Materials Today Bio 31 (2025) 101534

Contents lists available at ScienceDirect

Materials Today Bio

journal homepage: www.journals.elsevier.com/materials-today-bio

Nanomaterials for targeted therapy of kidney diseases: Strategies and advances

Zhiwen Wang, Chun Zhang *

Department of Nephrology, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, 430022, China

A B S T R A C T

The treatment and management of kidney diseases pose a significant global burden. Due to the presence of blood circulation barriers and glomerular filtration barriers, drug therapy for kidney diseases faces challenges such as poor renal targeting, short half-life, and severe systemic side effects, severely hindering therapeutic progress. Therefore, the research and development of kidney-targeted therapeutic agents is of great clinical significance. In recent years, the application of nanotechnology in the field of nephrology has shown potential for revolutionizing the diagnosis and treatment of kidney diseases. Carefully designed nanomaterials can exhibit optimal biological characteristics, influencing various aspects such as circulation, retention, targeting, and excretion. Rationally designing and modifying nanomaterials based on the anatomical structure and pathophysiological environment of the kidney to achieve highly specific kidney-targeted nanomaterials or nanodrug delivery systems is both feasible and promising. Based on the targeted therapy of kidney diseases, this review discusses the advantages and limitations of current nanomedicine in the targeted therapy of kidney diseases, and summarizes the application and challenges of current renal active/passive targeting strategies, in order to further promote the development of kidney-targeted nanomedicine through a preliminary summary of previous studies and future prospects.

1. Introduction

The kidneys play a pivotal role in maintaining human homeostasis, and their dysfunction can lead to hypertension, urinary tract infections, and inflammation-related diseases [1,2]. With the advancement of socioeconomic development, kidney disease has emerged as a global epidemic, ranking third among the leading causes of death worldwide and projected to become the fifth highest cause of death by 2040. Currently, 850 million individuals are affected, and the associated treatment costs are draining public health resources, with the US government-funded Medicare program alone spending an estimated $130 billion annually [3–6]. Kidney diseases can be broadly classified into acute kidney injury (AKI) and chronic kidney disease (CKD), with AKI being the predominant form in the former. The two types of diseases are closely linked, and recent studies have demonstrated that poor recovery from AKI is a major risk factor for CKD development. Moreover, the presence of CKD significantly increases the susceptibility to AKI [7]. From a mechanistic standpoint, oxidative stress, inflammation, ischemia-hypoxia, and fibrosis are all contributing factors to the malignant progression of kidney diseases [8]. For a long time, the clinical treatment of kidney disease is still based on non-steroidal drugs, hormones and dialysis. Although it can largely inhibit the progression of kidney disease, it still faces many problems such as poor kidney targeting, short half-life, low kidney utilization, serious systemic side effects and so on. This largely hinders the rapid intervention of kidney disease, leading to disease deterioration. Therefore, the development of kidney-targeted therapeutic drugs is of great clinical significance to solve the above clinical challenges.

The utilization of nanomaterials, with their unique optical, electrical, physical, and chemical properties, to construct novel nanomedicines for disease diagnosis and treatment is a burgeoning field of biomedical research, holding immense potential for addressing maladies such as cancer, cardiovascular diseases, bone repair, and neurological disorders [9–15]. In recent years, the integration of nanomaterials with therapeutic agents has demonstrated remarkable prospects and rapid progress in the realm of renal disease therapy. A diverse range of organic, inorganic, polymeric, and metallic nanomaterials, including liposomes, nanoparticles, low-dimensional nanomaterials, hydrogels, dendritic polymers, mesoporous materials, oncolytic viruses, micelles, and carbon nanotubes, have emerged as “delivery vehicles” for targeted delivery of therapeutic agents (e.g. drugs, mRNA, siRNA) to specific tissues [16–32], cells, and even subcellular compartments. Particularly for poorly soluble drugs with low absorption or short half-lives, nanocarrier-mediated delivery can achieve high-efficiency accumulation in targeted regions. By meticulously designing and modifying the nanomaterials, one can achieve spatiotemporal control over drug delivery, revolutionizing traditional approaches to renal disease therapy. This approach effectively addresses clinical challenges such as poor renal

* Corresponding author.
E-mail address: drzhangchun@hust.edu.cn (C. Zhang).

https://doi.org/10.1016/j.mtbio.2025.101534
Received 28 November 2024; Received in revised form 21 January 2025; Accepted 28 January 2025
Available online 29 January 2025

targeting, severe systemic side effects, and short half-lives, thereby significantly advancing the treatment of renal diseases.

The glomerular filtration barrier is the main obstacle to the delivery of nanomaterials. Therefore, the smooth passage of nanocarries through the glomerular filtration barrier is the prerequisite for the renal application of nanomaterials. As we know, the physical and chemical properties of nanomaterials (such as size, composition, geometry, surface charge, surface functional groups, hydrophilicity and hydrophobicity, rigidity and elasticity) largely determine their potential for renal applications [33–40]. These factors can directly or indirectly affect the uptake of materials or the efficiency of targeting specific cells or organs. Therefore, the development of kidney-targeted nanodrugs should not only have excellent biological safety, but also scientifically design the physical and chemical properties of nanomaterials based on the anatomical structure and physiological and pathological characteristics of the kidney. It is of great significance to learn from the targeting strategies reported in previous studies to promote the development of kidney-targeted nanodrugs.

Despite the rapid advancements in nanomedicine, its application in the realm of renal disease therapy remains in its nascent stages. To address this gap, this comprehensive review aims to critically summarize the strategies and research progress in nanomaterial-based targeted therapies for renal diseases. With a primary focus on renal targeting strategies, we provide a comprehensive overview of currently employed targeted nanomaterials for renal diagnosis and treatment. We categorize these targeting strategies, discuss their prospects and challenges, and highlight our current understanding and future contributions to the development of renal targeted therapies.

2. Anatomical and structural features of the kidney and filtration size requirements

The kidneys, pivotal organs of the urinary system, are situated retroperitoneally on either side of the lumbar spine, resembling bean-shaped structures. Blood enters the kidneys via the renal arteries and exits through the renal veins. The nephron, is a remarkable microscopic

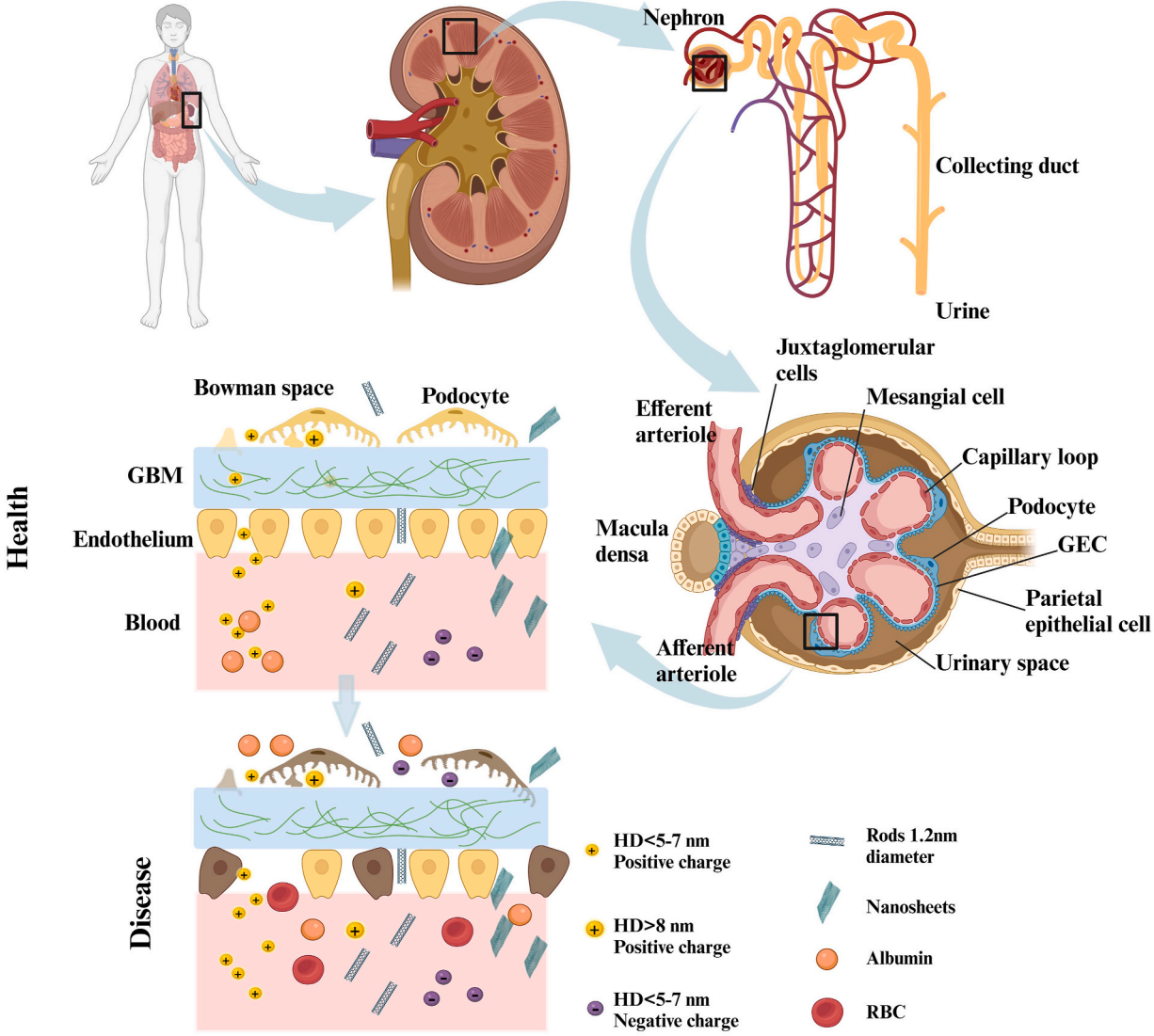

Fig. 1. Anatomical Structure of the Kidney and Various Cell Types. The nephron is the basic structural and functional unit of the kidney, consisting of the renal corpuscle and renal tubule. The renal corpuscle includes the glomerulus and Bowman's capsule, with the glomerulus comprising capillaries. The schematic illustrates the glomerulus and the glomerular filtration barrier in both healthy and diseased states. The latter is composed of glomerular endothelial cells, the glomerular basement membrane, and podocytes. All solutes and molecules with a molecular weight less than albumin (68 kDa) and a hydrodynamic diameter (HD) < 5–7 nm can pass through this barrier. The glomerular filtration barrier is negatively charged and repels negatively charged proteins and nanoparticles under healthy conditions. In disease states, podocyte damage leads to severe impairment of barrier function.

structure that orchestrates the filtration process. Adult kidneys harbor approximately 1–2.5 million nephrons, each composed of two intricate filtering components: the glomerulus and a hairpin-shaped tubule comprising the proximal tubule, the loop of Henle, the distal tubule, and the collecting duct. The glomerulus, a capillary network enveloped by Bowman's capsule, serves as the filtration site. It is composed of glomerular endothelial cells (GECs), a glomerular basement membrane (GBM), podocytes, mesangial cells, and parietal epithelial cells [41–48]. The glomerular filtration membrane (GFM) is the primary executor of the kidney's filtration function. As previously discussed, GFM filtration relies heavily on three distinct barrier components: the endothelium, the basement membrane, and the podocytes. The endothelium consists of a monolayer of endothelial cells with fenestrations of 70–90 nm and a basement membrane composed primarily of type IV collagen, laminin, and proteoglycans. These elements interweave to form a mesh with pore sizes of 2–8 nm. Podocytes, situated on the opposite side of the basement membrane and connected to Bowman's space, exhibit slit pores with diameters of 4–11 nm and are covered by a glycocalyx approximately 200 nm thick [49]. Given the intricate four-layer filtration system of the glomerulus, nanomedicines employed for renal disease therapy must undergo rigorous design and fabrication to minimize excessive losses during the circulation process (Fig. 1).

2.1. Nanoparticle size

The different size of nanoparticle largely determined their different organ distribution. It was found that 150–300 nm nanoparticle were mainly enriched in the liver and spleen, while larger than 1000 nm nanoparticle were mainly trapped in alveolar capillaries. In the case of the kidney, due to the unique structure of the glomerulus, the glomerular filtration of nanoparticles is strongly size-dependent, so the development of nanomedicine for biomedical applications needs to fully consider particle size [50]. As shown in the schematic diagram in Fig. 2, under normal circumstances, the fenestration of glomerular capillaries and the slit diaphragm formed by podocyte foot processes create a physical barrier for blood filtration. Nanoparticles with a particle size <10 nm can successfully pass through the glomerular filtration barrier, such as the ultra-small Tungsten-based nanodots (TWNDs) designed by Huang Q et al. [51]. It can successfully cross the glomerular filtration barrier to reach the renal tubular epithelial cells. However, nanoparticles larger than 10 nm may be trapped in the podocyte foot processes. Moreover, nanoparticles with hydrodynamic diameter (HD) $>$ 100 nm almost did not pass through the endothelium. Specifically, PEG-coated gold nanoparticle substrates with HD $>$ 100 nm could barely pass through the endothelium; However, HD gold nanoparticles in the 6–100 nm range were able to successfully filter through the endothelium and be intercepted by glomerular basement membrane (GBM), resulting in their accumulation in the mesangium, but not in the GBM [52–54]. Remarkably, nanoparticles with HD ranging from 1 to 6 nm can permeate the GFM and are efficiently cleared into the urine, with over 50 % elimination achieved within 4 h post-administration [55,56]. For example, Singh et al. found that silicon nanoparticles with a size of 2.4 $\pm$ 0.5 nm were almost 100 % cleared into urine within 24h [57]. Interestingly, among PEG-modified silica nanoparticles, those with HD of 3.3 nm exhibited significantly faster filtration compared to their 6 nm counterparts (73 % vs. 64 % at 48 h post-injection) [58]. Similarly, gold nanoparticles with HD of 6, 3, 2.4, and 1 nm demonstrated filtration rates of 4 %, 42 %, 52.5 %, and 51.6 %, respectively, at 24 h post-injection [59–61]. These observations underscore that within the 2–6 nm range, smaller nanoparticles exhibit faster filtration rates than larger ones. However, within the 1–2 nm range, nanoparticle clearance efficiency appears to plateau. Guo et al. conducted a classic study in which they prepared nanoparticles with three different diameters of 75/95 and 130 nm, and found that 95 nm nanoparticles had the highest accumulation efficiency, and the accumulation rates of 75 nm and 130 nm nanoparticles were only 56 % and 22 % of 95 nm particles, respectively. More importantly, their study showed that, the renal accumulation rate increased with the particle size of nanoparticles in the range of 100 nm, but the opposite was observed for nanoparticles larger than 100 nm [62]. When disease occurs, it has been shown that nanoparticles in the range of 70–100 nm are present within mesangial cells, which can subsequently pass through the apical membrane into the tubular epithelial cells [63]. Similarly, Yu et al. demonstrated that PLGA nanoparticles with a size of 100 nm were able to accumulate in the injured kidney after ischemia-reperfusion, but not with nanoparticles in the 200–300 nm range, which are not present in the normal kidney [64]. It has also been shown that nanoparticles in the size range of 300–400 nm are also able to accumulate in the kidney [65–68]. Therefore, in pathological conditions, the gap in the filtration barrier increases, which in part promotes the filtration of large nanoparticles. This may be closely related to the enhanced permeability and retention (EPR) effect at the lesion site after injury [69]. However, the specific situation is constantly variable due to the degree of kidney damage, so there is no clear explanation. Therefore, it is a better choice to design nanoparticles based on the barrier filtration requirements under physiological conditions to ensure kidney targeting.

Under pathological conditions, the interspaces of the filtration barrier may widen, potentially facilitating the filtration of larger

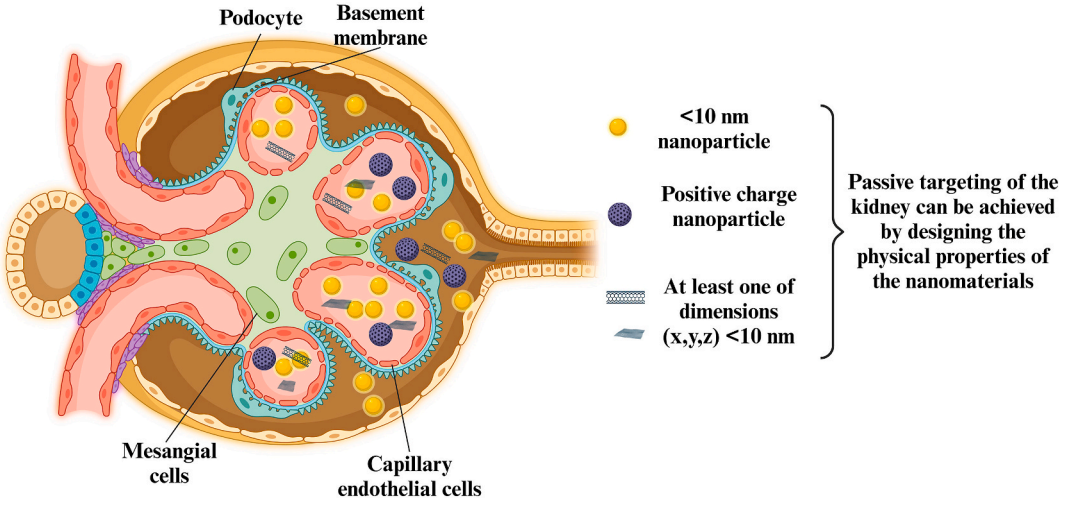

Fig. 2. Renal Passive Targeting of Nanomaterials. By designing the shape, size, and charge of nanomaterials, they can effectively passively traverse the glomerular filtration barrier, enter the Bowman's capsule, and reach the target cells.。

nanoparticles to some extent [70,71]. However, the specific details vary depending on the severity of kidney damage, precluding a definitive explanation. Therefore, designing nanoparticle size based on physiological barrier filtration requirements remains the optimal approach for ensuring renal targeting.

2.2. Nanoparticle shape

While nanoparticle size plays a paramount role in their renal filtration and targeted drug delivery potential, shape also exerts a significant influence on their behavior within the kidney. During transport, blood flow exerts a substantial force on nanoparticles, often surpassing the impact of Brownian motion. As a result, the shape of nanoparticles can influence their in vivo performance and biodistribution to a certain extent (Fig. 1) [72]. Typically, kidney-targeting nanoparticles are designed with a spherical shape. However, research has demonstrated that certain high-aspect-ratio nanomaterials, such as rods, tubes, and sheets, can also rapidly traverse the glomerulus and achieve renal accumulation. For instance, carbon nanotubes with lengths ranging from 100 to 1000 nm and diameters between 0.8 and 1.2 nm, despite having molecular weights of 350–500 kDa, can passively filter through the GFM while maintaining their structural integrity [73]. Similarly, novel two-dimensional nanomaterials, including black phosphorus nanosheets (thickness of 3–4 nm and lateral dimensions of 400–600 nm) and graphene oxide nanosheets (thickness of 1–2 nm and lateral dimensions of ~1 μm), have been shown to rapidly accumulate in the kidneys within a short timeframe [74,75]. A proposed mechanism to explain this phenomenon is that hydrodynamic forces orient these high-aspect-ratio nanomaterials perpendicular to the GBM, enabling them to insert into the interspaces and complete renal filtration. Therefore, beyond the conventional spherical design, high-aspect-ratio nanomaterials can also achieve rapid renal filtration and targeted drug delivery to the kidneys.

2.3. Nanoparticle charge

The glomerular filtration membrane (GFM), the primary barrier to renal filtration, exhibits a net negative charge due to the presence of anionic proteoglycans in the GBM and sulfated heparan sulfate in the podocyte glycocalyx. This inherent charge selectivity influences the filtration rates of nanoparticles with varying surface charges [56,76]. Generally, positively charged nanoparticles tend to favor glomerular filtration due to electrostatic attraction (Fig. 1). For instance, positively charged silica nanoparticles ($\zeta = 5.4$ mV, HD = 2.4 nm) demonstrated a remarkable renal clearance rate of 100 % within 24 h post-injection, while negatively charged gold nanoparticles ($\zeta = -30$ mV, HD = 2.9 nm) exhibited a clearance rate of only 45 % [60,77]. This suggests that a negative surface charge on nanoparticles may enhance their retention within the kidneys, potentially leading to improved therapeutic efficacy. However, the relationship between nanoparticle charge and renal filtration is not as straightforward as simply considering positive versus negative charges. Studies have shown that among negatively charged nanoparticles, the specific charge magnitude can also influence filtration behavior. For example, glutathione-coated gold nanoparticles (GS-AuNPs, HD = 3.0 nm, $\zeta = -50$ mV) and glutathione-cysteine-coated gold nanoparticles (GC-AuNPs, HD = 2.9 nm, $\zeta = -22$ mV) exhibited significantly different renal clearance rates of 28 % ID and ~10 % ID, respectively, within 1 h post-injection [78]. These findings highlight the importance of considering not only the polarity (positive or negative) but also the magnitude of the surface charge when designing kidney-targeting nanomedicines. A fine balance between charge-mediated filtration and retention is crucial for achieving optimal drug delivery to the kidneys. Although these nanoparticles are synthesized from different materials, the charge affects their renal clearance properties, and positively charged nanoparticles are generally cleared faster than negatively charged nanoparticles. A number of methods are commonly used to adjust the charge of nanoparticles, including conjugation of charged ligands such as peptides and application of surface coatings with amine or carboxyl/silanol groups [79]. For example, Hu et al. synthesized fluorescent carbon spots with amine-rich coatings and surface functionalization of carboxyl or silanol groups to obtain nanoparticles with charges varying from 36.6 mV to −52.3 mV [80].

3. Overview of kidney targeting nanomaterials: general mechanisms and influencing factors

3.1. Passive targeting of nanomaterials to the kidney

Passive targeting relies on the inherent physicochemical properties of nanomaterials to achieve kidney-specific localization. Following intravenous administration, nanomaterials navigate the circulatory system and selectively accumulate in the kidneys through glomerular filtration. As previously discussed, the four-layer filtration system of the glomerulus imposes stringent requirements on nanomaterial characteristics, including size, shape, and surface charge. These specific requirements have been elaborated upon in the preceding sections and will not be reiterated here. It is noteworthy that passive targeting of nanomaterials can significantly mitigate the obstacles posed by the circulatory and glomerular filtration barriers, thereby minimizing unnecessary losses of therapeutic agents and facilitating rapid renal accumulation. This approach holds immense promise for both renal drug delivery and targeted renal therapies. Ryan et al. found that polymer-based mesoscale nanoparticles (MNPS) with large diameters (350–400 nm) localized to the kidney 5 to 7 times more efficiently than any other organ when administered in the intravenous tail vein. This is because the nanomaterial is tubular and improves passive targeting of the kidney [81]. Therefore, designing and fabricating nanomaterials tailored to the GFM's characteristics is a fundamental prerequisite for successful kidney targeting therapy (Fig. 2).

3.2. Active targeting of nanomaterials to the kidney

Active targeting employs surface modifications to enhance the homing and retention of nanomaterials in target cells/tissues while improving their uptake. Compared to passive targeting, active targeting introduces a greater degree of "intentionality" by enabling researchers to design and fabricate nanocarriers equipped with specific ligands that impart targeted delivery capabilities. This approach facilitates site-specific therapy with minimal off-target toxicity (Fig. 3).

A common strategy for active kidney targeting involves conjugating targeting peptides to the surface of nanomaterials to facilitate specific anchoring to target cell/tissue-specific molecules. For instance, the kidney-targeting peptide (KKEEE)3K was identified to bind to megalin, a multiligand binding receptor expressed in proximal tubule cells [82]. Studies have demonstrated that PEGylated micelles conjugated with (KKEEE)3K exhibited 35 % renal fluorescence intensity 24 h post-intravenous injection, compared to total fluorescence intensity [83]. Similarly, (KKEEE)3K-conjugated ciprofloxacin also showed substantial accumulation in the kidneys [84]. In addition, modification of exosomal vesicles with KIM-1-targeting peptide LTH also promoted the rapid anchoring of the vesicles to the surface of injured renal tubular epithelial cells. The efficiency of the vesicles was up to five times higher than that of the non-targeted vesicles, and most of them were endocytozed in kim-1^+ cells [85].

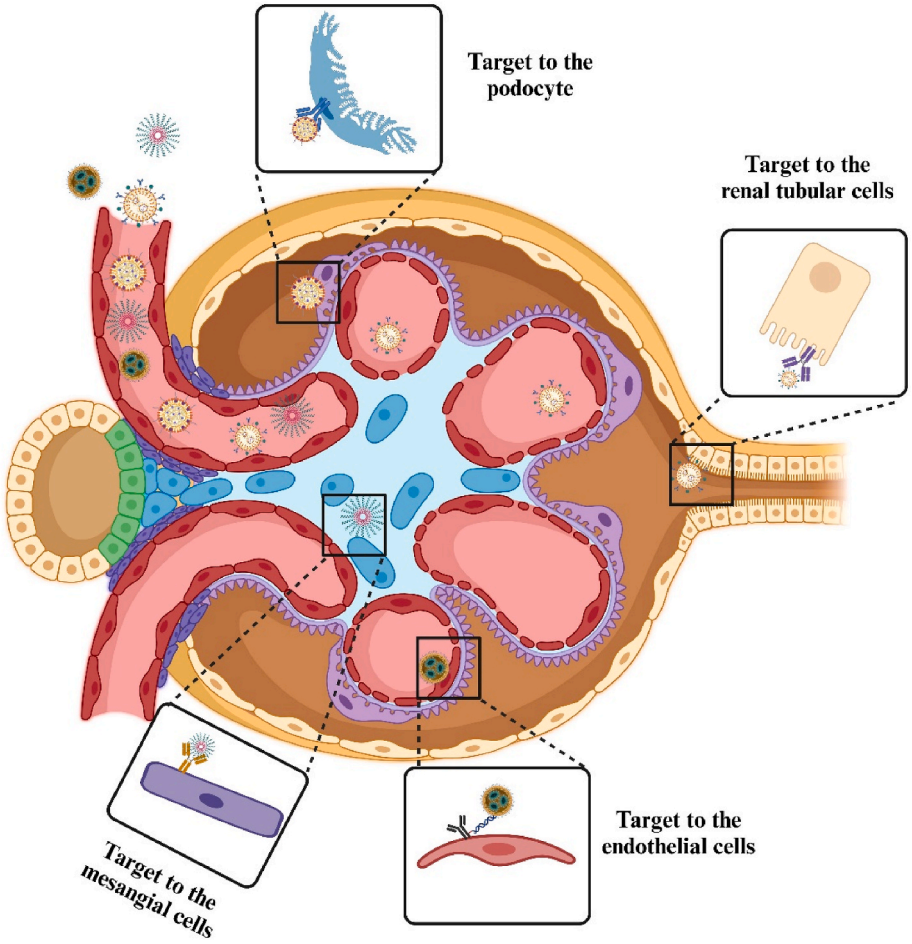

Fig. 3. Renal Active Targeting of Nanomaterials. By modifying the surface of nanomaterials or conjugating them with targeting peptides, nucleic acids, or other molecules, specific targeting of kidney cells can be achieved.

Aptamers, also known as chemical antibodies, are single-stranded DNA/RNA molecules with high specificity and affinity for a wide range of ligands [86–88]. Conjugating aptamers to nanomaterial surfaces to target specific cells is another effective strategy for renal active targeting. For example, NGAL specific aptamer NA53 modified polydopamine nanospheres could effectively bind NGAL protein on the surface of renal tubular epithelial cells after AKI. The limit of detection (LOD) was as low as 6.25 pg/mL^{-1}. The test is up to five times more sensitive than normal tests [89].

CD44, a transmembrane glycoprotein, is overexpressed on the surface of injured renal tubular epithelial cells [90,91]. Under physiological conditions, CD44 can effectively bind hyaluronic acid (HA) [92]. Sun et al. used HA-modified melanin nanoplatform to achieve effective targeting of damaged renal tubular epithelial cells with AKI induced by IRI. After HA modification, the in vitro targeting efficiency of the melanin nanoplatform was as high as 94 %, which was in sharp contrast to the unmodified (80 %) [93]. Therefore, HA-mediated surface modification of nanomaterials to anchor to CD44 receptors is another valuable strategy for targeting renal tubular epithelial cells.

4. Overview of kidney targeting nanomaterials and their current applications in renal diseases

As mentioned above, kidney disease has become one of the major hazards worldwide, and drug therapy for kidney disease has been faced with problems such as poor renal targeting, short half-life and serious systemic side effects. Therefore, drug research and development for kidney targeted therapy is of great clinical significance. In recent years, the development of nanomaterials has promoted more and more research and development of kidney-targeted therapeutic agents or drug delivery systems based on nanomaterials, which has greatly improved the kidney-targeting efficiency of drugs and improved the progress of disease. The types and applications of kidney-targeting nanomaterials are described in detail in the following aspects.

4.1. Nanoparticles: introduction, properties, preparation methods, and applications

Nanoparticles are nanoscale particles prepared from polymers, lipids, or metals [94]. They hold immense potential as drug delivery vehicles, with applications reported in cancer, cardiovascular diseases, respiratory diseases, and renal diseases. As nanotechnology advances, innovative engineered composite nanoparticles are continuously emerging. Through surface modification or functional group conjugation, these nanocarriers enable precise and rapid targeted drug delivery. In the context of renal diseases, designing and fabricating nanoparticles that conform to the glomerular filtration barrier can effectively promote kidney targeting and substantially reduce systemic toxicity. Nanoparticles can be broadly categorized into polymeric nanoparticles and inorganic nanoparticles, which will be discussed in detail below.

4.1.1. Polymeric nanoparticles

Polymeric nanoparticles can be synthesized from natural or synthetic materials, monomers, or preformed polymers, enabling a diverse range of potential structures and properties. Polymer-based nanoparticles are a prominent class of nanocarriers for drug delivery. They are often

arranged in specific sequences, conformations, and structural arrangements, essentially representing a flexible and tunable chemical molecular platform. The unique physicochemical properties of these polymers allow researchers to tailor nanoparticles by controlling their size, shape, and surface chemistry, thereby altering their in vivo biodistribution, loading efficiency, and release kinetics. Biomedically relevant polymeric nanoparticles are typically composed of polymers with excellent biocompatibility and biodegradability, such as poly (lactic-co-glycolic acid) (PLGA), polyethylene glycol (PEG), and chitosan. Currently, a mature set of methods exists for the synthesis of polymeric nanoparticles, including emulsification (solvent displacement or diffusion), nanoprecipitation, ionic gelation, and microfluidics. Therapeutic drugs can be encapsulated within the NP core, embedded within the polymeric matrix, chemically conjugated to the polymer, or attached to the NP surface. This ensures a wide range of deliverable agents, including hydrophobic and hydrophilic compounds, small molecules, biomacromolecules, proteins, and vaccines. Farideh et al. synthesized light-chain-conjugated PLGA NP (LC-NP) specifically designed to target the membrane protein giantin, which is expressed by renal proximal tubular epithelial and renal cell carcinoma cells. After entering the body, LC-NPs are selectively delivered to the kidneys in vivo. LC-NPs accumulated significantly higher in the kidney compared to injections of NPs or PBS alone. The fluorescence signal intensity of LC-NPs in the kidney was 2.7-fold, 3.4-fold, and 2.2-fold higher at 1, 2, and 7 days after injection, respectively. It then descends into the lumen of the renal tubules. The light chains selectively interact with the giant proteins on the membrane of proximal renal tubular epithelial cells, leading to the uptake of NP. This property of LC-NPs can effectively reduce the dose and off-target toxicity of LC-nps. Therefore, their study fully demonstrated the biosafety and biodegradability of PLGA [95]. Notably, polymeric nanoparticles can be pre-designed to control their composition, response conditions, surface charge, and stability, leading to differential drug loading efficiency and release profiles.

4.1.2. Inorganic nanoparticles

Inorganic nanoparticles are typically based on metals and non-carbon elements, with representative examples including gold nanoparticles, metal salts, quantum dots, and mesoporous silica nanoparticles. Due to their controllable nanostructure, large surface area, diverse surface chemistry, and unique optical and magnetic properties, inorganic nanoparticles have demonstrated immense potential in nanomedicine [96]. Notably, their ability to scavenge reactive oxygen species (ROS) has led to their widespread application in various ROS-related diseases [97,98], including acute kidney injury (AKI). For instance, Dalong Ni and colleagues reported molybdenum-based polyoxometalate (POM) nanoclusters as a new type of nanoantioxidant to protect the kidney with preferential renal uptake. Their findings demonstrated that POM nanoclusters with an average diameter of approximately 1 nm exhibited excellent renal uptake and effectively inhibited AKI progression [99]. As nanotechnology advances, the preparation techniques for inorganic nanoparticles are becoming increasingly mature and diverse. Common preparation methods include hydrothermal synthesis, precipitation, sol-gel, redox, and template methods [100]. However, the limited biocompatibility and targeting ability of inorganic nanoparticles have hindered their biomedical applications to some extent. To address this issue, researchers often employ surface modification techniques, the most common of which is PEGylation [101]. This approach not only reduces reticuloendothelial system (RES) uptake of nanoparticles but also enhances their tissue or cell targeting capabilities by anchoring targeting moieties to the PEGylated inorganic nanoparticle surface. Additionally, utilizing cell membrane-coated inorganic nanoparticles to evade the immune system has gained significant research attention in recent years. Examples include red blood cell membrane, platelet membrane, and macrophage membrane coatings [102–105]. As mentioned earlier, the composition of inorganic nanoparticles is largely based on metal elements, which may pose toxicological concerns in biomedical applications, presenting a significant challenge for clinical translation. However, recent research has revealed that specific metal ions or trace elements released from many inorganic nanoparticles can act as therapeutic agents or treatment modalities for various diseases in target tissues. Upon cellular uptake, these trace elements or metal ions can influence relevant intracellular mechanisms, such as redox balance, cell signaling, migration, and photothermal effects [106]. This not only alleviates researchers' concerns but also lays a better foundation for the broader biomedical applications of inorganic nanoparticles.

4.2. Nanogels

Hydrogels, crosslinked networks of hydrophilic polymers, can retain significant amounts of water, making them excellent carriers for drug loading and release [107,108]. Nanogels, as the name suggests, are hydrogel particles with nanoscale dimensions. Compared to macroscopic hydrogels, their nanometer size facilitates cellular uptake via receptor-mediated endocytosis, rendering them suitable carriers for various chemotherapeutic drugs, antisense nucleotides, siRNA, and peptides [109–112]. As a "fusion" of nanoparticles and hydrogels, nanogels possess the high water content and mechanical properties of hydrogels, along with the controllable size and large surface area characteristic of nanocarriers, making them an ideal choice for drug delivery.

4.2.1. Advantages of nanogels

Firstly, nanogels exhibit high biocompatibility and can easily disperse in aqueous media. In studies using injectable nanogels for the treatment of bone and joint injuries, no inflammatory reactions were observed, indicating excellent biocompatibility [113,114]. Additionally, the cross-linked network of nanogels can capture molecules of various sizes within the hydrophilic network, maintaining the proper spatial conformation of proteins and enzymes to preserve their biological activity [115,116]. Notably, the properties of nanogels can be customized by altering their size, cross-linking density, and surface characteristics [117,118]. For instance, when loading drug molecules smaller than the mesh size of the nanogel, drug molecules may be lost during loading, resulting in low loading efficiency. This issue can be addressed by changing the cross-linking density of the nanogel [119,120]. Similarly, strongly charged biotherapeutics (such as nucleic acids) can be loaded into nanogels with opposite charges, achieving stable fixation of drug molecules under physiological conditions and subsequently releasing them as the gel degrades, providing a sustained therapeutic effect [121–123].

Moreover, modifying the surface properties or selecting the components of nanogels can enable responsive degradation, such as ROS-responsive degradation and pH-responsive degradation. This allows rapid degradation of nanogels based on the physiological differences between intracellular and extracellular environments [118,124,125]. Such responsive degradation not only ensures effective drug release but also enables targeted release in diseased areas based on the characteristics of the disease microenvironment, thereby improving drug utilization efficiency.

4.2.2. Preparation of nanogels

The network structure of polymeric nanogels is composed of homopolymers or copolymers and can be linked through covalent bonds

(chemically crosslinked gels) or weak interactions (physically crosslinked gels) [126]. Covalent crosslinking generates a stable polymer network, and the size and morphology of the gel can be controlled by fine-tuning the hydrophilic and hydrophobic components [127]. Additionally, nanogels can be synthesized via physical interactions between polymers, such as hydrogen bonds, electrostatic interactions, and host-guest interactions. Compared to covalent crosslinking, physically crosslinked nanogels offer a simpler preparation process and enhanced biocompatibility [128]. For example, Kiyono et al. designed and prepared cholesterol-group branched starch that can form nanogels in water via physical crosslinking and capture proteins through hydrophobic interactions, enabling needle-free vaccine delivery [129].

4.2.3. Nanogels as therapeutic drug carriers

As discussed earlier, the high loading capacity, stability, and environmental responsiveness of nanogels make them an excellent choice for drug delivery systems. Biotherapeutics can be incorporated into nanogels via physical entrapment, covalent coupling, or self-assembly, leading to the formation of stable nanocarriers. Fujii et al. investigated the potential of cholesterol-cyclic amyloss self-assembled nanogels with spermine groups (CH-CA-Spe) to deliver vascular endothelial growth factor (VEGF) -specific short interfering RNA (siVEGF) to kidney cells. They co-cultured the nanogel and cells, and the results showed that the nanogel complex did not exhibit any significant toxicity to the cells [130]. With the advancement of nanogel technology, targeted delivery, efficient drug release, controlled release characteristics, biocompatibility, and biodegradability of nanogels as drug carriers have become research hotspots, continuously providing innovative solutions for disease treatment and enabling precision therapy for various ailments.

4.3. Liposomes

Liposomes are spherical vesicles primarily composed of lipids, featuring a lipid bilayer membrane and an aqueous core. Their typical size ranges from 100 to 200 nm, enabling the incorporation of hydrophobic drugs into the membrane while encapsulating hydrophilic drugs within the aqueous core [131]. The amphiphilic nature of the lipid membrane allows for surface modification with various targeting ligands or other small molecules, conferring targeted drug delivery to specific cells or organs [132]. Liposomes can be categorized based on their size, bilayer number, and composition. According to the number and thickness of their bilayers, liposomes are classified into two groups: unilamellar vesicles (ULVs) and multilamellar vesicles (MLVs). ULVs are surrounded by a single lipid bilayer and are further categorized based on their size into small unilamellar vesicles (SUVs), large unilamellar vesicles (LUVs), and giant unilamellar vesicles (GUVs), with respective sizes of 30–100 nm, 100–1000 nm, and 1–100 μm. MLVs consist of multiple lipid bilayers and typically reach diameters of hundreds of nanometers [133–135]. Different types of liposomes exhibit distinct properties in drug delivery applications. For instance, small-sized liposomes can effectively traverse various physiological barrier systems, enhancing passive targeting capabilities, while larger liposomes can improve drug encapsulation efficiency and be actively targeted through surface modifications.

4.3.1. Liposome properties

Liposomes offer several advantages as drug delivery systems, including excellent biocompatibility, high drug loading capacity, and tunable physicochemical properties. Additionally, liposomes can alter the pharmacokinetics of drugs by protecting them from premature inactivation, degradation, and dilution in the bloodstream, a crucial aspect for RNA therapeutics [136–139]. Naked RNA is a negatively charged hydrophilic macromolecule that is difficult for cells to uptake due to electrostatic repulsion from the cell membrane and is rapidly degraded by RNA enzymes. Encapsulation of RNA within liposomes provides an opportunity to deliver both the cell membrane and released RNA to the cytosol. The FDA-approved mRNA-LNP COVID-19 vaccine (Comirnaty) and Moderna's COVID-19 vaccine's emergency use authorization (EUA) further demonstrate the safety and applicability of LNP-based nucleic acid delivery methods for various therapeutic agents [140].

4.3.2. Liposome preparation methods

Various methods exist for liposome preparation, but all methods can be broadly categorized into two steps: drying lipids from an organic solvent and dispersing the lipids in an aqueous solution. Common preparation methods include lipid vesicle extrusion, lipid film rehydration, nanoprecipitation, and microfluidic mixing [141]. Conventional preparation involves rapid mixing of some form of aqueous and lipid components. However, microfluidic technology has gained increasing popularity in recent years due to its enhanced reproducibility and control over liposome size uniformity. Microfluidics enables precise modulation of liposome size and encapsulation volume by altering flow parameters [142]. Microfluidic liposome preparation techniques can be classified into droplet-based and continuous flow-based systems [143]. Liposome preparation relies on the power of self-assembly, where lipid components spontaneously organize into nanoscale structural entities based on intermolecular interactions. Liposome formation begins with electrostatic interactions between negatively charged nucleic acids and positively charged lipids, followed by growth driven by hydrophobic and van der Waals interactions between the lipid components [144].

4.3.3. Liposome applications in kidney diseases

The structural features of the kidney dictate that particles smaller than 10 nm can be rapidly cleared by the kidney, while particles larger than 150 nm are eliminated by phagocytosis of the immune barrier [145,146]. Therefore, liposomes in the range of 10–150 nm can achieve targeted drug delivery to the kidney. Additionally, the excellent biocompatibility, surface modification properties, membrane permeability, and cell-uptake capability of liposomes make them ideal candidates for kidney disease applications. Specific size tailoring of liposomes using microfluidic technology, surface ligand modification, or alteration of their composition can effectively achieve specific passive and active targeting to kidney diseases. For instance, surface modification with E-selectin antibody [147], integrin αIIbβ3 [148], glucose ligand [149], and CD44 receptor [150] has been employed to achieve active targeting in the kidney. Antibody-based targeting is another effective strategy for promoting kidney targeting of liposomes. For example, Fab fragments targeting the mesangial cell-specific ligand Thy1.1 demonstrated six-fold higher kidney accumulation of targeted liposomes compared to unmodified liposomes and effectively anchored and colocalized with mesangial cells [151]. Besides surface modification, altering liposome charge can also facilitate kidney active targeting. For instance, incorporating TRX-20 into the liposome surface generates a positive charge, which not only facilitates electrostatic attraction of negatively charged drugs (particularly nucleic acids) into the liposome assembly but also enhances liposome targeting to endothelial cells and mesangial cells [152]. Fang et al. designed a liposome-nanoparticle hybrid for co-delivery of dexamethasone and TGFβ1-siRNA to effectively inhibit glomerular inflammation and fibrosis. They comodified AuNPs with PEG and α8 integrin antibody to obtain gold nanoparticle immunoliposomes (Au-ILs). Next, Au-ILs were loaded with dexamethasone and TGFβ1 siRNA to obtain DXMS/siRNA@Au-ILs. The results of cell experiments showed that about 95 % of cells were still alive when

co-cultured with nanoparticles for 48–72 h. This indicates that liposomes have low cytotoxicity and good safety as a drug delivery system [153]. Overall, whether through size modulation or surface chemical modification, the targeted application of liposomes for kidney diseases holds immense promise.

4.4. Low-dimensional nanomaterials

Low-dimensional nanomaterials have attracted significant attention in the biomedical field due to their unique properties arising from their atomic thickness in one or more dimensions. These materials can exhibit exceptional flexibility and maintain excellent performance. Low-dimensional nanomaterials are classified as 0D, 1D, or 2D based on their size and aspect ratio. Their atomic structures and morphologies are shown in Fig. 1 [154]. Common examples of low-dimensional nanomaterials include carbon nanotubes, quantum dots, graphene, MXenes, and black phosphorus nanosheets. The rich binding sites, excellent cellular permeability, and high surface area of low-dimensional nanomaterials make them ideal materials for efficient drug and biomolecule loading, specific surface modification, and targeted cellular delivery [155]. Here, we focus on several representative low-dimensional nanomaterials and their applications and advantages in the kidney field.

4.4.1. Ceria nanoparticles

Ceria nanoparticles (CeNPs) are a type of zero-dimensional nanomaterial, meaning they are confined to the nanoscale in all three dimensions and exhibit uniform size characteristics in each dimension [156]. Unlike traditional lanthanide elements, cerium can exist in a stable form as both tetravalent and trivalent cations in physiological solutions. This is attributed to the relatively low reduction potential of Ce4+ (1.74 V at 1 m HClO4), which facilitates the redox switching between Ce3+ and Ce4+. As a result, CeNPs have been extensively studied as antioxidants in the biomedical field. In fact, the free radical scavenging properties of CeNPs can be compared to those of natural enzymes (such as SOD, CAT, and GPX) and non-enzymatic antioxidants (such as ascorbic acid and glutathione) [157]. For instance, CeNPs can convert superoxide anions into hydrogen peroxide or molecular oxygen [158]. Their redox cycling can eliminate various types of ROS, offering a significant advantage over natural enzymes. Numerous studies have demonstrated the therapeutic efficacy of CeNPs for various ROS-related diseases. However, the dosage and administration route vary depending on the disease type. In the context of kidney disease, oxidative stress plays a crucial role in the development and progression of acute kidney injury (AKI). Several studies have reported the use of CeNPs to mitigate the severe oxidative stress induced by excessive ROS following AKI. For example, Manne et al. [159] employed CeNPs (10–40 nm) intravenously injected to significantly alleviate peritonitis-induced AKI. The intervention led to remarkable improvements in glomerular capillary network damage and tubular injury in the kidneys of treated rats. Similarly, Zhang et al. [160] synthesized ultra-small CeNPs (3–4 nm) that effectively accumulated in the kidneys. They found that intervention with ultra-small CeNPs significantly restored serum creatinine and blood urea nitrogen levels and improved tubular injury and renal cell apoptosis in an rhabdomyolysis-induced AKI model. In addition, Yu et al. [25] and Weng et al. [161] demonstrated the efficacy of CeNPs in treating LPS-induced AKI and cancer chemotherapy-induced AKI, respectively. These findings collectively highlight the promising therapeutic potential of CeNPs for ROS-related kidney diseases and underscore the immense potential of zero-dimensional nanomaterials in the kidney field.

4.4.2. Carbon nanotubes

Carbon nanotubes (CNTs), as one of the most representative one-dimensional nanomaterials, are formed by rolling up single or multiple layers of graphite sheets and have a large specific surface area (50–1315 m2 g−1). Their radial dimensions are nanoscale, while their axial dimensions are microscale, resulting in an aspect ratio far exceeding that of traditional fiber materials, making them highly efficient drug carriers [162]. Additionally, the remarkable biocompatibility of CNTs enhanced by surface functionalization, along with their inherent low or no immunogenicity, has all contributed to their growing significance in drug delivery and tissue engineering [162–164]. The clinical application of biomaterials first and foremost requires addressing the toxicity, pharmacokinetics, and biodegradation or clearance of nanomaterials. Therefore, extensive research has focused on surface functionalization of CNTs to achieve their clinical safety. Through functionalization, CNTs can simultaneously accommodate both lipophilic [165] and hydrophilic drugs [166]. Moreover, CNTs can themselves enter the cytoplasm through various energy-dependent pathways, such as endocytosis and phagocytosis, significantly enhancing the ability to deliver drugs to cells [164,167]. The application of CNTs in the kidney field has already been reported. For instance, Alidori et al. employed ammonium-functionalized single-walled carbon nanotubes (fCNTs) to mediate the targeted and efficient delivery of siRNA to renal proximal tubule epithelial cells. Approximately 22 % of the dose was localized to the kidney within 1 h after injection, indicating good specificity and stability of the platform in vivo. The fCNT delivery system resulted in a 10-fold increase in siRNA accumulation in the kidney compared with the control. Compared to siRNA alone, fCNTs improved siRNA delivery efficiency and effectively knocked down the expression of several target genes, including Trp53, Mep1b, ctr1, and EGFP. Their findings demonstrated that fCNT-mediated siRNA delivery successfully reduced the expression of related mRNA and proteins in the kidney following cisplatin-induced AKI injury, minimized fibrosis and immune cell infiltration, and exhibited excellent blood clearance, biodistribution, and renal clearance in monkeys. Additionally, the results also showed good biocompatibility of fCNT and siRNA, and no nephrotoxicity was observed. The fCNT/si Trp53/si Mep1b combination was also able to maintain the message and protein expression of p53 and meprin-1β at baseline after nephrotoxic injury and pharmacologically protected mice from renal injury [168]. These results strongly support the potential of CNTs in the field of kidney disease therapy. Of course, if this study can further verify the therapeutic effect on AKI induced by different causes or other kidney disease models, it will be important to evaluate the long-term biological safety of this agent to promote further application.

4.4.3. Graphene and its derivatives

Graphene, a single layer of graphite, is one of the most prominent carbon nanomaterials alongside fullerenes and carbon nanotubes. It is a two-dimensional structure composed of sp2-hybridized carbon atoms [169]. Graphene-based nanosheets (GNS), including graphene nanosheets, graphene oxide nanosheets (GO), and reduced graphene oxide nanosheets (rGO), have nanoscale lateral dimensions [170,171]. Their exceptional surface area enables maximum adsorption of various compounds, including drugs, antibodies, proteins, and nucleic acids (such as aptamers) [171]. This property lays the foundation for the application of graphene-based nanosheets in drug delivery and immunoassays. Numerous methods exist for producing graphene-based nanosheets. While the initial physical exfoliation method is simple, its limited scalability restricts its applicability for large-scale production. Therefore, researchers predominantly employ chemical exfoliation methods, including GO and rGO, to synthesize graphene-based nanosheets. GO

possesses abundant oxygen-containing functional groups, such as carboxyl, hydroxyl, carbonyl, and epoxy groups, on its surface. These groups allow for the attachment of various molecules (e.g., proteins, peptides, nucleic acids) or nanomaterials to the GO surface via π-π interactions, hydrogen bonds, or chemical reactions (e.g., amination, esterification) [172]. Tyagi et al. developed cellulose acetate (CA)-functionalized graphene oxide (GO) beads (~1.5–2 mm) for direct hemoperfusion to treat kidney dysfunction. Their study demonstrated that CA-functionalized GO effectively adsorbs toxins from the bloodstream, including creatinine, urea, and bilirubin, while preserving red blood cells, white blood cells, and platelets. In vitro experiments revealed that the intervention effectively restored creatinine and urea levels within 2 h, offering a potential therapeutic strategy for patients with renal failure [173].

Furthermore, Fu et al. investigated the therapeutic efficacy of a fasudil (FSD)-loaded graphene oxide-bovine serum albumin (GO-BSA) biocomposite for treating sepsis-induced AKI. Their findings indicated that intraperitoneal injection of GO-BSA/FSD significantly improved serum creatinine and blood urea nitrogen levels following endotoxin-induced AKI. Histological evaluation revealed a marked reduction in glomerular and vascular pathology scores in the treated kidneys, demonstrating the substantial protective effect of GO-BSA/FSD against sepsis-induced AKI in rats. Furthermore, the cell viability was judged by morphological assessment of live/dead staining measurements, and the results showed that the structure of HEK293 cells was barely distinguishable from that of the control cells, indicating the good biocompatibility of the GO nanosheets [174].

4.4.4. MXenes

MXenes, a class of two-dimensional nanomaterials, are transition metal carbides, nitrides, and carbonitrides with a "concertina-like" microstructure. They are prepared by selectively etching the A atomic layer of the corresponding 3D MAX phase. The general chemical formula of MXenes is Mn+1XnTx, where M represents a transition metal (e.g., Ti, Y, Zr, Hf, V, W, Nb, Ta, Cr, Sc), X denotes C and/or N, and Tx represents surface functional groups (e.g., O, OH, F) determined by the starting materials and synthesis methods [175]. Two-dimensional nanomaterials have attracted considerable attention due to their exceptional loading capacity (for drugs, imaging agents, and 0D nanoparticles), photothermal conversion, and catalytic properties [176]. Compared to conventional two-dimensional nanomaterials, the properties of MXenes (e.g., bandgap, elemental composition, photothermal conversion efficiency) can be readily tuned by adjusting size, surface modification, and elemental composition [177,178]. Importantly, the abundant functional groups (e.g., OH/-F/-CL) on MXene surfaces facilitate the loading of other functional nanomaterials (e.g., imaging particles, nanozymes, and nanosensitizers), enabling them to acquire additional functionalities and achieve synergistic treatment of biological diseases [179]. In the context of kidney disease, Zhao et al. employed polyethylene pyrrolidone (PVP)-modified ultrathin single-layer Ti3C2 MXene nanosheets to construct a novel nanozyme for AKI therapy. PVP modification enhanced the colloidal stability and biocompatibility of MXene nanosheets. The TEM results indicate that the nanodots produced by MXene degradation can be rapidly excreted from the body, thus suggesting that the long-term toxicity of MXene nanosheets is negligible. In addition, intracellular degradation assays confirmed that MXene could be degraded by cells, and excretion routes such as urine and feces showed that nearly 35 % of the Ti content was excreted from the mice 24 h after intravenous injection. Therefore, Ti3C2 MXene generally exhibits good biocompatibility and biodegradability as a potential biomaterial for clinical demand. Additionally, leveraging the high reactive activity of MXene towards ROS, the nanozyme rapidly cleared excessive ROS in the injured areas of the kidney following AKI, effectively suppressing oxidative stress progression. Their findings further demonstrated that by eliminating excess ROS, MXene nanozymes could exert antioxidative and anti-inflammatory protection through the inhibition of the nf-kb signaling pathway [180]. Unfortunately, they only explored the inhibitory effect of MXene 's own ROS scavenging on AKI, ignoring the strong loading capacity of MXene, and did not carry out drug delivery for the treatment of kidney disease. With the deepening of research, we believe that MXene nanosheets can play a greater potential in the field of kidney disease treatment through surface modification and drug loading.

4.4.5. Black phosphorus nanosheets

Since its discovery in 2014, black phosphorus (BP) has garnered immense research interest due to its unique structure and remarkable properties [181]. As the most stable allotrope of phosphorus, BP consists of puckered honeycomb layers of phosphorus atoms held together by strong intra-layer P-P bonds and weak interlayer van der Waals forces [182]. Consequently, ultrathin single-layer or multilayered nanosheets can be exfoliated from bulk BP by disrupting the weak interlayer interactions. Common approaches include "top-down" or "bottom-up" methods [183]. Compared to other two-dimensional nanomaterials (e.g., graphene), the 2D puckered structure of BPNSs (black phosphorus nanosheets) results in a larger surface area, making them inherently advantageous for drug loading. Additionally, the abundant surface modification sites on BPNSs allow researchers to tailor their surface properties to suit specific experimental needs. This capability not only enables modulation of BPNSs' behavior in vivo, such as cellular uptake, transport, and clearance, but also permits their functionalization with multiple recognition molecules, imparting active targeting abilities. Notably, BPNSs can degrade in vivo to non-toxic phosphates, further promoting their biomedical applications [184–186]. In the context of kidney disease, BPNSs' high ROS (reactive oxygen species) scavenging activity, excellent biodegradability, and large surface area make them an ideal candidate for therapeutic intervention. Notably, the honeycomb-like structure of BPNSs resembles the architecture of glomerular filtration units, enabling passive transport to the kidneys and achieving efficient drug accumulation. This property significantly enhances the efficacy of kidney-specific drug delivery. Hou et al. pioneered the exploration of BPNSs for AKI (acute kidney injury) therapy. Their findings demonstrated that intravenous administration of BPNSs in rhabdomyolysis-induced AKI mice effectively suppressed AKI progression. As expected, BPNSs rapidly accumulated in the kidneys following injection, promptly scavenging excessive ROS and degrading into oxidized phosphorus upon ROS reaction. Further investigation revealed that BPNS intervention mitigated cellular apoptosis in the kidneys of AKI mice, significantly restored serum creatinine and blood urea nitrogen levels, and substantially reduced renal tissue structural damage [75]. Based on these findings, BPNSs can serve as kidney-targeted shape--dependent transporters, enabling precise drug delivery to the kidneys through therapeutic agent loading or surface modification. Additionally, BPNSs' inherent ROS scavenging activity effectively eliminates excessive ROS and suppresses oxidative stress progression, making them a promising nanomaterial for kidney disease therapy.

4.5. Functionalized framework nucleic acids

4.5.1. Tetrahedral framework nucleic acids

Since their successful development by Turberfield, tetrahedral framework nucleic acids (tFNAs) have garnered significant attention due to their versatile functionalization strategies and broad applications in various biomedical fields [187]. Considered the simplest polyhedron, tFNAs encompass both DNA and RNA tetrahedra. In the realm of

biomedical applications, tFNAs offer numerous inherent advantages, including biocompatibility, biodegradability, structural stability, exceptional programmability, functional diversity, and ease of cellular internalization. Compared to traditional nanomaterials, tFNAs exhibit superior cellular uptake properties. Fan et al. demonstrated that by orienting tFNAs with their corners attached to the cell membrane, electrostatic repulsion is minimized, leading to charge redistribution. Subsequently, tFNAs are internalized via a caveolin-mediated pathway and enter lysosomes through a microtubule-dependent mechanism [188]. This efficient cellular uptake significantly enhances intracellular drug delivery, rendering tFNAs natural drug delivery vehicles. Furthermore, tFNAs possess high ROS (reactive oxygen species) scavenging activity, effectively eliminating excessive ROS within cells under pathological conditions. Notably, tFNAs' shape and function can be tailored through programming techniques. Oligonucleotides can be incorporated into the ends of single-stranded DNA, and functional molecules can be inserted into double-stranded DNA during synthesis via extension, chemical crosslinking using complementary sequences, or electrostatic interactions, imbuing tFNAs with novel functionalities [189]. The most common method for tFNA fabrication is the single-strand annealing method, where at least four specially designed complementary single strands can rapidly hybridize upon annealing to form a tetrahedral structure. In 2023, Yan et al. developed a Typhaneoside-Tetrahedral Framework Nucleic Acids System (TTC) for AKI (acute kidney injury) therapy. By encapsulating Typhaneoside (Typ) within 20 nm tFNAs, the bioavailability of Typ was significantly enhanced. Their results showed that TTC could precisely target mitochondria in renal tubular epithelial cells after AKI. In vitro and in vivo results showed that TTC could effectively restore mitochondrial function and ameliorate apoptosis, thereby inhibiting kidney injury and restoring kidney function with non-nephrotoxicity both in vitro and in vivo [190]. While the application of tFNAs in kidney disease therapy remains relatively unexplored, their exceptional ROS scavenging capabilities and remarkable programmability hold immense promise for this therapeutic area.

5. Microenvironment-responsive delivery systems

With the advancement of nanotechnology, the development of microenvironment-responsive drug delivery systems has gained significant attention. By loading drugs or biomolecules onto responsive delivery systems, targeted delivery can be achieved in specific regions under specific microenvironments, maximizing the bioavailability of drugs or biomolecules. The localization and release of drugs at specific sites can be accomplished through the stimuli-responsive delivery system in response to specific pathological and physiological microenvironments (e.g., ROS, pH, and enzymes). Details are as follows.

5.1. ROS-responsive strategies

ROS (reactive oxygen species) play a crucial role in damage repair processes by regulating oxidative stress and inflammatory signaling pathways. Common ROS include superoxide (O2 -), hydrogen peroxide (H2O2), peroxide anion (HO2 -), •OH, 1O2, peroxynitrite (ONOO -), and hypochlorite (OCl -) [191]. Under physiological conditions, a certain level of ROS is necessary to promote cell survival, proliferation, and growth, as well as vascular reactivity in the kidneys. Additionally, ROS serve as oxygen sensors for cells. However, in pathological states, excess ROS can be generated by NADPH oxidases (NOX) enzymes, leading to oxidative stress imbalance and triggering the progression of pathological lesions. Notably, ROS can also influence the extent of macrophage infiltration [192], thereby affecting the progression of inflammation. Previous studies have demonstrated that oxidative stress imbalance caused by ROS overload is a major factor contributing to the progression of kidney diseases, including diabetic nephropathy, hypertension-associated kidney injury, ischemia-reperfusion injury (IRI), toxic nephropathy, and various forms of inflammatory syndromes. During oxidative stress imbalance, renal tubular epithelial cells are the most vulnerable. As the primary participants in active transport within the kidney, renal tubular epithelial cells are highly dependent on ATP to drive the transport of various factors, with ATP generated from glucose metabolism being the main source. This necessitates the maintenance of a highly active state of the mitochondrial electron transport chain, which is extremely sensitive to oxidative stress. Consequently, renal tubular epithelial cells become the most susceptible to oxidative stress-induced damage [193]. Moreover, ROS overload-induced oxidative stress can also cause significant damage to the glomeruli. As ROS overload occurs, mitochondrial oxidative stress intensifies, leading to the activation of various kinase pathways in mesangial cells [194,195], such as protein kinase C [196] and protein kinase B/Akt [197]. These changes alter gene expression within mesangial cells, ultimately leading to autophagy and apoptosis of podocytes [198] and mesangial cells [199], promoting fibrosis progression and glomerulosclerosis. Therefore, timely and effective clearance of ROS to curb oxidative stress imbalance is an effective strategy for treating kidney diseases. Based on this principle, researchers have employed antioxidants such as vitamin C, N-acetylcysteine, coenzyme Q10, and curcumin, or nanomaterials with ROS scavenging activity (e.g., DNA origami and CeO2 nanoparticles) for kidney disease treatment with promising results.

Despite the promising potential of antioxidants and antioxidant nanomaterials for kidney disease treatment, several challenges remain, including low kidney accumulation efficiency, short half-lives, and severe systemic side effects. To address these limitations, researchers have shifted their focus to developing ROS-responsive antioxidant formulations/materials that can trigger localized high-efficiency drug release in response to the elevated ROS levels in damaged kidney regions. Commonly employed ROS-responsive functional groups include thioethers, oxalates, and thioaldehydes, which can undergo cleavage under high ROS conditions [200]. Du et al. encapsulated atorvastatin and triphenylphosphine (TCeria NPs)-modified ceria nanoparticles within an ROS-responsive organic polymer (mPEG-TK-PLGA). This formulation achieved targeted and responsive drug release in the high-ROS regions of damaged tissues following AKI, significantly suppressing AKI progression [25]. However, the authors only carried out the animal model verification of sepsis-related AKI, and it will undoubtedly be more beneficial for the further promotion and application of the agent if more pathogenic AKI models can be verified. Similarly, Liu et al. utilized ROS-sensitive thioketal modification of SS31 (a mitochondria-targeted antioxidant) to enable its ROS-responsive release. This approach effectively mitigated mitochondrial damage, reduced oxidative stress, suppressed inflammation, and inhibited cellular apoptosis following AKI, substantially enhancing the therapeutic efficacy of SS31. More importantly, the cytotoxicity of SS31 on HK-2 cells in vitro was determined by MTT assay, and the survival rate of treated cells was still higher than 95 % when the concentration of SS31 was up to 500 μg/ml, indicating that SS31 had excellent biological safety [201]. These studies highlight the potential of ROS-responsive drug delivery vehicles to effectively target the damaged areas associated with kidney disease progression, enabling precise and localized drug release. By maximizing drug utilization, ROS-responsive drug delivery systems represent a promising strategy for targeted kidney disease therapy.

5.2. PH-responsive strategies

PH-responsiveness is another widely employed targeting strategy for responsive drug delivery systems, apart from ROS-responsiveness. Unlike the physiological pH of 7.4, the pH of pathological areas (e.g., cancer, bacterial infections, inflammation) can undergo significant alterations. Utilizing differential pH to trigger targeted drug release in specific regions has gained increasing popularity. pH-responsive drug delivery systems encompass liposomes, micelles, hydrogels, dendritic macromolecules, and organic-inorganic hybrid nanoparticles. In the context of kidney disease, numerous studies have demonstrated the efficacy of pH-responsive drug release for targeted therapy of kidney lesion areas. Liu et al. successfully constructed a pH-responsive CD44-targeted nanoparticle by modifying mitochondria-targeting peptide SS-31 with cationic chitosan (CS) and anionic HA. Their findings revealed that under physiological pH (7.4), SS-31 remained confined within the nanoparticles and was not released. However, at pH 5 or 4.5, SS-31 was rapidly released. In vivo experiments demonstrated that the nanoparticles effectively targeted the kidneys following AKI and released SS-31 under specific pH conditions. This targeted mitochondrial delivery effectively improved mitochondrial function, mitigated cellular apoptosis, and suppressed AKI progression [202]. Yoshitomi et al. proposed a novel therapeutic strategy for AKI treatment, termed "Environmental-Signal-Enhanced Polymer Drug Therapy" (ESEPT). Based on this concept, they developed a poly(ethylene glycol)-b-poly (methylstyrene) (PEG-b-PMS) block copolymer attached to 2,2,6,6-tetramethylpiperidine-N-oxyl (TEMPO) via an amine linkage (PEG-b-PMNT). PEG-b-PMNT self-assembles into core-shell polymeric micelles in aqueous media. Under acidic conditions, the micelles disintegrate due to the protonation of amino groups located in the core of the nitroxide-radical-containing particle (RNPpH). Simultaneously, RNPpH exposes the nitroxide radicals, which can catalytically scavenge ROS. The efficacy of these nanoparticles was demonstrated in an IRI-induced AKI model, representing another approach for pH-responsive targeted therapy in the kidneys [203]. However, the overall organ distribution and in vivo biosafety of PEG-b-PMNT have not been studied in detail by the authors, and the efficiency of PEG-b-PMNT to reach the kidney has not been tested, which hinders the possible clinical application of PEG-b-PMNT to a certain extent. Similarly, Lee et al. fabricated pH-sensitive poly(2-(diisopropylamino)ethyl methacrylate (PDPA) polymers to encapsulate a NO donor, a dinitrosyl iron complex (DNIC; $(Fe_2(\mu\text{-}SEt)_2(NO)_4)$). Under physiological conditions, the nanoparticles remained stable. However, upon exposure to pH 4.0–6.0, they rapidly disintegrated, releasing NO to inhibit fibrosis progression. Moreover, the cytotoxicity results showed that free DNIC exhibited higher cytotoxicity, while DNIC encapsulated in PBA-NO and PLGA-NO significantly reduced cytotoxicity due to its slower drug release rate [204]. These studies collectively demonstrate the promising potential of pH-responsive targeted drug release strategies for kidney-targeted drug delivery and therapy.

6. Enzyme-responsive strategies

Enzyme-responsive drug delivery systems (ERDDS) combine the unique properties of nanomaterials with the responsiveness of biological enzymes, offering immense potential in bioimaging, disease diagnosis and treatment, drug delivery, and cellular internalization [205,206]. Compared to other responsive delivery systems, utilizing biological enzymes as trigger conditions holds inherent advantages. First, biological enzymes are naturally occurring within the body, eliminating the need for external stimuli such as magnetic fields, ultrasound, or light, ensuring enhanced biocompatibility and safety. Enzymes exhibit remarkable specificity for their substrates, ensuring controlled chemical and biological reactions [207]. Different enzymes exhibit distinct expression patterns under various pathological conditions. By leveraging these differences, enzyme-responsive drug delivery systems can achieve targeted and specific drug release at designated sites. Currently, proteases, esterases, phosphatases, kinases, and oxidoreductases are the most widely explored enzyme-responsive categories [208]. ERDDS typically comprise two components: enzyme-responsive moieties and the therapeutic agent to be delivered. The enzyme-responsive moiety, typically a nanomaterial scaffold, undergoes degradation upon interaction with the target enzyme. The therapeutic agent can be attached to the carrier via biodegradable bonds (e.g., ester linkages), electrostatic interactions between the active ingredient and charged carriers, or incorporated into the outer lipid membrane or lipid core [209]. ERDDS have gained significant traction in cancer therapy, capitalizing on the unique characteristics of tumor tissues, including leaky vasculature and diverse enzyme expression profiles. For instance, Zhang et al. designed and synthesized MMP-2/9-cleavable stimulus-responsive drug delivery systems for chemotherapeutic drug delivery to solid tumors [210]. Their approach involved inserting an MMP-2/9-cleavable oligopeptide (GPVGLIGK-NH2, GK8) as a spacer between α-tocopherol succinate (α-TOS) and methoxy-polyethylene glycol (mPEG2K-NHS) to generate mPEG2K-GK8-α-TOS (TGK) as the primary component of MMP-2/9-sensitive micelles composed of d-α-tocopheryl polyethylene glycol 1000 succinate (TPGS) and TGK (n:n = 40:60). Their results demonstrated the efficacy of ERDDS in achieving maximized tumor therapy with minimal systemic toxicity. Similarly, in the context of atherosclerosis, ERDDS have gained attention. Fang et al. developed integrin αvβ3-targeted and CTSK-responsive nanoparticles to control localized release of rapamycin (RAP) based on the observation of CTSK enrichment in atherosclerotic lesions [211]. These targeted and responsive nanoparticles (T/R NPs) were self-assembled from the targeted polymer PLGA-PEG-c (RGDfC) and the CTSK-sensitive polymer PLGA-Pep-PEG. Their findings revealed that elevated CTSK expression in lesion areas effectively accelerated RAP release, significantly suppressing OX-LDL uptake and cytokine release by inflammatory macrophages, thereby effectively inhibiting AS progression. In addition, the in vitro cytotoxicity results showed that even high concentration of T/R NP did not cause any damage to HUVEC and RAW264.7 cells, indicating that the NPS had good biocompatibility. While ERDDS have not yet been explored in kidney disease diagnosis and treatment, the kidney disease pathological microenvironment exhibits rapid upregulation of enzymes such as hyaluronidase and matrix metalloproteinases under certain disease conditions. Therefore, ERDDS hold promising potential for targeted therapy of kidney diseases.

The preparation of responsive degradation nanomaterials based on the characteristics of different pathological microenvironment of kidney diseases can effectively realize the targeted accumulation and release of drugs/nucleic acid molecules in the kidney, and effectively improve the bioavailability of the kidney. However, it is worth noting that the implementation of the microenvironment responsive degradation strategy also destroyed the stability of nanomaterials to a certain extent. Whether it is PH response, enzyme response or ROS response, excessive design may lead to high microenvironment sensitivity, which may cause a large number of degradation of nanomaterials in the circulation process, seriously reducing their in vivo stability and bioavailability. Therefore, effective balance between microenvironment response and stability of nanomaterials is also the premise and basis for ensuring the kidney targeting of nanomaterials. As Zhu L et al. added high molecular weight hyaluronic acid (HMW-HA) to the surface of the responsive degradation MPN coating, the balance between the responsive degradation and the stability of the nanomaterials was maximized, and the

targeting efficiency was further improved [212].

7. Cell targeting

7.1. Proximal tubule epithelial cells

The proximal tubule (PT) is the most crucial component of the nephron, both anatomically and functionally, playing a pivotal role in urine filtration and reabsorption. Activated proximal tubule epithelial cells (PTECs) can lead to tubulointerstitial nephropathy (TIN), renal dysfunction, interstitial inflammation, and fibrosis development through chemotaxis, antigen presentation, and autocrine and paracrine cytokine secretion modes [213,214]. Therefore, targeted drug delivery to PTECs holds significant clinical implications for kidney disease treatment. Numerous studies have demonstrated that efficient targeting of PTECs can be achieved through rational design and surface modification. Examples include carriers modified with receptor-ligand binding proteins or targeting peptides, water-soluble polymer carriers, prodrugs, nanoparticles, and more. Low molecular weight proteins (LMWPs) exhibit remarkable kidney targeting properties, with approximately 80 % of the injected dose being absorbed by the kidneys and exhibiting minimal accumulation in other parts of the body. Additionally, most LMWPs are non-immunogenic and possess functional groups that enable covalent conjugation to therapeutic drugs. Among LMWPs, lysozyme with a molecular weight of 14 kDa is the most widely employed. Zhang et al. developed 14-succinyl triptolide-lysozyme (TPS-LZM) for specific delivery of triptolide (TP) to PTECs. Compared with free TP, TPS-LZM demonstrated a significantly enhanced overall targeting efficiency (TE) from 11.74 % to 95.54 %. At extremely low concentrations, TPS-LZM effectively suppressed ischemia/reperfusion (I/R)-induced AKI progression, while a mixture of free TP and LZM was ineffective [215]. Other LMWPs include albumin, cytochrome C, and angiotensinogen [216–219]. Bidwell GL 3rd et al. designed a drug delivery system with high PTEC targeting specificity. They modified elastin-like polypeptides (ELPs) at their NH2-terminus with a cyclic, seven-amino acid kidney-targeting peptide (KTP). Validation in rat and pig models revealed that KTP-ELP accumulation in PTECs was over five times higher than that of ELP, with kidney accumulation 15–150 times higher compared to other organs [220]. However, the insufficiency is that the authors only carried out in vivo verification of normal animal models, lack of relevant verification of disease animal models, and lack of systematic detection of the overall biological safety in vivo, which also lays a hidden danger for the possible clinical application of KTP-ELP.

Theoretically, a wide range of nanomedicine delivery systems, including macromolecular nanoparticles, liposomes, polymeric micelles, and inorganic nanoparticles, can be employed for kidney targeting. Their ability to overcome biological barriers and achieve specific targeting of particular cells is largely dependent on factors such as nanoparticle size, surface charge, shape, and density. For instance, Kim et al. developed hydrophobically modified glycol chitosan (HGC) nanomicelles (HGC-TAC) loaded with tacrolimus (TAC) to target PTECs for lupus nephritis treatment. Their findings demonstrated that HGC-TAC nanomicelles with a diameter of 370 ± 22 nm exhibited a significantly higher distribution in the kidneys than in other organs in vivo. Additionally, HGC-TAC effectively alleviated renal dysfunction, proteinuria, and tissue damage in LN mice compared to TAC alone, showcasing superior therapeutic efficacy due to enhanced PTEC targeting [221].

7.2. Podocytes

Podocytes, terminally differentiated cells derived from renal mesenchymal stem cells, have emerged as a pivotal target for the treatment of kidney diseases, particularly those characterized by proteinuria. As research into podocytes deepens, it has become increasingly evident that podocyte injury underlies the molecular mechanisms of many proteinuric glomerular diseases, including FSGS and diabetic nephropathy. Podocyte dysfunction and subsequent cell death drive the initiation and progression of these diseases, representing a significant paradigm shift in our understanding of the pathophysiology of glomerular diseases. This realization has fueled the pursuit of early, targeted therapies against podocyte lesions as a potential strategy to reverse CKD [222]. Podocytes are characterized by a unique morphology with a cell body adorned with primary and secondary foot processes. Adjacent foot processes interdigitate, forming approximately 10–70 nm slit pores, which are bridged by a zipper-like protein structure called the slit diaphragm (SD) [54]. As a crucial component of the glomerular basement membrane (GBM), podocytes firmly anchor to the GBM via α3β1 integrin, while cytoskeletal proteins bridge the integrins at the GBM and the SD proteins at the podocyte membrane, maintaining podocyte morphology [223]. Current treatment strategies for podocyte injury-induced glomerular proteinuria primarily involve immunosuppressive agents such as glucocorticoids (e.g., prednisolone) and tacrolimus [224]. However, these therapies are often associated with adverse effects, including disease recurrence upon drug withdrawal or discontinuation. Therefore, targeted drug delivery to podocytes holds great promise for treating podocyte-induced kidney diseases. Common approaches for podocyte-targeted therapy include antibody-modified carriers or the design of specific nanoparticles. For instance, Visweswaran et al. capitalized on the upregulated expression of VCAM-1 on podocytes under inflammatory conditions to design a VCAM-1-targeted lipid nanoparticle carrier called SAINT-O-Somes. Compared with non-targeted rapamycin-loaded SAINT-O-Somes, VCAM-1-modified rapamycin-loaded SAINT-O-Somes demonstrated superior efficacy in suppressing AB8/13 podocyte migration [225]. This finding highlights VCAM-1-based targeted delivery as a viable strategy for podocyte targeting. Hauser et al. developed a specific antibody that effectively binds rat/mouse podocytes in vivo. The antibody was conjugated to biotin via single-chain IgG before complexing with siRNA using protamine, a polycationic nuclear protein commonly used as an siRNA carrier. Their in vivo studies demonstrated that the complex specifically bound to podocytes without triggering glomerular complement deposition and subsequent glomerulosclerosis [226]. The results in vivo showed that the complex could bind podocytes effectively and did not trigger glomerular complement deposition to induce glomerulosclerosis injury. However, the authors only verified it in normal animal models, but not in disease models, and the efficiency of podocyte targeting under pathological conditions remains to be explored.

Podocyte targeting by nanoparticles primarily relies on tuning their particle size and charge to maximize their specific interactions with podocytes. Bruni et al. synthesized four-armed star polymers with/without hydrophobic polyε-caprolactone cores and brush-like poly (ethylene glycol) (PEG) hydrophilic shells via controlled/living polymerization (ROP and ATRP) to form stable ultrafine colloidal nanomaterials. They controlled the particle size range between 5 and 30 nm to facilitate GFB penetration and podocyte accumulation. Their findings demonstrated that the ultrafine colloidal nanomaterials exhibited excellent biocompatibility without any detrimental effects on podocytes. Further cytotoxicity tests on the nanomaterials also confirmed the safe cytotoxic characteristics of these polymeric nanomaterials. Moreover, controlled delivery of dexamethasone significantly ameliorated cytoskeletal disruption and reduced albumin permeability. These studies pave the way for the development of podocyte-targeted nanotherapies [30].

7.3. Mesangial cells

Mesangial cells, matrix-producing cells residing in the glomerulus, play a crucial role in maintaining glomerular homeostasis and orchestrating the glomerular injury response. Emerging research highlights the involvement of mesenchymal matrix cells in regulating physiological processes such as development, angiogenesis, and cell fate specification. Through crosstalk with neighboring cells and indirect effects mediated by matrix remodeling, matrix cells can also modulate pathological processes like immunity, inflammation, regeneration, and maladaptive responses (fibrosis). Mesangial cell proliferation and extracellular matrix accumulation are pivotal contributors to CKD progression. Therefore, targeted drug delivery to mesangial cells represents a promising approach for kidney disease therapy. The primary goal of mesangial cell-targeted drug delivery is to suppress their activation and proliferation. Common carriers for mesangial cell targeting include liposomes and polymeric nanoparticles. For instance, Morimoto et al. designed and synthesized TRX-20 (3,5-dipentadecyloxybenzamidine hydrochloride)-modified liposomes for targeted delivery to mesangial cells. These liposomes primarily accumulated in inflamed glomeruli and effectively inhibited mesangial cell proliferation, thereby curbing fibrosis progression [227]. The drug characteristics of TRX liposomes, coupled with their superior mesangial cell targeting, make them a promising option for mesangial cell-targeted strategies in kidney disease therapy. However, it is worth mentioning that although the authors have effectively demonstrated the effective mesangial cell targeting of TRX-20, from the results of the authors, there is a lack of validation of the distribution of other organs and the overall animal biosafety, which is the most important prerequisite to ensure the possible future clinical application of TRX-20. Similarly, Tuffin et al. developed OX7-coupled immunoliposomes (OX7-IL) by coupling liposomes with Fab' fragments of OX7 mAb directed against Thy1.1 antigen. Their findings demonstrated that a single injection of low-dose doxorubicin encapsulated in OX7-IL in rats induced extensive glomerular injury without affecting other parts of the kidney or other organs [151]. For nanoparticles, particle size is a critical determinant of mesangial cell targeting. Guo et al. designed and synthesized three different sized ANs (75/95/130 nm). Using immunofluorescence staining for the mesangial cell marker α8-integrin, they found that AN95 exhibited superior mesangial cell targeting (targeting efficiency of 53.4 %) [29]. Furthermore, surface modification with targeting ligands, such as proteins, peptides, antibodies, and aptamers, can further enhance nanoparticle targeting to mesangial cells. Manil et al. prepared ampicillin-loaded poly (isobutylcyanoacrylate) nanoparticles (ADNPs). Both in vitro and in vivo experiments demonstrated the excellent mesangial cell targeting properties of ADNPs. In vitro experiments confirmed that glomerular mesangial cells internalized ADNPs about five times more efficiently than epithelial cells [228].

8. Biomimetic engineering

8.1. Cell membrane-camouflaged nanoparticles

Harnessing the inherent functionalities of cell membranes, cell membrane-camouflaged nanoparticles have emerged as promising tools for diagnostics and therapeutics in various diseases. These biomimetic nanoparticles offer several advantages, including prolonged blood circulation, active cellular targeting, and enhanced drug delivery. Of course, unlike natural exosomes, cell membrane-coated nanoparticles are based on artificial design. Cell membrane proteins are used to endob

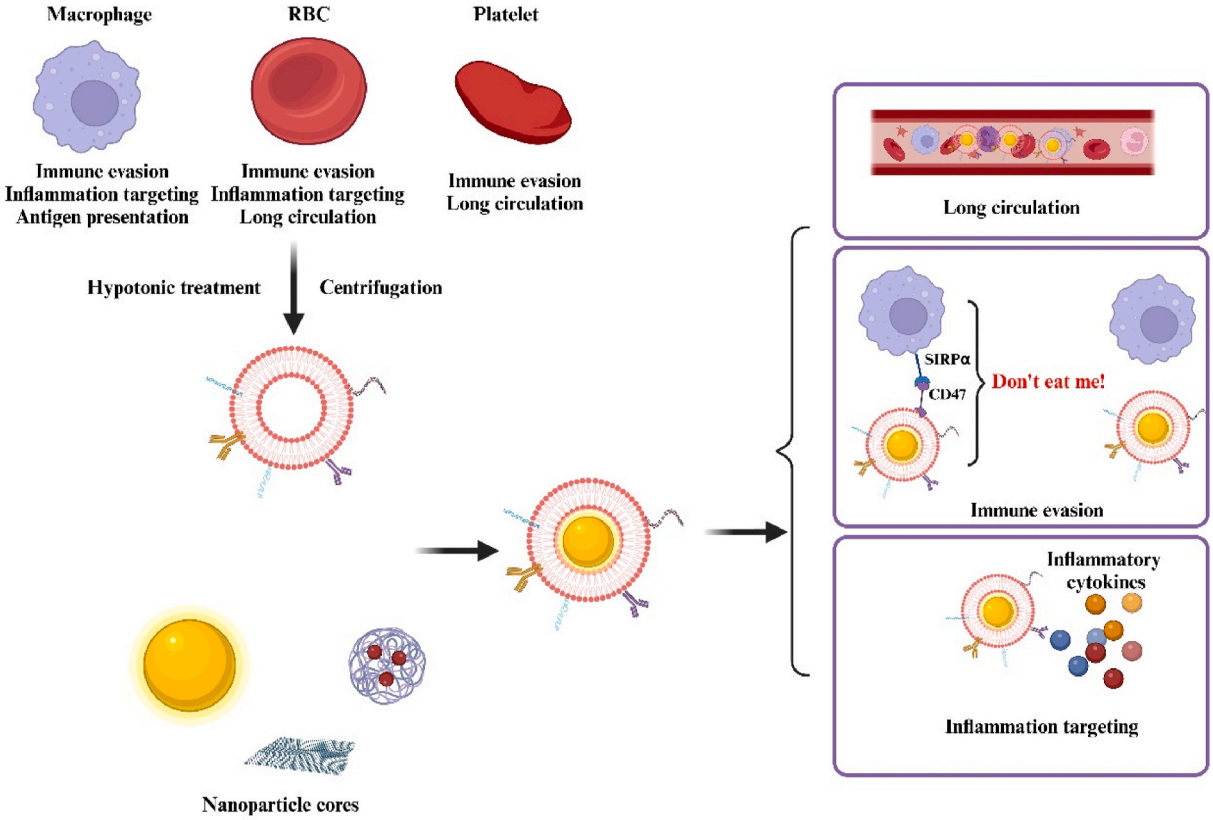

Fig. 4. Cell Membrane-Coated Nanoparticles. Biomimetic modification of nanoparticles with cell membranes can specifically achieve long circulation, immune evasion, and inflammation targeting of the nanoparticles.

nanoparticles with different targeting properties or recycling properties to achieve the best drug delivery. Currently, with the growing exploration of cell membrane mimicry/camouflage nanotechnology and the increasing demand for more specific cell membrane functionalities, strategies to engineer cell membranes beyond their natural properties through physical engineering, chemical modification, and biofunctionalization have gained widespread attention. Here, we discuss the application of cell membrane-camouflaged nanoparticles for targeted therapy in kidney diseases (Fig. 4).

8.2. Red blood cell membrane camouflage

Effective drug delivery hinges on the ability to evade immune clearance and maintain extended in vivo circulation. Red blood cells (RBCs), with their unique 120-day half-life, serve as valuable models for long-circulating injectable carriers [229]. Additionally, RBCs are the most abundant cells in the human body, with an average of 50 billion RBCs per milliliter of blood. Mature RBCs lack a nucleus and other organelles, facilitating the extraction and purification of cell membranes with minimal interference from impurities [230]. RBCs express several biomarkers that enable immune cells to recognize them as "self." These include the "don't eat me" signals CD47 and SIRP-α receptors that prevent phagocytic degradation, as well as the surface membrane proteins CD59 (a membrane cofactor protein) and complement receptor 1 (CR1) that suppress complement system component attachment [231]. These biomarkers effectively shield RBCs from immune clearance. Leveraging RBC membrane-camouflaged nanoparticles can significantly reduce inherent immune system clearance. Zhang et al. pioneered the RBC membrane coating strategy. They isolated RBCs from blood and employed a two-step method to obtain RBC membrane-camouflaged nanoparticles: (1) hypotonic treatment to remove intracellular components, followed by extrusion through porous membranes to generate RBC membrane-derived vesicles; (2) fusion of RBC vesicles with poly (lactic-co-glycolic acid) (PLGA) nanoparticles using mechanical extrusion to yield RBC-camouflaged PLGA nanoparticles [102,232]. Studies have demonstrated that RBC membrane-camouflaged gold nanoparticles [233] and Fe3O4 nanoparticles [234] effectively evade macrophage uptake and immune clearance. While RBC membrane-camouflaged nanoparticles have been extensively explored for drug delivery, imaging, phototherapy, nanovaccination, and nano-detoxification, their application in the kidney field remains limited. Given the advantages of RBC membrane camouflage, we believe that utilizing this approach to prolong nanoparticle circulation and evade immune clearance can significantly enhance kidney drug delivery efficiency. Combining the merits of RBC membrane camouflage with the physicochemical properties of nanoparticles holds great promise as a potential strategy for targeted kidney therapy.

8.3. Macrophage membrane camouflage

Immune cell membrane coating nanotechnology has emerged as a hot research topic in biomimetic nanotechnology in recent years, utilizing good biocompatibility, longer blood circulation time, and enhanced immune cell-specific migration to inflammatory sites [235,236]. Among these, macrophage membrane camouflage is the most commonly used. Macrophages are multifunctional phagocytic cells that play a crucial role in regulating innate and adaptive immune responses by recognizing and eliminating foreign invaders (e.g., bacteria, viruses) from the body through phagocytosis and antigen presentation. Macrophages also specifically target tumors, inflammation, and infection sites through chemotaxis [103]. Their ability to actively recognize and bind inflammatory cells through cell adhesion makes them an attractive cell for improving inflammatory diseases while reducing unnecessary systemic toxicity. Macrophages communicate with their surrounding environment and different cells by activating or inhibiting specific signals through surface markers. The cell adhesion molecules (e.g., integrins and selectins) and chemokine receptors on their cell surface can bind to specific adhesion molecules and inflammatory chemokines to target specific diseased cells. This has led to increasing research into utilizing macrophage membrane properties to modify nanoparticles for targeted therapy of diseases. In general, cell membrane-camouflaged nanoparticles typically consist of a thin layer of cell membrane encapsulating a nanoparticle core, forming a "shell-core" structure. The construction of macrophage membrane nanoparticles can be broadly summarized as a two-step process: preparation of macrophage membranes and encapsulation of nanoparticle cores with macrophage membranes. Specifically, a large number of cells are obtained from culture plates, blood, or tissues. After hypotonic treatment, freeze-thaw cycles, and sonication, the cells are centrifuged, and the precipitate is collected. The cell suspension is then disrupted with ultrasound of appropriate power, and the resulting membrane vesicles are extruded through a polycarbonate membrane [237]. Four main methods are currently used to coat nanoparticles with macrophage membranes: incubation, membrane extrusion, sonication, and electroporation. Each method has its own advantages and disadvantages, but electroporation is currently the most advantageous. The nanoparticle core and cell membrane vesicles are injected into a microfluidic chip, and then electrical pulses are used to generate transient pores in the membrane, facilitating the entry of nanoparticles into the membrane vesicles. This method has been shown to be more effective in maintaining vesicle integrity and improving encapsulation efficiency [238]. The many advantages of macrophage membrane-camouflaged nanoparticles have led to the application of this biomimetic nanomaterial in the diagnosis and treatment of various diseases, including cancer, infectious diseases, cardiovascular diseases, central nervous system diseases, immune diseases, and inflammation. Through their surface receptors, macrophage membrane-camouflaged nanoparticles have demonstrated excellent targeting ability to inflammatory tissue regions. In the context of the kidney, kidney disease development is inextricably linked to inflammatory responses. The degree of inflammatory development in renal tissue, whether in acute or chronic kidney disease, determines the extent of tissue damage. Therefore, effective targeting of inflammatory regions within renal tissue is a powerful approach for targeted therapy of kidney diseases. In 2019, Tang et al. utilized macrophage membrane-camouflaged dexamethasone (named MV-DEX) to target inflammatory regions within renal tissue. Dexamethasone was encapsulated in macrophage membranes by co-incubation. Their findings demonstrated that MV-DEX could effectively bind to inflammatory tissues in the kidney using integrins αLβ2 (LFA-1) and α4β1 (VAL-4). Compared with free DEX treatment, an equimolar dose of MV-DEX significantly reduced kidney injury and largely suppressed LPS- or ADR-induced renal inflammation and fibrosis progression. Mv-dex-treated mice showed a higher survival rate of 45 % compared with 30 % of free DeX-treated mice. In vitro results further demonstrated that MV-DEX achieved significant anti-inflammatory effects by inhibiting NF-κB activity with approximately 1/5 the dose of free DEX [239]. This study highlights the promising potential of macrophage membrane-camouflaged nanoparticles for targeted therapy of kidney diseases.

8.4. Platelet membrane camouflage

Over the past few decades, platelet (PLT)-camouflaged nanoparticles have garnered significant attention due to the unique properties of PLTs in immune evasion, subendothelial adhesion, and pathogen interactions, with numerous applications reported in cancer and inflammatory diseases [240–243]. To better understand the potential of PLT-camouflaged nanoparticles for targeted drug delivery in kidney diseases, it is crucial to first delve into the structure and functions of PLTs. PLTs are disc-shaped, anucleate cell fragments with an average diameter of 2–4 μm, produced by mature megakaryocytes in the bone marrow and with a lifespan of 7–10 days. Traditionally, PLTs have been primarily associated with hemostasis; however, recent research has revealed their extensive involvement in various disease processes, including inflammation, immune responses, wound healing, and cancer [244]. Given the close association between kidney diseases and inflammation, we will focus on the role of PLTs in inflammatory responses. In summary, upon inflammation, activated leukocytes and other cells release soluble mediators such as chemokines, interleukins, and platelet activating factor (PAF) into the circulation, effectively activating PLTs. Notably, PLTs can keenly detect pathogens or pathogenic inflammation and interact with immune effector cells. By recognizing pathogen-associated molecular patterns (PAMPs) or damage-associated molecular patterns (DAMPs), PLTs can efficiently target inflammatory sites/cells through receptors such as Toll-like receptors (TLRs) and C-type lectin receptors.

Nanoparticles based on PLT membranes enable nanoparticles to effectively target inflamed tissues without compromising their intrinsic properties, and can be designed for controlled drug release, such as in response to reactive oxygen species (ROS). Compared to other biomembranes, PLT membranes facilitate immune evasion and prolong in vivo circulation. In the context of kidney diseases, PLT membrane-camouflaged nanoparticles hold promising potential for targeted therapy. In 2024, Fei et al. developed PLGA nanoparticles camouflaged with PLT membranes (PMVs@siRNA NPs) for targeted delivery of TGF-β1-siRNA. The aim was to achieve kidney-specific targeting and modulate the TGF-β1 pathway in damaged renal tissue. Their findings demonstrated that PMVs@siRNA NPs efficiently accumulated in the kidneys of unilateral ureteral obstruction (UUO) mice and ischemia/reperfusion injury (I/R) mice 1 h after injection, significantly surpassing accumulation in other organs. Further validation confirmed that by blocking the TGF-β1/Smad3 pathway, PMVs@siRNA NPs effectively downregulated TGF-β1 expression, mitigating inflammation and fibrosis progression [245]. Yao S et al. prepared Platelet membrane-ICG-SS31-PLGA (PISP) by means of the natural adhesion property of platelet membrane to the vascular injury site to achieve the specific targeting of the damaged kidney after AKI. This is a good example of platelet membrane properties endow nanoparticles with kidney targeting, but it would be interesting if the authors could further verify the effect of application in different cause-induced AKI or other kidney disease models [246]. In addition, Yang et al. also used the impaired vascular convergence property of platelet membrane to fabricate platelet membrane-coated hybrid microbubbles (Pla-MBs) to achieve kidney-targeted therapy for sepsis-induced AKI model [247]. These findings highlight the remarkable potential of PLT membrane-camouflaged nanoparticles for targeted therapy in kidney diseases. While current research is limited, the future prospects for this approach in kidney disease management appear promising.

9. Conclusion and outlook

With the development of nanotechnology, the application of nanomaterials in the biomedical field has received increasing research and support. The major challenges in the clinical diagnosis and treatment of kidney diseases have always been poor kidney targeting and low drug delivery efficiency. The maturity of nanotechnology offers potential solutions to these problems. Many studies have demonstrated that kidney-specific targeted nano-drug delivery systems can be prepared through surface modification, shape regulation, and size control [248]. These systems have shown excellent therapeutic effects in kidney diseases. A variety of nano therapies have entered clinical trials, demonstrating their translational potential. For example, liposomal formulations targeting renal inflammation have shown promising efficacy and safety in early clinical trials. Furthermore, dual-targeting nanoparticles that combine passive EPR effects with active ligand targeting mechanisms have significantly improved therapeutic efficiency in pre-clinical models of kidney disease [249]. However, despite these advancements, very few kidney-specific targeted nano-drug delivery systems have been effectively translated into clinical practice. The main factors can be summarized as follows.

1. Biocompatibility and Biosafety: Achieving physiological standards for biocompatibility and biosafety remains challenging. Although many researchers have improved the biocompatibility and biosafety of nanomaterials through surface modification or biomimetic cell membrane encapsulation, proving excellent in vitro and in vivo biosafety, almost all nanomaterials still fail to meet clinical sterile standards fully. Additionally, the safe use of nanomaterial delivery systems in the human body cannot be guaranteed 100 %. Therefore, further addressing the sterile standards of targeted delivery systems is necessary and crucial. Meeting stringent regulatory standards is key to driving clinical translation. Cgmp-compliant manufacturing processes ensure that products meet high quality requirements in terms of safety and efficacy. For application scenarios such as chronic kidney disease that require long-term treatment, a comprehensive long-term safety assessment is essential, especially in terms of biodistribution, metabolism, and non-target organ accumulation of nanomaterials. Collaboration among researchers, regulators, and industry will help streamline the approval pathway.
2. Commercial Mass Production: Besides biocompatibility and biosafety issues, another significant challenge for clinical translation is the commercial mass production to meet clinical demands. Although nanotechnology is increasingly mature, and the preparation and production methods of various nanomaterials are continuously updated, a method for high-standard mass production of certain nanomaterials is still unachievable. Achieving large-scale and reproducible production of nanomaterials is essential for their clinical applications. Microfluidic synthesis technology significantly improves batch-to-batch consistency by precisely controlling particle size, shape, and surface properties, providing reliable technical support for clinical applications [250]. In addition, spray drying and extrusion processes have been gradually applied to the preparation of nanoparticles, further improving the feasibility of industrial production [251]. Addressing the high-standard mass production of nanomaterials has been a consistent focus for researchers. We believe that achieving high-standard mass production of nanomaterials will significantly promote clinical translation. Moreover, economic factors have a significant impact on the clinical promotion of nanomedicine. The use of biodegradable polymers such as PLGA as substrates not only enhances biocompatibility but also reduces production costs. In addition, the application of efficient production processes such as solvent evaporation and self-assembly greatly reduces resource consumption and improves economy.

All in all, specific targeted treatment of kidney diseases based on nanomaterials is a possible and feasible strategy. We believe that with the advancement of nanotechnology, the targeted drug delivery of nanomaterials in the kidney field will eventually achieve clinical translation.

	Nanomaterial Type	Targeting Mechanism	Clinical Applications	Key Features
Mesoscale Nanoparticles (MNPs) [81]	Polymeric	**Passive targeting** to renal tubules	Potential treatments for AKI and CKD	- High renal selectivity (26-fold over other organs) - Biocompatible and FDA-approved PLGA core - Encapsulates both hydrophobic and hydrophilic cargo - Long renal retention (up to 28 days)
Extracellular Vesicles (EVs) [85]	Liposomes	**Active targeting** via Kim-1 receptor binding	Treatment of AKI	- Kim-1 receptor targeting improves specificity for damaged renal tubules - Ability to deliver RNAi therapeutics (e.g., siRNA) effectively
HA-MNP-DXM [93]	Polymeric	**Active targeting** to CD44 receptor on damaged renal tubular epithelial cells	Treatment of AKI, especially caused by ischemia/reperfusion (I/R) injury	- Strong targeting via HA-CD44 receptor interaction
Light Chain-Conjugated PEGylated PLGA Nanoparticles (LC-NPs) [95]	Polymetric	**Active targeting** via megalin receptor expressed on proximal tubule epithelial cells (PTECs) and RCC cells	Treatment of renal cell carcinoma (RCC) and proximal tubular injury in kidney diseases	- Specific renal and RCC targeting through megalin interaction; Biodegradable and biocompatible polymer
Molybdenum-based polyoxometalate (POM) [99]	Inorganic	**Passive targeting** via size (<10 nm) enabling glomerular filtration and renal accumulation	Treatment of AKI	- High renal uptake, robust ROS scavenging
Cycloamylose-Cholesteryl-Spermine (CH-CA-Spe) [130]	Polymetric	**Active targeting** via endocytosis to tumor cells, VEGF silencing	Treatment of renal cell carcinoma (RCC)	- Biodegradable, efficient siRNA delivery, anti-angiogenesis
Dual-Regulated Functionalized Liposome–Nanoparticle Hybrids (Liposome–NP Hybrids) [153]	Liposomes	**Active targeting** via TGF-β1 silencing and interaction with glomerular endothelial cells	Treatment of glomerulonephritis, focusing on reducing inflammation and fibrosis	- Dual-regulated system ensuring targeted delivery - Combination of siRNA and dexamethasone for enhanced therapeutic efficacy
Cerium Oxide Nanoparticles (CeO_2 NPs) [159]	Inorganic	**Passive targeting** to the kidneys by reducing oxidative stress and inflammation	Treatment of AKI induced by polymicrobial peritonitis	- Potent reactive oxygen species (ROS) scavenger - Reduces inflammation and apoptosis in renal cells
Cerium Oxide Nanozymes (Ceria Nanozymes) Zhang	Inorganic	**Passive targeting** via preferential renal uptake due to optimal size and surface charge	Alleviation of AKI caused by oxidative stress	- High antioxidant activity via ROS scavenging - Preferential renal accumulation and low systemic toxicity
Catalytic Activity Tunable Cerium Oxide Nanoparticles (CNPs) [160]	Inorganic	**Passive targeting** via preferential renal uptake due to small size (~3 nm) and surface modification	Prevention of chemotherapy-induced AKI	- Context-dependent ROS scavenging ability - Protects renal tissue without compromising chemotherapy efficacy
Fibrillar Nanocarbon-Based RNA Interference Delivery System (fCNT RNAi) [168]	Low-Dimensional	**Active targeting** to proximal tubular epithelial cells (PTECs) via enhanced cellular uptake and Trp53/Mep1b silencing	Prevention and treatment of cisplatin-induced AKI	- Highly efficient and specific renal targeting - Co-delivery of siRNA for Trp53 and Mep1b for synergistic nephroprotection
Cellulose Acetate Functionalized Graphene Oxide Beads (CAGO) [173]	Low-Dimensional	**Passive targeting** by leveraging surface adsorption and electrostatic/van der Waals interactions to bind toxins.	Treatment of CKD by removing uremic toxins	- High adsorption efficiency, biocompatibility, selective removal of medium and large molecules, suitable for hemoperfusion.
Fasudil Hydrochloride-Modified Graphene Oxide-Bovine Serum Albumin Biocomposite (GO-BSA/FSD) [174]	Inorganic	**Passive targeting** via adsorption of extracellular matrix proteins and local retention in renal tissues	Treatment of septicopyemia-induced AKI	- Enhanced renal repair through ECM adsorption - Sustained drug release and improved therapeutic efficacy
Titanium Carbide Polyvinylpyrrolidone Nanosheets (TPNS) [180]	Low-Dimensional	**Passive targeting** via renal accumulation due to nanosheet geometry and surface modification	Treatment of AKI by mitigating oxidative stress and inflammation	- Broad-spectrum ROS scavenging through redox reactions - Excellent biocompatibility and enzyme-triggered biodegradability
Black Phosphorus Nanosheets (BPNSs) [75]	Low-Dimensional	**Passive targeting** via accumulation in the kidney due to flake-like framework and optimal size for renal filtration.	Treatment of AKI	- Efficient ROS scavenger with high biocompatibility and degradability. - Degrades into non-toxic phosphorus oxides, offering protection against oxidative damage in ROS-related diseases
Tetrahedral DNA Nanostructures (TDNs) [188]	Low-Dimensional	**Active targeting** via receptor-mediated endocytosis (caveolin-dependent pathway)	Potential use in targeted drug delivery for lysosome-related cellular processes	- Biocompatible and structurally stable - Efficient cellular uptake without transfection agents
Typhaneoside-Tetrahedral Framework Nucleic Acids Complex (tFNA-Typ Complex, TTC) [190]	Low-Dimensional (Tetrahedral Framework Nucleic Acids)	**Active targeting** via dual mechanisms: mitochondria-specific delivery and renal tubular targeting.	Treatment of AKI	- Enhances bioavailability of typhaneoside - Prevents cell apoptosis and restores kidney function.
Atorvastatin/Triphenylphosphine-Modified Ceria Nanoparticles (Atv/PTP-TCeria NPs) [25]	Inorganic	**Both Active and Passive targeting**: Passive accumulation in inflamed kidneys due to enhanced permeability; Active targeting to mitochondria via triphenylphosphine (TPP) modification.	Treatment of sepsis-induced AKI	- ROS-responsive drug delivery system. - Antioxidant and anti-inflammatory effects. - Protects mitochondrial structure and function.
Serine-Chitosan-TK-SS31 Nanoparticles (SC-TK-SS31 NPs) [201]	Polymetric	**Active targeting** via interaction with Kidney Injury Molecule-1 (Kim-1) on renal tubule epithelial cells and mitochondrial targeting through SS31.	Treatment of ischemia-reperfusion (IR)-induced AKI	- ROS-responsive drug release. - Dual-targeting to renal tubules and mitochondria.

(*continued on next page*)

(*continued*)

	Nanomaterial Type	Targeting Mechanism	Clinical Applications	Key Features
pH-Responsive Hyaluronic Acid-Chitosan-SS31 Nanoparticles (HA-CS-SS31 NPs) [202]	Polymetric	**Active targeting** via CD44 receptor interaction on renal tubular cells and mitochondrial targeting through SS31	Treatment of AKI	- Effective reduction of oxidative stress and cell apoptosis. - Dual-targeting (renal tubular cells and mitochondria) - pH-responsive drug release - Enhanced antioxidant and anti-inflammatory effects.
pH-Responsive Nitroxide Radical-Containing Nanoparticles (RNPpH) [203]	Polymetric	**Passive targeting** to the renal ischemic lesion via enhanced permeability and retention (EPR) effect, and **active targeting**through pH-triggered disintegration in acidic environments.	Treatment of renal ischemia-reperfusion (IR)-induced AKI	- pH-sensitive disintegration for ROS scavenging. - Minimized side effects by compartmentalizing nitroxide radicals.
pH-Responsive Poly (Diisopropylamino)ethyl Methacrylate Nitric Oxide Nanoparticles (PDPA-NO) [204]	Polymetric	**Active targeting** via pH-sensitive disassembly in acidic fibrotic kidney microenvironments	Treatment of renal fibrosis caused by unilateral ureteral obstruction	- Efficient antifibrotic effects through NO delivery. - pH-responsive release for controlled targeting. - Low systemic toxicity and high biocompatibility.
Matrix Metalloproteinase-Responsive Micelles (MMP-Responsive Micelles, TGK Micelles) [210]	Polymetric	**Active targeting** via matrix metalloproteinase-2/9 (MMP-2/9)-triggered drug release at tumor sites.	Treatment of solid tumors, particularly MMP-2/9-overexpressing cancers	- Stimuli-responsive release at tumor sites. - Enhanced tumor accumulation via EPR effect.
Cathepsin K-Responsive and Integrin αvβ3-Targeted Nanoparticles (T/R NPs) [211]	Polymetric	**Active targeting** via integrin αvβ3 receptor binding and cathepsin K-triggered drug release.	Treatment of atherosclerosis	- Dual-targeting mechanism. - Controlled rapamycin (RAP) release for enhanced efficacy.
14-Succinyl Triptolide-Lysozyme Conjugate (TPS-LZM) [215]	Polymetric	**Active targeting** via megalin receptor-mediated uptake in proximal renal tubular epithelial cells (PTECs).	Treatment of renal ischemia-reperfusion (I/R) injury and immunological renal diseases	- High renal specificity with reduced systemic toxicity. - Enhanced therapeutic efficacy compared to free triptolide.
Kidney-Targeted Biopolymer (KTP-ELP Conjugate) [220]	Polymetric	**Active targeting** via kidney-targeting peptide (KTP) to proximal tubules.	Treatment of chronic kidney disease, acute kidney injury	- High renal specificity. - Low toxicity and biodegradable.
Hydrophobically Modified Glycol Chitosan-Tacrolimus Nanomicelles (HGC-TAC Nanomicelles) [221]	Polymetric	**Passive targeting** via enhanced permeability and retention (EPR) effect in inflamed kidney tissues.	Treatment of kidney transplant rejection	- High biocompatibility with reduced systemic toxicity. - Enhanced drug accumulation in the kidneys.
Hydrophobically Modified Glycol Chitosan-Tacrolimus Nanomicelles (HGC-TAC Nanomicelles) [225]	Polymetric	**Passive targeting** via enhanced permeability and retention (EPR) effect in inflamed kidney tissues.	Treatment of kidney transplant rejection	- High biocompatibility with reduced systemic toxicity. - Enhanced drug accumulation in the kidneys.
Sheep Anti-Mouse Podocyte Transporter (Shamporter) [226]	Polymetric	**Active targeting** via podocyte-specific antibody binding and internalization through endocytosis.	Treatment of glomerular diseases	- Specific siRNA delivery to podocytes. - Minimal off-target effects and immune activation.
Four-Arm Star-Shaped Polymeric Nanocarriers (Star-Polymers) [30]	Polymeric	**Passive and Active targeting**: Crosses the glomerular filtration barrier (GFB) and interacts with podocytes via charge selectivity.	Treatment of CKD, focusing on proteinuria-related conditions.	- Ultrasmall size (5–30 nm) for effective filtration. - Biodegradable hydrophobic core with a PEG shell for high stability.
Polyethylene Glycol-Modified Liposomes with TRX-20 (TRX-Liposomes) [227]	Liposomes	**Active and Passive targeting**: Active targeting to chondroitin sulfate proteoglycans on mesangial cells; passive accumulation via EPR effect.	Treatment of glomerulonephritis by reducing mesangial cell proliferation.	- Enhanced glomerular accumulation. - Effective at lower doses compared to conventional formulations.
Polystyrene Nanoparticles (PS-NPs) [228]	Inorganic	**Passive targeting** via enhanced accumulation in glomerular mesangial cells	Investigational tool for studying mesangial cell dynamics in glomerular diseases.	- High uptake efficiency by mesangial cells. - Tunable size and charge for targeted studies.
Red Blood Cell Membrane-Coated Polymeric Nanoparticles (RBC-NPs) [102]	Polymetric	**Passive targeting** via prolonged circulation through immune evasion, mimicking red blood cells.	Treatment of cancer by improving drug delivery and minimizing immune system clearance.	- Long circulation time through immune evasion. - Biomimetic coating ensures high biocompatibility.
P-selectin Binding Peptide-Modified Extracellular Vesicles (PBP-EVs) [232]	Low-Dimension	**Active targeting** via P-selectin binding peptide to injured renal endothelial cells.	Treatment of ischemic AKI	- Targeted delivery for renal repair. - Reduces fibrosis and enhances therapeutic outcomes.
Macrophage-Derived Microvesicle-Dexamethasone (MV-DEX) [239]	Liposomes	**Active targeting** via surface integrins (LFA-1, VLA-4) binding to ICAM-1 and VCAM-1 on inflamed endothelial cells.	Treatment of renal inflammation and fibrosis in nephropathy.	- Enhanced kidney-specific drug delivery. - Reduced systemic glucocorticoid side effects.
Platelet Membrane-Vesicle Coated Poly (lactic-co-glycolic acid)-siRNA Nanoparticles (PMVs@siRNA NPs) [245]	Polymetric	**Active targeting** via platelet membrane's affinity for damaged kidney sites.	Treatment of AKI and CKD.	- Enhanced renal targeting through platelet membrane coating. - Reduces renal fibrosis and inflammation.

CRediT authorship contribution statement

Zhiwen Wang: Writing – original draft, Conceptualization. **Chun Zhang:** Writing – review & editing, Conceptualization.

Availability of data and materials

No datasets were generated or analysed during the current study.

Consent for publication

All authors agree to the submission and publication of this paper.

Ethics approval and consent to participate

Not applicable.

Funding

C.Z. greatly acknowledges the financial support from the National Key Research and Development Program of China (2024YFC3044900), National Natural Science Foundation of China (82370728, 81974097, 82170773, 82100729, 82100794, 82200808, 82200841, 81800610, 82300843, 82300851, and 82300786), Key Research and Development Program of Hubei Province (2023BCB034), and National Key Research and Development Program of China (2021YFC2500200).

Declaration of competing interest

All authors declare no conflict of interest.

Acknowledgement

All the schematic figures were Created with BioRender.com.

Data availability

No data was used for the research described in the article.

References

[1] J.A. Kellum, R. Bellomo, C. Ronco, Definition and classification of acute kidney injury, Nephron Clin. Pract. 109 (4) (2008) c182–c187.
[2] M. Haase, J.A. Kellum, C. Ronco, Subclinical AKI–an emerging syndrome with important consequences, Nat. Rev. Nephrol. 8 (12) (2012) 735–739.
[3] A. Francis, M.N. Harhay, A.C.M. Ong, S.L. Tummalapalli, A. Ortiz, A.B. Fogo, D. Fliser, P. Roy-Chaudhury, M. Fontana, M. Nangaku, C. Wanner, C. Malik, A. Hradsky, D. Adu, S. Bavanandan, A. Cusumano, L. Sola, I. Ulasi, V. Jha, N. American Society of, A. European Renal, N. International Society of, Chronic kidney disease and the global public health agenda: an international consensus, Nat. Rev. Nephrol. 20 (7) (2024) 473–485.
[4] K.J. Foreman, N. Marquez, A. Dolgert, K. Fukutaki, N. Fullman, M. McGaughey, M.A. Pletcher, A.E. Smith, K. Tang, C.W. Yuan, J.C. Brown, J. Friedman, J. He, K. R. Heuton, M. Holmberg, D.J. Patel, P. Reidy, A. Carter, K. Cercy, A. Chapin, D. Douwes-Schultz, T. Frank, F. Goettsch, P.Y. Liu, V. Nandakumar, M.B. Reitsma, V. Reuter, N. Sadat, R.J.D. Sorensen, V. Srinivasan, R.L. Updike, H. York, A. D. Lopez, R. Lozano, S.S. Lim, A.H. Mokdad, S.E. Vollset, C.J.L. Murray, Forecasting life expectancy, years of life lost, and all-cause and cause-specific mortality for 250 causes of death: reference and alternative scenarios for 2016-40 for 195 countries and territories, Lancet 392 (10159) (2018) 2052–2090.
[5] A. Ortiz, EKPF and ALCER, FRIAT, .RDIR, RICORS2040: the need for collaborative research in chronic kidney disease, Clin Kidney J 15 (3) (2022) 372–387.
[6] Time to sound the alarm about the hidden epidemic of kidney disease, Nature 628 (8006) (2024) 7–8.
[7] Z. Wang, C. Zhang, From AKI to CKD: maladaptive repair and the Underlying mechanisms, Int. J. Mol. Sci. 23 (18) (2022).
[8] S. Kishi, H. Nagasu, K. Kidokoro, N. Kashihara, Oxidative stress and the role of redox signalling in chronic kidney disease, Nat. Rev. Nephrol. 20 (2) (2024) 101–119.
[9] O.C. Farokhzad, R. Langer, Impact of nanotechnology on drug delivery, ACS Nano 3 (1) (2009) 16–20.
[10] S. Senapati, R. Thakur, S.P. Verma, S. Duggal, D.P. Mishra, P. Das, T. Shripathi, M. Kumar, D. Rana, P. Maiti, Layered double hydroxides as effective carrier for anticancer drugs and tailoring of release rate through interlayer anions, J. Contr. Release 224 (2016) 186–198.
[11] D. Peer, J.M. Karp, S. Hong, O.C. Farokhzad, R. Margalit, R. Langer, Nanocarriers as an emerging platform for cancer therapy, Nat. Nanotechnol. 2 (12) (2007) 751–760.
[12] N.K. Singh, S.K. Singh, D. Dash, B.P.D. Purkayastha, J.K. Roy, P. Maiti, Nanostructure controlled anti-cancer drug delivery using poly(ε-caprolactone) based nanohybrids, J. Mater. Chem. 22 (34) (2012) 17853–17863.
[13] Z. Zhou, T. Wang, T. Hu, H. Xu, L. Cui, B. Xue, X. Zhao, X. Pan, S. Yu, H. Li, Y. Qin, J. Zhang, L. Ma, R. Liang, C. Tan, Synergistic interaction between metal single-atoms and defective WO(3-) (x) nanosheets for enhanced sonodynamic cancer therapy, Adv. Mater. 36 (23) (2024) e2311002.
[14] J. Zhang, Y. Yang, F. Qin, T. Hu, X. Zhao, S. Zhao, Y. Cao, Z. Gao, Z. Zhou, R. Liang, C. Tan, Y. Qin, Catalyzing generation and stabilization of oxygen vacancies on CeO(2-x) nanorods by Pt nanoclusters as nanozymes for catalytic therapy, Adv. Healthcare Mater. 12 (31) (2023) e2302056.
[15] Q.Y. Huang, Y. Chen, M. Ye, S.Z. Zhuang, A.G. Zhong, J.Q. Liu, G. Maduraiveeran, Y.Q. Peng, Y. Huang, Metal-organic framework-based dressings: application and opportunities in wound healing, Mater. Today Chem. 40 (2024).
[16] M. Gu, L. Lu, Q. Wei, Z. Miao, H. Zhang, L. Gao, L. Li, Improved oral bioavailability and anti-chronic renal failure activity of chrysophanol via mixed polymeric micelles, J. Microencapsul. 38 (1) (2021) 47–60.
[17] X. Qin, Y. Xu, X. Zhou, T. Gong, Z.R. Zhang, Y. Fu, An injectable micelle-hydrogel hybrid for localized and prolonged drug delivery in the management of renal fibrosis, Acta Pharm. Sin. B 11 (3) (2021) 835–847.
[18] H. Qiao, M. Sun, Z. Su, Y. Xie, M. Chen, L. Zong, Y. Gao, H. Li, J. Qi, Q. Zhao, X. Gu, Q. Ping, Kidney-specific drug delivery system for renal fibrosis based on coordination-driven assembly of catechol-derived chitosan, Biomaterials 35 (25) (2014) 7157–7171.
[19] D.F. Chen, S.P. Han, Y.Q. Zhu, F. Hu, Y.H. Wei, G.W. Wang, Kidney-targeted drug delivery via rhein-loaded polyethyleneglycol- -polycaprolactone- -polyethylenimine nanoparticles for diabetic nephropathy therapy, Int. J. Nanomed. 13 (2018) 3507–3527.
[20] G.H. Zhou, W.C. Zhao, C.Y. Zhang, X.Y. Gao, Q.L. Cheng, F.P. Gao, Manganese carbonyl-loaded hollow mesoporous silica nanoparticles coated with neutrophil membranes for acute kidney injury therapy, ACS Appl. Nano Mater. 5 (3) (2022) 4130–4145.
[21] R.M. Williams, J. Shah, B.D. Ng, D.R. Minton, L.J. Gudas, C.Y. Park, D.A. Heller, Mesoscale nanoparticles selectively target the renal proximal tubule epithelium, Nano Lett. 15 (4) (2015) 2358–2364.
[22] X. Lai, X. Geng, L. Tan, J. Hu, S. Wang, A pH-responsive system based on fluorescence enhanced gold nanoparticles for renal targeting drug delivery and fibrosis therapy, Int. J. Nanomed. 15 (2020) 5613–5627.
[23] Z. Binkhathlan, R. Ali, W. Qamar, H. Al-Lawati, A. Lavasanifar, Pharmacokinetic and tissue distribution of orally administered cyclosporine A-loaded poly (ethylene oxide)-block-Poly(epsilon-caprolactone) micelles versus sandimmune ((R)) in rats, Pharm. Res. (N. Y.) 38 (1) (2021) 51–65.
[24] H. Kobayashi, S.K. Jo, S. Kawamoto, H. Yasuda, X.Z. Hu, M.V. Knopp, M. W. Brechbiel, P.L. Choyke, R.A. Star, Polyamine dendrimer-based MRI contrast agents for functional kidney imaging to diagnose acute renal failure, J. Magn. Reson. Imag. 20 (3) (2004) 512–518.
[25] H. Yu, F. Jin, D. Liu, G. Shu, X. Wang, J. Qi, M. Sun, P. Yang, S. Jiang, X. Ying, Y. Du, ROS-responsive nano-drug delivery system combining mitochondria-targeting ceria nanoparticles with atorvastatin for acute kidney injury, Theranostics 10 (5) (2020) 2342–2357.
[26] H. Katsumi, R. Takashima, H. Suzuki, N. Hirai, S. Matsuura, H. Kimura, M. Morishita, A. Yamamoto, S-nitrosylated l-serine-modified dendrimer as a kidney-targeting nitric oxide donor for prevention of renal ischaemia/reperfusion injury, Free Radic. Res. 54 (11–12) (2020) 841–847.
[27] S.J. Han, R.M. Williams, V. D'Agati, E.A. Jaimes, D.A. Heller, H.T. Lee, Selective nanoparticle-mediated targeting of renal tubular Toll-like receptor 9 attenuates ischemic acute kidney injury, Kidney Int. 98 (1) (2020) 76–87.
[28] S. Liu, M. Zhao, Y. Zhou, L. Li, C. Wang, Y. Yuan, L. Li, G. Liao, W. Bresette, Y. Chen, J. Cheng, Y. Lu, J. Liu, A self-assembling peptide hydrogel-based drug co-delivery platform to improve tissue repair after ischemia-reperfusion injury, Acta Biomater. 103 (2020) 102–114.
[29] L. Guo, S. Luo, Z. Du, M. Zhou, P. Li, Y. Fu, X. Sun, Y. Huang, Z. Zhang, Targeted delivery of celastrol to mesangial cells is effective against mesangioproliferative glomerulonephritis, Nat. Commun. 8 (1) (2017) 878.
[30] R. Bruni, P. Possenti, C. Bordignon, M. Li, S. Ordanini, P. Messa, M.P. Rastaldi, F. Cellesi, Ultrasmall polymeric nanocarriers for drug delivery to podocytes in kidney glomerulus, J. Contr. Release 255 (2017) 94–107.
[31] T. Hu, B. Xue, F. Meng, L. Ma, Y. Du, S. Yu, R. Ye, H. Li, Q. Zhang, L. Gu, Z. Zhou, R. Liang, C. Tan, Preparation of 2D polyaniline/MoO(3-) (x) superlattice nanosheets via intercalation-induced morphological transformation for efficient chemodynamic therapy, Adv. Healthcare Mater. 12 (11) (2023) e2202911.
[32] S. Huang, H. Lu, J. Chen, C. Jiang, G. Jiang, G. Maduraiveeran, Y. Pan, J. Liu, L. E. Deng, Advances in drug delivery-based therapeutic strategies for renal fibrosis treatment, J. Mater. Chem. B 12 (27) (2024) 6532–6549.
[33] K. Saha, A. Bajaj, B. Duncan, V.M. Rotello, Beauty is skin deep: a surface monolayer perspective on nanoparticle interactions with cells and bio-macromolecules, Small 7 (14) (2011) 1903–1918.

[34] Q. Mu, G. Jiang, L. Chen, H. Zhou, D. Fourches, A. Tropsha, B. Yan, Chemical basis of interactions between engineered nanoparticles and biological systems, Chem. Rev. 114 (15) (2014) 7740–7781.
[35] S.E. Gratton, P.A. Ropp, P.D. Pohlhaus, J.C. Luft, V.J. Madden, M.E. Napier, J. M. DeSimone, The effect of particle design on cellular internalization pathways, Proc. Natl. Acad. Sci. U. S. A. 105 (33) (2008) 11613–11618.
[36] A.C. Anselmo, S. Mitragotri, Impact of particle elasticity on particle-based drug delivery systems, Adv. Drug Deliv. Rev. 108 (2017) 51–67.
[37] J. Wang, J.D. Byrne, M.E. Napier, J.M. DeSimone, More effective nanomedicines through particle design, Small 7 (14) (2011) 1919–1931.
[38] A. Albanese, C.D. Walkey, J.B. Olsen, H. Guo, A. Emili, W.C. Chan, Secreted biomolecules alter the biological identity and cellular interactions of nanoparticles, ACS Nano 8 (6) (2014) 5515–5526.
[39] N. Kamaly, Z. Xiao, P.M. Valencia, A.F. Radovic-Moreno, O.C. Farokhzad, Targeted polymeric therapeutic nanoparticles: design, development and clinical translation, Chem. Soc. Rev. 41 (7) (2012) 2971–3010.
[40] A.E. Nel, L. Madler, D. Velegol, T. Xia, E.M. Hoek, P. Somasundaran, F. Klaessig, V. Castranova, M. Thompson, Understanding biophysicochemical interactions at the nano-bio interface, Nat. Mater. 8 (7) (2009) 543–557.
[41] S.J. Shankland, B. Smeets, J.W. Pippin, M.J. Moeller, The emergence of the glomerular parietal epithelial cell, Nat. Rev. Nephrol. 10 (3) (2014) 158–173.
[42] J.H. Miner, The glomerular basement membrane, Exp. Cell Res. 318 (9) (2012) 973–978.
[43] A. Singh, S.C. Satchell, C.R. Neal, E.A. McKenzie, J.E. Tooke, P.W. Mathieson, Glomerular endothelial glycocalyx constitutes a barrier to protein permeability, J. Am. Soc. Nephrol. 18 (11) (2007) 2885–2893.
[44] M.C. Menon, P.Y. Chuang, C.J. He, The glomerular filtration barrier: components and crosstalk, Internet J. Nephrol. 2012 (2012) 749010.
[45] H.E. Abboud, Mesangial cell biology, Exp. Cell Res. 318 (9) (2012) 979–985.
[46] S. Armelloni, A. Corbelli, L. Giardino, M. Li, M. Ikehata, D. Mattinzoli, P. Messa, C. Pignatari, S. Watanabe, M.P. Rastaldi, Podocytes: recent biomolecular developments, Biomol. Concepts 5 (4) (2014) 319–330.
[47] B. Haraldsson, J. Nystrom, W.M. Deen, Properties of the glomerular barrier and mechanisms of proteinuria, Physiol. Rev. 88 (2) (2008) 451–487.
[48] S. Satchell, The role of the glomerular endothelium in albumin handling, Nat. Rev. Nephrol. 9 (12) (2013) 717–725.
[49] B.J. Du, M.X. Yu, J. Zheng, Transport and interactions of nanoparticles in the kidneys, Nat. Rev. Mater. 3 (10) (2018) 358–374.
[50] H.T. Cheng, Y.N. Ngoc Ta, T. Hsia, Y. Chen, A quantitative review of nanotechnology-based therapeutics for kidney diseases, Wiley Interdiscip Rev Nanomed Nanobiotechnol 16 (2) (2024) e1953.
[51] Q. Huang, Y. Yang, T. Zhao, Q. Chen, M. Liu, S. Ji, Y. Zhu, Y. Yang, J. Zhang, H. Zhao, Y. Nan, K. Ai, Passively-targeted mitochondrial tungsten-based nanodots for efficient acute kidney injury treatment, Bioact. Mater. 21 (2023) 381–393.
[52] W.D. Comper, E.F. Glasgow, Charge selectivity in kidney ultrafiltration, Kidney Int. 47 (5) (1995) 1242–1251.
[53] J. Tencer, I.M. Frick, B.W. Oquist, P. Alm, B. Rippe, Size-selectivity of the glomerular barrier to high molecular weight proteins: upper size limitations of shunt pathways, Kidney Int. 53 (3) (1998) 709–715.
[54] C.H. Choi, J.E. Zuckerman, P. Webster, M.E. Davis, Targeting kidney mesangium by nanoparticles of defined size, Proc. Natl. Acad. Sci. U. S. A. 108 (16) (2011) 6656–6661.
[55] H.S. Choi, W. Liu, F. Liu, K. Nasr, P. Misra, M.G. Bawendi, J.V. Frangioni, Design considerations for tumour-targeted nanoparticles, Nat. Nanotechnol. 5 (1) (2010) 42–47.
[56] H.S. Choi, W. Liu, P. Misra, E. Tanaka, J.P. Zimmer, B.I. Ipe, M.G. Bawendi, J. V. Frangioni, Renal clearance of quantum dots, Nat. Biotechnol. 25 (10) (2007) 1165–1170.
[57] G. Singh, J.L.Z. Ddungu, N. Licciardello, R. Bergmann, L. De Cola, H. Stephan, Ultrasmall silicon nanoparticles as a promising platform for multimodal imaging, Faraday Discuss 222 (0) (2020) 362–383.
[58] A.A. Burns, J. Vider, H. Ow, E. Herz, O. Penate-Medina, M. Baumgart, S. M. Larson, U. Wiesner, M. Bradbury, Fluorescent silica nanoparticles with efficient urinary excretion for nanomedicine, Nano Lett. 9 (1) (2009) 442–448.
[59] B.J. Du, X.Y. Jiang, A. Das, Q.H. Zhou, M.X. Yu, R.C. Jin, J. Zheng, Glomerular barrier behaves as an atomically precise bandpass filter in a sub-nanometre regime, Nat. Nanotechnol. 12 (11) (2017), 1096-+.
[60] C. Zhou, M. Long, Y. Qin, X. Sun, J. Zheng, Luminescent gold nanoparticles with efficient renal clearance, Angew Chem. Int. Ed. Engl. 50 (14) (2011) 3168–3172.
[61] C. Zhou, G. Hao, P. Thomas, J. Liu, M. Yu, S. Sun, O.K. Oz, X. Sun, J. Zheng, Near-infrared emitting radioactive gold nanoparticles with molecular pharmacokinetics, Angew Chem. Int. Ed. Engl. 51 (40) (2012) 10118–10122.
[62] L. Guo, S. Luo, Z. Du, M. Zhou, P. Li, Y. Fu, X. Sun, Y. Huang, Z. Zhang, Targeted delivery of celastrol to mesangial cells is effective against mesangioproliferative glomerulonephritis, Nat. Commun. 8 (1) (2017) 878.
[63] Y. Huang, J. Wang, K. Jiang, E.J. Chung, Improving kidney targeting: the influence of nanoparticle physicochemical properties on kidney interactions, J. Contr. Release 334 (2021) 127–137.
[64] H. Yu, T. Lin, W. Chen, W. Cao, C. Zhang, T. Wang, M. Ding, S. Zhao, H. Wei, H. Guo, X. Zhao, Size and temporal-dependent efficacy of oltipraz-loaded PLGA nanoparticles for treatment of acute kidney injury and fibrosis, Biomaterials 219 (2019) 119368.
[65] R.M. Williams, J. Shah, B.D. Ng, D.R. Minton, L.J. Gudas, C.Y. Park, D.A. Heller, Mesoscale nanoparticles selectively target the renal proximal tubule epithelium, Nano Lett. 15 (4) (2015) 2358–2364.
[66] R.M. Williams, J. Shah, H.S. Tian, X. Chen, F. Geissmann, E.A. Jaimes, D. A. Heller, Selective nanoparticle targeting of the renal tubules, Hypertension 71 (1) (2018) 87–94.
[67] C.S. Kim, A.P. Mathew, S. Uthaman, M.J. Moon, E.H. Bae, S.W. Kim, I.K. Park, Glycol chitosan-based renal docking biopolymeric nanomicelles for site-specific delivery of the immunosuppressant, Carbohydr. Polym. 241 (2020) 116255.
[68] S.J. Han, R.M. Williams, V. D'Agati, E.A. Jaimes, D.A. Heller, H.T. Lee, Selective nanoparticle-mediated targeting of renal tubular Toll-like receptor 9 attenuates ischemic acute kidney injury, Kidney Int. 98 (1) (2020) 76–87.
[69] N. Kamaly, J.C. He, D.A. Ausiello, O.C. Farokhzad, Nanomedicines for renal disease: current status and future applications, Nat. Rev. Nephrol. 12 (12) (2016) 738–753.
[70] H. Pavenstadt, W. Kriz, M. Kretzler, Cell biology of the glomerular podocyte, Physiol. Rev. 83 (1) (2003) 253–307.
[71] C.P. Liu, Y. Hu, J.C. Lin, H.L. Fu, L.Y. Lim, Z.X. Yuan, Targeting strategies for drug delivery to the kidney: from renal glomeruli to tubules, Med. Res. Rev. 39 (2) (2019) 561–578.
[72] R. Toy, P.M. Peiris, K.B. Ghaghada, E. Karathanasis, Shaping cancer nanomedicine: the effect of particle shape on the journey of nanoparticles, Nanomedicine-Uk 9 (1) (2014) 121–134.
[73] A. Ruggiero, C.H. Villa, E. Bander, D.A. Rey, M. Bergkvist, C.A. Batt, K. Manova-Todorova, W.M. Deen, D.A. Scheinberg, M.R. McDevitt, Paradoxical glomerular filtration of carbon nanotubes, P Natl Acad Sci USA 107 (27) (2010) 12369–12374.
[74] D.A. Jasim, S. Murphy, L. Newman, A. Mironov, E. Prestat, J. McCaffrey, C. Ménard-Moyon, A.F. Rodrigues, A. Bianco, S. Haigh, R. Lennon, K. Kostarelos, The effects of extensive glomerular filtration of thin graphene oxide sheets on kidney physiology, ACS Nano 10 (12) (2016) 10753–10767.
[75] J.J. Hou, H. Wang, Z.L. Ge, T.T. Zuo, Q. Chen, X.G. Liu, S. Mou, C.H. Fan, Y. Xie, L.H. Wang, Treating acute kidney injury with antioxidative black phosphorus nanosheets, Nano Lett. 20 (2) (2020) 1447–1454.
[76] J.B. Liu, M.X. Yu, C. Zhou, J. Zheng, Renal clearable inorganic nanoparticles: a new frontier of bionanotechnology, Mater. Today 16 (12) (2013) 477–486.
[77] X.T. Deng, T. Zeng, J.W. Li, C.L. Huang, M. Yu, X. Wang, L.S. Tan, M.B. Zhang, A. Q. Li, J.Q. Hu, Kidney-targeted triptolide-encapsulated mesoscale nanoparticles for high-efficiency treatment of kidney injury, Biomater Sci-Uk 7 (12) (2019) 5312–5323.
[78] M.X. Yu, C. Zhou, L. Liu, S.R. Zhang, S.S. Sun, J.D. Hankins, X.K. Sun, J. Zheng, Interactions of renal-clearable gold nanoparticles with tumor microenvironments: vasculature and acidity effects, Angew. Chem., Int. Ed. 56 (15) (2017) 4314–4319.
[79] Y. Huang, K. Jiang, X. Zhang, E.J. Chung, The effect of size, charge, and peptide ligand length on kidney targeting by small, organic nanoparticles, Bioeng Transl Med 5 (3) (2020) e10173.
[80] P. Hu, J. An, M.M. Faulkner, H. Wu, Z. Li, X. Tian, J.P. Giraldo, Nanoparticle charge and size control foliar delivery efficiency to plant cells and organelles, ACS Nano 14 (7) (2020) 7970–7986.
[81] R.M. Williams, J. Shah, H.S. Tian, X. Chen, F. Geissmann, E.A. Jaimes, D. A. Heller, Selective nanoparticle targeting of the renal tubules, Hypertension 71 (1) (2018) 87–94.
[82] A. Wischnjow, D. Sarko, M. Janzer, C. Kaufman, B. Beijer, S. Brings, U. Haberkorn, G. Larbig, A. Kübelbeck, W. Mier, Renal targeting: peptide-based drug delivery to proximal tubule cells, Bioconjugate Chem. 27 (4) (2016) 1050–1057.
[83] J. Wang, C. Poon, D. Chin, S. Milkowski, V. Lu, K.R. Hallows, E.J. Chung, Design and characterization of kidney-targeting multimodal micelles for renal drug delivery, Nano Res. 11 (10) (2018) 5584–5595.
[84] J.W. Zuo, S.M. Wang, X. Jiang, M.X. Cao, Z.W. Zhang, T.L. Shi, H.L. Qin, W. J. Tang, Design, synthesis and biological evaluation of novel arylpropionic esters for the treatment of acute kidney injury, Bioorg. Chem. 105 (2020).
[85] T.T. Tang, B. Wang, Z.L. Li, Y. Wen, S.T. Feng, M. Wu, D. Liu, J.Y. Cao, Q. Yin, D. Yin, Y.Q. Fu, Y.M. Gao, Z.Y. Ding, J.Y. Qian, Q.L. Wu, L.L. Lv, B.C. Liu, Kim-1 targeted extracellular vesicles: a new therapeutic platform for RNAi to treat AKI, J. Am. Soc. Nephrol. 32 (10) (2021) 2467–2483.
[86] E.J. Cho, J.W. Lee, A.D. Ellington, Applications of aptamers as sensors, Annu. Rev. Anal. Chem. 2 (2009) 241–264.
[87] K.H. Trinh, U.S. Kadam, S. Rampogu, Y. Cho, K.A. Yang, C.H. Kang, K.W. Lee, K. O. Lee, W.S. Chung, J.C. Hong, Development of novel fluorescence-based and label-free noncanonical G4-quadruplex-like DNA biosensor for facile, specific, and ultrasensitive detection of fipronil, J. Hazard Mater. 427 (2022) 127939.
[88] K.H. Trinh, U.S. Kadam, J. Song, Y. Cho, C.H. Kang, K.O. Lee, C.O. Lim, W. S. Chung, J.C. Hong, Novel DNA aptameric sensors to detect the toxic insecticide fenitrothion, Int. J. Mol. Sci. 22 (19) (2021).
[89] Y. Hu, X.A. Yu, Y. Zhang, R. Zhang, X. Bai, M. Lu, J. Li, L. Gu, J.H. Liu, B.Y. Yu, J. Tian, Rapid and sensitive detection of NGAL for the prediction of acute kidney injury via a polydopamine nanosphere/aptamer nanocomplex coupled with DNase I-assisted recycling amplification, Analyst 145 (10) (2020) 3620–3625.
[90] J.B. Hu, S.J. Li, X.Q. Kang, J. Qi, J.H. Wu, X.J. Wang, X.L. Xu, X.Y. Ying, S. P. Jiang, J. You, Y.Z. Du, CD44-targeted hyaluronic acid-curcumin prodrug protects renal tubular epithelial cell survival from oxidative stress damage, Carbohydr. Polym. 193 (2018) 268–280.
[91] Z.W. Huang, Y. Shi, Y.Y. Zhai, C.C. Du, J. Zhai, R.J. Yu, L. Kou, J. Xiao, Y.Z. Zhao, Q. Yao, Hyaluronic acid coated bilirubin nanoparticles attenuate ischemia reperfusion-induced acute kidney injury, J. Contr. Release 334 (2021) 275–289.
[92] N. Liu, X. Liang, C. Yang, S. Hu, Q. Luo, H. Luo, Dual-targeted magnetic mesoporous silica nanoparticles reduce brain amyloid-beta burden via

depolymerization and intestinal metabolism, Theranostics 12 (15) (2022) 6646–6664.
[93] J. Sun, X. Zhao, H. Shen, J. Dong, S. Rong, W. Cai, R. Zhang, CD44-targeted melanin-based nanoplatform for alleviation of ischemia/reperfusion-induced acute kidney injury, J. Contr. Release 368 (2024) 1–14.
[94] I. Khan, K. Saeed, I. Khan, Nanoparticles: properties, applications and toxicities, Arab. J. Chem. 12 (7) (2019) 908–931.
[95] F. Ordikhani, V. Kasinath, M. Uehara, A. Akbarzadeh, O.A. Yilmam, L. Dai, H. Aksu, S. Jung, L. Jiang, X. Li, J. Zhao, B. Bahmani, T. Ichimura, P. Fiorina, N. Annabi, R. Abdi, Selective trafficking of light chain-conjugated nanoparticles to the kidney and renal cell carcinoma, Nano Today 35 (2020).
[96] T.M. Sun, Y.S. Zhang, B. Pang, D.C. Hyun, M.X. Yang, Y.N. Xia, Engineered nanoparticles for drug delivery in cancer therapy, Angew. Chem., Int. Ed. 53 (46) (2014) 12320–12364.
[97] C.K. Kim, T. Kim, I.Y. Choi, M. Soh, D. Kim, Y.J. Kim, H. Jang, H.S. Yang, J. Y. Kim, H.K. Park, S.P. Park, S. Park, T. Yu, B.W. Yoon, S.H. Lee, T. Hyeon, Ceria nanoparticles that can protect against ischemic stroke, Angew. Chem., Int. Ed. 51 (44) (2012) 11039–11043.
[98] A. Watanabe, M. Kajita, J. Kim, A. Kanayama, K. Takahashi, T. Mashino, Y. Miyamoto, In vitro free radical scavenging activity of platinum nanoparticles, Nanotechnology 20 (45) (2009) 455105.
[99] D.L. Ni, D.W. Jiang, C.J. Kutyreff, J.H. Lai, Y.J. Yan, T.E. Barnhart, B. Yu, H.J. Im, L. Kang, S.Y. Cho, Z.F. Liu, P. Huang, J.W. Engle, W.B. Cai, Molybdenum-based nanoclusters act as antioxidants and ameliorate acute kidney injury in mice, Nat. Commun. 9 (2018).
[100] C.N. Rao, H.S. Ramakrishna Matte, R. Voggu, A. Govindaraj, Recent progress in the synthesis of inorganic nanoparticles, Dalton Trans. 41 (17) (2012) 5089–5120.
[101] R. Gref, M. Luck, P. Quellec, M. Marchand, E. Dellacherie, S. Harnisch, T. Blunk, R.H. Muller, 'Stealth' corona-core nanoparticles surface modified by polyethylene glycol (PEG): influences of the corona (PEG chain length and surface density) and of the core composition on phagocytic uptake and plasma protein adsorption, Colloids Surf. B Biointerfaces 18 (3–4) (2000) 301–313.
[102] C.M. Hu, L. Zhang, S. Aryal, C. Cheung, R.H. Fang, L. Zhang, Erythrocyte membrane-camouflaged polymeric nanoparticles as a biomimetic delivery platform, Proc. Natl. Acad. Sci. U. S. A. 108 (27) (2011) 10980–10985.
[103] N. Khatoon, Z. Zhang, C. Zhou, M. Chu, Macrophage membrane coated nanoparticles: a biomimetic approach for enhanced and targeted delivery, Biomater. Sci. 10 (5) (2022) 1193–1208.
[104] W. Pei, B. Huang, S. Chen, L. Wang, Y. Xu, C. Niu, Platelet-mimicking drug delivery nanoparticles for enhanced chemo-photothermal therapy of breast cancer, Int. J. Nanomed. 15 (2020) 10151–10167.
[105] C. Gao, Z. Lin, Z. Wu, X. Lin, Q. He, Stem-cell-membrane camouflaging on near-infrared photoactivated upconversion nanoarchitectures for in vivo remote-controlled photodynamic therapy, ACS Appl. Mater. Interfaces 8 (50) (2016) 34252–34260.
[106] Q.Q. Liu, Y.J. Kim, G.B. Im, J.T. Zhu, Y.Z. Wu, Y.J. Liu, S.H. Bhang, Inorganic nanoparticles applied as functional therapeutics, Adv. Funct. Mater. 31 (12) (2021).
[107] S.J. Buwalda, K.W.M. Boere, P.J. Dijkstra, J. Feijen, T. Vermonden, W.E. Hennink, Hydrogels in a historical perspective: from simple networks to smart materials, J. Contr. Release 190 (2014) 254–273.
[108] N.A. Peppas, J.Z. Hilt, A. Khademhosseini, R. Langer, Hydrogels in biology and medicine: from molecular principles to bionanotechnology, Adv. Mater. 18 (11) (2006) 1345–1360.
[109] K. Raemdonck, J. Demeester, S. De Smedt, Advanced nanogel engineering for drug delivery, Soft Matter 5 (4) (2009) 707–715.
[110] J.K. Oh, R. Drumright, D.J. Siegwart, K. Matyjaszewski, The development of microgels/nanogels for drug delivery applications, Prog. Polym. Sci. 33 (4) (2008) 448–477.
[111] A.V. Kabanov, S.V. Vinogradov, Nanogels as pharmaceutical carriers: finite networks of infinite capabilities, Angew. Chem., Int. Ed. 48 (30) (2009) 5418–5429.
[112] S. Mavuso, T. Marimuthu, Y.E. Choonara, P. Kumar, L.C. du Toit, V. Pillay, A review of polymeric colloidal nanogels in transdermal drug delivery, Curr. Pharmaceut. Des. 21 (20) (2015) 2801–2813.
[113] Y. Han, J. Yang, W. Zhao, H. Wang, Y. Sun, Y. Chen, J. Luo, L. Deng, X. Xu, W. Cui, H. Zhang, Biomimetic injectable hydrogel microspheres with enhanced lubrication and controllable drug release for the treatment of osteoarthritis, Bioact. Mater. 6 (10) (2021) 3596–3607.
[114] M.D. Moya-Ortega, C. Alvarez-Lorenzo, A. Concheiro, T. Loftsson, Cyclodextrin-based nanogels for pharmaceutical and biomedical applications, Int. J. Pharm. 428 (1–2) (2012) 152–163.
[115] Y. Li, D. Maciel, J. Rodrigues, X. Shi, H. Tomas, Biodegradable polymer nanogels for drug/nucleic acid delivery, Chem. Rev. 115 (16) (2015) 8564–8608.
[116] H. Zhang, Y. Zhai, J. Wang, G. Zhai, New progress and prospects: the application of nanogel in drug delivery, Mater Sci Eng C Mater Biol Appl 60 (2016) 560–568.
[117] H.Q. Wu, C.C. Wang, Biodegradable smart nanogels: a new platform for targeting drug delivery and biomedical diagnostics, Langmuir 32 (25) (2016) 6211–6225.
[118] K.S. Soni, S.S. Desale, T.K. Bronich, Nanogels: an overview of properties, biomedical applications and obstacles to clinical translation, J. Contr. Release 240 (2016) 109–126.
[119] M. Gregoritza, A.M. Goepferich, F.P. Brandl, Polyanions effectively prevent protein conjugation and activity loss during hydrogel cross-linking, J. Contr. Release 238 (2016) 92–102.
[120] N. Hammer, F.P. Brandl, S. Kirchhof, V. Messmann, A.M. Goepferich, Protein compatibility of selected cross-linking reactions for hydrogels, Macromol. Biosci. 15 (3) (2015) 405–413.
[121] L. Nuhn, L. Braun, I. Overhoff, A. Kelsch, D. Schaeffel, K. Koynov, R. Zentel, Degradable cationic nanohydrogel particles for stimuli-responsive release of siRNA, Macromol Rapid Comm 35 (24) (2014) 2057–2064.
[122] K. Raemdonck, T.G. Van Thienen, R.E. Vandenbroucke, N.N. Sanders, J. Demeester, S.C. De Smedt, Dextran microgels for time-controlled delivery of siRNA, Adv. Funct. Mater. 18 (7) (2008) 993–1001.
[123] L. Nuhn, L. Kaps, M. Diken, D. Schuppan, R. Zentel, Reductive decationizable block copolymers for stimuli-responsive mRNA delivery, Macromol Rapid Comm 37 (11) (2016) 924–933.
[124] Y. Sasaki, K. Akiyoshi, Nanogel engineering for new nanobiomaterials: from chaperoning engineering to biomedical applications, Chem. Rec. 10 (6) (2010) 366–376.
[125] P. Lavrador, V.M. Gaspar, J.F. Mano, Stimuli-responsive nanocarriers for delivery of bone therapeutics - barriers and progresses, J. Contr. Release 273 (2018) 51–67.
[126] N.A. Peppas, P. Bures, W. Leobandung, H. Ichikawa, Hydrogels in pharmaceutical formulations, Eur. J. Pharm. Biopharm. 50 (1) (2000) 27–46.
[127] L. Nuhn, S. Tomcin, K. Miyata, V. Mailander, K. Landfester, K. Kataoka, R. Zentel, Size-dependent knockdown potential of siRNA-loaded cationic nanohydrogel particles, Biomacromolecules 15 (11) (2014) 4111–4121.
[128] M. Hamidi, A. Azadi, P. Rafiei, Hydrogel nanoparticles in drug delivery, Adv. Drug Deliv. Rev. 60 (15) (2008) 1638–1649.
[129] T. Nochi, Y. Yuki, H. Takahashi, S. Sawada, M. Mejima, T. Kohda, N. Harada, I. G. Kong, A. Sato, N. Kataoka, D. Tokuhara, S. Kurokawa, Y. Takahashi, H. Tsukada, S. Kozaki, K. Akiyoshi, H. Kiyono, Nanogel antigenic protein-delivery system for adjuvant-free intranasal vaccines, Nat. Mater. 9 (7) (2010) 572–578.
[130] H. Fujii, M. Shin-Ya, S. Takeda, Y. Hashimoto, S.A. Mukai, S. Sawada, T. Adachi, K. Akiyoshi, T. Miki, O. Mazda, Cycloamylose-nanogel drug delivery system-mediated intratumor silencing of the vascular endothelial growth factor regulates neovascularization in tumor microenvironment, Cancer Sci. 105 (12) (2014) 1616–1625.
[131] M. Kolter, M. Wittmann, M. Köll-Weber, R. Süss, The suitability of liposomes for the delivery of hydrophobic drugs - a case study with curcumin, Eur. J. Pharm. Biopharm. 140 (2019) 20–28.
[132] A.A. Khan, K.S. Allemailem, S.A. Almatroodi, A. Almatroudi, A.H. Rahmani, Recent strategies towards the surface modification of liposomes: an innovative approach for different clinical applications, 3 Biotech 10 (4) (2020) 163.
[133] S.M. Gruner, R.P. Lenk, A.S. Janoff, M.J. Ostro, Novel multilayered lipid vesicles: comparison of physical characteristics of multilamellar liposomes and stable plurilamellar vesicles, Biochemistry 24 (12) (1985) 2833–2842.
[134] J. Liu, X. Li, L. Liu, Q. Bai, N. Sui, Z. Zhu, Self-assembled ultrasmall silver nanoclusters on liposome for topical antimicrobial delivery, Colloids Surf. B Biointerfaces 200 (2021) 111618.
[135] D. Lichtenberg, T. Markello, Structural characteristics of phospholipid multilamellar liposomes, J. Pharmaceut. Sci. 73 (1) (1984) 122–125.
[136] L. Sercombe, T. Veerati, F. Moheimani, S.Y. Wu, A.K. Sood, S. Hua, Advances and challenges of liposome assisted drug delivery, Front. Pharmacol. 6 (2015) 286.
[137] A. Nagelkerke, M. Ojansivu, L. van der Koog, T.E. Whittaker, E.M. Cunnane, A. M. Silva, N. Dekker, M.M. Stevens, Extracellular vesicles for tissue repair and regeneration: evidence, challenges and opportunities, Adv. Drug Deliv. Rev. 175 (2021) 113775.
[138] S. Zhang, H. Gao, G. Bao, Physical principles of nanoparticle cellular endocytosis, ACS Nano 9 (9) (2015) 8655–8671.
[139] K. Sakai-Kato, K. Yoshida, Y. Takechi-Haraya, K.I. Izutsu, Physicochemical characterization of liposomes that mimic the lipid composition of exosomes for effective intracellular trafficking, Langmuir 36 (42) (2020) 12735–12744.
[140] Y. Eygeris, M. Gupta, J. Kim, G. Sahay, Chemistry of lipid nanoparticles for RNA delivery, Acc. Chem. Res. 55 (1) (2022) 2–12.
[141] M.J.W. Evers, J.A. Kulkarni, R. van der Meel, P.R. Cullis, P. Vader, R. M. Schiffelers, State-of-the-Art design and rapid-mixing production techniques of lipid nanoparticles for nucleic acid delivery, Small Methods 2 (9) (2018).
[142] V.V.S.N.L. Andra, S.V.N. Pammi, L.V.K.P. Bhatraju, L.K. Ruddaraju, A comprehensive review on novel liposomal methodologies, commercial formulations, clinical trials and patents (vol 26, pg 1, 2022), Bionanoscience 12 (2) (2022) 660, 660.
[143] T.A. Balbino, N.T. Aoki, A.A.M. Gasperini, C.L.P. Oliveira, A.R. Azzoni, L. P. Cavalcanti, L.G. de la Torre, Continuous flow production of cationic liposomes at high lipid concentration in microfluidic devices for gene delivery applications, Chem. Eng. J. 226 (2013) 423–433.
[144] J. Kim, Y. Eygeris, M. Gupta, G. Sahay, Self-assembled mRNA vaccines, Adv. Drug Deliv. Rev. 170 (2021) 83–112.
[145] M. Uchida, B. Maier, H.K. Waghwani, E. Selivanovitch, S.L. Pay, J. Avera, E. Yun, R.M. Sandoval, B.A. Molitoris, A. Zollman, T. Douglas, T. Hato, The archaeal Dps nanocage targets kidney proximal tubules via glomerular filtration, J. Clin. Invest. 129 (9) (2019) 3941–3951.
[146] A. Akhtar, S.X. Wang, L. Ghali, C. Bell, X. Wen, Effective delivery of arsenic trioxide to HPV-positive cervical cancer cells using optimised liposomes: a size and charge study, Int. J. Mol. Sci. 19 (4) (2018).
[147] S.A. Asgeirsdottir, P.J. Zwiers, H.W. Morselt, H.E. Moorlag, H.I. Bakker, P. Heeringa, J.W. Kok, C.G. Kallenberg, G. Molema, J.A. Kamps, Inhibition of proinflammatory genes in anti-GBM glomerulonephritis by targeted dexamethasone-loaded AbEsel liposomes, Am. J. Physiol. Ren. Physiol. 294 (3) (2008) F554–F561.

[148] J. Yang, X. Miao, Y. Guan, C. Chen, S. Chen, X. Zhang, X. Xiao, Z. Zhang, Z. Xia, T. Yin, Z. Hei, W. Yao, Microbubble functionalization with platelet membrane enables targeting and early detection of sepsis-induced acute kidney injury, Adv. Healthcare Mater. 10 (23) (2021) e2101628.
[149] Z. Chen, W. Li, L. Shi, L. Jiang, M. Li, C. Zhang, H. Peng, Kidney-targeted astaxanthin natural antioxidant nanosystem for diabetic nephropathy therapy, Eur. J. Pharm. Biopharm. 156 (2020) 143–154.
[150] J. Huang, J. Guo, Y. Dong, H. Xiao, P. Yang, Y. Liu, S. Liu, S. Cheng, J. Song, Y. Su, S. Wang, Self-assembled hyaluronic acid-coated nanocomplexes for targeted delivery of curcumin alleviate acute kidney injury, Int. J. Biol. Macromol. 226 (2023) 1192–1202.
[151] G. Tuffin, E. Waelti, J. Huwyler, C. Hammer, H.P. Marti, Immunoliposome targeting to mesangial cells: a promising strategy for specific drug delivery to the kidney, J. Am. Soc. Nephrol. 16 (11) (2005) 3295–3305.
[152] Z.X. Yuan, L. Jia, L.Y. Lim, J.C. Lin, G. Shu, L. Zhao, G. Ye, X.X. Liang, H. Ji, H. L. Fu, Renal-targeted delivery of triptolide by entrapment in pegylated TRX-20-modified liposomes, Int. J. Nanomed. 12 (2017) 5673–5686.
[153] P. Fang, L. Han, C. Liu, S. Deng, E. Zhang, P. Gong, Y. Ren, J. Gu, L. He, Z.X. Yuan, Dual-Regulated functionalized liposome-nanoparticle hybrids loaded with dexamethasone/TGFbeta1-siRNA for targeted therapy of glomerulonephritis, ACS Appl. Mater. Interfaces 14 (1) (2022) 307–323.
[154] Z.L. Shaw, S. Kuriakose, S. Cheeseman, M.D. Dickey, J. Genzer, A. J. Christofferson, R.J. Crawford, C.F. McConville, J. Chapman, V.K. Truong, A. Elbourne, S. Walia, Antipathogenic properties and applications of low-dimensional materials, Nat. Commun. 12 (1) (2021) 3897.
[155] L.F. Wang, Y.J. Zhang, Y.Y. Li, J.H. Chen, W.Q. Lin, Recent advances in engineered nanomaterials for acute kidney injury theranostics, Nano Res. 14 (4) (2021) 920–933.
[156] G.B. Hwang, H. Huang, G. Wu, J. Shin, A. Kafizas, K. Karu, H.D. Toit, A. M. Alotaibi, L. Mohammad-Hadi, E. Allan, A.J. MacRobert, A. Gavriilidis, I. P. Parkin, Photobactericidal activity activated by thiolated gold nanoclusters at low flux levels of white light, Nat. Commun. 11 (1) (2020) 1207.
[157] I. Celardo, J.Z. Pedersen, E. Traversa, L. Ghibelli, Pharmacological potential of cerium oxide nanoparticles, Nanoscale 3 (4) (2011) 1411–1420.
[158] I. Fridovich, Superoxide radical and superoxide dismutases, Annu. Rev. Biochem. 64 (1995) 97–112.
[159] N.D. Manne, R. Arvapalli, N. Nepal, T. Shokuhfar, K.M. Rice, S. Asano, E. R. Blough, Cerium oxide nanoparticles attenuate acute kidney injury induced by intra-abdominal infection in Sprague-Dawley rats, J. Nanobiotechnol. 13 (2015) 75.
[160] D.Y. Zhang, H. Liu, C. Li, M.R. Younis, S. Lei, C. Yang, J. Lin, Z. Li, P. Huang, Ceria nanozymes with preferential renal uptake for acute kidney injury alleviation, ACS Appl. Mater. Interfaces 12 (51) (2020) 56830–56838.
[161] Q. Weng, H. Sun, C. Fang, F. Xia, H. Liao, J. Lee, J. Wang, A. Xie, J. Ren, X. Guo, F. Li, B. Yang, D. Ling, Catalytic activity tunable ceria nanoparticles prevent chemotherapy-induced acute kidney injury without interference with chemotherapeutics, Nat. Commun. 12 (1) (2021) 1436.
[162] C. Gao, P. Feng, S. Peng, C. Shuai, Carbon nanotube, graphene and boron nitride nanotube reinforced bioactive ceramics for bone repair, Acta Biomater. 61 (2017) 1–20.
[163] N.K. Mehra, N.K. Jain, Multifunctional hybrid-carbon nanotubes: new horizon in drug delivery and targeting, J. Drug Target. 24 (4) (2016) 294–308.
[164] L. Lacerda, J. Russier, G. Pastorin, M.A. Herrero, E. Venturelli, H. Dumortier, K. T. Al-Jamal, M. Prato, K. Kostarelos, A. Bianco, Translocation mechanisms of chemically functionalised carbon nanotubes across plasma membranes, Biomaterials 33 (11) (2012) 3334–3343.
[165] Z. Sobhani, R. Dinarvand, F. Atyabi, M. Ghahremani, M. Adeli, Increased paclitaxel cytotoxicity against cancer cell lines using a novel functionalized carbon nanotube, Int. J. Nanomed. 6 (2011) 705–719.
[166] B. Anbarasan, S.V. Babu, K. Elango, B. Shriya, S. Ramaprabhu, pH responsive release of doxorubicin to the cancer cells by functionalized multi-walled carbon nanotubes, J. Nanosci. Nanotechnol. 15 (7) (2015) 4799–4805.
[167] M. Chakrabarti, R. Kiseleva, A. Vertegel, S.K. Ray, Carbon nanomaterials for drug delivery and cancer therapy, J. Nanosci. Nanotechnol. 15 (8) (2015) 5501–5511.
[168] S. Alidori, N. Akhavein, D.L. Thorek, K. Behling, Y. Romin, D. Queen, B.J. Beattie, K. Manova-Todorova, M. Bergkvist, D.A. Scheinberg, M.R. McDevitt, Targeted fibrillar nanocarbon RNAi treatment of acute kidney injury, Sci. Transl. Med. 8 (331) (2016) 331ra39.
[169] N.D. Quyen Chau, C. Menard-Moyon, K. Kostarelos, A. Bianco, Multifunctional carbon nanomaterial hybrids for magnetic manipulation and targeting, Biochem. Biophys. Res. Commun. 468 (3) (2015) 454–462.
[170] S. Park, R.S. Ruoff, Chemical methods for the production of graphenes, Nat. Nanotechnol. 4 (4) (2009) 217–224.
[171] A.K. Geim, K.S. Novoselov, The rise of graphene, Nat. Mater. 6 (3) (2007) 183–191.
[172] C.X. Zhao, J.N. Liu, B.Q. Li, D. Ren, X. Chen, J. Yu, Q. Zhang, Multiscale construction of bifunctional electrocatalysts for long-lifespan rechargeable zinc-air batteries, Adv. Funct. Mater. 30 (36) (2020).
[173] A. Tyagi, Y.W. Ng, M. Tamtaji, I.H. Abidi, J. Li, F. Rehman, M.D. Hossain, Y. Cai, Z. Liu, P.R. Galligan, S. Luo, K. Zhang, Z. Luo, Elimination of uremic toxins by functionalized graphene-based composite beads for direct hemoperfusion, ACS Appl. Mater. Interfaces 13 (5) (2021) 5955–5965.
[174] J. Fu, L. Chang, Fabrication of fasudil hydrochloride modified graphene oxide biocomposites and its defensive effect acute renal injury in septicopyemia rats, J. Photochem. Photobiol., B 186 (2018) 125–130.
[175] X. Zhao, J. Xuan, Q. Li, F. Gao, X. Xun, Q. Liao, Y. Zhang, Roles of low-dimensional nanomaterials in pursuing human-machine-thing natural interaction, Adv. Mater. 35 (50) (2023) e2207437.
[176] L. Cheng, X. Wang, F. Gong, T. Liu, Z. Liu, 2D nanomaterials for cancer theranostic applications, Adv. Mater. 32 (13) (2020) e1902333.
[177] D.X. Xu, Z.D. Li, L.S. Li, J. Wang, Insights into the photothermal conversion of 2D MXene nanomaterials: synthesis, mechanism, and applications, Adv. Funct. Mater. 30 (47) (2020).
[178] Y. Wang, T. Guo, Z. Tian, K. Bibi, Y.Z. Zhang, H.N. Alshareef, MXenes for energy harvesting, Adv. Mater. 34 (21) (2022) e2108560.
[179] A. Maleki, M. Ghomi, N. Nikfarjam, M. Akbari, E. Sharifi, M.A. Shahbazi, M. Kermanian, M. Seyedhamzeh, E.N. Zare, M. Mehrali, O. Moradi, F. Sefat, V. Mattoli, P. Makvandi, Y. Chen, Biomedical applications of MXene-integrated composites: regenerative medicine, infection therapy, cancer treatment, and biosensing, Adv. Funct. Mater. 32 (34) (2022).
[180] X. Zhao, L.Y. Wang, J.M. Li, L.M. Peng, C.Y. Tang, X.J. Zha, K. Ke, M.B. Yang, B. H. Su, W. Yang, Redox-mediated artificial non-enzymatic antioxidant MXene nanoplatforms for acute kidney injury alleviation, Adv. Sci. 8 (18) (2021) e2101498.
[181] Z.Q. Yan, W. Zhang, The development of graphene-based devices for cell biology research, Front. Mater. Sci. 8 (2) (2014) 107–122.
[182] X. Ling, H. Wang, S. Huang, F. Xia, M.S. Dresselhaus, The renaissance of black phosphorus, Proc. Natl. Acad. Sci. U. S. A. 112 (15) (2015) 4523–4530.
[183] S. Anju, J. Ashtami, P.V. Mohanan, Black phosphorus, a prospective graphene substitute for biomedical applications, Mater Sci Eng C Mater Biol Appl 97 (2019) 978–993.
[184] X.Y. Yang, D.Y. Wang, Y.H. Shi, J.H. Zou, Q.S. Zhao, Q. Zhang, W. Huang, J. J. Shao, X.J. Xie, X.C. Dong, Black phosphorus nanosheets immobilizing Ce6 for imaging-guided photothermal/photodynamic cancer therapy (vol 10, pg 12431, 2018), Acs Appl Mater Inter 11 (46) (2019) 43797, 43797.
[185] T. Zhang, Y. Wan, H. Xie, Y. Mu, P. Du, D. Wang, X. Wu, H. Ji, L. Wan, Degradation chemistry and stabilization of exfoliated few-layer black phosphorus in water, J. Am. Chem. Soc. 140 (24) (2018) 7561–7567.
[186] X.T. Meng, X.H. Wang, Z.C. Cheng, N. Tian, M.C. Lang, W.J. Yan, D.M. Liu, Y. Z. Zhang, P. Wang, Photoluminescence lifetime of black phosphorus nanoparticles and their applications in live cell imaging, Acs Appl Mater Inter 10 (37) (2018) 31136–31145.
[187] R.P. Goodman, I.A. Schaap, C.F. Tardin, C.M. Erben, R.M. Berry, C.F. Schmidt, A. J. Turberfield, Rapid chiral assembly of rigid DNA building blocks for molecular nanofabrication, Science 310 (5754) (2005) 1661–1665.
[188] L. Liang, J. Li, Q. Li, Q. Huang, J. Shi, H. Yan, C. Fan, Single-particle tracking and modulation of cell entry pathways of a tetrahedral DNA nanostructure in live cells, Angew Chem. Int. Ed. Engl. 53 (30) (2014) 7745–7750.
[189] T. Zhang, T. Tian, Y. Lin, Functionalizing framework nucleic-acid-based nanostructures for biomedical application, Adv. Mater. 34 (46) (2022) e2107820.
[190] R. Yan, W. Cui, W. Ma, J. Li, Z. Liu, Y. Lin, Typhaneoside-tetrahedral framework nucleic acids system: mitochondrial recovery and antioxidation for acute kidney injury treatment, ACS Nano 17 (9) (2023) 8767–8781.
[191] D. Andre-Levigne, A. Modarressi, M.S. Pepper, B. Pittet-Cuenod, Reactive oxygen species and NOX enzymes are emerging as key players in cutaneous wound repair, Int. J. Mol. Sci. 18 (10) (2017).
[192] N.R. Madamanchi, Z.S. Hakim, M.S. Runge, Oxidative stress in atherogenesis and arterial thrombosis: the disconnect between cellular studies and clinical outcomes, J. Thromb. Haemostasis 3 (2) (2005) 254–267.
[193] L.J. Mandel, Metabolic substrates, cellular energy production, and the regulation of proximal tubular transport, Annu. Rev. Physiol. 47 (1985) 85–101.
[194] A. Yadav, S. Vallabu, S. Arora, P. Tandon, D. Slahan, S. Teichberg, P.C. Singhal, ANG II promotes autophagy in podocytes, Am. J. Physiol. Cell Physiol. 299 (2) (2010) C488–C496.
[195] S. Lodha, D. Dani, R. Mehta, M. Bhaskaran, K. Reddy, G. Ding, P.C. Singhal, Angiotensin II-induced mesangial cell apoptosis: role of oxidative stress, Mol. Med. 8 (12) (2002) 830–840.
[196] B. Lassegue, D. Sorescu, K. Szocs, Q. Yin, M. Akers, Y. Zhang, S.L. Grant, J. D. Lambeth, K.K. Griendling, Novel gp91(phox) homologues in vascular smooth muscle cells : nox1 mediates angiotensin II-induced superoxide formation and redox-sensitive signaling pathways, Circ. Res. 88 (9) (2001) 888–894.
[197] Y. Gorin, J.M. Ricono, N.H. Kim, B. Bhandari, G.G. Choudhury, H.E. Abboud, Nox4 mediates angiotensin II-induced activation of Akt/protein kinase B in mesangial cells, Am. J. Physiol. Ren. Physiol. 285 (2) (2003) F219–F229.
[198] Z. Ren, W. Liang, C. Chen, H. Yang, P.C. Singhal, G. Ding, Angiotensin II induces nephrin dephosphorylation and podocyte injury: role of caveolin-1, Cell. Signal. 24 (2) (2012) 443–450.
[199] T. Böhler, J. Waiser, H. Hepburn, J. Gaedeke, C. Lehmann, P. Hambach, K. Budde, H.H. Neumayer, TNF-α and IL-1α induce apoptosis in subconfluent rat mesangial cells.: evidence for the involvement of hydrogen peroxide and lipid peroxidation as second messengers, Cytokine 12 (7) (2000) 986–991.
[200] S.J. Peng, F.F. Xiao, M.W. Chen, H.L. Gao, Tumor-microenvironment-responsive nanomedicine for enhanced cancer immunotherapy, Adv. Sci. 9 (1) (2022).
[201] D. Liu, G. Shu, F. Jin, J. Qi, X. Xu, Y. Du, H. Yu, J. Wang, M. Sun, Y. You, M. Zhu, M. Chen, L. Zhu, Q. Shen, X. Ying, X. Lou, S. Jiang, Y. Du, ROS-responsive chitosan-SS31 prodrug for AKI therapy via rapid distribution in the kidney and long-term retention in the renal tubule, Sci. Adv. 6 (41) (2020).
[202] D. Liu, F. Jin, G. Shu, X. Xu, J. Qi, X. Kang, H. Yu, K. Lu, S. Jiang, F. Han, J. You, Y. Du, J. Ji, Enhanced efficiency of mitochondria-targeted peptide SS-31 for acute kidney injury by pH-responsive and AKI-kidney targeted nanopolyplexes, Biomaterials 211 (2019) 57–67.

[203] T. Yoshitomi, A. Hirayama, Y. Nagasaki, The ROS scavenging and renal protective effects of pH-responsive nitroxide radical-containing nanoparticles, Biomaterials 32 (31) (2011) 8021–8028.
[204] T.Y. Lee, H.H. Lu, H.T. Cheng, H.C. Huang, Y.J. Tsai, I.H. Chang, C.P. Tu, C. W. Chung, T.T. Lu, C.H. Peng, Y. Chen, Delivery of nitric oxide with a pH-responsive nanocarrier for the treatment of renal fibrosis, J. Contr. Release 354 (2023) 417–428.
[205] R. de la Rica, D. Aili, M.M. Stevens, Enzyme-responsive nanoparticles for drug release and diagnostics, Adv. Drug Deliv. Rev. 64 (11) (2012) 967–978.
[206] A. Razgulin, N. Ma, J. Rao, Strategies for in vivo imaging of enzyme activity: an overview and recent advances, Chem. Soc. Rev. 40 (7) (2011) 4186–4216.
[207] M. Zelzer, S.J. Todd, A.R. Hirst, T.O. McDonald, R.V. Ulijn, Enzyme responsive materials: design strategies and future developments, Biomater. Sci. 1 (1) (2013) 11–39.
[208] J. Mu, J. Lin, P. Huang, X. Chen, Development of endogenous enzyme-responsive nanomaterials for theranostics, Chem. Soc. Rev. 47 (15) (2018) 5554–5573.
[209] J. Majumder, T. Minko, Multifunctional and stimuli-responsive nanocarriers for targeted therapeutic delivery, Expet Opin. Drug Deliv. 18 (2) (2021) 205–227.
[210] X. Zhang, X. Wang, W. Zhong, X. Ren, X. Sha, X. Fang, Matrix metalloproteinases-2/9-sensitive peptide-conjugated polymer micelles for site-specific release of drugs and enhancing tumor accumulation: preparation and in vitro and in vivo evaluation, Int. J. Nanomed. 11 (2016) 1643–1661.
[211] F. Fang, Y. Ni, H. Yu, H. Yin, F. Yang, C. Li, D. Sun, T. Pei, J. Ma, L. Deng, H. Zhang, G. Wang, S. Li, Y. Shen, X. Liu, Inflammatory endothelium-targeted and cathepsin responsive nanoparticles are effective against atherosclerosis, Theranostics 12 (9) (2022) 4200–4220.
[212] L. Zhu, T. Yu, W. Wang, T. Xu, W. Geng, N. Li, X. Zan, Responsively degradable nanoarmor-assisted super resistance and stable colonization of probiotics for enhanced inflammation-targeted delivery, Adv. Mater. 36 (18) (2024) e2308728.
[213] Z.Y. Zou, B. Chung, T. Nguyen, S. Mentone, B. Thomson, D. Biemesderfer, Linking receptor-mediated endocytosis and cell signaling - evidence for regulated intramembrane proteolysis of megalin in proximal tubule, J. Biol. Chem. 279 (33) (2004) 34302–34310.
[214] E.I. Christensen, J. Gburek, Protein reabsorption in renal proximal tubule-function and dysfunction in kidney pathophysiology, Pediatr. Nephrol. 19 (7) (2004) 714–721.
[215] Z. Zhang, Q. Zheng, J. Han, G. Gao, J. Liu, T. Gong, Z. Gu, Y. Huang, X. Sun, Q. He, The targeting of 14-succinate triptolide-lysozyme conjugate to proximal renal tubular epithelial cells, Biomaterials 30 (7) (2009) 1372–1381.
[216] G. Schlag, J. Seifert, Fibrin sealant, aprotinin, and immune response in children undergoing operations for congenital heart disease, J Thorac Cardiov Sur 116 (6) (1998) 1082, 1082.
[217] X.L. Wu, Q.Q. Zhu, X.J. Cheng, J. Xiao, H. Xu, Z.G. Liu, Investigation for relationship between heat treatment process and immunogenicity of lysozyme in egg by spectroscopic method, Chin. J. Anal. Chem. 39 (2) (2011) 198–202.
[218] R.F.G. Haverdings, M. Haas, A.R. Greupink, P.A.M. de Vries, F. Moolenaar, D. de Zeeuw, D.K.F. Meijer, Potentials and limitations of the low-molecular-weight protein lysozyme as a carrier for renal drug targeting, Ren. Fail. 23 (3–4) (2001) 397–409.
[219] E. Vegt, J.E.M. van Eerd, A. Eek, W.J.G. Oyen, J.F.M. Wetzels, M. de Jona, F.G. M. Russel, R. Masereeuw, M. Gotthardt, O.C. Boerman, Reducing renal uptake of radiolabeled peptides using albumin fragments, J. Nucl. Med. 49 (9) (2008) 1506–1511.
[220] G.L. Bidwell, F. Mahdi, Q. Shao, O.C. Logue, J.P. Waller, C. Reese, A.R. Chade, A kidney-selective biopolymer for targeted drug delivery, Am J Physiol-Renal 312 (1) (2017) F54–F64.
[221] C.S. Kim, A.P. Mathew, A. Vasukutty, S. Uthaman, S.Y. Joo, E.H. Bae, S.K. Ma, I. K. Park, S.W. Kim, Glycol chitosan-based tacrolimus-loaded nanomicelle therapy ameliorates lupus nephritis, J. Nanobiotechnol. 19 (1) (2021).
[222] J. Reiser, S. Sever, Podocyte biology and pathogenesis of kidney disease, Annu. Rev. Med. 64 (2013) 357–366.
[223] L. Barisoni, H.W. Schnaper, J.B. Kopp, Advances in the biology and genetics of the podocytopathies: implications for diagnosis and therapy, Arch. Pathol. Lab Med. 133 (2) (2009) 201–216.
[224] G. Fernandez-Juarez, J. Villacorta, G. Ruiz-Roso, N. Panizo, I. Martinez-Marin, H. Marco, P. Arrizabalaga, M. Diaz, V. Perez-Gomez, M. Vaca, E. Rodriguez, C. Cobelo, L. Fernandez, A. Avila, M. Praga, C. Quereda, A. Ortiz, Therapeutic variability in adult minimal change disease and focal segmental glomerulosclerosis, Clin Kidney J 9 (3) (2016) 381–386.
[225] G.R. Visweswaran, S. Gholizadeh, M.H. Ruiters, G. Molema, R.J. Kok, J.A. Kamps, Targeting rapamycin to podocytes using a vascular cell adhesion molecule-1 (VCAM-1)-Harnessed SAINT-based lipid carrier system, PLoS One 10 (9) (2015) e0138870.
[226] P.V. Hauser, J.W. Pippin, C. Kaiser, R.D. Krofft, P.T. Brinkkoetter, K.L. Hudkins, D. Kerjaschki, J. Reiser, C.E. Alpers, S.J. Shankland, Novel siRNA delivery system to target podocytes in vivo, PLoS One 5 (3) (2010) e9463.
[227] K. Morimoto, M. Kondo, K. Kawahara, H. Ushijima, Y. Tomino, M. Miyajima, J. Kimura, Advances in targeting drug delivery to glomerular mesangial cells by long circulating cationic liposomes for the treatment of glomerulonephritis, Pharm. Res. (N. Y.) 24 (5) (2007) 946–954.
[228] L. Manil, J.C. Davin, C. Duchenne, C. Kubiak, J. Foidart, P. Couvreur, P. Mahieu, Uptake of nanoparticles by rat glomerular mesangial cells in vivo and in vitro, Pharm. Res. (N. Y.) 11 (8) (1994) 1160–1165.
[229] D. Shemin, D. Rittenberg, The life span of the human red blood cell, J. Biol. Chem. 166 (2) (1946) 627–636.
[230] C.M.J. Hu, R.H. Fang, L.F. Zhang, Erythrocyte-inspired delivery systems, Adv. Healthcare Mater. 1 (5) (2012) 537–547.
[231] P.A. Oldenborg, A. Zheleznyak, Y.F. Fang, C.F. Lagenaur, H.D. Gresham, F. P. Lindberg, Role of CD47 as a marker of self on red blood cells, Science 288 (5473) (2000), 2051-+.
[232] R.H. Fang, C.M.J. Hu, L.F. Zhang, Nanoparticles disguised as red blood cells to evade the immune system, Expet Opin. Biol. Ther. 12 (4) (2012) 385–389.
[233] W.W. Gao, C.M.J. Hu, R.H. Fang, B.T. Luk, J. Su, L.F. Zhang, Surface functionalization of gold nanoparticles with red blood cell membranes, Adv. Mater. 25 (26) (2013) 3549–3553.
[234] L. Rao, L.L. Bu, J.H. Xu, B. Cai, G.T. Yu, X.L. Yu, Z.B. He, Q.Q. Huang, A. Li, S. S. Guo, W.F. Zhang, W. Liu, Z.J. Sun, H. Wang, T.H. Wang, X.Z. Zhao, Red blood cell membrane as a biomimetic nanocoating for prolonged circulation time and reduced accelerated blood clearance, Small 11 (46) (2015) 6225–6236.
[235] F. Oroojalian, M. Beygi, B. Baradaran, A. Mokhtarzadeh, M.A. Shahbazi, Immune cell membrane-coated biomimetic nanoparticles for targeted cancer therapy, Small 17 (12) (2021) e2006484.
[236] D. Wang, S. Wang, Z. Zhou, D. Bai, Q. Zhang, X. Ai, W. Gao, L. Zhang, White blood cell membrane-coated nanoparticles: recent development and medical applications, Adv. Healthcare Mater. 11 (7) (2022) e2101349.
[237] Y. Zhai, J. Su, W. Ran, P. Zhang, Q. Yin, Z. Zhang, H. Yu, Y. Li, Preparation and application of cell membrane-camouflaged nanoparticles for cancer therapy, Theranostics 7 (10) (2017) 2575–2592.
[238] L.Y. Chou, K. Ming, W.C. Chan, Strategies for the intracellular delivery of nanoparticles, Chem. Soc. Rev. 40 (1) (2011) 233–245.
[239] T.T. Tang, L.L. Lv, B. Wang, J.Y. Cao, Y. Feng, Z.L. Li, M. Wu, F.M. Wang, Y. Wen, L.T. Zhou, H.F. Ni, P.S. Chen, N. Gu, S.D. Crowley, B.C. Liu, Employing macrophage-derived microvesicle for kidney-targeted delivery of dexamethasone: an efficient therapeutic strategy against renal inflammation and fibrosis, Theranostics 9 (16) (2019) 4740–4755.
[240] A. Narain, S. Asawa, V. Chhabria, Y. Patil-Sen, Cell membrane coated nanoparticles: next-generation therapeutics, Nanomedicine (Lond) 12 (21) (2017) 2677–2692.
[241] J.R. Fitzgerald, T.J. Foster, D. Cox, The interaction of bacterial pathogens with platelets, Nat. Rev. Microbiol. 4 (6) (2006) 445–457.
[242] B. Nieswandt, S.P. Watson, Platelet-collagen interaction: is GPVI the central receptor? Blood 102 (2) (2003) 449–461.
[243] M.R. Yeaman, Platelets in defense against bacterial pathogens, Cell. Mol. Life Sci. 67 (4) (2010) 525–544.
[244] S.S. Smyth, R.P. McEver, A.S. Weyrich, C.N. Morrell, M.R. Hoffman, G. M. Arepally, P.A. French, H.L. Dauerman, R.C. Becker, P. Platelet Colloquium, Platelet functions beyond hemostasis, J. Thromb. Haemostasis 7 (11) (2009) 1759–1766.
[245] S. Fei, Y. Ma, B. Zhou, X. Chen, Y. Zhang, K. Yue, Q. Li, Y. Gui, T. Xiang, J. Liu, B. Yang, L. Wang, X. Huang, Platelet membrane biomimetic nanoparticle-targeted delivery of TGF-beta1 siRNA attenuates renal inflammation and fibrosis, Int. J. Pharm. 659 (2024) 124261.
[246] S. Yao, D. Wu, X. Hu, Y. Chen, W. Fan, X. Mou, Y. Cai, X. Yang, Platelet membrane-coated bio-nanoparticles of indocyanine green/elamipretide for NIR diagnosis and antioxidant therapy in acute kidney injury, Acta Biomater. 173 (2024) 482–494.
[247] J. Yang, X. Miao, Y. Guan, C. Chen, S. Chen, X. Zhang, X. Xiao, Z. Zhang, Z. Xia, T. Yin, Z. Hei, W. Yao, Microbubble functionalization with platelet membrane enables targeting and early detection of sepsis-induced acute kidney injury, Adv. Healthcare Mater. 10 (23) (2021) e2101628.
[248] Q. Chen, Y. Nan, Y. Yang, Z. Xiao, M. Liu, J. Huang, Y. Xiang, X. Long, T. Zhao, X. Wang, Q. Huang, K. Ai, Nanodrugs alleviate acute kidney injury: manipulate RONS at kidney, Bioact. Mater. 22 (2023) 141–167.
[249] T. Zeng, A.Q. Li, A modular intracellular hierarchical-responsive nanocarrier enables dual targeting for high therapeutic efficacy in kidney disease, Nephrol. Dial. Transplant. 38 (2023) I117. I117.
[250] C.F. Yin, R.N. Wang, Y. Sun, S. Li, X.K. Zhang, J. Gu, W. Wu, X.Q. Jiang, The in vitro and in vivo properties of ringlike polymer brushes, Nano Today 41 (2021).
[251] K. Park, Science the endless frontier, J. Contr. Release 308 (2019) 240.