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Review

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Promising future: a review of clinical applications of biopolymers in renal cell carcinoma

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Abstract

Renal cell carcinoma (RCC), being the most common type of renal malignancy, accounting for 85% of its incidence, poses a significant threat to human health. Although progress has been made in RCC diagnosis and management, problems of delayed detection and treatment failure remain in traditional methods. In the development of material research, biopolymers have emerged as significant players in medical practices, demonstrating considerable potential in the management of kidney cancer. Specifically, bioactive polymers have been proven to have numerous advantages over traditional methods, finding prosperous applications in diverse areas such as imaging detection, chemotherapy carrier, and prognostic estimation. However, the clinical value of some biopolymers still needs to be fully recognized in the RCC clinical pathway. This review summarizes recent studies about bioactive polymers'

application in RCC and further discusses its significance and constraints in clinical translational medicine and clinical trials. As our understanding of biopolymers grows, more advancements can be carried out in clinical practices.

Keywords: Renal cell carcinoma, kidney cancer, bioactive polymers, clinical application

INTRODUCTIONS

Globally, kidney cancer constitutes approximately 5% of all malignancies and ranks as the sixth most prevalent cancer among males[1]. Given recent advancements in diagnostic methodologies, malignancies originating from unknown primary sites (CUP), constituting approximately 1%-3% of all malignant neoplasms, are occasionally managed as renal cell carcinoma (RCC), which is the main type of kidney cancer. This practice could potentially contribute to the observed rise in kidney cancer incidence rates[2]. It also accounts for 3% of malignancies and ranks as the tenth most prevalent cancer among women[1]. It has been reported that pregnancy-related hormonal changes, especially high estrogen levels, may stimulate renal cell proliferation either directly or through paracrine growth factors, thereby promoting malignancy. Therefore, gynecologists should be alert to the possibility of malignancy in renal masses found during pregnancy[3]. Kidney cancer is the eighth most common new tumor in women and the fifth most common new tumor in males. According to the Global Cancer Statistics in 2023, the incidence of kidney cancer in males and females was 23.5 per 10,000 and 12 per 10,000 during 2015-2019, while the mortality from 2016-2020 was 5.1 per 10,000 and 2.2 per 10,000, respectively[4]. Compared to other tumorous malignancies, the mechanisms underlying kidney cancers are still poorly known. Although hematuria, lumbar masses, and lumbar discomfort are common symptoms in typical situations, renal cell carcinoma is notorious in clinical practice for its sneaky signs and covert presentation. They are frequently found by accident during routine physical examinations of patients. As a result, RCC patients often have delayed diagnosis and treatment, leading to missed opportunities for optimal surgical intervention and timely therapy.

A growing number of academics and businesses are undertaking in-depth investigations into medical polymer materials and integrating them into clinical practice due to the rise of polymer materials in medical applications. Meanwhile, nanoparticles are at the forefront of current medical polymer research investigating RCC. Nanobiotechnology facilitates precise molecular-level material manipulation to produce biocompatible products targeted for desired tissues and locations. Since the last century, there have been reports exploring the use of biopolymers, such as natural polymers, as drug carriers in disease treatment[5]. However, the application and development of biopolymers have not yet been widely acknowledged. With the continuous development of polymer materials and nanotechnology, in 2017, Nizioł *et al.* utilized gold nanoparticles to enhance target binding matrix-assisted laser desorption/ionization (MALDI) imaging mass spectrometry, enabling rapid visualization of differences between RCC and normal kidney tissue without the need for pathology[6]. This research has ignited interest and enthusiasm in the application of biopolymers for the diagnosis and treatment of RCC. In the context of RCC management, biopolymers demonstrate great potential over traditional solutions. Carefully designed bioactive nanoparticles can cross traditional biological barriers *in vivo* and bind selectively to biomarkers[7]. In addition, two or more therapeutic agents can be carried for synergistic effects and can be modulated to provide suitable circulation durations[8]. Those features are greatly effective in the therapy and diagnosis of kidney cancer. However, challenges persist, such as controlled drug release and cytotoxicity[9]. We present this review in the hope that it will serve as a guide for future clinical research in RCC.

Biopolymer materials in renal cell carcinoma research

Polymeric nanoparticles, lipid-based nanoparticles, inorganic nanoparticles, and mega polymers (such as plastics) are the most often employed biopolymer materials in RCC research[10]. In recent years, perioperative adjuvant therapy for high-risk RCC and advanced treatment have been hot topics in clinical research. The choice of immune-based combination therapy is increasingly supported in first-line treatment. Notably, the downregulation of lactotransferrin, an important protein in the innate immune system, promotes clear cell RCC metastasis. This downregulation made clear cell RCC tumor cells more sensitive to mTOR inhibitors, suggesting that it might serve as a predictor of the efficacy of immune-targeted therapies[11,12]. Combining basic cancer signaling research with biopolymer material studies to guide and develop novel diagnosis and treatment systems in RCC is a substantial challenge to all researchers in this field. Here, we present a summary of the studies investigating the role of different classes of biopolymers in the diagnosis and management of RCC. A brief illustration is given in Figure 1.

POLYMERIC NANOPARTICLES IN RENAL CELL CARCINOMA

Introduction of polymeric nanoparticles

Polymeric nanoparticles include a class of multifunctional polymer materials polymerized with organic substances, biologically active macromolecules (antibodies, nucleic acids), organic small molecules (vitamins), and other substances. Due to their diverse synthetic route options, polymeric nanoparticles possess easily modifiable and selectable physicochemical properties. These include various naturally occurring and synthetic materials, monomers or pre-formed polymers, and simple formulation parameters. They make excellent contenders for drug delivery as they possess traits such as biodegradability, water solubility, biocompatibility, biomimicry, storage stability, and ease of surface modification for further targeting. Furthermore, they have the capability to transport payloads of different molecular sizes, spanning from small compounds to biological macromolecules, including proteins and vaccines[13-15].

Polymeric NPs in targeted drug delivery

The hypoxic microenvironment and associated signaling pathways within RCC significantly influence their advancement, metastatic potential, and resistance to therapy. Extensive evidence suggests that within the hypoxic core of tumors, there exist highly aggressive, drug-resistant stem-like cells capable of surviving conventional drug treatments, infiltrating surrounding normal tissues, and establishing secondary tumors at distant locations. Vascular abnormalities, which are an important component of the tumor microenvironment, largely contribute to malignant phenotype, immune system evasion, and drug resistance in RCC carcinoma. Thus, targeting the RCC tumor microenvironment, such as current VEGFR-targeted therapies, holds great promise in preventing metastasis, overcoming acquired drug resistance, and improving efficacy. Monotherapy with tyrosine kinase inhibitors (TKIs) continues to be a suitable initial treatment for a significant subset of patients who are ineligible for immunotherapy, and the findings from the STAR study are directly relevant to this population. For other patients who do not undergo TKI therapy as a first-line option, it may be considered as monotherapy for second-line treatment. While treatment interruptions for these individuals might be contemplated, caution is warranted as they typically experience shorter progression-free survival compared to those receiving TKIs as initial therapy[16].

However, many patients' tumors develop resistance to VEGFR-targeted drugs, resulting in poorer outcomes. How to solve the problem of drug resistance has become a hot issue in the treatment of RCC. The intractable reaction to anti-VEGFR treatment in most RCC patients is ultimately attributed to inadequate vascularization within the tumor core, which is linked to tumor hypoxia[17]. Carbonic anhydrase IX (CA IX) is a transmembrane protein that exhibits heightened expression on the surface of numerous cancerous cells within hypoxic conditions[18]. CA IX has a favorable distribution in RCC and is esteemed as a superb candidate for diagnostic applications and potentially for precision-targeted therapeutic

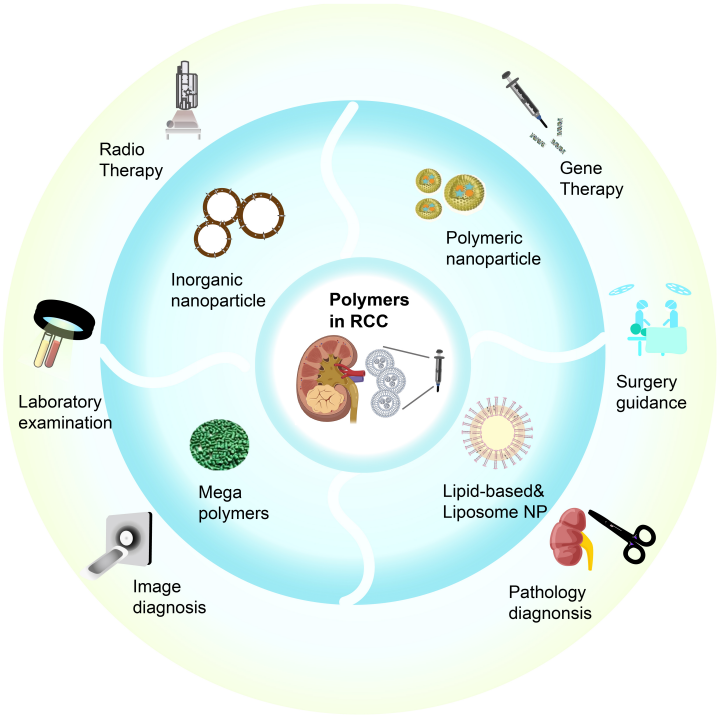

Figure 1. For renal cell carcinoma, all four major classes of polymers play a role in its clinical pathway. The giant polymer materials can also serve as a separate branch due to their remarkable properties. Polymers are used not only for laboratory diagnostics and diagnostic imaging, but also for radiation therapy, surgical markers, and so on. More innovatively, polymeric materials are also involved in gene therapy.

modalities[19,20]. Alsaab *et al.* utilized a nanoparticle (NP) loaded with CFM 4.16 (C4.16), an apoptosis inducer, termed CA IX-C4.16, in conjunction with targeted tumor hypoxia delivery[21]. This NP was designed to transport the payload specifically to the hypoxic core of tumors, thereby inducing enhanced cellular death in both parental and Everolimus-resistant RCC cells, while selectively modulating tumor causing M2 macrophages. The simple procedure of this experiment is described briefly in Figure 2. For conjugation, "click" chemistry without copper linked SMA-TPGS with Acetazolamide, specifically targeting CA IX. Furthermore, the NP was labeled with a clinically approved near-infrared dye (S0456) to evaluate penetration into the hypoxic tumor cores and organ distributions. Imaging studies of tumor spheroids treated with NIR dye-labeled CA IX-SMA-TPGS demonstrated significant penetration into the tumor core, facilitated by CA IX which is targeting in hypoxic A498 cells. The synergistic combination of CA IX-C4.16 and Sorafenib (Sor) displayed a substantial cell-killing effect, indicating efficient reversal of Evr-resistance in A498 cells. Additionally, the CA IX-directed nanoplatform combined with Sor presented multiple advantages in overcoming drug resistance, including inhibition of p-AKT, upregulation of tumoricidal M1 macrophages which leads to the caspase enzyme 3/7-mediated apoptosis of Evr-res A498 cells in a macrophage-RCC co-culturing condition, significant *in vitro/vivo* inhibition of Evr-res A498 tumor growth compared to individual treatment, and negligible liver and kidney toxicity in mice. Near-infrared (NIR) imaging of CA IX-SMA-TPGS-S0456 in the Evr-res A498 model revealed a significant accumulation of CAIX-oligomer in the tumor core, with over three times higher tumor uptake compared to the control. In summary, this proof of concept study presents a multi-purpose tumor hypoxia-targeted nanoplatform capable of synergizing with existing medicines to reverse pharmacological resistance in RCC, along with the rebuilding of tumor-infiltrating macrophages, potentially applicable to various hypoxic tumors.

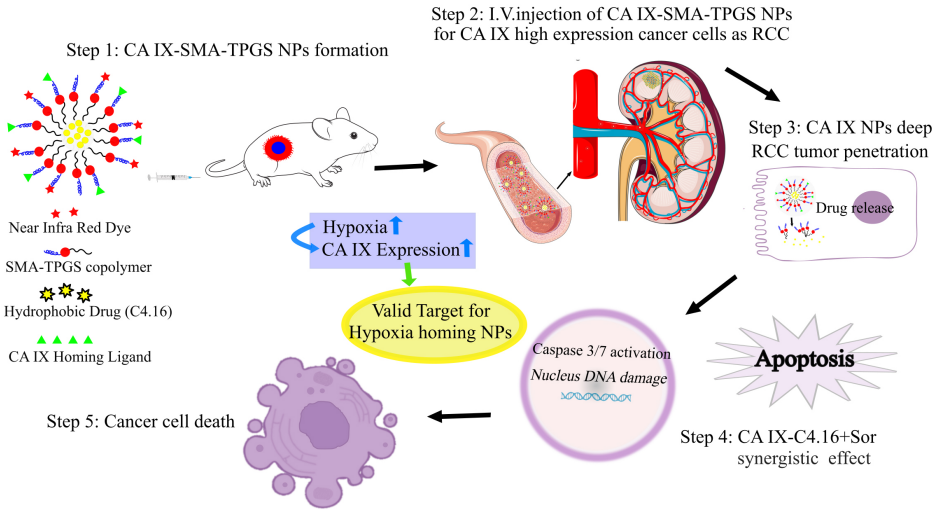

Figure 2. Synopsis of tumor hypoxia-targeted nanotherapy combined with Sorafenib, demonstrating manifold advantages against cancer, including overcoming drug resistance, triggering apoptosis, and reshaping macrophage function[21].

Chen *et al.* innovatively developed H-NPs, an oxygen nanocarrier based on hemoglobin, to address hypoxia-induced drug resistance in RCC when used in conjunction with DAC[22]. These H-NPs, as shown in Figure 3, characterized by their hemoglobin-based composition, were crafted with meticulous attention using poly (lactic-co-glycolic acid) (PLGA) to encapsulate hemoglobin via hydrophobic interactions. Additionally, a specialized coating of low molecular weight hydroxyethyl chitosan was applied to facilitate renal targeting, thus enhancing the nanocarrier's therapeutic efficacy in the context of RCC. Western blotting analysis of ENT1, which was treated with oxygen nanocarriers in 769-P under hypoxia, demonstrated a reduction in The hypoxia-induced downregulation phenotype of ENT1. This serves as evidence for the capacity of H-NPs to mitigate the diminution of DAC efficacy and enhance the sensitivity of RCC cells to consecutive combination therapy involving DAC and oxaliplatin. The above findings established an important base of clinic translational research and treatment studies in RCC.

Sunitinib represents an orally administered, multitargeted receptor tyrosine kinase inhibitor (TKI) that specifically inhibits the signaling pathways of vascular endothelial growth factor and platelet-derived growth factor receptors. As a representative of targeted therapy, sunitinib remains the recommended treatment option for patients with metastatic renal cell carcinoma (mRCC). However, approximately 60%-70% of patients with mRCC exhibit inherent resistance to sunitinib therapy, and even responding patients may relapse after 14 months of treatment. Zeng *et al.* synthesized an amphipathic conjugate known as sialic acid-poly-ibuprofen, which is capable of self-assembling into nanomicelles and encapsulating sunitinib in a watery solution[23]. Ibuprofen is a nonsteroidal anti-inflammatory drug and it is usually utilized to decrease COX-2 manufacturing. Notably, COX-2 has been implicated in both tumorigenesis and metastasis, and ibuprofen has shown some effectiveness in cancer treatment. Sialic acid (SA), another constituent of the conjugate, is a derivative of neuraminic acid that specifically targets E-selectin receptors. To evaluate the biodistribution of SPI nanomicelles, DiR-laden SPI nanomicelles and free DiR were administered intravenously to tumor-bearing mice. *In vivo* infrared imaging was conducted at specific time intervals (3, 6, 12, 24 h) post-administration to observe the biodistribution of the nanomicelles. The fluorescence signal of SPI/DiR nanomicelles within tumoral tissues was significantly stronger than that of the free DiR, indicating the superior tumor-targeting capability of SPI nanomicelles. Following this, the tumor treatment effects of sunitinib-loaded SA-PEG-IBU and control groups were evaluated in tumor-bearing nude mice models. Every group, including free sunitinib, free ibuprofen, SPI/SU, and PI/SU, exhibited a tumor suppression

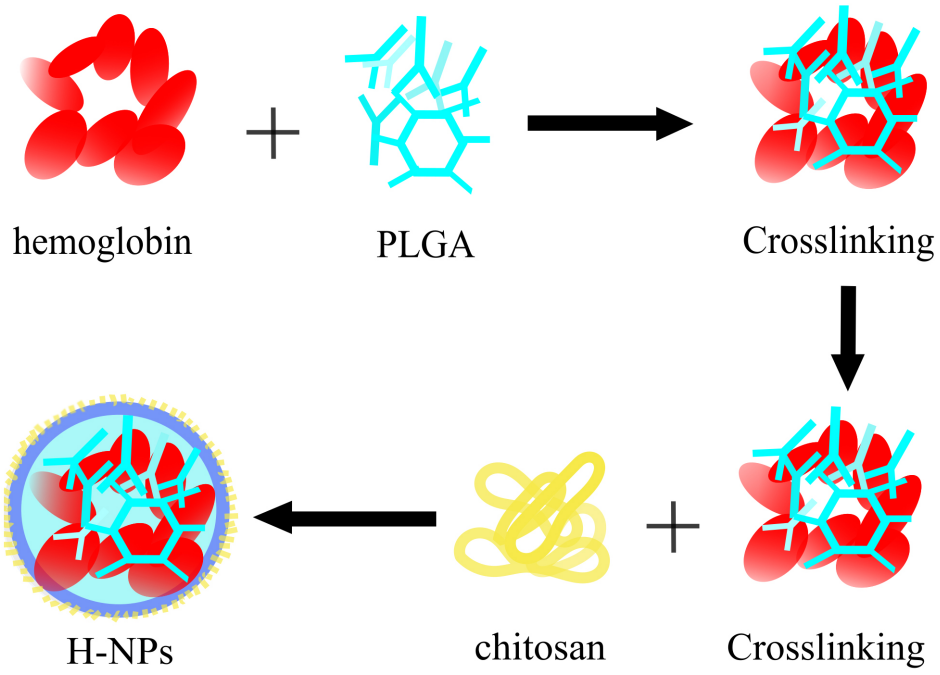

Figure 3. Diagram illustrating the fabrication process and architecture of hemoglobin-derived nanocarriers[22]. PLGA: poly (lactic-co-glycolic acid).

rate exceeding half. Remarkably, SPI/SU nanomicelles exhibited the most robust suppression of tumor proliferation, achieving an average inhibition rate of 80%. While the group of free sunitinib displayed tumoral inhibition, it was accompanied by significant body weight loss, suggesting systemic side effects or cachexia induced by free sunitinib. In contrast, body weight loss was not observed in the SPI/SU group during the 21-day treatment period, indicating minimal adverse effects. The remarkable efficacy in inhibiting tumor growth and reducing side effects may be attributed to the specific targeting of E-selectin and the synergistic effects of ibuprofen conjugation.

We believe that the discovery of these new signaling pathways or targets has important guiding significance for the development of future polymer-related therapies. However, how to link these targets or signals with polymers-targeted therapies is still a key problem in translational medicine research. In this case, seeking a more accurate polymers-based targeted delivery system is particularly important and, for the major biopolymers in Figure 4, has great development prospects.

LIPID-BASED NPS IN RENAL CELL CARCINOMA

Introduction of lipid-based NPs

Though lipid-based NPs encompass various component configurations, lipid-based NPs are spherical platforms comprising at least one lipid bilayer surrounding at least one internal aqueous compartment[24]. Lipid-based NPs have many benefits as drug delivery vehicles, including formulation simplicity, self-assembly, biocompatibility, high bioavailability, ability to carry large payloads, and various physicochemical characteristics that can be controlled to vary their biological features[25]. Figure 5 demonstrates surface modifications of lipid-based NPs, as well as internal and external stimulatory factors.

Lipid-based NPs in gene therapy

The primary characteristic of liposomal polymeric materials is the presence of bipolar molecules that are

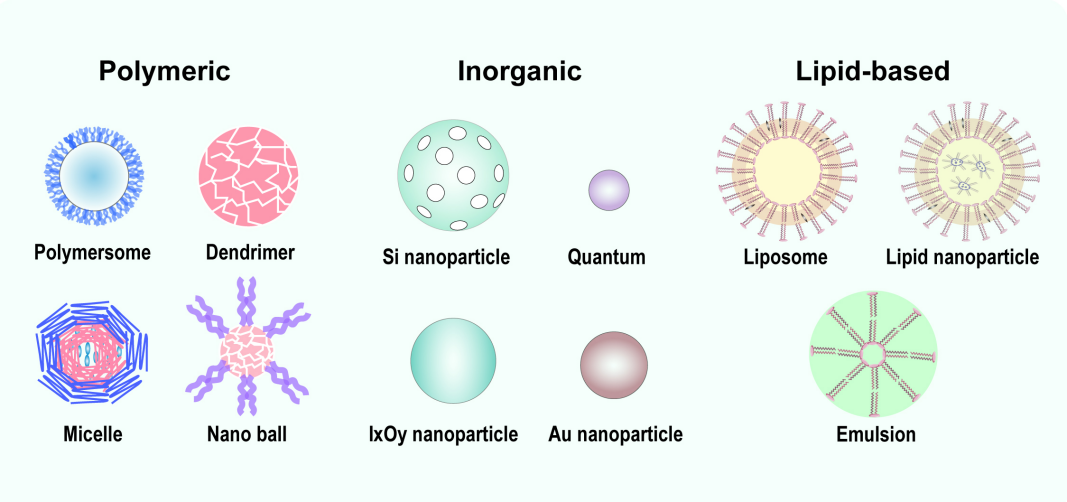

Figure 4. The main classifications of nanopolymers are divided into two categories based on their organic and inorganic properties; inorganic NPs are mainly named based on their compounds, such as silicon NPs, iodine oxides NPs, and so on, while organic NPs can be divided into many categories. In this article, organic NPs are classified into two categories: Polymeric and Lipid-based. Polymeric mainly includes Polymersome, Dendrimer, Micelle, and Nanoball. For Lipid-based, they mainly include liposomes, lipids, nanoparticles, emulsions, *etc.*

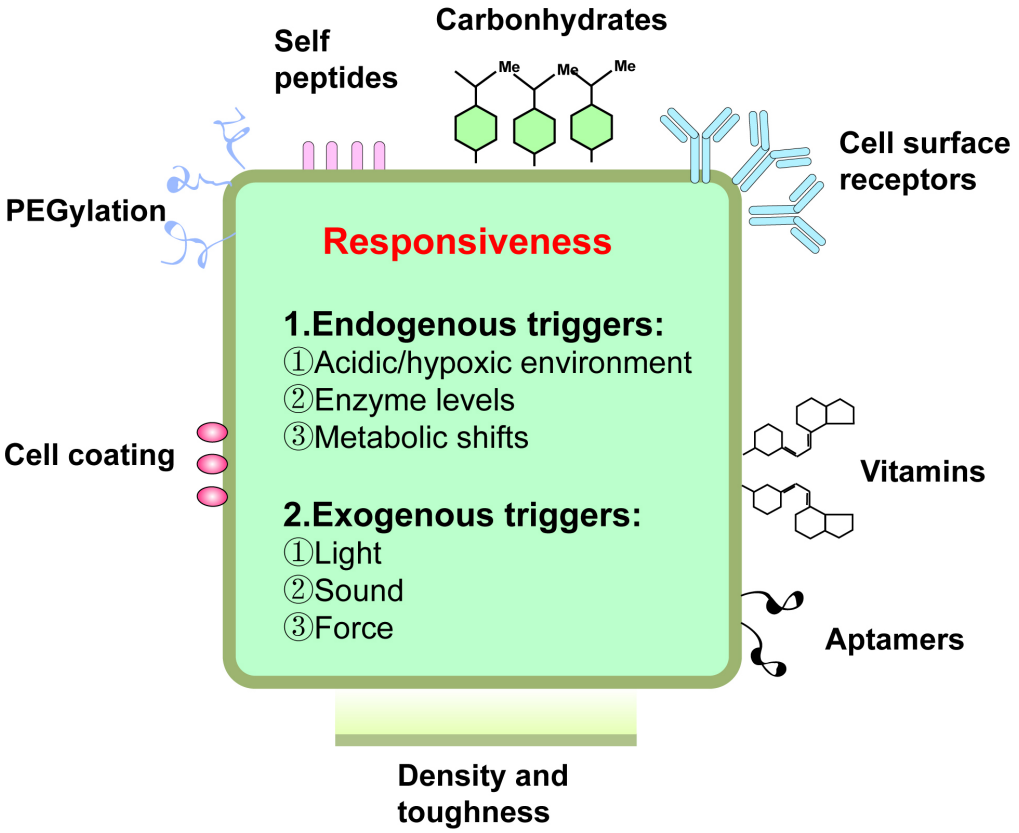

Figure 5. Lipid-based NPs have flexible surface modification options, including cell coating, Vitamin, *etc.*; they can also change the surface toughness to suit different drug delivery needs for lipid-based. Meanwhile, lipid-based NPs can receive intrinsic or extrinsic stimuli to produce a response (usually rupture), with intrinsic motivations including various enzyme levels, metabolic changes, and other precision regulation, and extrinsic stimuli including physical stimuli such as sound, light, and electricity.

both hydrophilic and lipophilic. These molecules can self-assemble into spherical polymer nanoparticles, encapsulating medicines, biologically active components like RNA and DNA, and metal particles. Additionally, to act as specific medication carriers, their surfaces can be altered with pertinent antibodies, vitamins, and other guiding molecules[26]. Retroviruses, adenoviruses, and lentiviruses are among the viral vectors employed in gene therapy as delivery systems[27]. However, due to safety issues such as carcinogenic potentials, immunological detection of the viral capsid proteins, and induction of diverse immune responses *in vivo*, viral vectors have limited their clinical applicability[28].

Fortunately, non-viral carriers are increasingly widely utilized for secure and effective delivery of nucleic acids, such as a prominent subset of lipid-based NPs known as lipid nanoparticles (LNPs) - liposome-like structures. LNPs typically consist of four main parts: cationic or ionizable lipids, phospholipids for particle structure, cholesterol for stability and membrane fusion, and PEGylated lipids to enhance stability and circulation. These lipids interact with genetic material that has a negative charge to aid in the escape of endosomes[29,30]. Ionizable LNPs, which have nearly neutral charges at physiological pH but become set in acidic endosomal compartments, are excellent for intracellularly delivering nucleic acid therapy. LNPs are particularly crucial in implementations related to tailored genetic therapy due to their nucleic acid delivery effectiveness and their straightforward manufacturing, diminutive size, and serum stability.

The condensation of plasmid DNA with positively charged substances (polycations or liposomes) has been a prevalent strategy ever since the initial documentation of effective plasmid DNA (pDNA) transfection using a positively charged lipoplex[31]. This approach is founded on the premise that the positively charged attribute plays a pivotal role in cellular interaction, facilitated by the negatively charged heparan sulfate present on the cell membrane surface[32]. Akita *et al.* developed a plasmid DNA (pDNA)-encapsulating liposomal nanoparticle (LNP) as a gene vector platform for targeting RCC[33]. The critical component is a SS-cleavable and pH-activated lipid-like material (ssPalm) that mounts dual sensing motifs (tertiary amines and disulfide bonds) to respond to various intracellular environments and surface-modified with polyethylene glycol to enhance its blood circulation stability. The study also highlighted the use of vitamin E as a hydrophobic scaffold, which showed synergistic anti-tumor function with encoded pDNA. According to reports, LNPssPalmE had a much more significant anti-tumor effect than LNPssPalmM while only slightly outperforming LNPssPalmM in transfection activity. Hama *et al.* demonstrated that the apoptotic activity against cancer cells of α-tocopherol succinate, derived from the degradation of ssPalmE, is noteworthy[34]. Additionally, tumor growth inhibition was pronounced upon administration of completely CpG-free pDNA encoding the soluble form of VEGFR (fms-like tyrosine kinase-1: sFlt-1), especially when delivered through lipid nanoparticle (LNP) formulations containing ssPalmE (LNPssPalmE). Hence, the PEG-modified LNP ssPalmE emerges as a promising vehicle for gene therapy directed at RCC.

DNA immunization presents another auspicious avenue for tumor immunotherapy. Following intramuscular injection, plasmid DNA can prompt the expression of the encoded antigen within the human system, thus eliciting both cellular and humoral immune responses. He *et al.* selected Nesprin-2 L4492R (Nes2LR) from 20 novel epitopes and packaged it in immunogenic liposomes[35]. In a murine model of RCC, their findings indicated that Nes2LR vaccination combined with immune checkpoint blockade effectively mitigated or reversed the disease progression across subcutaneous, experimental lung metastasis, and orthotopic tumor models. Additionally, the Nes2LR neoepitope holds promise for preclinical investigations pertaining to immunotherapeutic interventions against RCC.

Lipid-based NPs in targeted drug delivery

Liposomes are a distinct subset of lipid-based nanoparticles with the most members. They are commonly made up of phospholipids, which can form unilamellar and multilamellar vesicular structures. Therefore, liposomes can transport and encapsulate hydrophilic, hydrophobic, and lipophilic medications[36]. However, liposome carriers confront challenges including multiple defense systems of the human body, especially reticulo-endothelial system (RES) leading to shortened liposome circulation time and tumor accumulation[37] and low drug-loading capacity[25]. Improving the effectiveness of liposomes in drug delivery is a major focus of research in this field.

A hydrophobically modified chitosan (HMC) coat can increase particle stability and overall circulation time. Additionally, it enhances tumor cell uptake due to the interaction force of differently charged surfaces of the HMC shell and tumor cell[38]. Liu *et al.* conducted a comparative analysis of various biocompatible nanoparticle formulations incorporating Sorafenib, a targeted agent for RCC[39]. The nanoparticle models under scrutiny included poly (lactic & glycolic) acid, liposomes, and HMC-coated liposomes. Flow cytometry data comparing DiI-Lip and flu-HMC DiI-Lip treatments showed that cells treated with flu-HMC DiI-Lip exhibited higher DiI intensity than those treated with DiI-Lip alone or unstained cells, indicating that additional HMC coating improved the delivery of the RCC drug Sorafenib by liposomes.

On the other hand, combining therapies could be a valuable approach to address the challenge of low liposomal drug-loading capacity. Pal *et al.* employed phospholipids, cholesterol, DSPE-(PEG)2000-Ome, and a proprietary tumor-targeting peptide (TTP)-conjugated lipopeptide to encapsulate two distinct medications, everolimus and vinorelbine, within a tumor-directed liposomal formulation[8]. Figure 6 illustrates the process of preparation of this tumor-directed liposome formulation. The combination therapy comprising everolimus and vinorelbine successfully inhibited *in vitro* proliferation and *in vivo* tumor growth and lung metastasis. In the single mouse trial, eight-week-old male SCID mice were subcutaneously injected with 5×10^6 786-O cells on their right flanks. The tumors could grow until they reached an average size of ~400-500 mm^3. Afterward, drug-loaded liposomes were administered to the mice (one mouse per treatment group) thrice a week for three weeks. Tumor dimensions were assessed on a weekly basis, and their respective growth curves were plotted accordingly. In both experimental settings, it was noted that liposomes loaded with two drugs exhibited noteworthy inhibition, surpassing the efficacy observed with liposomes carrying only a single drug, a trend consistent with the outcomes observed in A498 xenografts. Notably, this tumor suppression was accomplished at reduced dosages of the drugs (everolimus at 1-5 mg/kg/day and vinorelbine at 4.8-5 mg/kg/week, typically) than those typically administered. The internalization of TTP-conjugated liposomes (TL) exhibited markedly higher levels in both the A498 and 786-O cell lines compared to the control liposome (CL), which was formulated with the identical lipid composition excluding the TTP-conjugated lipopeptide. In the *in vivo* experiment, at both 24 and 48 h post-administration, TL demonstrated a heightened tumor-specific signal in both 786-O and A498 xenograft models compared to CL. The findings indicate that attaching targeting ligands to liposomes could be a practical approach to enhance their targeting ability. To summarize, this liposome, loaded with two drugs and decorated with targeting ligands, exhibits notable uptake in tumor cells, more significant inhibition of growth, and decreased lung metastasis in both *in vitro* and *in vivo* settings.

In addition, doxorubicin, one of the important chemotherapeutic agents for RCC, was packaged as a model cargo following the process shown in Figure 7 in a MITO-Porter to make DOX-MITO-Porter by Yamada *et al.* Compared with bare DOX and conventional DOX liposomal formulations, DOX-MITO-Porter inhibits mitochondrial functions such as the maintenance of the mitochondrial membrane potential and significantly reduces cell viability[40]. This provides an alternative therapeutic strategy for treating drug-resistant cancers.

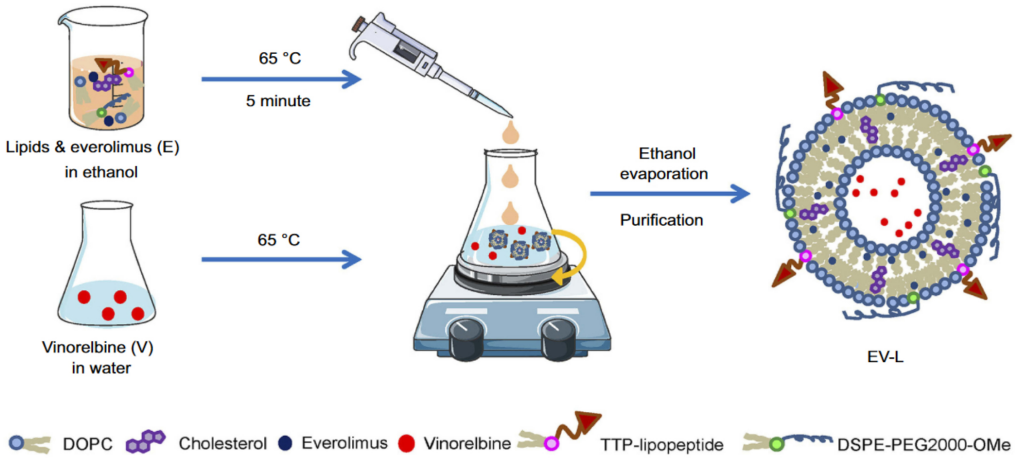

Figure 6. Illustration depicting the synthesis process of drug-incorporated liposomes[8]. DOPC: 1,2-dioleoyl-sn-glycero-3-phosphocholine; TTP: tumor targeting peptide; DSPE-PEG2000-Ome: 1,2-distearoyl-sn-glycero-3-phosphoethanolamine-N-[methoxy(polyethylene glycol)-2000] (ammonium salt).

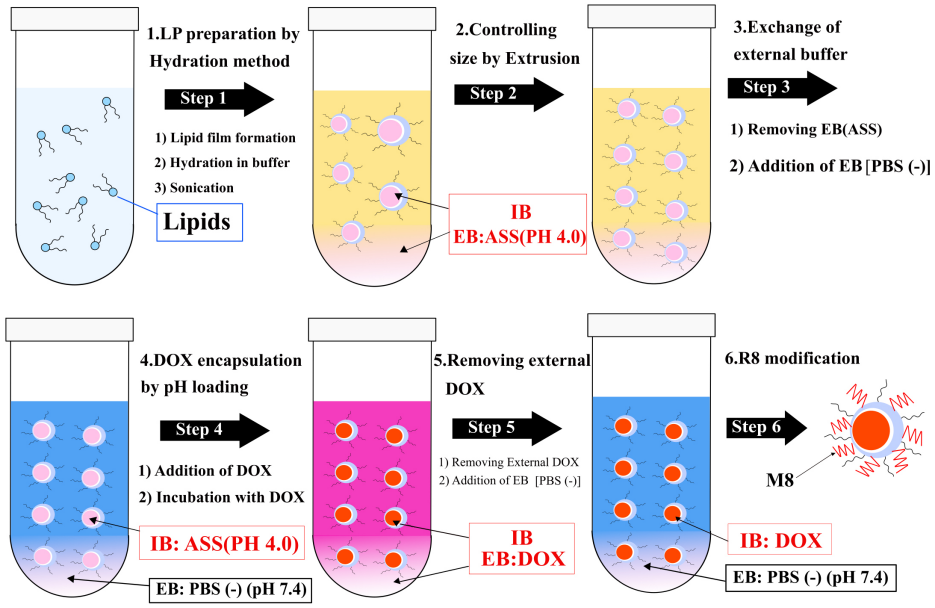

Figure 7. Schematic diagram showing the preparation of the DOX-MITO-Porter using a pH loading method[40]. DOX: Doxorubicin; IB: internal buffer; EB: external buffer; ASS: assay buffer.

Liposome-loaded drug delivery and antigen-antibody targeted conjugation for enhanced ultrasound imaging of RCC xenografts for differentiation of non-cancerous and cancerous lesions in renal masses. The G250 antigen represents a transmembrane protein abundantly expressed in the majority of RCCs while remaining absent in healthy renal tissue[20]. Yu *et al.* formulated targeted nanobubbles (anti-G250 NTNs) functionalized with anti-G250 nanobodies by coupling them with lipid nanobubbles[41]. Their study validated the targeting specificity and binding efficacy of these nanobubbles to RCC cells expressing the G250 antigen, as well as their ability to enhance ultrasound imaging of RCC xenografts[41]. *In vitro* experiments demonstrated the specific attachment of anti-G250 NTNs to G250-positive 786-O and HeLa cells, while no binding was observed with G250-negative ACHN cells. *In vivo* investigations exhibited a

significant improvement in ultrasound imaging of xenograft tumors originating from 786-O and HeLa cells following the administration of anti-G250 NTNs compared to control nanobubbles. However, there was no discernible enhancement in tumors derived from ACHN cells. Immunofluorescence imaging of the tumor tissue sections confirmed the infiltration of anti-G250 nanobodies into tissues through the tumor blood vessels, where they selectively adhered to tumor cells. Overall, the use of anti-G250 nanobodies holds excellent promise as a solution to distinguishing between benign and malignant changes in kidney masses, as they specifically bind to G250-positive RCC cells and enhance the ultrasound imaging of G250-positive masses.

As a means of drug transportation, lipid-based nanoparticles (NPs) present numerous benefits, such as straightforward formulation, self-assembly, biocompatibility, elevated bioavailability, extensive cargo capacity, and a diverse array of physicochemical attributes that can be modulated to modify their biological properties. Lipid-based NPs are one of the most widely used and recognized delivery systems in targeted therapy or gene therapy. However, as a delivery system, lipid-based NPs also have some unavoidable shortcomings due to their characteristics, such as inaccurate load, difficulties in ensuring the uniform physical size of the delivery body, and difficulty in implementing multiple target modifications for various targets.

INORGANIC NPS IN RENAL CELL CARCINOMA

Introduction of inorganic polymer NPs

Inorganic polymer nanoparticles have been used not only as contrast agents in computed tomography (CT) and magnetic resonance imaging (MRI) in clinical practice, but also as probes in laboratory tests and pathological examinations to detect tumor biomarkers due to their improved electrical conductivity, biophilicity, photothermal effect, X-ray blocking effect, and magnetic resonance effect. Inorganic polymer nanoparticles have also been used to help surgeons define the tumor site[42].

Inorganic materials such as gold, iron, and silica have been utilized in the fabrication of nanostructured materials for various applications, including drug delivery and imaging. Inorganic nanoparticles precisely manipulate their size, structure, and geometry. Primarily, inorganic NPs possess distinctive physical, electrical, magnetic, and optical characteristics attributed to the material's inherent properties. For instance, gold nanoparticles have unbound electrons on their surface that constantly vibrate at a frequency that relies on their size and shape, conferring upon them photothermal characteristics[43].

Inorganic NPs in surface-assisted laser desorption ionization method

MALDI MSI has been successfully employed to analyze the spatial distribution of proteins and lipids within the kidney tissue of patients with RCC[44,45]. However, the use of low molecular weight organic acids as matrices by conventional methods is limited due to the generation of numerous high background peaks in the low mass range (up to m/z 800), low mass determination accuracy due to the large thickness of the sample and the sweet spot effect. Due to various limitations and subjective evaluations, MALDI is not the optimal technique for identifying, analyzing, and imaging low-molecular-weight compounds, including cellular metabolites. This method offers a promising alternative for low-molecular-weight biomarker research. To address these constraints, a novel matrix-free laser desorption-ionization approach has been introduced based on the principle basis of the MALDI assay in Figure 8, which utilizes a steel platform coated with positively charged silver or gold nanoparticles (AgNPs/AuNPs)[6,46]. The latter represents a surface-assisted laser desorption ionization method (SALDI) that, unlike MALDI, is matrix-free. Nizioł *et al.* elucidated the utilization of gold nanoparticle-enhanced target (AuNPET), a surface-assisted laser desorption/ionization (SALDI) mass spectrometric technique, for the examination and imaging of

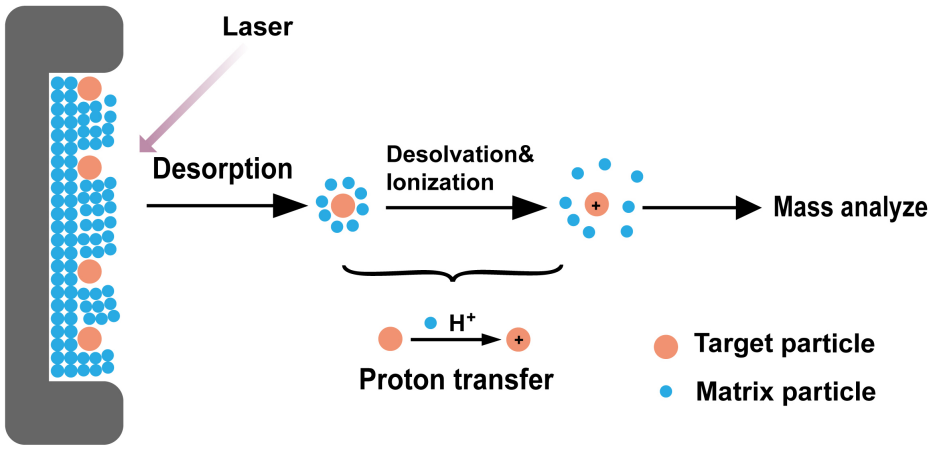

Figure 8. The MALDI technique is based on a series of matrix substances surrounding the particles to be detected, after which the laser irradiates the detection plane, and the matrix-wrapped particles to be seen are desorbed from the overall material. Then, the particles to be seen and the surrounding matrix particles undergo desolvation and ionization, whereby the matrix substances transfer positive charges to the particles to be caught to form a Particle for Mass Spectrometry.

renal tissue, distinguishing between normal and cancerous specimens[6]. LDI MS and MS/MS experiments were conducted on healthy and RCC tissues, utilizing a time-of-flight mass spectrometer in reflection mode. Upon analysis, diglyceride DG(18:1/20:0) and octadecanamide were identified with significantly higher intensities in the cancerous regions of the examined tissue, representing potential biomarkers.

Inorganic NPs *in vitro* detection

Regarding diagnosis methods, renal mass biopsy may have some benefits but is at risk of sampling error, invasiveness, and morbidity. Consequently, it is crucial to explore alternative, non-intrusive techniques, such as those employing unique chemical compounds found in body fluids that could reveal the presence of a tumor. Regrettably, significant efforts have been invested over the past few decades to pinpoint microscopic molecule markers peculiar to RCC. However, no reliable markers guide more effective therapies, diagnosis, or tumoral prognosis. Over the past few decades, there has been a significant increase in the use of metabolomics applications in cancer research. Urine has become a preferred biospecimen source for the examination of kidney cancer using metabolomics because of its strong association with the disease's origin. Metabolic profiling was conducted on urine samples collected from fifty patients diagnosed with kidney cancer and fifty healthy people. This profiling employed high-resolution proton nuclear magnetic resonance spectroscopy and silver-109 nanoparticle-enhanced steel target laser desorption/ionization mass spectrometry[47]. Four metabolites with significantly altered levels in both cancer patients and non-cancer controls were putatively identified using 109AgNPET LDI MS metabolite profiling. The study has revealed the capacity of mass spectrometry to detect informative urinary biomarkers for RCC. In conclusion, monitoring alterations in urinary metabolite concentrations could emerge as a valuable approach for screening and monitoring the progression of RCC in a less invasive manner.

Inorganic NPs in photodynamic therapy and photothermal therapy

Photodynamic therapy (PDT) and photothermal therapy (PTT) are effective means of cancer treatment. Ever since the discovery of the photocatalytic properties of titanium dioxide in 1972, TiO_2-based materials have garnered extensive research attention as photosensitizers in photodynamic therapy[48]. Under irradiation, TiO_2 can generate ROS by reacting with water to cause cell damage. Yang *et al.* developed a core-shell structured formulation consisting of titanium dioxide@red phosphorus nanorods (TiO_2@RP NRs) as shown in Figure 9, serving as a photosensitizer, driving PDT and PTT for RCC[49]. The

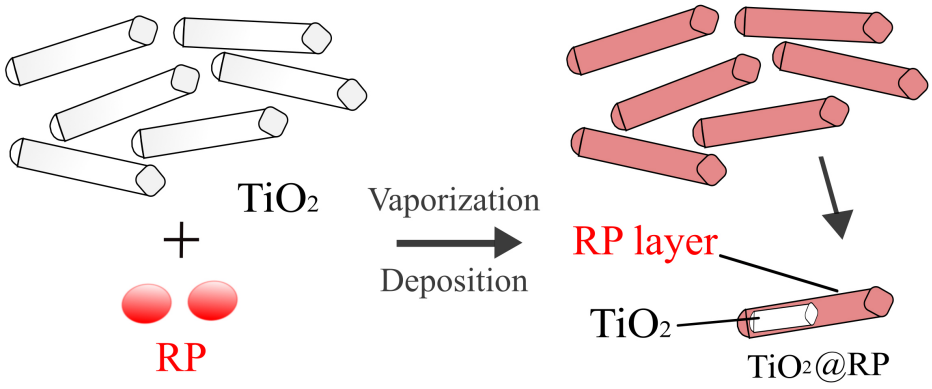

Figure 9. Illustration depicting the synthesis process of the TiO_2@RP heterostructure[49]. TiO_2: Titanium dioxide; RP: red phosphorus.

research demonstrates that synchronous PDT and PTT treatments are feasible and effective for RCC[49]. The investigation focused on the *in vivo* ability of TiO_2@RP NRs to kill RCC tumors. Promisingly, the results imply that these nanomaterials have the potential for RCC treatment and offer novel ideas for treatment approaches. Furthermore, the study highlights the medical utility of synchronous PDT and PTT treatment in RCC.

Above all, numerous studies have investigated the potential applications of nanoparticles in cancer management, mainly when employed as drug delivery systems. These investigations have yielded significant findings indicating that nanoparticles can offer reduced toxicity and improved pharmacokinetics over traditional cancer therapies. Additionally, due to their adjustable structures that provide the possibility of encapsulating the drug or conjugating it on the surface and their unique sizes, they can effectively target cancer cells and deliver therapeutic payloads with high precision and efficacy. In recent years, significant developments in the clinical application of nanoparticles, including biomimetic nanocarriers and metal-organic frameworks, have emerged to tackle existing challenges. Notably, given the ever-increasing number of different formulations and the vast amount of research on nanomaterials, the number of candidates reaching clinical trials or commercialization is minimal[50]. Thus, further research is required to fully understand the clinical potential of nanoparticle-based cancer therapies.

MEGA-POLYMERS IN RENAL CELL CARCINOMA-RELATED CLINIC STUDIES

While the application of biopolymers in RCC has focused on nanomaterials, we will present some noteworthy studies involving the clinical applications of mega-polymers. As their natural analogs, the favorable biological, physical, and chemical properties of mega-polymers have led to their use in many fields, including tissue engineering materials, and therapeutic and diagnostic applications. *In vitro*, von Rundstedt *et al.* used 3D printing technology to print a 1:1 renal model of a patient in silicon-based material for rehearsal before robot-assisted laparoscopic partial nephrectomy[51]. Models were fabricated utilizing blends of silicone rubber [with a shore hardness of 10A, a Die B tear strength of 17.863 N/mm (equivalent to 102 pounds per linear inch), and a tensile strength of 3.2750 MPa (475 psi)], along with silicone oil as a diluent. The tumor was formulated using a composition comprising 85% silicone rubber and 15% diluent, exhibiting an orange hue. These formulations yield a tumor with marginally elevated shore hardness, tensile strength, and tear strength in comparison to the renal parenchyma. Their recent study generated a patient-specific soft tissue model that not only provides a three-dimensional representation of the tumor anatomy, but also allows tumor resection to be performed on the model with high fidelity. The volume of the renal mass removed during surgery was similar to the modeled and computer-assessed

resection volume. The time to surgically remove the mass was greatly reduced by adequate preoperative testing. This simulation technique utilizing polymeric materials to aid in surgical decision-making improved surgical efficiency.

RCC has a biological predisposition to direct vascular invasion, with 4% to 10% involving the venous system, of which 22% to 70% involve the inferior vena cava (IVC). The median life expectancy of patients with untreated RCC with inferior vena cava thrombosis is 5 months, with a 1-year disease-specific survival rate of 29%[52]. The applications of mega-polymers provide worthwhile new ideas and methods for this situation. Using a circular polytetrafluoroethylene (PTFE) cannula, Ciancio *et al.* graft-reconstructed the inferior vena cava of a patient with RCC with tumor thrombus (TT) invasion of the IVC, with simultaneous placement of an IVC filter[53]. The novelty of this approach is that an IVC filter can be deployed before completing the distal IVC anastomosis. During the postoperative follow-up period, thrombosis did not occur in any of the patients' IVC grafts and the PTFE graft in each patient was patent at last follow-up. This implies that PTFE, a synthetic vascular substitute made of polymer, offers a positive clinical outlook and serves as a safe and viable vascular channel in RCC's treatment.

DISCUSSION

Currently, renal cell carcinoma faces challenges such as late diagnosis and poor prognosis, particularly in patients with metastatic RCC. Surgical procedures like direct resection, radiofrequency ablation, and interventional embolization are common treatments for localized RCC. However, treatment decisions must consider individual patient health and the balance between postoperative benefits and risks. Since sorafenib's approval for metastatic RCC treatment in 2005, targeted therapy has revolutionized treatment. Nevertheless, dose-dependent side effects remain a concern. Moreover, increasing early screening and diagnosis rates for kidney cancer is essential to reduce the burden of advanced stages. Significant progress has been made in developing biopolymers, especially nanomedicines, offering potential solutions to these challenges in clinical diagnosis and treatment.

In clinical diagnosis, Table 1 summarizes some of the uses of biopolymers for laboratory liquid tests, pathology, and imaging tests. Notably, they hold vast potential in liquid biopsy, as demonstrated in ongoing collaborative studies. These studies explore using single-molecule biomarkers to nucleate and assemble large-scale polymers, enhancing detection signals. Biopolymers' characteristics enable early screening of tumors like RCC with subtle symptoms. Further research aims to unlock the full potential of this method. Additionally, biopolymers can enhance the accuracy and visibility of pathological and imaging detection by serving as delivery carriers.

Nanomedicine carriers, with their excellent physical and chemical properties, offer promise in improving the efficacy of chemotherapeutic drugs. Targeted nanoparticles, for instance, can precisely deliver drugs to tumor cores, minimizing toxicity to normal tissues. Table 2 demonstrates the *in vivo* and *in vitro* applications of some of the polymers. However, transitioning these advancements to the clinical stage presents challenges. Current tumor animal models may not accurately reflect drug pharmacokinetics and the tumor microenvironment's complexity, hindering in-depth investigations into drug release control[82].

Recent research by Yamamoto *et al.* highlights the importance of considering the tumor microenvironment in nanoparticle delivery. They found that inhibiting VEGFR2 enhances macrophage infiltration, improving nanoparticle delivery in highly vascularized RCC[89]. This underscores the necessity of targeting both cancer cells and the tumor microenvironment in treatment strategies. Additionally, the role of extracellular vesicles in cancer treatment is significant, influencing various aspects like angiogenesis and metastasis[90].

Table 1. Polymers for clinical diagnosis

Diagnostic type	Target substance	Diagnostic agent	Experiment type	Dominance
Laboratory examination of bodily fluids	Circulating tumor cells	CELLection™ Dynabeads®[54]	*In vitro*	Circulating tumor cells in metastatic RCC
Laboratory examination of bodily fluids	Soluble biomarker	Borosilicate micropipettes and complementary γ-peptide nucleic acid (γ-PNA) probes linked to polystyrene beads[55]	*In vitro*	Safely detect miR-204 and miR-210 associated with ccRCC
Laboratory examination of bodily fluids	Soluble biomarker	Gold nanoparticles-assisted laser desorption/ionization mass spectrometry[56]	*In vitro*	Compared the LOD and the LMW of different analytical methods
Laboratory examination of bodily fluids	Soluble biomarker	Silver-109 nanoparticle enhanced steel target laser desorption/ ionization mass spectrometry[57]	*In vitro*	Prospects for clinical diagnosis/differential diagnosis
Laboratory examination of bodily fluids	Circulating tumor cells	PPy-Ag@BSA[58]	Human study	Efficient capture of circulating tumor cells in RCC
Pathology	Circulating tumor cells	Shell-isolated nanoparticle--enhanced Raman spectroscopy in microfluidic device[59]	*In vitro*	High diagnostic accuracy of circulating tumor cells
Pathology	Patient tissue	AgNPET/Laser desorption/ ionization MS imaging[60]	*In vitro*	Facilitated swift visualization of the disparities between ccRcc and the healthy segment of kidney tissues
Pathology	Patient tissue	Biotin-streptavidin binding and fluorescence active magnetic nanocarriers[61]	Human study	The detection of trace miRNA 15a
Pathology	Patient tissue	Peptide-coated gold clusters exhibiting inherent red fluorescence and a distinct mass signal[62]	*In vitro & vivo* & human study	Prognosis evaluation
Pathology	patient tissue	EVs identified through nanoparticle tracking analysis[63]	*In vitro* & human study	The detection of CA9/CD70/CD147
Imaging	Tumor cells	mAb G250-SPIO molecular nanoprobe[64]	*In vitro*	Contrast agent in specific tumor cells
Imaging	Lymph node	Lymphotropic nanoparticle-enhanced magnetic resonance imaging-monocrystalline iron oxide nanoparticle[65] (ferumoxtran-10 Combidex],AMAG harmaceuticals, Inc.)	Human study	Contrast agent for lymph node
Imaging	Lymph node	99mTc-nanocolloid[66]	Human study	Mapping of sentinel lymph nodes
Imaging	Whole tumor	Fe3O4 @mSiO2 /PDDA/ BSA-Gd2O3 nanocomplex[67]	Human study	Being a T1-T2 dual-mode contrast agent
Imaging	Tumor cells	AS1411 Aptamer Modified Mn-MoS2 QDs[7]	*In vitro & in vivo*	Fluorescently label RCC cells and enhance MRI signal
Imaging	Lymph node	Hydrophilic manganese oxide nanoparticles modified AS1411 aptamer[67]	*In vitro & in vivo*	High T1 relaxivity
Imaging	Tumor cells	Anti-G250 nanobody-functionalized targeted nanobubbles for ultrasound[41]	*In vitro & in vivo*	Specific contrast agent for G250(+) RCC cells
Imaging	Whole tumor & tumor cells	Targeted nanobubbles carrying CAIX polypeptides/aptamer[68]	*In vitro & in vivo*	Specific contrast agent in CAIX(+) tumor tissues

Extracellular vesicles are small vesicles found in the extracellular space, consisting of a lipid bilayer membrane structure. They are actively excreted by both normal cells and cancer cells, containing proteins, nucleic acids, lipids, and various other bioactive compounds. These proteins play a crucial role in cell-to-cell

Table 2. Polymers research for therapy *in vitro* and *vivo*

Category		Polymers	Therapeutic strategies	Dominance	Experiment type
Nanodrugs	Lipid-based NPs	DOX-MITO-Porter[40]	Chemotherapy	Suppress mitochondria functions	*In vitro*
		Tumor-targeted liposomal formulation[8]	Chemotherapy	Dual drug-loaded and targeting ligand-decorated liposome	*In vitro & vivo (subcutaneous)*
		Hydrophobically modified chitosan-coated liposomes[39]	Chemotherapy	HMC coat promotes more interaction between cell membrane and particle	*In vitro*
		Liposomes[35]	Tumor vaccine	Enhancement of anti-tumor immunity	*In vitro & vivo*
		LNPssPalmE[33]	Gene therapy	Collaborative action of gene products encoded in plasmid DNA (pDNA) and LNPssPalmE	*In vitro & vivo (subcutaneous)*
	Polymeric NPs	Chlorambucil-conjugated PI polyamide[69]	Chemotherapy	Induce proliferation arrest depending on p21 expression	*In vitro*
		CA IX-SMA-TPGS (combined with Sor)[21]	Chemotherapy	Target hypoxia core using CA IX (tumor core penetration)	*In vitro & vivo*
		Sialic acid-poly-ibuprofen[23]	Chemotherapy	Synergistic anti-tumor effect of ibuprofen due to COX-2 reduction	*In vitro & vivo (subcutaneous)*
		Poly acid[39]	Chemotherapy	A highly effective drug transport system facilitating gradual and uniform drug release while suspended	*In vitro*
		Poly acid[70]	Chemotherapy	Notable preclinical antimetastatic impacts on lung metastatic cells of RCC	*In vivo (orthotopic)*
		PH1/pHGFK1[71]	Gene therapy	HGFK1 could counteract sorafenib-induced stemness of RCC, thus alleviating Sor resistance	*In vitro & vivo*
		CH-CA-Spe nanogel[72]	Gene therapy	Enable successful transfection of siRNA	*In vitro & vivo (subcutaneous)*
		PLGA-HB-NPs[22]	Adjuvant therapy	Marginally attenuate the resistance of RCC cells to oxaliplatin under hypoxic conditions	*In vitro*
		Sunitinib-loaded micellar nanocomplex[73]	Chemotherapy	Combined anticancer efficacy of SU and the carrier containing PEG-EGCG exhibited synergistic effects	*In vitro & vivo (subcutaneous)*
		Magnetic-core-based silibinin nanopolymeric carriers[74]	Chemotherapy	show a greater inhibitory effect compared to free SLB	*In vitro & vivo*
		CRLX101[75]	Chemotherapy	No additive toxicity of the combination was observed	Clinical trial
		Purified glycogen Polycationic derivatives[76]	Gene therapy	Gene carrier	*In vitro & vivo*
		P1-DBCO combined doxorubic[77,78]	Chemotherapy	Antitumor and metastasis	*In vitro & vivo*
		Polyion complex-loaded miRNA-143#12[79]	Gene therapy	Inhibition KRAS	*In vitro & vivo*
		H1/pAIM2[80]	Gene therapy	Enhance the inflammasome pathway to suppress malignancies associated with RCC	*In vitro & vivo (subcutaneous)*
	Inorganic NPs	MIL-101(Fe) NPs[81]	Chemotherapy	Apart from supplying iron ions to cancer cells, MIL-101(Fe) nanoparticles can function as a delivery platform for RSL3	*In vitro & vivo (subcutaneous)*
Megapolymers	Chitosan oligosaccharide[82]		Chemotherapy	Repress human renal carcinoma growth and induce apoptosis via ROS-dependent ER stress pathways	*In vitro & vivo (orthotopic)*
	Pegilodecakin[83]		Chemotherapy	Induces intratumoral antigen-specific CD8(+) T cells and upregulates IFN γ and MHC I & II	Clinical trial
Interventional and surgical agents	Polymeric NPs	tLyP-1/PR-619/Fe3O4@PCM (tPF@PCM)[84]	Photothermal therapy	Induce ERS and cause apoptosis	*In vitro & vivo*
		Gold nanorod encapsulated albumin[85]	Photothermal therapy	Synergistic tumor necrosis	*In vitro & vivo*

Inorganic NPs	99mTc-nanocolloid[66,86]	Image-guided surgery	Localization of sentinel lymph nodes	Human body (clinical trial)
	X-ray irradiation and quantum dots composed of black phosphorus[87]	Radiotherapy	Enhance apoptotic of tumor cells	*In vitro & vivo*
	TiO_2@red phosphorus nanorods (TiO_2@RP NRs)[49]	Photothermal therapy	Antitumor thermal effect	*In vitro & vivo*
	Mesoporous silica nanoparticles[88]	Photothermal therapy	Enhance antiproliferative effect	*In vitro & vivo*
	Gold nanorods[85]	Photothermal therapy	Simultaneous observation of cell death as a photothermal therapy drug	*In vitro*

communication by liberating bioactive compounds that either merge with receptor cell membranes or adhere to receptors on the cell surface, facilitating intercellular information exchange[91-94].

Patient-derived xenograft (PDX) models offer a promising approach to address challenges in cancer research. The PDX model is established by transplanting fresh tumor tissue, cut from human cancers, into mice[95]. In contrast, it more accurately reflects cancer characteristics and can simulate the progression and evolution of tumors in human patients. PDX models have produced the most compelling preclinical results and are regarded as one of the most promising models for addressing challenges faced by clinicians. Consequently, PDX models, with their aforementioned advantages, have gained increasing attention and development in recent years. We are actively developing a PDX model system for kidney cancer, aiming to further validate key aspects such as the efficiency and safety of biopolymer drug delivery, which is the focal point of our research efforts.

Several nanomedicines have been approved for clinical use in tumoral treatment, but their indications need expansion. Some novel nanomedicines have entered clinical trials, demonstrating feasibility and effectiveness in clinical settings[75,96-98]. However, they also present a typical drawback compared to traditional drugs: low drug loading, resulting in poor efficacy, necessitating increased doses and/or dosing frequencies, thereby increasing systemic toxicity[73]. To prolong drug circulation time and accumulation in tumors or reduce drug doses, various strategies have been proposed, including tumor-targeting ligands[21], surface modification[39], dual-drug delivery[8], and constructing drug carriers with synergistic therapeutic effects[23,73]. To the best of our knowledge, there is currently no FDA-approved liposome formulation utilizing active targeting ligands[8]. This suggests that translating these methods from theory into clinical practice will require extensive clinical trials and exploration of new carrier development.

The tremendous potential demonstrated by biopolymers in various fields fuels our anticipation for their further development and application. Meanwhile, in the face of the aforementioned challenges, we aim to connect a plethora of studies exploring significant new biomarkers and mechanistic pathways of RCC. Recent research has identified CD133+/CD24+ cell subsets in RCC specimens with self-renewal ability and clonal multipotentiality[99]. Previously, we reported the phenomenon of "slimming"[100] in RCC cells, characterized by tumor cell volume reduction and lipid titration. Through related work, the mechanisms of action of HIF2a and its downstream regulatory molecule NUDT1 have been explored[101,102]. The potential of biopolymers in targeting these signaling pathways offers a new approach to RCC treatment beyond traditional therapies. Additionally, advancements such as DNA Origami provide a fresh perspective for biopolymer delivery systems. These are areas that require our focused attention and efforts in the future.

CONCLUSION

In this review, we focus on the advanced progress of applying biopolymers in the treatment of RCC, particularly in material classification and clinical pathways. With the rapid development of biomedical

engineering, research into the adjunctive use of biopolymers alongside current frontline clinical therapies and diagnostics offers new hope. Although the clinical application may still be at a distance, the future intersection of medical science with biology and chemistry will become increasingly important. We believe that by leveraging the design and biophysical and chemical properties of biopolymers, in conjunction with extensive foundational work on classical targets and pathway signaling molecules in RCC, as well as the construction of PDX models, we can accelerate the clinical translation of biopolymers for RCC, thereby achieving effective diagnosis and treatment for RCC patients as soon as possible.

DECLARATIONS

Authors' contributions

Made substantial contributions to the design and completion of the study and performed the illustrative drawings: Zhou X, Xue K, Xu R

Performed literature acquisition and data analysis: Huang F, Li Q, Huang Y

Performed academic guidance: Xiao W, Wang K, Zhang X

Availability of data and materials

Not applicable.

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Conflicts of interest

Xiao W is an Editorial Board member of the journal *Journal of Cancer Metastasis and Treatment*. while the other authors have declared that they have no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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