countries due to the food habits, environmental pollutions, work stress, domestic problems, financial problems and many more [25].

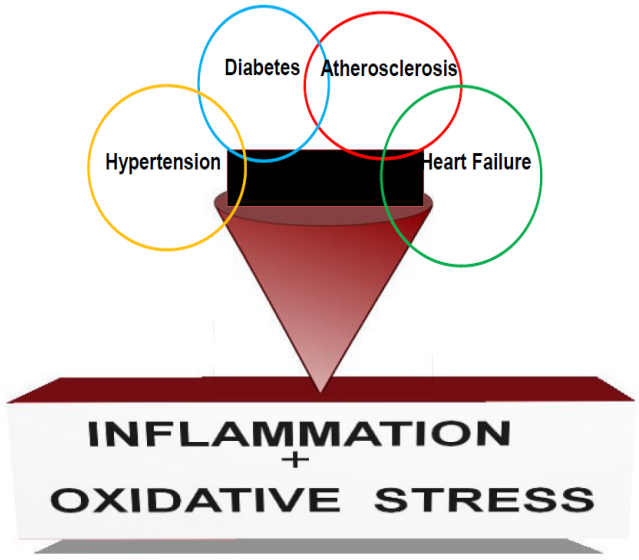

Figure 2. Hypertension, diabetes and atherosclerosis are the major disease which can leadto chronic kidney disease (CKD). Cardiovascular disease such as heart failure is the majorcause of death in patients with CKD. However, CKD can also worsen prognosis ofhypertension, diabetes, atherosclerosis and heart failure. Inappropriate inflammation andtolerance of oxidative stress plays a significant role in the development and prognosis ofthese disease processes [25].

The majority of nano-medicines produced so far have been developed for cancer therapy, as compromised endothelial barriers in tumours facilitate NP retentionow). Over a dozen NP platforms based on liposomes [26-32], albumin [33-37], polymeric micelles [38-41], and nanosized polymer-drug conjugates [42-45] have been ratified by the FDA (Table 1). A few targeted NPs including Her2 scFv-targeted liposomes (MM-302) [46], the first targeted controlled-release polymeric NP BIND-014 [47], and the first targeted short interfering (si) RNA NP CALAA-01 [48] are currently being tested in clinical trials for cancer therapy. Although many nano-medicines improve the pharmacokinetics and bio-distribution of drugs, so far, only one nano-medicine, CPX351, has increased survival in patients with cancer when directly matched with the conventional parent drug [49]. These findings emphasize the need to reconsider strategies for the improvement of NPs, including potential patient selection to identify those most likely to respond to nano-medicines. Nanotechnology-enabled diagnostic and therapeutics based on dendrimers [50-51], gold [52-53], silica [54-55], iron oxide [53,56-57] and hafnium oxide [58-59] are also currently under clinical analysis, with the majority intended for oncological applications. For example gold NPs decorated with a surface of PEG conjugated to TNFα molecules are in phase I/II trials for solid tumour therapy [60]. Silica NPs in combination with gold are being tested in thermal ablation therapy of head and neck cancers [61]. Two MRI contrast agent iron-oxide NPs (Ferumoxtran-10® and Ferumoxytol®) are in clinical trials for cancer imaging [62-63]. A therapeutic version of iron oxide NPs termed NanoTherm® was approved in Europe in 2010 for the thermal ablation of glioblastomas (magnetic hyperthermia treatment) [64]. Clinical trials have begun for the investigation of hafnium oxide NPs (phase I), which will be used as radio-sensitizers in patients with soft-tissue sarcomas [58].

Nano-medicines are also undergoing clinical translation for gene therapy [65], RNA interference [66-68], and immunotherapy [69-70]. Viral NPs have found utility in the delivery of a range of therapeutics and have been clinically confirmed for gene therapy applications [71-73].

Kidney failure results in a build up of toxins and excess waste in the body. Dialysis is the most common treatment, performed daily either at home or in hospital. Nonetheless, dialysis machines require electricity and careful maintenance, and are therefore more readily available in developed countries than poorer nations [73]. Around one million people die each year worldwide from potentially preventable end-stage renal disease.In addition to this, in the aftermath of disasters such as the Japanese earthquakes and tsunami of 2011, dialysis patients are frequently left without treatment until normal hospital services are resumed. With this in mind, Mitsuhiro Ebara and co-workers at the International Center for Materials Nanoarchitectonics, National Institute for Materials Science in Ibaraki, Japan, have developed a way of removing toxins and waste from blood using a cheap, easy-to-produce nano-fiber mesh. The mesh could be incorporated into a blood purification product small enough to be worn on a patient's arm, reducing the need for expensive, time-consuming dialysis [74].

A blood-compatible primary matrix polymer made from polyethylene-co-vinyl alcohol, or EVOH, and several different forms of zeolites - naturally occurring aluminosilicates. Zeolites have

Table 1. Clinical use of nanoparticle [14-24].

Nanoplatform	Composition	Size	Examples of nanoparticles applied to the clinic	Disease indication	Active pharmaceutical ingredient	Clinical status in 2016
Hafnium oxide-based 	HfO_2 NPs	~50 nm	Non-targeted: NBTXR3	Adult soft tissue sarcoma, head and neck cancer	NA (Radiotherapy)	Phase I
Viral 	Viral and virus-like nanoparticles	20–50 nm	Non-targeted: Oncolytic poxvirus JX-594	Stimulation of anti-tumour immune response	Granulocyte colony-stimulating factor	Phase I, Phase II
Exosomes 	Naturally secreted cell-derived vesicles	30–100 nm	Targeted or non-targeted: various biologically derived nanosized exosomes	Immunotherapy of melanoma, colon cancer, diabetes, wound-healing, oral mucositis, gastric cancer (biomarker), oropharyngeal cancer (biomarker), thyroid cancer (biomarker)	Various biological payloads	Phase 0, Phase I, Phase II
Carbon-based 	Polycyclic aromatic hydrocarbons	>1 µm	Targeted or non-targeted: Nanospheres, nanotubes, nanosheets	Breast cancer, lung cancer, other solid tumours	Various poorly soluble therapeutics in high concentrations	Preclinical

microporous structures capable of adsorbing toxins such as creatinine from blood.

The researchers generated the mesh using a versatile and cost-effective process called electrospinning - using an electrical charge to draw fibers from a liquid. Ebara and his team found that the silicon-aluminum ratio within the zeolites is critical to creatinine adsorption [74]. Beta type 940-HOA zeolite had the highest capacity for toxin adsorption, and shows potential for a final blood purification product. Although the new strategy is still in its early stages and not yet ready for production, Ebara and his team are confident that a product based on their nano-fiber mesh will soon be a feasible, compact and cheap alternative to dialysis for kidney failure patients across the world [75].

The newly-fabricated nano-fiber mesh for the removal of toxins from the blood, made by WPI-MANA researchers, may be incorporated into wearable blood purification systems for kidney failure patients [76].

The kidney is aoutstanding organ for targeting of NPs due to its characteristic ability to rapidly clearparticles that are smaller than 10 nm in diameter 12 which is discussed above. This is accounted for by the glomerular filtration unit, the basement membrane, and the interdigitating podocytes. Within the renalcorpuscle, there exists a fenestrated endothelium separating the mesangium from the extracellular matrix. Therefore, 2 nm particles are readily cleared by the kidney, but significantly decreased when size is 6 nm and virtually no renal excretion at 11 nmdiameter [74].

Choi *et al.* [12-13], devised gold-loaded nanoparticles of serial core diameters entrapped by PEGpolymer of various sizes 12. They demonstrated that NPs of 80-100 nm target the mesangium of the kidney, where smaller particles are seen only in the peritubular capillariesand the largest particles are taken up by the Kupffer cells in the RES of the liver and spleen.

Choi *et al.* [12-13] have synthesized pores for in vitro testing; they reported the fabrication of membrane with the pores in it; and we're in the process of working on the scale of methodology to produce a device. One way is the ability to miniaturize the components of the device including the membranes which permits itto be wearable and eventually implantable so that it will be transparent to the patient. Using a nano thickness G membrane, it will eliminate the blood pump and run off the patient's own blood pressure [75-76].

It can be nano-manufactured the G membrane and engineer it in a way to make it completely biocompatible so the interaction of blood with this membrane will be such that author hope to obviate the need for anticoagulation and also eradicate membrane-induced inflammation. In addition, by using this very open G membrane, it should be able to remove all of the important uremic toxins without regard to molecular weight at least up to the molecular weight of albumin [76].

It can be manufacture using nanotechnology the T membrane to make sure we reabsorb necessary substances and if we start seeing depletion syndromes, we can reengineer the pores to eliminate that problem [77-79].

It is hopefully can produce about 60 cc a minute of glomerular filtration, which would restore patients up to early stage 3 chronic kidney disease and hopefully this would be a cost-saving approach. Still it has to be demonstrated that the membrane functions in vitro the way we modeled it on a computer. Then finally if it is a successful, it has the potential for being truely transformational or disruptive technology because it will permit patients to move out of the dialysis center into an ambulatory or home setting and that's something that we need to consider as well [78].

Conclusions

This mini review highlights about application of Nano particle in the treatment of Kidney disease. NPs have unique sizes everything in linking nanotechnology together with biotechnology. NPS size, shape structure play key role in curing kidney disease when compared dialysis which takes more time, and its not guaranteed whether the disease is cured, in order to replace this techniques NP's will play greater role in the treatment of Kidney disease. To a large scope biotechnology relies greatly on biomolecules such as proteins and DNA. Research in the field of neuroscience will definitely benefit with the advent of chemical and materials synthesis (e.g. multifunctional nanoparticle systems) that allows incorporation of these biomolecules to nanostructured inorganic and organic materials. In conclusion as the field of nano-medicine rapidly expands, with several NPs already marketed and many undergoing clinical trials, our accumulated experience and the clinical successes to date form a framework for the creation of a simple technology to irradicate this dreadful disease by utilizing NP's the next generation of Kidney nanomedicines.

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