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Nanoparticles modified by polydopamine: Working as "drug" carriers

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ABSTRACT

Inspired by the mechanism of mussel adhesion, polydopamine (PDA), a versatile polymer for surface modification has been discovered. Owing to its unique properties like extraordinary adhesiveness, excellent biocompatibility, mild synthesis requirements, as well as distinctive drug loading approach, strong photothermal conversion capacity and reactive oxygen species (ROS) scavenging facility, various PDA-modified nanoparticles have been desired as drug carriers. These nanoparticles with diverse nanostructures are exploited in multifunctions, consisting of targeting, imaging, chemical treatment (CT), photodynamic therapy (PDT), photothermal therapy (PTT), tissue regeneration ability, therefore have attracted great attentions in plenty biomedical applications. Herein, recent progress of PDA-modified nanoparticle drug carriers in cancer therapy, antibiosis, prevention of inflammation, theranostics, vaccine delivery and adjuvant, tissue repair and implant materials are reviewed, including preparation of PDA-modified nanoparticle drug carriers with various nanostructures and their drug loading strategies, basic roles of PDA surface modification, etc. The advantages of PDA modification in overcoming the existing limitations of cancer therapy, antibiosis, tissue repair and the developing trends in the future of PDA-modified nanoparticle drug carriers are also discussed.

1. Introduction

Nanoparticles (NPs) are the particles in size of 1–100 nm with a contiguous interfacial layer which behave as a whole unit concerning their transport and biomedical properties [1]. Over the past few years, thanks to the robust advancement of nanotechnology, a great number of nanoparticles have emerged as a promising platform to deliver drugs to specific cells for achieving lower side-effects and circumventing multidrug resistance (MDR) [2–8]. As numerous researchers devote themselves to fabricating new and more efficient nanoparticles for drug delivery, it remains to be a great challenge to combine all the desired properties into one single system, thus results in the hindrance of biomedical applications of those mono-functional nanoparticles [9–12]. Therefore, appropriate modification of such nanoparticles is required for endowing the nanoplatform with ideal biocompatibility, various functionalization, colloidal stability and additional attributes such as photothermal conversion ability, etc [13–17].

In recent years, the innovative discovery of a versatile biomaterial, polydopamine (PDA), has shed new light on the surface functionalization and biomedical applications of nanoparticles as drug carriers [18,19]. This pioneering work was put forward by Lee et al. [20] in 2007, who was inspired by the adhesive proteins secreted in mussels which can attach to nearly all kind of surfaces. They found the clues to mussels' adhesive versatility may lie in lysine amino acids as well as 3,4-dihydroxy-L-phenylalanine (DOPA) [21]. Thus, they identified that dopamine, a derivative of DOPA belonging to the class of catecholamines which was proved to be crucial for mussels' achieving adhesion, tended to strongly interact with multiple substrates via both covalent and noncovalent binding. And its polymerization product, PDA, was able to form on and attach to almost all material surfaces, including metals, ceramics, semiconductors, and synthetic polymers [22]. Notably, this marked the very first attempt to prepare PDA coating by means of stirring dopamine hydrochloride in a Tris-HCl buffer saline solution under alkali condition. Despite that the specific synthetic mechanism of PDA polymerization remains unclear, numerous researches have been pursuing the fabrication of delicate and multifunctional PDA-modified nanoparticles with various nanostructure for biomedical applications during the past decade [23]. It is worth noting that besides the coating of PDA shell on the outer layer of the nanoparticles, there are other approaches for PDA modification where PDA can be either

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coated on various templates followed by the exclusion of the sacrificial template nanoparticles to prepare PDA hollow nanoparticles, or bonded with other bioactive components to form “building block” of the PDA co-assembly nanoparticles [24–26].

Comparing to other materials for surface functionalization, the advantages and roles of PDA modification on these nanoparticle drug carriers are outstanding and promising. Primarily, the synthesis requirement of PDA is simple and mild with no need for organic solvent owing to its unique adhesion property. In addition, via altering the essential parameters such as pH, temperature, concentration of dopamine, oxidants and reaction time, it is highly controllable to prepare PDA surface modification in diverse particle size, film thickness and so on [27]. Secondly, when working as drug carriers, the drug loading ability of the nanoparticles can be significantly improved by PDA modification because of its richness of catechol/quinone moieties, which offers the potential to either anchor functional molecules onto the nanoparticles by physical bonding (π-π stacking or hydrogen bond) or chemical bonding (Michael addition or Schiff base reactions) [20,28]. Moreover, it is convenient to achieve secondary modification such as PEGylation with the help of PDA, for it is capable of reacting with thiol or amino group-containing compounds through Michael addition or Schiff base reactions [29]. Lastly, the intriguing properties of PDA modification provide the nanoparticles with increased hydrophilicity, excellent biocompatibility, appropriate biodegradability, strong photothermal conversion capacity and Reactive oxygen species (ROS) scavenging facility. As a result, thanks to the characteristics of the various anchored bioactive molecular combined with the intrinsic properties of PDA, PDA modification have endowed the nanoparticles with multifunction, including targeting, imaging, chemical treatment (CT), photodynamic therapy (PDT), photothermal therapy (PTT), tissue regeneration ability, anti-inflammatory and antioxidant effect. With such prominent multifunction, PDA-modified nanoparticle drug carriers have aroused great interests in cancer therapy, antibacterial application, theranostic, tissue repair and so on [30–34].

This review aims to summarize current advances of PDA-modified multifunctional nanoparticle drug carriers on cancer therapy, antibiosis, prevention of inflammation, theranostics, vaccine delivery and adjuvant, tissue repair and implant material usage. We firstly comply the preparation of diverse PDA-modified nanoparticles working as drug carriers with various nanostructures, where five typical drug loading strategies of these drug systems are highlighted. Afterwards, the basic roles of PDA surface modification in these drug systems are discussed. Finally, the recent progress in biomedical applications of these drug carriers, especially the advantages of PDA modification in overcoming the existing limitations of present treatment, theranostics and the approaches to enhance their tumor/microbes-killing effect or tissue repair bioactivity are illustrated.

2. Preparation of PDA-modified nanoparticle drug carriers

Polydopamine (PDA), as an insoluble biopolymer, is obtained by the polymerization of its dopamine monomers. The definite mechanism of dopamine polymerization remains ambiguous. Up till now, the most wide-accepted theory of the mechanism of dopamine polymerization was proposed by Lee et al. [35] who considered both covalent oxidative polymerization and physical self-assembly pathways were existed during dopamine polymerization (Fig. 1). The catechol group of dopamine can get easily oxidized to form dopamine-benzoquinone. In alkaline condition, the equilibrium of phenol and quinone in aqueous medium moves towards quinone. Subsequently, dopamine-benzoquinones undergo intramolecular cyclization to form colorless dopamine derivatives, and colorless dopamine derivatives are further oxidized to form pink intermediate dopamine derivatives. However, pink dopamine derivatives are unstable and will soon undergo further oxidative rearrangement to produce 5, 6-dihydroxyindole, which occurs intermolecular and intramolecular rearrangement end up with cross-linking to form a dark brown dopamine oxidative polymer-PDA. In addition to it, (dopamine)2/5,6-dihydroxyindole trimers are thought to be involved in the formation of PDA as well for the reason that they are closely adsorbed with oxidative polymerization products through non-covalent interactions including hydrogen-bonding, T-shape interaction, and cation−π interaction. Employing single-molecule force spectroscopy (SMFS), Messersmith et al. [36] found that PDA contain high-molecular-weight polymer chains with covalently linked subunits, which provided direct evidence for demonstrating PDA as an actual polymer.

Solution oxidation, enzymatic oxidation, and electropolymerization are three common approach to synthesis PDA, among which solution oxidation is most widely used [37]. The solution oxidation method refers to dissolve the DA hydrochloride in an alkaline solution and the self-polymerization procedure begins immediately in the presence of atmospheric oxygen without requiring any strict reaction conditions [38]. Unfortunately, some insoluble black precipitate is inclined to deposit at the bottom of the reaction vessel during the solution oxidation, resulting lacking in uniformity and thickness of the PDA surface modification. The electropolymerization method is considered to be the best procedure for maintaining a desired coating thickness [39]. However, only the minority of substrates are conductive to carry out the electropolymerization. Recently, Li et al. [40] reported their progress in the synthesis of PDA nanoparticles using an enzymatic reaction method to avoid harsh chemical conditions. This method can fabricate PDA similar to the naturally occurring melanin with the aid of tyrosinase enzyme. The preparing condition, advantages and disadvantages of each method are demonstrated in Table 1. By providing the appropriate reaction conditions and utilizing flexible drug loading strategies, the PDA surface modification can be prepared in diverse morphology and structures composed of core@shell nanostructures, hollow nanoparticles and PDA co-assembly nanoparticles with various “drugs” loaded. Therefore, the nanoparticles, the PDA modification and the loading “drugs” make up the whole drug system, as what we call “PDA-modified nanoparticles working as drug carriers” here.

2.1. PDA core@shell nanoparticles

The synthesis of PDA core@shell nanoparticles is simply executed via stirring dopamine hydrochloride in a Tris-HCl buffer saline solution at pH 8.5. Due to the novel adherent ability and multiple biochemical properties, PDA has been most broadly used for the coating of both organic and inorganic nanoparticles.

2.1.1. Inorganic core

In terms of PDA-coated inorganic nanoparticles, both metallic cores such as gold nanoparticles, magnetic nanoparticles and nonmetallic cores such as mesoporous silica nanoparticles (MSN), reduced graphene oxide nanoparticles (RGO) can be coated with PDA in a simple way (Fig. 2) [41–44].

2.1.1.1. • Metallic elements containing. Gold nanoparticles of different shapes with different biological properties have been explored as the core where PDA plays different part in them. Firstly, PDA coating directs the growth of spherical gold nanoparticles called “Core-Petal Nanostructure”. Via coating PDA and adding gold chloride to the system to induce oxidative disassembly and rupture of the PDA shell, the anisotropic growth of Au nanopetals can be accomplished [41]. Secondly, PDA acts as a surface passivation layer and confers vigorous photothermal stability to spiky gold nanoparticles coated with PDA [45,46]. As for PDA-coated hyperbranched gold plasmonic blackbody, PDA helps to prepare the blackbody in a straightforward one-pot method for photothermal therapy [47]. Thirdly, gold nanorods coated by PDA can also be proposed where PDA represses the cytotoxicity of cetyltrimethylammonium bromide (CTAB) meanwhile improves the loading efficacy of drugs as well as chelator-free radioisotopes

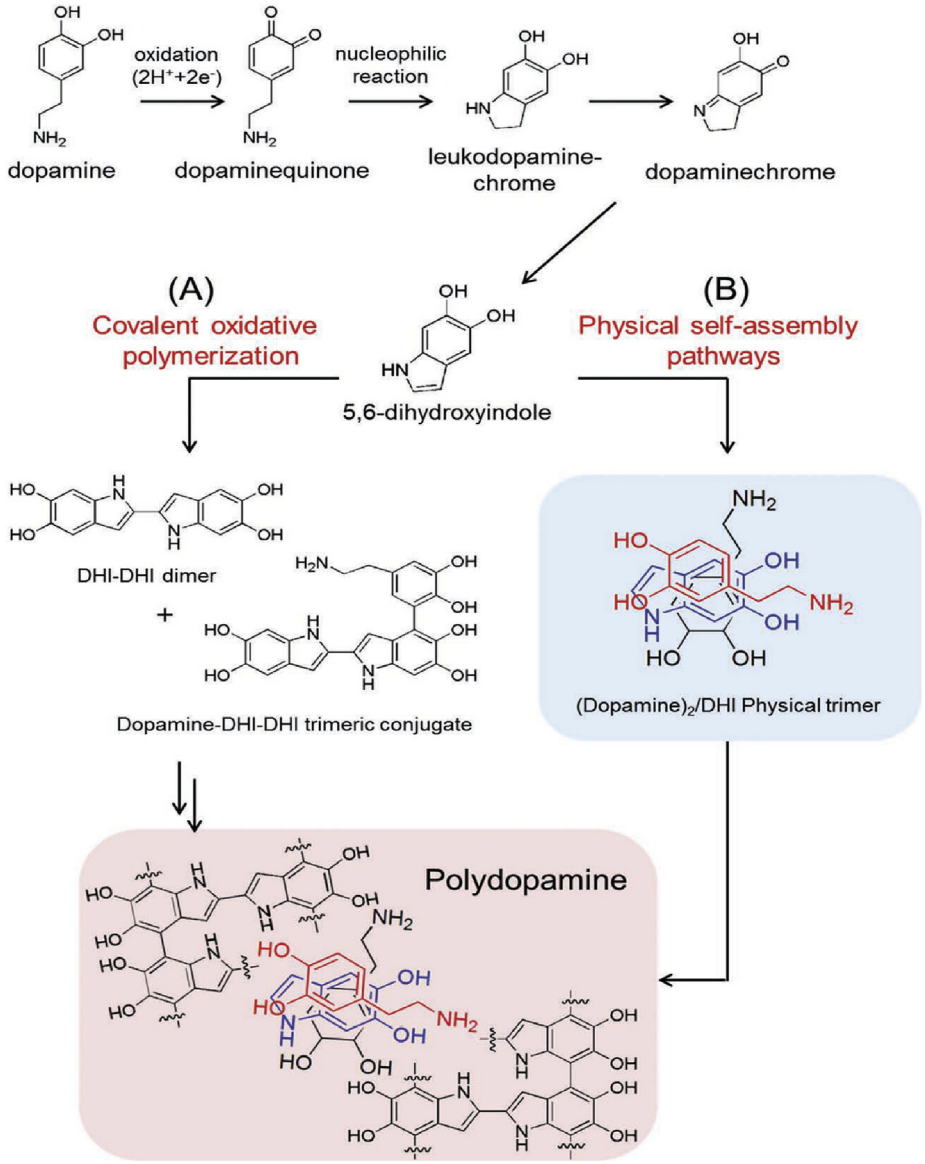

Fig. 1. Polydopamine synthesis occurs through two possible pathways: a) oxidative polymerization via covalent bonding and b) physical self-assembly of dopamine and DHI. Reproduced from Ref. [35], Advanced Functional Materials.

Table 1
Summary and comparison of various methods used for PDA synthesis.

Method	Main conditions	Advantages	Disadvantages	Ref.
Solution oxidation	pH > 7.5 Oxygen Dopamine > 2 mg/ml	Simplicity Mildness Extensive useage	Lack of thickness	[37]
Electropolymerization	Cyclic voltammetry Oxygen-free	Simplicity Considerable thickness	Require electrode to conduct	[39]
Enzymatic oxidation	Enzyme-catalyzed Oxygen	Environmentally friendly	Need further study	[40]

labeling and RGD (Arg-Gly-Asp) peptide modification [48,49]. Moreover, the PDA shell of gold nanorods can be doped with Cu (II) for endowing this nanoparticles with not only magnetic resonance imaging function, but also chemotherapeutic performance [50]. Finally, in addition to one layer, the shell of gold nanoparticles can be designed as bilayer or multilayer, for example, antibodies can be embedded in PDA-modified gold nanoparticles with silver shell as the inner layer and PDA as the outer one [51].

Magnetic nanomaterials including Fe_2O_3 as well as Fe_3O_4 are of great potentials to fabricate multifunctional nanosystems for drug carriers, thus numerous researchers are working on surface functionalization of this kind of material for fusing more desired factors into one nanoplatform. Up till now, PDA has been the functional shell of either magnetic nanoparticles [52] or nanoclusters [53] serving as the core. For instance, Wang et al. [54] presented Fe_3O_4 colloidal nanocrystal clusters (CNCs) core coated with PDA shell which was functionalized with triphenylphosphonium (TPP). Moreover, Fe_3O_4@PDA core@shell nanoparticles can be designed as a versatile nanoplatform by means of proceeding different molecular immobilization or second modification [55]. The shell of magnetic nanoparticles can also be prepared as multilayer, and the inner layer is usually the SiO_2 nanoparticles with mesopores for drug loading [56,57]. Co–P nanocomposites which display inherent magnetic behavior were also chosen to be the core coated by PDA to improve their biocompatibility and the photothermal conversion efficiency [58].

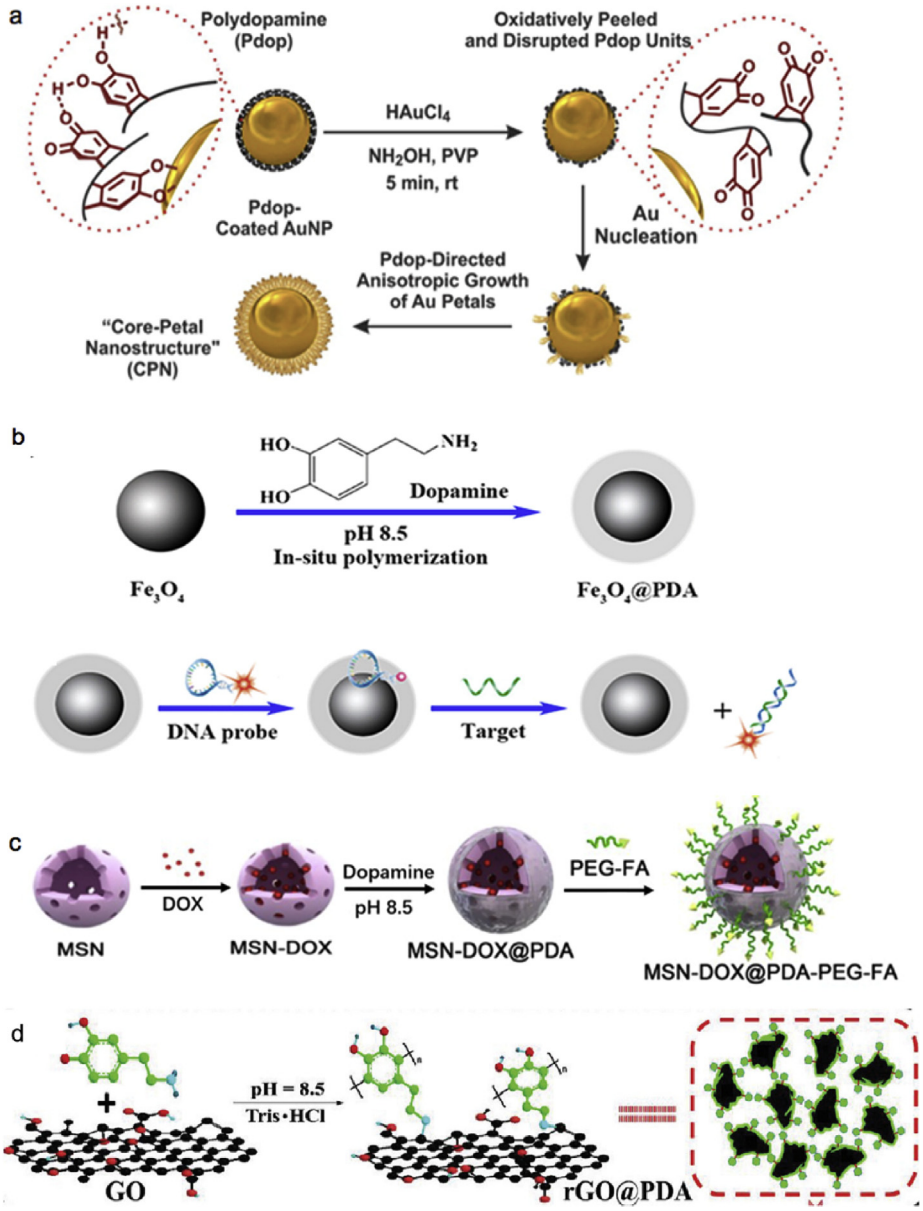

Fig. 2. Schematic illustration of the synthesis of PDA-coated inorganic nanoparticles, (a) core-petal nanoparticles by oxidative nanopeeling of PDA on gold nanoparticles; (b) Fe_3O_4@PDA NCs for RNA detection; (c) DOX-loaded MSN-DOX@PDA-PEG-FA; and (d), rGO@PDA. Reprinted with permission from Refs. [41], Journal of the American Chemical Society, Copyright (2014) American Chemical Society; [42], ACS Nano, Copyright (2014) American Chemical Society; [43], ACS Applied Materials & Interfaces, Copyright (2017) American Chemical Society; and [44], Small, respectively. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

Other metal nanoparticles have also been developed as the inner core of drug carriers. Recently TiO_2 nanotubes (TNTs) have received considerable attentions in the fields like drug delivery owing to their porous structures, tubular architectures, controllable dimensions and good mechanical properties, but their biocompatibility and drug loading efficiency need to be necessarily improved. Enduringly binding with TNTs and drug molecules, PDA shell in the meanwhile, can significantly improve biocompatibility of metal ions as well as drug loading efficiency [59,60]. Mn-based metal nanoparticles have been widely explored as candidates for magnetic resonance imaging (MRI)-guided chemical therapy agents while they frequently suffered from low relaxation rate [61]. Benefiting from surface coating with PDA, Mn-based nanoparticles such as Mn_3O_4, $MnCO_3$, MnCoO, core@shell nanocomposites obtained enhanced longitudinal relaxation rate as well as high photothermal conversion efficiency and remarkable drug loading capability [62–65]. In the meantime, combinational photothermal therapy and immunotherapy application of PDA-coated Al_2O_3 nanoparticles, co-administrated with cytosine-guanine (CpG), was inspired by the practice of aluminum compounds treatment as the immune adjuvants in human vaccines and enabled by excellent biocompatibility from PDA shell coating [66]. Biodegradable ZnO nanoparticles has good antibacterial activity but obvious cytotoxicity. By coated with PDA shell which was covalent immobilized with RGDC peptide, the biocompatibility of ZnO nanorods was significantly improved through the radical scavenging of PDA and the chelation between PDA and Zn^{2+} [67,68]. In terms of Bi_2Se_3 two-layer nanoplates@PDA/doxorubicin (DOX)/human serum albumin (HSA), the PDA shell improved the biocompatibility and photothermal properties of this nanoagent and HSA layer could be coated on the PDA shell for drug loading and circulatory half-life prolonging [69]. Similarly, coating with PDA shell endowed MoS_2 core with enhanced photothermal conversion efficiency and could further immobilize with other active molecules to gain multifunction [70].

2.1.1.2. • Metallic elements free. As for nonmetallic cores, mesoporous silica nanoparticles (MSNs) are optimistic drug carriers thanks to their distinctive mesoporous structure, decent biocompatibility, chemical stability, and compelling drug release competence [71]. PDA shell has been used as pH-responsive "gate keeper" to block the pores of MSNs and regulate the encapsulation and release of cationic

amphiphilic drug molecules (such as DOX and paclitaxel, etc.) which were previously loaded in the mesoporous [42,72,73]. Based on this, Cheng et al. [74] anchored functional ligands d-a-tocopheryl polyethylene glycol 1000 succinate (TPGS) on PDA shell to overcome multidrug resistance in chemical therapy. Other silica-based nanoparticles such as solid SiO_2 [75], tubular mesoporous silica (SBA-15) [76] were investigated as the inner cores coated with PDA for drug delivery as well.

Compared with graphene, graphene oxide (GO) shows better water dispersity but lower conductivity [77]. Fortunately, the generation of PDA coating on the surfaces of GO core is synchronized with the reduction of GO, as a result, forming reduced GO (RGO)@PDA nanoparticles to improve the conductivity, dispersity and bioactivity of GO [44,78]. In Shervedani's work, the PDA shell was reported to stabilize and protect RGO, while further acted as the anchor where bovine serum albumin (BSA) biopolymer could be grafted onto it through catechol chemistry and formed a RGO-PDA-BSA system [79]. Carboxyl graphene (CG) nanosheet could be coated with PDA as well to load free-radical initiator for phototherapy [80].

Hydroxyapatite (HAp) is extensively utilized for tissue regeneration because of its impact on cell behaviors, adhesion, proliferation and differentiation. Yet, HAp nanoparticles or wear debris from its coating can induce inflammation so far as to hinder the growth of osteoblasts [81]. PDA modification shed light on overcoming the limitations of HAp-based nanomaterials in tissue repair for improving their biocompatibility and enhancing the osteogenic differentiation ability by grafting bioactive peptide or protein, for instance, bone morphogenetic protein-2 (BMP-2) [82].

2.1.2. Organic core

When it comes to organic core, coating of poly (d, l-lactic-co-glycolic acid) (PLGA)-based nanoparticles with PDA shell has gained some attentions for overcoming the drawbacks of PLGA including weak hydrophilicity, poor cell adhesion and cytotoxicity. In addition to solve these problems, PDA coating can endow the organic cores with other functions. By means of immobilizing hepatitis B surface antigen (HbsAg) as well as immunoreaction-activating ligands, PLGA@PDA nanoparticles could simulate both the morphology and the function of pathogen, endowing the PLGA core immune-stimulation properties [83]. Another research team fabricated core@shell nanoparticles with hierarchically patterned organic cores (Fig. 3) [84]. They combined the amphiphilic co-polymer P (MEO_2MA-co-OEGMA-co-DMAEMA)-b-PLGA with hydrophilic core and hydrophobic inner layer as the building block which encapsulated drugs and absorbed small interfering RNAs. The drug loading building blocks were finally functionalized with PDA shell.

2.1.3. Metal–organic (MOF) core

Besides organic and inorganic cores, PDA-coated metal–organic nanoparticles (MOF NPs) were also reported. Lately, encapsulating various bioactive molecules in MOFs material opens up a novel avenue to acquire smart drug delivery [85,86]. However, diverse shortcomings such as cytotoxicity and unproper degradability rate still exist. Therefore, coating MOFs with PDA shell, for example, Mn-IR825@PDA–PEG [87], H-ZIF-8/PDA [88] and MIL-100@HA/PDA [89] is of great significance (Fig. 4). Wu et al. [90] proposed self-assembly zeolitic imidazolate frameworks (ZIFs) coated with PDA-PCM where DOX was encapsulated in pores of ZIF-8 for thermo-chemotherapy against cancer. Not only was the biocompatibility of ZIFs greatly improved by PDA coating, but the degradability was subtly regulated as well. Meanwhile, PDA exploited photothermal transfer activity for realizing near-infrared light (NIR) controlled drug release.

2.1.4. Drug self-assembly core

There are certain kinds of drugs who have the ability to get self-assembled. These drug self-assembly cores, for instance, DOX nanoparticles [91], paclitaxel (PTX) nanoparticles [92], and tanshinone IIA nanoparticles [93] can be coated with PDA to prolong the blood circulation time as well as keep the cargo from preleakage (Fig. 5). More importantly, the thiolate and quinone groups on PDA could chemically crosslinked with –SH or $–NH_2$ terminated molecules to form hydrogel meanwhile the core@shell drug self-assembly nanoparticles could be conveniently entrapped in the hydrogel to enhance its mechanical property [93].

To better demonstrate and compare the characters of various PDA core@shell nanoparticles discussed in ***2.1.1–2.1.4***, we further summarize the representative PDA core@shell nanoparticles and their advantages in Table 2.

2.2. PDA hollow nanoparticles

PDA hollow nanoparticles are interesting hollow assemblies using as drug carriers which are typically assembled via the PDA coating on various templates followed by the exclusion of the sacrificial core. The

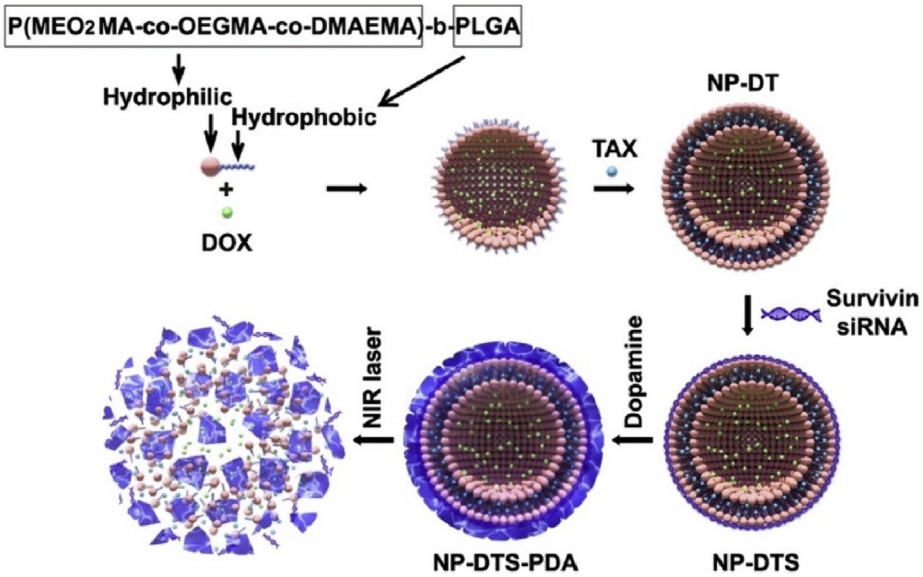

Fig. 3. Schematic illustration of the synthesis of PDA-coated organic nanoparticles, NP-DTS-PDA. Reproduced from Ref. [84], Biomaterials.

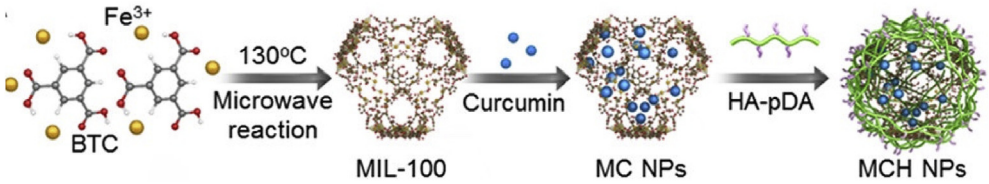

Fig. 4. Schematic illustration of the preparation procedure of PDA-coated metal–organic nanoparticles (MOF NPs), MIL-100@HA/PDA. Reprinted with permission from Ref. [89], ACS Applied Materials & Interfaces. Copyright (2018) American Chemical Society.

typical stepwise processes of fabricating PDA hollow nanoparticles are as follows [95]. Firstly, template nanoparticles should be synthesized for the hollow nanostructure. Secondly, the template nanoparticles are immersed into a dopamine-containing Tris buffer at pH 8.5 for enough time to obtain the PDA coating. Thirdly, etching process is carried out to remove the core from the core@PDA nanoparticles. For instance, PDA/mesoporous calcium phosphate (PDA/mCaP)-coated poly (acrylic acid) hollow Janus nanoparticles (H-JNPs): PEG–ICG–PDA/mCaP H-JNPs with image-guided chemo-photothermal capabilities could be proposed [96]. The PDA region could be utilized for secondary functional modification for imaging while the mesoporous cavity could accommodate drugs (Fig. 6).

Those template-based PDA hollow nanoparticles require a chemical or physical treatment to remove the core which might be a limitation for bioactive cargo loading. The very first attempt to manufacture template-free PDA hollow nanoparticles was carried out by Yeroslavsky et al. [97] in 2013. They chased for a distinctive strategy to construct PDA hollow nanoparticles via engaging a sonochemical approach using a two-phase system including n-dodecane or canola oil as well as a dopamine-containing Tris buffer. Water-insoluble compounds could be encapsulated in the hollow nanoparticles for drug loading.

2.3. PDA co-assembly nanoparticles

In addition to PDA core@shell nanoparticles prepared via coating PDA onto the inner core, and the PDA hollow nanoparticles regularly obtained by removing the core of PDA-coated nanoparticles, there are another kind of PDA-modified nanoparticles where PDA plays a role in the assembly of the "building block" of the nanostructure by bonding with another bioactive component other than coating on the surface.

The component that bonded with PDA to form "building block" varies from drug itself, inorganic compounds, proteins to MOF. For instance, PDA can be accommodated in the pores of MOF and further gained PEGylation and RGD targeting modification for multifunctional theranostic purpose [98]. Moreover, PDA can not only chemically bond with DOX to obtain PDA−DOX conjugate nanoparticles (PDCNs) [99], but also link with alginate to form PEGylated manganese-chelated nanogels [100]. Hybrid $CaCO_3$−PDA hollow nanoparticles which are furthered objected to surface modification with lipid bilayers, Ce6 (chlorin e6) @$CaCO_3$−PDA−PEG hollow nanoparticles was carried out by Dong et al. [101]. PDA skeleton could chelate with metal ions for imaging as well as quench the photosensitivity of the photosensitizer and make it reactivated under reduced pH.

In Liu's work, the concept of aggressive "man-made red blood cells" was practiced as PDA-hemoglobin (Hb) hybrid nanoparticles formed by noncovalent bonding with PDA and Hb [102]. Such "man-made red blood cells" consisted of RBC membrane encapsulating PDA-Hb hybrid nanoparticles loading methylene blue. PDA was supposed to function as antioxidant to protect Hb from oxidation and the carrier for other biomolecules loading (Fig. 7).

2.4. Drug loading strategies in PDA-modified nanoparticles

Owing to the distinctive biomedical properties, PDA surface modification offers the possibility of loading various "drugs" on nanoparticles. It needs to be mentioned here that the word "drugs" we use here is a generalized concept which refers to the diverse functional molecules including chemotherapeutics, antibiotics, metal ions, fluorochrome, targeting ligands, antibodies, cytokines and other bioactive peptides or proteins anchored in the nanoparticles [103]. The as fabricated drug system consisting of the nanoparticles, the PDA modification and the loading "drugs" possess multiple functions such as targeting, imaging, chemical treatment (CT), photodynamic therapy (PDT), photothermal therapy (PTT) and tissue repair [104], etc., as summarized in Table 3.

There are primary five strategies for drug loading (Fig. 8):

(1) The first one is to anchor the drugs onto the surface of the PDA-modified nanoparticles through physical adsorption (van der Wool's force or hydrogen bond) or chemical bonding (Michael addition or Schiff base reaction) [106,110]. This surface anchoring strategy is a classical method for drug loading in PDA modified core@shell nanoparticles [48,107,108].
(2) The second strategy is embedding and imprinting the drugs in the matrix either via physical adsorption or chemical bonding [119]. This matrix imprinting strategy can be utilized in multi-layer PDA-modified nanoparticles.
(3) The third approach is encapsulating the drugs in the PDA hollow nanoparticles or load them in the mesoporous of MSN or MOF where PDA is utilized as the "gate keeper" [120,121].
(4) The fourth one is through the formation of drug-PDA conjugates via chemical linking [122].
(5) Lastly, some drugs, for example, DOX [91] and paclitaxel (PTX) [92] have the ability to get self-assembled. Thus, these drug self-assembly nanoparticles can be coated with PDA to elongate the blood circulation time as well as prevent the preleakage of the cargo.

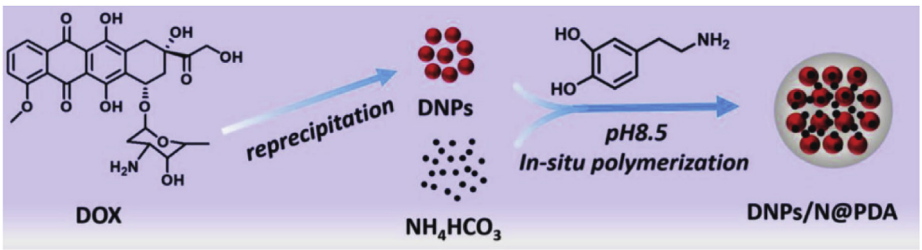

Fig. 5. Schematic illustration of the manufacture of PDA-coated drug self-assembly nanoparticles, DNPs/N@PDA. Reproduced from Ref. [91], Advanced Science.

Table 2
Summary of advantages of PDA core@shell nanoparticles with various cores.

Types of the core	Representative nanoparticles	Advantages of PDA modification	Ref.
Metal core	Au@PDA	Direct the growth of Au nanopetals Surface passivation Photothermal stability Improve the biocompatibility	[41,45,46]
	Fe_2O_3@PDA Fe_3O_4@PDA	Anchor bioactive molecules Secondary modification Photothermal conversion	[52,53]
	TiO_2 NT@PDA	Improve the biocompatibility Enhance drug loading efficiency	[59,60]
	Mn_3O_4@PDA $MnCO_3$@PDA	Improve the relaxation rate Enhance drug loading efficiency	[62–65]
	ZnO@PDA	Improve the biocompatibility	[67,68]
Nonmetal core	MSN@PDA	pH-responsive “gate keeper”	[42,72,73]
	RGO@PDA	Improve conductivity Enhance bioactivity	[44,78]
	HAp@PDA	Improve biocompatibility Enhance bioactivity	[81,82]
Organic core	PLGA@PDA	Improve biocompatibility Enhance hydrophilicity	[83]
	BSA@PDA	Enhance drug loading efficiency	[94]
MOF core	MIL-100@PDA	Improve the biocompatibility	[88–90]
	ZIF-8@PDA	Tune the biodegradability	
Drug self-assembly core	DOX@PDA PTX@Au@PDA/DOX TIIA@PDA	Prolong the blood circulation time pH-responsive “gate keeper”	[91–93]

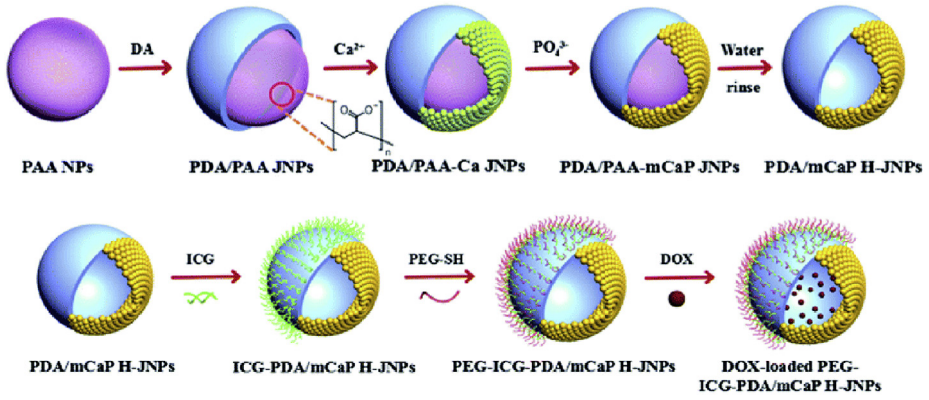

Fig. 6. Schematic illustration of the synthesis of PDA hollow nanoparticles, template-based PEG–ICG–PDA/mCaP H-JNPs. Reproduced from Ref. [96], Chemical Science.

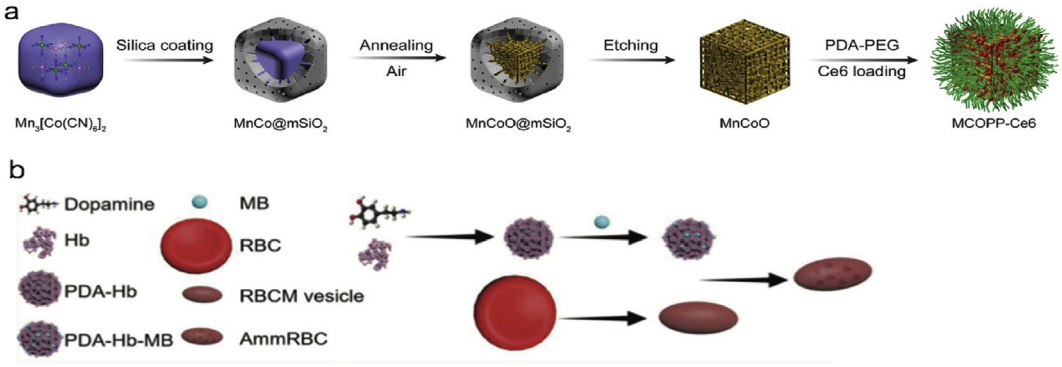

Fig. 7. Schematic illustration of the synthesis of PDA co-assembly nanoparticles, (a) (MCP)MOF/PDA-PEG-RGD, (b) PDA-hemoglobin (Hb) hybrid nanoparticles; Reproduced from Ref. [98], Advanced Science; and [102], Advanced Materials.

3. Roles of PDA in the modified nanoparticle drug carriers

3.1. Improving hydrophilicity

The surface characteristics of biomaterials determine the biological response of the materials [123]. It has become a consensus that PDA surface modification is an efficient way of hydrophilicity improving with no need for further functionalization. The contact angle of PDA coating on various substrates is in the range of 40–60° [20]. With the outstanding hydrophilic property, PDA surface modification offers

Table 3
Multifunction of the PDA-modified nanoparticle drug carrier working as a drug system.

Function of the drug system	Contributing portion	Classes of the portion	Representative agents	Reference
Targeting	Nanoparticle	Nanoparticle	Fe_3O_4 nanoparticles	[54]
	Loading "drug"	Ligand	RGD peptides	[48]
			Antibodies	[105,106]
			Folic acid	[37,48,65,107,108]
			TPP	[54]
Imaging	Nanoparticle	Nanoparticle	Au nanostructure	[50]
	Loading "drug"	Radionuclide	^{125}I	[48]
		Metal ion	Cu^{2+}	[50]
			Mn^{2+}	[63]
			Bi_2Se_3	[69]
		Fluorochrome	Cy5-SE	[109]
		Photosensitizer	Indocyanine green	[32]
Chemical treatment (CT)	Nanoparticle	Nanoparticle	Au nanostructure	[82]
	Loading "drug"	Chemotherapeutics	DOX	[54,56,69,74,96,99]
			Cisplatin	[48,53]
		Metal ion	Cu^{2+}	[50]
			Ag^{+}	[70,76,78,109]
		Antibiotic	Daptomycin	[105]
			Doxycycline	[44]
		Gas molecular	NO	[52]
		Protein	Lysozyme	[57]
Photodynamic therapy (PDT)	Loading "drug"	Photosensitizer	Ce6	[56]
		Organic compound	Methylene blue	[102]
Photothermal therapy (PTT)	Nanoparticle	Nanoparticle	Au nanostructure	[109,110]
		Nanosheet	Black phosphorus	[111]
	Loading "drug"	Organic compound	2-phenylethynesulfonamide	[112]
	PDA modification	Organic compound	PDA	[82,105,110]
Immunotherapy	Loading "drug"	Antigen	HbsAg	[83]
		Ligand	CpG	[66,83]
Gene therapy	Loading "drug"	Nucleic acid	small interfering RNA	[84,111]
			hairpin DNA	[68]
Bone regeneration	Nanoparticle	Nanoparticle	HAp	[82,113]
	Loading "drug"	Protein	BMP-2	[94,114]
	PDA modification	Organic compound	PDA	[44]
Anti-inflammatory/Antioxidant	Loading "drug"	Glucocorticoid	DEX	[59]
		Flavonoids	Tanshinone IIA	[93]
			Hesperetin	[115]
	PDA modification	Organic compound	PDA	[116–118]

DEX, Dexamethasone sodium phosphate; O, Nitric oxide; ICG, indocyanine green.

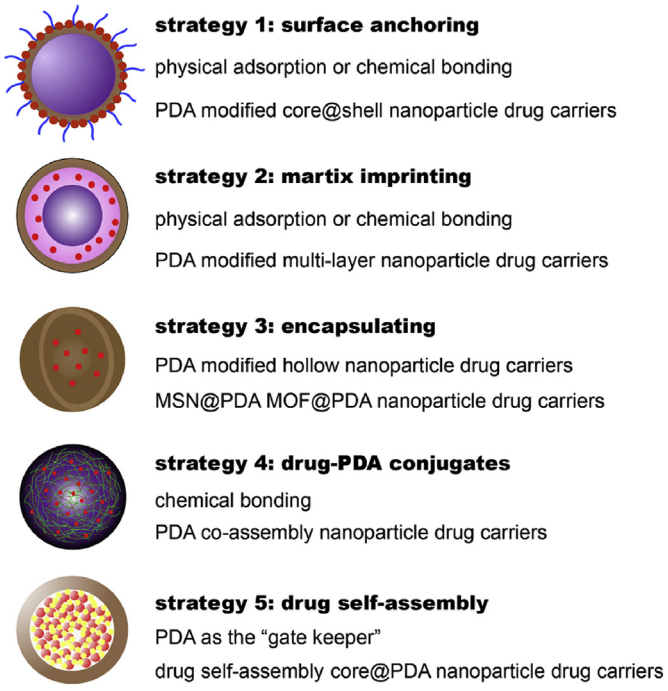

Fig. 8. Schematic illustration of the five strategies for drug loading.

benefitting interface for both protein-biomaterial and cell-biomaterial interaction. When the PDA-modified nanoparticles come in contact with the physiological environment, their surface with appropriate hydrophilicity provide ideal interface for the adsorption of adhesive proteins, thus promoting cell adhesion, which is of great importance in cell proliferation, migration and differentiation [124,125]. As the accumulation of protein and cells adhered, a favorable microenvironment for targeted drug delivery can be formed.

3.2. Enhancing biocompatibility

It is of great significance to ensure excellent biocompatibility of the materials for biomedical application. As a nature-inspired biomaterial, PDA surface modification can increase the biocompatibility of the materials effectively. MTT assay testing the cytotoxicity of the PDA-modified nanoparticles in various type of cells, such as tumor cell lines (A549 [126], HeLa [127] and 4T1 [128], etc.) and normal cell lines (RLE-6TN [126], MC3T3-E1 [129] and MG-63 [130], etc.) has proved remarkable biocompatibility of PDA surface modification.

3.3. Tuning biodegradation

Proper biodegradability to realize the gradual disassembly of the nanoparticle drug carriers when the drug delivery is accomplished is highly required, since rapid disassembly products of the nanocarriers may be toxic to cells and organs, while nanoparticles which degrade too slow can lead to long-lasting accumulation of the nanoparticles in normal tissue. Plenty of researches have verified that modification of

Table 4
Diverse PDA-modified nanoparticle drug systems and their biomedical application.

Classification		Drug system	"Drugs"	Loading strategy	Multifunction	Application	Ref.
PDA core@shell nanoparticles	Inorganic core	AuNR@PDA − PEG − DOX	DOX	Adsorption on surface	Imaging, CT, PTT	Theranostics	[110]
		AuNR@PDA-Ag^+-GCS	Cy5-SE	Linking on surface	Imaging, CT, PTT	Theranostics	[109]
			Ag^+	Adsorption on surface			
		Fe_2O_3@PDA-HP-NO	NO	Linking on surface	Targeting, CT	Antibacterial	[52]
		Fe_3O_4@m-SiO_2@PDA@HSA	DOX	Encapsulate in mesopores	Targeting, CT, PDT	Cancer therapy	[56]
			Ce6	Adsorption in matrix			
		Fe_3O_4 CNCs@PDA/DOX-TPP-PEG	DOX	Adsorption on surface	Targeting, CT, PTT	Cancer therapy	[54]
			TPP	Linking on surface			
		TiO_2 NT@PDA-Zn-Ag	Zn nanoparticles	Adsorption on surface	CT	Antibacterial	[60]
		ZnO@PDA-hpDNA	Hairpin DNA	Adsorption on surface	Gene therapy	Cancer therapy	[68]
		Bi_2Se_3@PDA/DOX/HSA	DOX	Adsorption in matrix	Imaging, CT, PTT	Theranostics	[69]
		FA-Mn_3O_4@PDA@PEG-DOX	Folic acid	Linking on surface	Imaging, CT, PTT	Theranostics	[65]
			DOX	Adsorption on surface			
		MoS_2@PDA-Ag	Ag nanoparticles	Adsorption on surface	CT, PTT	Antibacterial	[70]
		DOX–siRNA-BP-R-D@PDA-PEG-Apt	P-gp siRNA	Adsorption on surface	CT, PTT	Cancer therapy	[111]
			DOX	Adsorption on surface			
		MSN/DOX@PDA-TPGS	DOX	Encapsulate in mesopores	CT	Cancer therapy	[74]
			TPGS	Linking on surface			
		SBA-15@PDA-Ag	Ag nanoparticles	Adsorption on surface	CT	Antibacterial	[76]
		RGO nanosheet@Ag-PDA	Ag nanoparticles	Adsorption on surface	CT	Antibacterial	[78]
		HAp@PDA-BMP-2	BMP-2	Adsorption on surface	Bone regeneration	Tissue repair	[114]
	organic core	NP-DTS-PDA	DOX	Encapsulate in core	CT, PTT, gene therapy	Cancer therapy	[84]
			PTX siRNA	Adsorption in matrix			
				Linking in core			
		PLGA@PDA-HBsAg-CpG	HBsAg	Linking on surface	Immunotherapy	Vaccine adjuvants	[83]
			CpG	Linking on surface			
		BSA/BMP-2@PDA	BMP-2	Encapsulate in core	Bone regeneration	Tissue repair	[94]
	MOF core	PDA-PCM@ZIF-8/DOX	DOX	Encapsulate in pores	CT, PTT	Cancer therapy	[90]
		MIL-100@HA/PDA	Curcumin	Encapsulate in pores	Imaging, CT, PTT	Theranostics	[89]
	drug self-assembly core	DNPs/N@PDA	DOX	Self-assembly as core	CT, PTT	Cancer therapy	[91]
		BV/PTX@Au@PDA/DOX	DOX	Adsorption on surface	CT, PTT	Cancer therapy	[92]
			PTX	Self-assembly as core			
		TIIA@PDA	Tanshinone IIA	Self-assembly as core	Anti-inflammatory, antioxidant	Prevention of inflammation	[93]
PDA hollow nanoparticles	template-based	PDA-NO	NO	Linking on surface	CT	Antibacterial	[95]
		PEG–ICG–PDA/mCaP H-JNPs	ICG	Linking on surface	Imaging, CT, PTT	Theranostics	[96]
			DOX	Encapsulate in mesopores			
	template-free	PDA-Cu	Cu^{2+} ions	Chelating on surface	CT	Antibacterial	[97]
PDA co-assembly nanoparticles		(MCP)MOF/PDA-PEG-RGD	RGD peptides	Linking on surface	Imaging, PTT	Theranostics	[98]
		Mn^{2+}/Ce6@$CaCO_3$ − PDA − PEG nanocapsules	Mn^{2+}	Chelating on surface	Imaging, PDT	Theranostics	[101]
			Ce6	Adsorption on surface			
		PDA/DOX conjugate NPs (PDCNs)	DOX	Linking as building block	CT; PTT	Cancer therapy	[99]
		PDA/Hb-MB	Hb	Adsorption as building block	PDT	Cancer therapy	[102]
			Methylene blue	Adsorption on surface			

P-gp siRNA, permeability glycoprotein small interfering RNA; PTX, paclitaxel.

PDA can be used to regular the degradation rate of nanoparticle drug carriers, for instance, MOF, HAp nanoparticles and magnesium-based biomaterials [90,114,131].

3.4. Anchoring bioactive molecules

PDA is rich in catechol/quinone moieties as well as imine, which endows PDA surface modification with the capability to anchor drugs, peptides or proteins onto the nanoparticles either by physical bonding (π-π stacking or hydrogen bond) or chemical bonding (Michael addition or Schiff base reactions) [20,28]. Moreover, by means of oxidization of the catechol moieties into the quinone form, metal nanoparticles such as Au, Ag, Pt can be deposited on the surface of PDA [132]. Other metal ions including Cu^{2+}, Fe^{3+}, Mn^{2+}, Zn^{2+} can chelate with PDA by reacting with the catechol groups [133,134].

3.5. Secondary modification for drug delivery

As PDA plays the part as the first modification, other compounds which do not directly work as bioactive coating or grafting can be adsorbed (π-π stacking or hydrogen bond) or linked (Michael addition or Schiff base reactions) onto PDA, that is what we described as “secondary modification”. The secondary modification is usually desired for loading drugs, improving the physicochemical property, or adjusting the dynamics of the nanosystem. The typical secondary modification are thiol or amino group-containing compounds which tend to react with PDA via chemical linking, for example, PEG-SH or PEG-NH_2 utilized as second modification to prolong the circulation half-life of the nanoparticles [135]. HSA, which can be physically absorbed onto PDA, is another practical second modification for not only loading hydrophobic drugs but improving biocompatibility and prolonging circulatory half-life as well [56,69].

3.6. Photothermal conversion

Thanks to the similar structure with natural eumelanin, PDA can provide a high photothermal conversion efficiency (40%), which turns out to be an outstanding property for not only PTT, but also for photothermal conversion to generate thermal reaction shift of phase transformation materials aiming at delivering drugs in a near-infrared light controlled manner [136].

3.7. On-demand drug release

PDA modification makes the dream of on-demand drug delivery come true. Due to the particular drug loading pattern of PDA discussed in **3.4** and **3.5**, the bonding between drugs and PDA tends to weaken in the acidic and high glutathione (GSH) condition. Therefore, PDA is capable of anchoring drugs at neutral pH (usually in normal tissue), releasing them at lower pH (usually in tumor cite or inflammatory area), and resulting drug releasing in a pH and GSH responsive manner [53,137–140]. In addition, the photothermal response of PDA can be used as NIR controlled drug delivery. Therefore, PDA-modified nanocarriers achieve pH, GSH and NIR triggered drug release profile.

3.8. Scavenging reactive oxygen species (ROS)

As naturally occurring biopolymers, PDA is rich in reductive functional groups consisting of catechol and imine. As a result, PDA shows the prominent capacities in scavenging various radical species such as ROS as well as reducing ROS-induced inflammation [116,141,142]. Therefore, PDA modified nanoparticles can be a promising candidate as a radical scavenger for anti-inflammatory treatment [118].

4. Applications of PDA-modified nanoparticle drug carriers

One can notice that modification those ordinarily used nanoparticles with PDA followed by various drug loading can transform them into novel drug systems with multifunction such as targeting, imaging, chemical treatment (CT), photodynamic therapy (PDT), photothermal therapy (PTT), bone regeneration and anti-inflammatory. The as-fabricated PDA-modified multifunctional nanoparticle drug systems have opened a fresh door to the application of cancer therapy, antibacterial therapy, prevention of oxidative stress and inflammation, theranostics, vaccine delivery and adjuvant, tissue repair and implant materials. Diverse PDA-modified nanoparticles working as drug carriers and their biomedical applications are summarized in Table 4.

4.1. Cancer therapy

As we all know, cancer has become a major threat to human health. In order to fight against cancer, a great number of therapeutic drug loading nanoparticles have been developed for achieving CT, PDT and PTT [143].

It is worth noting that the particular microenvironment of tumor including enhanced vascular permeability, lower pH, increased GSH level and extreme hypoxia have great impact on drug loading nanoparticles-based cancer therapy. Thanks to the remarkable properties of PDA, the coating thickness can be modulated to obtain proper size of the nanoparticles for improved permeability and retention (EPR) effect; the loading efficiency of chemotherapeutic agents, especially those hydrophobic drugs can be significantly developed for enhanced CT effect; various functional molecules like targeting ligand can be anchored for multifunctional combined tumor killing. Moreover, PDA can also prevent the preleakage of the drugs as well as achieve pH, GSH level and NIR responsive release of the cargo. Additional functions such as strong photothermal conversion capacity, ROS scavenging facility and fluorescence quenching ability can also be realized due to the intrinsic properties of PDA. Therefore, the study of PDA-modified nanoparticle anticancer drug carriers has gained much interest of many researchers.

4.1.1. Monotherapy

Although a great number of nanoparticle drug systems have been explored for CT, PDT and PTT, each of them has its own drawbacks. Chemotherapy uses one or more chemotherapeutic agents to kill tumor cells while most of the chemotherapeutics are lacking in selectivity of the tumor cite, resulting in serious harms to the normal tissues. PDT takes the advantage of photosensitizer molecules which transform $^3O_2$ to $^1O_2$ and ROS for killing cancer cells in the context of site-selective exposure of a particular light wavelength. However, the oxygen-deficient environment of tumor hinders the effect of PDT that requires oxygen to realize photodynamic transduction. What's more, the phototoxicity and the photodecomposition under long-term light exposure during PDT require to be solved. PTT makes efforts to use electromagnetic radiation for the treatment of cancer in which a photosensitizer is excited with specific band light, resulting in releasing heat to ablate the cancer cells [69]. There are two main shortcomings of PTT. For one thing, the requirement for direct access to the light irradiation limits its usage to fight against advanced metastatic tumors [45]; for another, the heat produced by NIR irradiation shows dissatisfactory soft tissue penetration, leading to failure of avoiding tumor recurrence [48]. For making up for the disadvantages of each therapy, monotherapy based on PDA-modified drug loading nanosystem specific to the tumor microenvironment has been proved to be a promising candidate.

In order to solve the problem of lacking in selectivity of the tumor cite, tissue-targeted chemotherapy has been accomplished through the targeting ligands such as folic acid (FA) anchoring on PDA via Michael addition or Schiff base reactions [48,65,107,108]. Moreover, due to the specific drug loading pattern of PDA, the bonding between drugs and

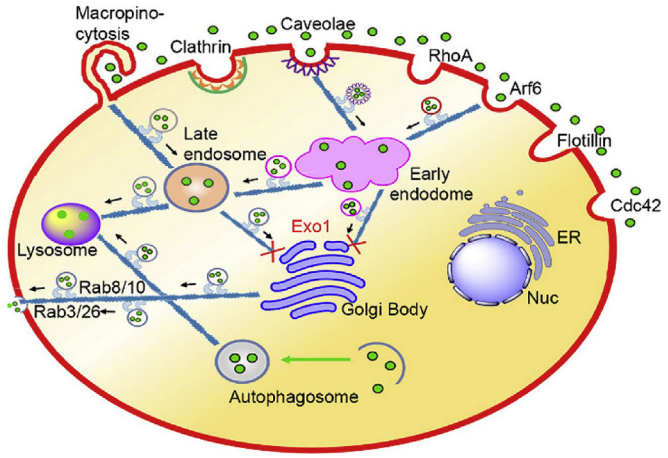

Fig. 9. Schematic illustration of the intracellular trafficking network of PDNPs. Reprinted with permission from Ref. [73], Nano Letters. Copyright (2017) American Chemical Society.

PDA tends to weaken in the acidic and high GSH microenvironment of tumor, resulting drug releasing in a pH and GSH responsive manner, thus achieving tissue-targeted controlled drug release profile [53]. There are researchers focusing on targeting cell organelle in order to achieve more effective tumor killing. Lysosomes are dynamic organelles containing a variety of enzymes which play an important role in the cell death pathways, making them prominent pharmacological target for killing cancer cells. An innovative chemotherapy strategy was proposed by Ding et al. [73] by means of PTX-loaded MSNs with PDA coating. Making use of the PDA-mediated internalization of nanoparticles, the MSNs@PDA nanocarriers were uptake by HeLa cells through energy-dependent endocytosis. The subsequent peeling of PDA under the circumstance of acid environment in lysosome induced the targeted release of PTX, thus, killing cancer cells via lysosome impairment mediated pathways. Furthermore, by means of pretreating HeLa cells with 2-(4-Fluorobenzoylamino)-benzoic acid methyl ester (Exo1), the exocytosis of PDA-coated MSNs was basically inhibited, thus the drug concentrations were significantly increased within cancer cells (Fig. 9).

To deal with the oxygen deficiency in tumor cite for PDT, oxygen should be delivered by the nanoparticles for providing sufficient local oxygen concentration to realize photodynamic transduction. Due to the outstanding drug loading ability as well as the antioxidative property of PDA, Liu et al. [102] created a man-made red blood cell (AmmRBC) consisted of RBC membrane encapsulating PDA-hemoglobin (Hb) hybrid nanoparticles loading methylene blue (Hb/PDA-MB) via π-π stacking, where PDA could protect the loading oxygen from auto-oxidation. Such universal AmmRBCs which tended to accumulate in tumor site and boost $^1O_2$ generation, could serve as an oxygen-self-supplied magnificent PDT system.

4.1.2. Chemo-photothermal combined therapy

Aimed at enhancing the tumor killing efficacy, chemotherapy can be combined with photothermal therapy (CT-PTT) to realize synergistic or combined effects. Guaranteeing the proper thickness of PDA coating for tumor tissue accumulation via the enhanced EPR effect, PDA-modified chemotherapeutics loading nanoparticles which introduced photothermal conversion agents together with the inherent photothermal transformation capability of PDA to increase the photothermal therapeutic efficiency have been developed.

Gold nanoparticles have gained much interest as agents for photothermal therapy. Spiky gold nanoparticles (SGNPs) coated with PDA were proposed by Nam et al. [45]. Serving as a surface passivation layer, PDA coating have proven to overcome the limitation of instability of SGNPs. After delivery of the nanoparticles in combination with DOX, this “in situ cancer vaccination” based nanoplatform was capable of triggering robust anti-tumor immunity, therefore eliminating local as well as untreated and disseminated tumors.

Coming up with a novel design strategy of nanocarriers, Li et al. [91] fabricated a “nanobomb” for in situ on-demand CT-PTT. This delicate “nanobomb” consisted of DOX co-assembly with NH_4HCO_3 nanoparticles. After moving to the tumor cite, the PDA shell was fragmented by carbon dioxide and ammonia gases generated by the decomposition of NH_4HCO_3 under NIR irradiation. Simultaneously, DOX were released in a “bomb-like” style because of the photothermal conversion efficiency of PDA, thus presenting a CT-PTT synergistic therapy of cancer.

Additionally, some researchers have made combination of CT-PTT and gene therapy [84,111,144]. Zeng et al. [111] used PDA coating to not only protect the black phosphorus nanosheet from air and water but endow the nanoplatform with photothermal therapy ability and NIR-triggered, pH-responsive properties as well. NH_2-PEG-aptamers (Apt), permeability glycoprotein (P-gp) small interfering RNA (siRNA) and DOX were absorbed on the surface playing the role of targeting, gene therapy and chemotherapy agents, respectively.

4.1.3. Chemo-photodynamic combined therapy

Several researchers committed themselves to chemo-photodynamic combined therapy by loading chemotherapeutic drugs and immobilization photosensitizer molecules with the help of PDA. Fe_3O_4@$mSiO_2$(DOX)@HSA (Ce6) nanoparticles was built based on the magnetic targeting ability of the Fe_3O_4 core and the PDT effect of the photosensitizer Ce6 [56]. DOX were loaded into mesoporous silica blocked by PDA coating while Ce6 was embedded in the HSA bonded with PDA. This novel nanoplatform showed a synergistic ablation of tumor cells.

4.2. Antibacterial

Nowadays, the growing emergence of bacterial infection, which usually caused by the formation of biofilms, has become a serious threat to public health. The biofilms are formed by the adhered bacteria aggregating in a hydrated matrix of extracellular polymeric substances including polysaccharides and proteins, and they act as sophisticated shelter for the bacterial inside via blocking the penetration of antibiotics and preventing the attack of host immune system [60]. Hence, it is in abundant need to develop nanosystem with improved anti-biofilm activity for efficient treatment of bacterial infection.

Antibacterial treatment requires the ablation of microbes and biofilms in the case of minimizing damage to the cells and tissues as well as reducing the drug resistance of the bacteria. However, a spectrum of current antibacterial materials fails to meet all these desires, especially when dealing with the biofilms [57]. To solve these problems, surface functionalization of the nanoparticle drug carriers and combining antibiotics treatment with physical treatment together are two considerable strategies. As a versatile insoluble biomaterial, PDA has moved into spotlight in the field of antibacterial applications not only because of its regulable drug loading and releasing abilities but also owing to PDA itself as a novel bactericide for enhancing both chemical and physical antibacterial effects [145]. One of the mechanisms of PDA antibacterial activity is that PDA can entrap the bacterial efficiently not only because of its superior absorbability but also its positive charge under the acidic condition in the bacterial infection site involving the biofilms. After entrapping the microbes, PDA would physically communicate with the surface of bacterial cells, interacting with their secreted proteins and hampering the metabolisms of bacterial for living [52]. It is worth noting that under near-irradiation light, the photothermal conversion capability endows PDA with photothermal antibacterial ability to destroy the matrix of biofilms, which can be another mechanism of antibacterial activity contributed from PDA. Moreover, by constructing a two-step shaking-assisted coating technique reported by Forooshani et al. [146], PDA couldq sustainedly generate hydrogen

peroxide (H_2O_2) and achieve excellent antimicrobial effect. This finding helped to pinpoint a potential new strategy for PDA-modified drug loading nanoparticles in terms of antibacterial treatment.

Similar to cancer therapy, the principles of antibacterial can be divided into chemotherapy, physiotherapy, immunotherapy and combined therapy which take the advantages of chemical and physical treatment strategies together.

4.2.1. Chemical antibiosis

As is known to all, silver demonstrate great bactericidal activity mainly through ROS generating and bacterial membrane destruction. The weakness of silver nanoparticles in antibiosis is that their antibacterial activities will decline when they are accumulating. What's more, the poor biocompatibility of silver nanoparticles is another drawback, especially when delivered in high concentration. Numerous studies devoted to improving the antibacterial effect of Ag have been done. Ding et al. [60] prepared PDA-Zn-Ag on TiO_2 nanotubes. Owing to the unique structure of quinone-Zn structure, the deposited Ag nanoparticles were much uniformed scaling from 10 to 30 nm, which were beneficial for increasing the antibacterial activity. Moreover, such PDA-Zn-Ag coating on TiO_2 nanotubes presented lower cell cytotoxicity and better biocompatibility. Similarly, Jatoi et al. [147] embedded TiO_2@PDA-Ag in cellulose acetate nanofibers for improved antibacterial activities and decreased silver leaching. The antibacterial test demonstrated this CA/TiO_2/Ag nanofiber with outstanding bactericidal behaviors for 36 h and considerable bacterial growth depression for 72 h. To evaluate the antibacterial activity between different structures of Ag nanostructure, nanosilver encapsulated in mesoporous SiO_2 nanoparticles (Ag-MSN) and Ag^+ ions deposited on SiO_2@PDA nanoparticles were compared by Liu et al. [75]. It was discovered that prompt bacterial eradication was accomplished by SiO_2@PDA-Ag nanoparticles verified by bacterial growth curves and ROS assays. However, the antibacterial effect of Ag-MSN was better at advanced time point. In another study, Song et al. [76] fabricated silver-incorporated PDA coating rodlike mesoporous silica of SBA-15 in order to compare its inhibitory effect against bacterial with solid core-shell SiO_2@PDA-Ag nanoparticles. They reached a conclusion that SBA-15@PDA-Ag displayed prolonged antibacterial activities compared to SiO_2@PDA-Ag nanoparticles.

Nitric oxide (NO) is an effective bacterial biofilm eradicator capable of fighting against multidrug-resistant and biofilm-forming bacteria. Yet there are many limitations in NO donors, such as unstable and unspecific delivery of NO. It has been demonstrated that PDA helps to immobilize NO efficiently for NO donating. Adnan et al. [52] fabricated a polymer protected N-diazeniumdiolates (NONOate)-functionalized PDA-coated iron oxide nanoparticles (IONPs) where PDA conjugated P (OEGMA)-b-P (ABA) for improving the colloidal stability and NONOate was anchored by PDA as NO donor onto the IONPs. These nanoparticles were able to disperse bacterial biofilms at low NO concentrations. PDA nanocapsules can be utilized as NO carriers as well [95]. After exposing to high pressure NO (g), NO was successfully loaded on the surface of PDA nanocapsules. *In vitro* assay verified that these nanocapsules could inhibit the gram-negative bacterial efficiently together with excellent biocompatibility.

Different from common antibiotics or antibacterial metal ions, lysozyme exhibits wide spectrum antibacterial activity with great biocombatility and low drug-resistance. Loading lysozyme efficiently and ensuring the high bioactivity of released lysozyme has been the major concern of its application. Chen et al. [57] presented lysozyme-imprinted Fe_3O_4@SiO_2@PDA nanoparticles, which could realize NIR-controllable on-demand release of lysozyme in order to decompose bacterial. The mesopores in the fibrous SiO_2 made a high surface area which turned out to have a high saturation adsorption capacity of lysozyme. Owing to the photothermal conversion ability of the PDA shell, the rebinding lysozyme could be released triggered by NIR and the released lysozyme remained remarkable antibacterial ability that could break the *E. coli.* cell walls.

4.2.2. Physical antibiosis

Physical antibacterial treatments consist of photodynamic and photothermal therapy where a photosensitizer is excited with specific band light to generate reactive oxygen species or heat for killing microbes. Different from traditional chemical antibiosis, physiotherapy has less possibility to trigger drug resistance of the bacteria. But the most prominent shortcoming of physiotherapy is that it is hard to reach complete ablation of bacteria when using conservative power density of irradiation for protecting the normal cells and tissues nearby. PDA modification for loading auxiliary bioactive molecules to enhance the PTT or PDT effects can be a promising strategy.

To enhance the bactericidal effect of NIR irradiation-immediate photothermal therapy, Fe_3O_4 nanoparticles were coated with PDA to load a small molecule HSP70 inhibitor, 2-phenylethynesulfonamide (PES) [112]. Under NIR irradiation, PES was released and precisely interfered with HSP70 of the pathogens, reducing the bacterial tolerance to thermal damage. Thus, the bacterial killing efficacy of PTT could be significantly improved.

As we have discussed above, producing reactive oxygen species is largely dependent on oxygen. When it comes to the treatment of bacteria-infected wounds, some multidrug-resistant microbes are inclined to generate hypoxia microenvironment, which significantly inhibits the antibacterial efficiency of photodynamic therapy. Yu et al. [80] proposed a light-induced free radical generation nanoplatform consisted of PDA-coated carboxyl graphene loading with a free-radical initiator, AIBI and conjugating with glycol chitosan (GCS) which made this nanosystem turned positively charged in the acid microenvironment, resulting their gathering in the bacterial infection area. Under the near-infrared light irradiation, the initiator decomposed and generated alkyl radical (R•), therefore elevated oxidative stress around the area and finally targeted multidrug-resistant bacteria eradication (Fig. 10).

4.2.3. Combined antibiosis

In order to take advantage of both conventional antibiotic therapy and physiotherapy for realizing synergistic or combined antibacterial effects, a number of studies have been done for achieving the combination of chemical and physical therapies. To overcome relatively high power density and off-target effects using MoS_2 Nanosheets (NS) alone in bacteria PPT treatment, Yuwen et al. [70] prepared silver nanoparticles (AgNPs) anchored on the surface of PDA-coated MoS_2 NS. They proposed that the hyperthermia induced by NIR could disrupt the structural integrity of biofilms and permeability of bacteria membrane, thus facilitate the antibacterial effect of AgNPs. For achieving targeted chemical-physical combined antibiosis, Meeker et al. [105] proposed PDA-coated gold nanoparticles for loading of the antibiotic daptomycin and conjugating antibodies against staphylococcal protein A (aSpa) to target methicillin-resistant S. aureus, therefore creating a photoactivatable, highly selective nanodrug to obtain synergistic photothermal and chemotherapy. Similarly, Black et al. [106] reported an Au@Ag nanorods (Au@Ag NRs) system, upon irradiation, which could localize sliver releasing and plasmonic heating to bacteria cell walls and target both gram-negative and gram positive bacteria. This combined bactericidal effect was realized by PDA priming onto the Au NRs surface, along with conjugating antibodies and passivating polymers.

4.3. Prevention of oxidative stress and inflammation

A variety of factors may contribute to the development of inflammation, for instance, bacterial infection and trauma, etc. After pathogen invasion, oxidative stress occurs. The imbalance of oxidation and anti-oxidation leads to neutrophil infiltration along with the mass production of leukotriene, thrombin, ROS and other pro-inflammatory mediators, thus triggering inflammatory response. Therefore, inhibition of oxidative stress can be a promising approach to anti-inflammatory

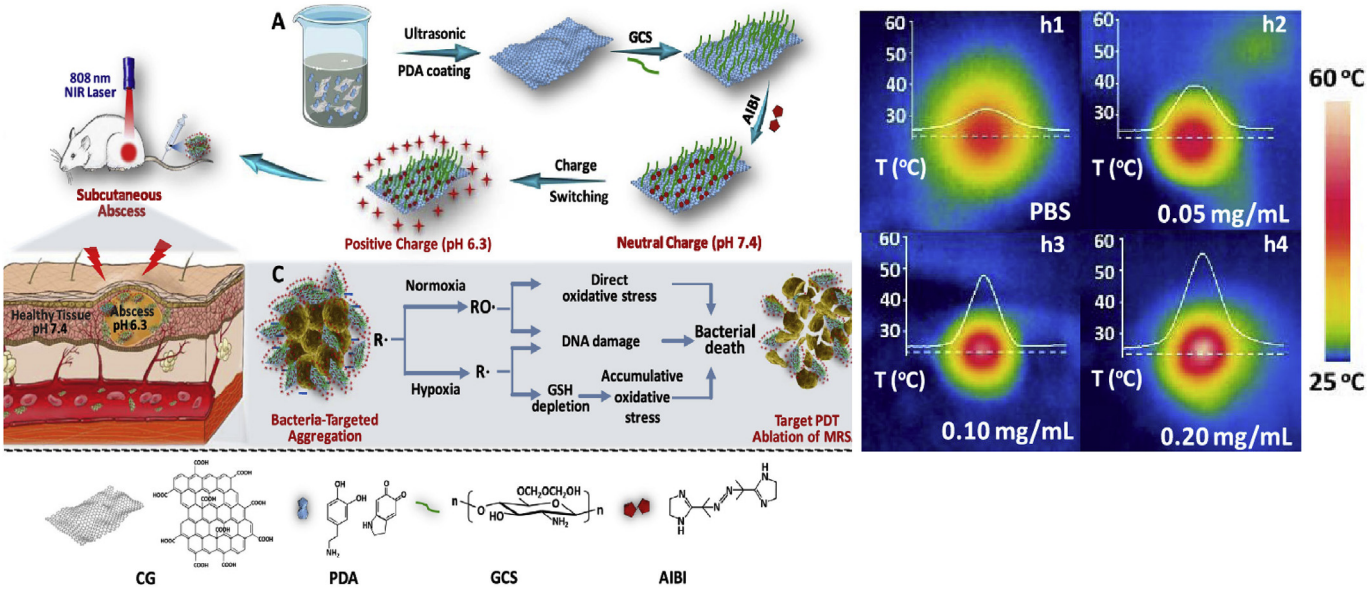

Fig. 10. Schematic illustration of AIBI-GCS-PDA@CG fabrication and the photothermal ablation of bacteria. Reprinted with permission from Ref. [80], ACS applied materials & interfaces. Copyright (2018) American Chemical Society.

treatment.

As we have mentioned before, PDA shows the prominent capacities in scavenging various radical species such as ROS for oxidative stress prevention which may ultimately suppress ROS-induced inflammation [116,141,142]. The possible mechanism of PDA mediated anti-inflammatory effect was reported by Jin et al. [117] During the inflammatory reaction, the degradation products of PDA were investigated and TLR-4-MYD88, NF-κB, and HO-1 signaling pathways were researched for revealing the role of PDA in anti-inflammatory. They demonstrated that through reducing the expression of TLR-4/MYD88 and inhibiting NF-κB signaling pathway, PDA could control the generation of ROS, repress the release of pro-inflammatory cytokines and activate the HO-1-related antioxidant signaling pathway, which might be the mechanism of PDA mediated anti-inflammatory effect.

A number of PDA-based antioxidant and anti-inflammatory nanoplatforms were simply composed of mere PDA nanoparticles and used PDA itself as the nanodrug [116,118]. When it comes to the antioxidant and anti-inflammatory application of PDA-modified nanoparticle drug carriers, a few of relative researches have been reported. A hyperbranched ROS-sensitive macromer Poly (β-amino esters) (HB-PBAEs) have been suggested as potent antioxidant biomaterials in applications of postinfracted myocardial function rebuilding. However, there are some distinct shortcomings relating to HB-PBAEs,such as low gel fraction and slow gelation rate. Meanwhile, the exploring of Tanshinone IIA (TIIA) nanoparticles as active cardioprotection, anti-oxidation, and anti-inflammation agents is impeded by their short half-life in blood and poor solubility. To address these problems altogether, Wang et al. [93] prepared and co-injected TIIA@PDA nanoparticles and HB-PBAE with crosslinking reagent thiolate-modified hyaluronic acid (HA-SH) into the infracted heart to form an in-situ hydrogel. This hydrogel brought a significant improvement in terms of increased ejection fraction and a sharp decline in infarction size. This PDA-modified nanosystem exhibited ROS-sensitive drug release profile and *in vivo* experiment showed a significant inhibition of inflammation response with a remarkable improvement of cardiac functions in terms of increased ejection fraction and a sharp decline in infarction size. Ouyang et al. [115] reported another condition of anti-inflammation for the treatment of osteoarthritis (OA). By the surface coating of PDA onto the $Gd_2(CO_3)_3$ core, hesperetin (Hes) was successfully loaded for alleviating chondrocyte apoptosis and inflammation meanwhile cartilage affinity peptide (CAP, DWRVIIPPRPSA) was grafted for cartilage targeted drug release. The biocombatility of the nanoparticle was also notably improved via the modification of PDA.

4.4. Theranostics

Theranostics, as the combination of treatment and diagnosis, requires efficient imaging guidance of therapy to monitor the targeted tissue accurately, and to detect the drug loading and release profile as well as the therapeutic efficacy [148]. A variety of imaging-based diagnostic tools, such as magnetic resonance imaging (MRI), computed tomography imaging (CT), photoacoustic imaging (PA), optical imaging and nuclear imaging can be combined with therapeutic method as theranostic platform [149]. As a versatile biomaterial for surface functionalization, PDA offers an active surface for anchoring diverse imaging agents including MRI contrast metal ions, radionuclide, photosensitizer, fluorochrome either through physical bonding (π-π stacking or hydrogen bond) or chemical bonding (Michael addition or Schiff base reactions) and prolonging their retention time. Additionally, PDA modification endows the diagnostic agents-loaded nanoparticles with improved biocompatibility, therefore reducing their side effect. Moreover, to better demonstrate various strategies of combining diagnostic tools with therapeutic methods, the typical theranostic platforms based on PDA-modified nanoparticle drug systems are summarized as Table 5.

4.4.1. Magnetic resonance imaging guided therapy

Magnetic resonance imaging (MRI) is a widespread diagnosis technique to acquire images of the body via stimulating nuclear spins through radiowaves. The past several years has observed plenty researches working on the combination of MRI with chemotherapy and spatially precise PTT or PDT because of its simplicity, noninvasiveness, high spatial resolution as well as targeting and remote-control characters.

For the purpose to combine MRI along with PTT, metallic nanocores with MRI contrast ability coated with PDA shells are exploited for secondary photothermal materials decorating, i.e. Fe_3O_4@PDA [43], $MnCO_3$@PDA [62], PDA-coated $NaYF_4$:Nd^{3+}@$NaLuF_4$ nanocomposites [150]. A novel one-pot way was designed by Wang et al. [98] to synthetize metal–organic framework (MOF)-based, PDA-modified "MOF-polydopamine-PEG-RGD hybrid nanogels" for realizing MRI guided along with photothermal therapy enhanced targeted cancer therapy.

Table 5
Summary of the typical theranostic platforms based on PDA-modified nanoparticle drug systems.

Diagnostic tool	Therapeutic method	Theranostic platform	Representative drug system	Ref.
MRI	PTT	MRI-PTT	$MnCO_3$@PDA	[62]
	PDT	MRI-PDT	Ce6@$CaCO_3$ − PDA − PEG	[101]
CT	PTT- chemotherapy	CT-PTT- chemotherapy	Bi_2Se_3@PDA/DOX/HSA	[69]
	PDT-PTT	CT-PDT-PTT	Au@PDA	[41]
PA	PTT	PA-PTT	Fe_3O_4@PDA	[43]
Optical imaging	PTT- chemotherapy	Optical imaging -PTT- chemotherapy	GNRs@GCS@PDA	[109]
Nuclear imaging	PTT- chemotherapy	Nuclear imaging -PTT- chemotherapy	RGD-PEG-^{125}I/Pt-PDA@GNR	[48]

MRI-guided PDT can be realized by the anchoring of both MRI contrast metal ions and photosensitizer molecules. Dong et al. [101] designed hybrid $CaCO_3$ − PDA nanocapsules which were furthered objected to surface modification with lipid bilayers and coated with PEG for efficient Mn^{2+} and Ce6 loading. The photosensitivity of Ce6 was quenched by PDA before arriving tumor cite. When transforming to the tumor tissue motivated by MRI, Ce6 was subsequently activated with recovered fluorescence and enhanced $^1O_2$ generation ability, facilitating the effective image-guided PDT with reduced phototoxicity.

4.4.2. Computed tomography imaging guided therapy

X-ray computed tomography (CT) was the first tool of slice-imaging modalities and have been widely used in clinical diagnosis. Recently, metallic nanoparticle core with high density, high atomic number and high X-ray attenuation coefficient such as gold nanoparticles, Bi_2Se_3 nanoparticles have been investigated as new CT imaging agents where PDA plays a part in improving biocompatibility, reducing side effect and loading of the therapeutic drugs.

As for PDA modified-gold nanoparticles in image-guided PDT-PTT which can generate moderate hyperthermia together with ROS-mediated intracellular destruction, Kumar et al. [41] offered a novel method called oxidative “nanopeeling” chemistry where PDA shell directing the growth of highly-branched Au nanopetals. This PDA-coated gold nanoparticles displayed an outstanding NIR induced PDT − PTT efficiency and could also be used as surface-enhanced Raman scattering probes for censoring the variations of the DNA in cancer cells.

PDA-modified Bi_2Se_3 nanoparticles were fabricated by Li et al. [69] for image-guided CT-PTT. Through adding DOX with Bi_2Se_3@PDA into HSA solution, the HSA layer were adsorbed onto the surfaces and DOX was embedded in the matrix of HSA. This nanocomposite acted as a high-contrast agent for X-ray computed tomography due to the contrast properties of the Bi_2Se_3 core and PTT efficacy was achieved owing to the photothermal conversion capability of both the core and the PDA shell.

4.4.3. Photoacoustic imaging guided therapy

Photoacoustic imaging (PA) is a new non-invasive and non-ionizing biomedical imaging method exploited in recent years. Principally, when the pulse laser irradiates biological tissues, a partial of energy is absorbed and converted into heat, leading to transient thermoelastic expansion and thus wideband ultrasonic emission that can be detected. Nanosystem with photothermal conversion ability can be employed to realize light-induced theranostics, therefore PDA modification is a promising candidate for photoacoustic imaging guided PTT or PDT.

Due to the excellent photothermal conversion capacity, PDA modification itself can be excellent agent for combining PA imaging with PTT. Lin et al. [43] assembled Fe_3O_4@PDA core-shell nanoparticles as theranostic nanosystem for intracellular mRNA detection and PA/MRI imaging-guided PTT. PDA shell could both adsorb and quench fluorescent dye-labeled single-strand DNA probes. In the presence of the target, the specific binding between the dye-labeled ssDNA probe and its target induced the formation of a duplex structure, resulting in the release of the probe from PDA and subsequent recovery of the fluorescence.

Photosensitizer can be anchored on the nanoparticles for amplifying PA and PTT effects. Hu et al. [32] coated PDA on the surface of rGO in order to load indocyanine green (ICG) molecules, quench its fluorescence, and enhance the optical absorption of the nanosystem at 780 nm for enhancing PA guided PTT for cancer theranostics. ICG could not only increased the optical absorption in the NIR region, but also improved the PA contrast ability and PTT efficacy.

4.4.4. Optical imaging guided therapy

Optical imaging combined with chemical therapy or physiotherapy benefiting from PDA-mediated grafting of fluorochrome is able to accomplish more controllable therapeutic effect with high sensitivity and spatial resolution. Liu et al. [109] proposed such GNRs@chitosan (GCS) @PDA where PDA played a role in efficiently Ag^+ ions loading as well as Cy5SE grafting. In addition, the hyperthermia generated by GNRs could trigger more Ag^+ ions release, improving the antibacterial efficiency of chemotherapy which could be monitored by fluorescence imaging.

4.4.5. Nuclear imaging guided therapy

Nuclear imaging is a form of medical imaging in which nuclear isotopes, also known as radionuclides, are used as the imaging agent. Zhang et al. [48] prepared a novel RGD-PEG-^{125}I/Pt-PDA@GNRs nanosystem where cisplatin and radioisotope iodine-125 were loaded on the surface of the PEGylated PDA@GNRs and RGD peptide was conjugated to the GNRs. Both *in vitro* and *in vivo* assay showed excellent angiogenesis targeting, satisfied tumor ablation and inhibition of tumor recurrence (Fig. 11).

4.5. Vaccine delivery and adjuvant

Immunotherapy which is able to trigger immune defense systems in the tumor or bacterial infection microenvironment, is another approach to fight against cancer or bacterial. Plenty of nanoparticles have been used as adjuvants and antigen carriers to improve the immunogenicity of subunit vaccines. However, it remains to be a challenge to fabricate vaccine delivery and adjuvant nanosystem with both nice biocompatibility and considerable activation effect of immune responses. As a nature-inspired biomaterial with excellent molecular loading ability, PDA modification endows the nanoparticles with great biocompatibility as well as enhanced antigen and adjuvant anchoring efficiency [119,151]. Liu et al. [83] reported the synthesis of pathogen-mimicking PLGA@PDA-HBsAg-CpG nanoparticles for vaccine hepatitis B surface antigen delivering. PDA based surface functionalization endowed the PLGA core with morphology to mimic pathogen structure and the loading of CpG which gave rise to molecular immune-activating properties could mimic pathogen function. Such novel vaccine delivery nanoparticles were capable of enhancing humoral and cellular immune responses *in vivo* and the biocompatibility and biosafety were validated by bone marrow-derived dendritic cells *in vitro*.

4.6. Tissue repair

Tissue regeneration requires orchestrated cell and tissue responses

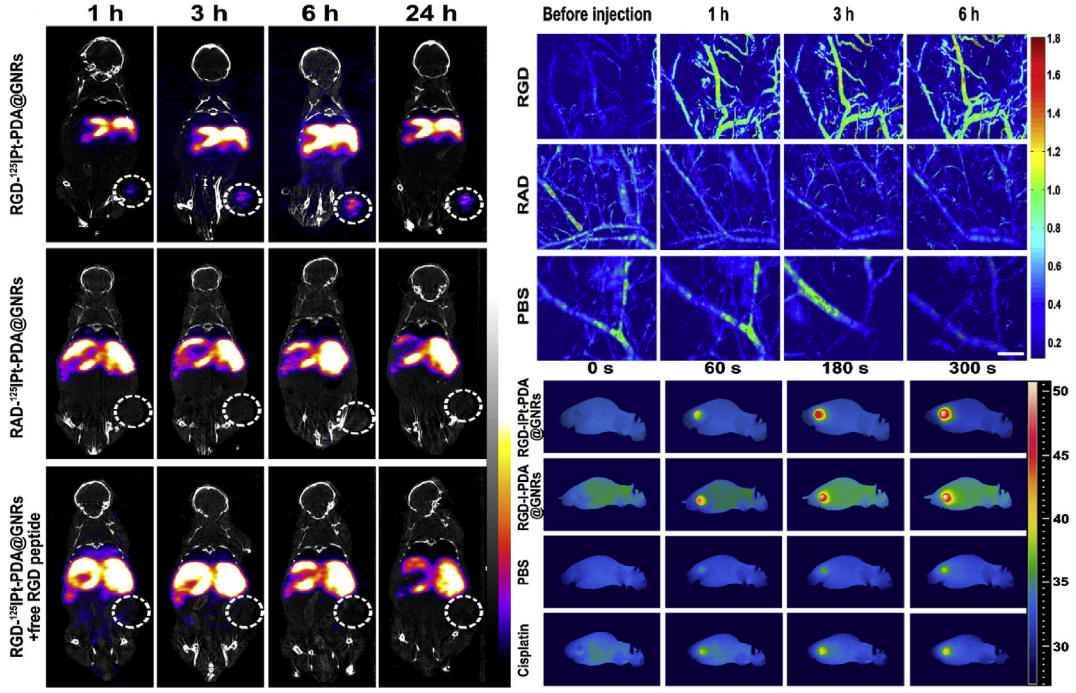

Fig. 11. Schematic illustration of image-guided angiogenesis-targeted combined chemo-thermal therapy effect of RGD-^{125}IPt-PDA@GNRs. Reprinted with permission from Ref. [48], ACS Nano. Copyright (2016) American Chemical Society.

for modulation of cell adhesion, proliferation, differentiation as well as prevention of excessive immune reactions and bacterial infection [123,152–160]. As we have mentioned before, owing to its particular structure and component, PDA provides superior adhesive properties for promoting and spatial controlling of cellular adhesion as well as affecting cell fate. In addition, due to the multifunction including biosafety, adhesiveness, antioxidant and antibacterial of PDA surface modification, it has been extensively explored for tissue regeneration and repair. Since PDA films coated on scaffolds and implants can be referred in several excellent reviews already [124], here we mainly focus on the discussion about the application of PDA-modified nanoparticles in tissue repair and implant materials.

4.6.1. Hard tissue

Notably, PDA itself has the ability to stimulate biomineralization because of its strong adsorption of calcium and phosphate ions, accelerating the formation of hydroxyapatite (HAp) crystals [161]. Our previous work [162] has revealed that PDA coating exhibited direct enhancing on the adhesion, proliferation and osteogenic differentiation of bone marrow mesenchymal stem cells (BMSCs) via FAK and p38 signaling pathways, which was in accordance with augmented new bone formation and improved osseointegration of PDA-coated implants *in vivo*. More importantly, various osteogenic biomolecules or drugs can be immobilization in the presence of PDA surface modification for refining osteogenesis.

For bone regeneration, Sun et al. [113] prepared PDA-coated HAp nanoparticles and subsequently immobilized bone forming peptide on the surface through catechol linking with PDA. Such peptide-conjugated HAp@PDA nanoparticles were validated to promote the adhesion and proliferation of MG-63 cells while maintaining the osteogenic activity of the grafted peptide. Aiming at manufacturing various nanoparticles to form composite surface coatings for producing artificial extracellular matrix (ECM) microenvironments with hierarchical nanostructures, Wang et al. [94] developed PDA-modified BSA-MS@PDA co-assembled with HAp@PDA encapsulating BMP-2 taking advantage of the adhesive properties of PDA. *In vitro* BMSC culturing and *in vivo* implantation demonstrated that these nanoparticles were beneficial to osteoinductivity.

In order to improve corrosion resistance and bone formation of Mg implant, Jiang et al. [114] developed a biocompatible coating strategy by PDA-coated HAp nanoparticles and simultaneously immobilized with BMP-2 on the surface of AZ31 Mg alloys. *In vivo* implantation analyses indicated that with the synergistic effects of HAp, PDA and BMP-2, not only the degradation rate of the alloys was reduced, but bone regeneration was induced as well with no additional inflammatory response.

Promoting bone regeneration while preventing bacterial infection, in other words, balancing the competition between bacterial and cell is highly required in tissue repair. An ingenious nanoplatform composed of ZnO@PDA-RGDC nanorods were designed and prepared on titanium (Ti) implants for balancing bacterial-osteoblast competition by means of selective physical puncture and the biofunctionalization of the nanoparticles to observably increase the osteoinductivity and efficiently kill bacteria [67]. ZnO@PDA-RGDC nanorods could puncture bacteria but not damage osteoblasts due to the large difference in size between osteoblasts and bacteria. Meanwhile, PDA endowed this nanosystem with improved cytocompatibility *via* the repression of both ROS and Zn^{2+} concentration.

4.6.2. Soft tissue

Acceleration of wound healing is a complex process involving promoting re-epithelialization, increasing angiogenesis, regulating extracellular matrix remodeling, preventing bacterial infection and enhancing the migration of mesenchymal stem cells (MSCs). Li et al. [163] developed Fe_3O_4@PDA nanoparticles which could be internalized by MSCs without any negative effects on their stem cell properties. Such Fe_3O_4@PDA labeled-MSCs system increased the recruitment of MSCs through SDF-1/CXCR4 axis and attenuated local inflammation response after implantation at the burn skin. Xu et al. [82] reported improving of wound healing through a combination of PTT and peroxidase catalytic activity utilizing PDA-coated HAp nanorods merged with gold nanoparticles. Gold nanoparticles endowed the nanoplatform with brilliant PDT activity, PDA assisted with sufficient photothermal conversion efficiency, while HAp accelerated cell adhesion, proliferation and

differentiation. The tissue repairing-related gene expression were up-regulated, therefore promoting wound healing. Recently, PDA conjunct silica nanoparticles was developed for hemorrhage control as well as antibacterial activity in wound healing [145]. This PDA/Si nanoparticle could clearly stimulate the extrinsic coagulation cascade, accelerating the blood clotting procedure. In addition, excellent antibacterial effect was observed besides hemorrhage control owing to the bactericidal ability of PDA as we have mentioned above.

5. Summary and outlooks

In summary, some of the recent advances in PDA-modified nanoparticles working as "drug" carriers with diverse nanostructures for cancer therapy, antibiosis, prevention of inflammation, theranostics, vaccine delivery and adjuvant, tissue repair and implant materials are presented. It needs to be emphasized that the "drug" we discuss in this review is a generalized concept which refers to the diverse functional molecules including chemotherapeutics, antibiotics, metal ions, fluorochromes, targeting ligands, antibodies, cytokines and other bioactive peptides or proteins. These PDA-modified nanoparticles working as drug carriers compose of the nanoparticle core, the PDA modification and the loading "drugs" work as a whole drug system, and can be divided into three classifications based on their different nanostructures:

(1) PDA core@shell nanoparticle drug systems where drugs can be anchored onto the surface, embedded in the matrix, encapsulated in the mesopores or self-assembly as the nanocores.
(2) PDA hollow nanoparticle drug systems where drugs can be bonded to the surface of PDA or encapsulated in the hollow of the nanoparticles.
(3) PDA co-assembly nanoparticle drug systems where PDA-drug conjugates play a part in the assembly of the "building block" of the nanostructure.

Owing to the intrinsic properties of PDA, the PDA modification can not only vest the nanoparticles with increased hydrophilicity, excellent biocompatibility, appropriate biodegradability, but also offer a bioactive surface for anchoring bioactive molecules, realizing second modification and achieving pH, GSH, NIR triggered drug release profiles. Additional attributes such as strong photothermal conversion capacity, ROS scavenging facility and fluorescence quenching ability can also be obtained. The as-fabricated PDA-modified nanoparticles with multifunction such as targeting, imaging, chemical treatment, photodynamic therapy, photothermal therapy, bone regeneration and anti-inflammatory can serve as promising drug systems in various biomedical fields and show great potentials in overcoming the limits of present mode, from treatment to theranostics, and from vaccine adjuvants to tissue repair. Although prominent progress has been made in fabrication, functionalization and biomedical applications of PDA-modified nanoparticle drug carriers, there are still challenges that remain to be faced, as demonstrated in Fig. 12.

Current studies mostly focused on the PDA-modified nanoparticle drug carriers for cancer diagnosis and therapy. It is worth to note that in addition to cancer therapy, these drug systems possess various potential biomedical applications to be explored. Firstly, bacterial infection has become a serious threat to public health in which the formation of biofilms plays the key role. Compared to planktonic bacteria, biofilms are more tough to be eliminated by antibiotics because they can block the penetration of antibiotics and preventing the attack of host immune system. It is required to utilize the efficient molecular immobilization ability, photothermal conversion efficiency and superior absorbability of PDA for designing multiple antimicrobial agents-loaded nanoparticle drug carriers. Such PDA-modified nanoparticles can be promising antibiofilm drug systems combining imaging guidance, biofilm destruction, bacteria targeting, chemical and physical antibiosis for realizing synergistic or combined antibacterial effect. Secondly, in terms of tissue repair, PDA coating on scaffolds or implants to form a PDA film has become a common practice, while PDA-modified nanoparticles working as enhanced bioactive drug systems blended in hydrogels or other scaffolds for tissue repair and implant materials are relatively less developed. Since these PDA-modified nanoparticles not only provide more flexible drug loading pattern for activating tissue regeneration, but also can be internalized into stem cells and involved in cell fate determination, it is intriguing to witness more versatile PDA-modified nanoparticle drug carriers applied in tissue repair, especially in soft tissue repair such as wound healing. Additionally, striking a balance in cell behavior and immune reactions as well as bacterial infection is also significant for tissue repair. Since there are reports about the potential of photothermal therapy to induce osteogenesis, whether PDA modification can be a candidate for promoting bone regeneration and killing bacterial simultaneously deserves further researches. Last but not least, it remains to be a challenge to fabricate vaccine delivery and adjuvant platform with both nice biocompatibility and considerable activation effect of immune responses. Therefore, it is of great importance to explore more pathogen-mimicking PDA-modified nanoparticles for antigen and adjuvant anchoring to obtain "all in one" vaccine system.

Given that there are numerous potential applications of PDA-modified nanoparticle drug carriers, bringing PDA-based nanomaterials into commercialization becomes a logical challenge. Safety and effectiveness are major considerations. Since dopamine itself act as a neurotransmitter, the biodegradation process of PDA in human body, the interactions of PDA with human cells, and its immunogenicity need to be revealed. The lack of understanding of the biodegradation and immunogenicity of PDA-modified nanoparticles may hinder the transformation of these nanoparticles as drug carriers from the laboratory investigation to clinical trials. Besides, in order to improve the effectiveness, further research is required on figuring out the exact polymerization mechanism of PDA and its precise structure. Based on this, researchers can explore and synthetize better PDA-mimicking surface functionalization materials, even tailor the properties of these materials according to different requirements.

In conclusion, PDA-modified nanoparticle drug carriers with various nanostructures and multifunctional capabilities have received abundant

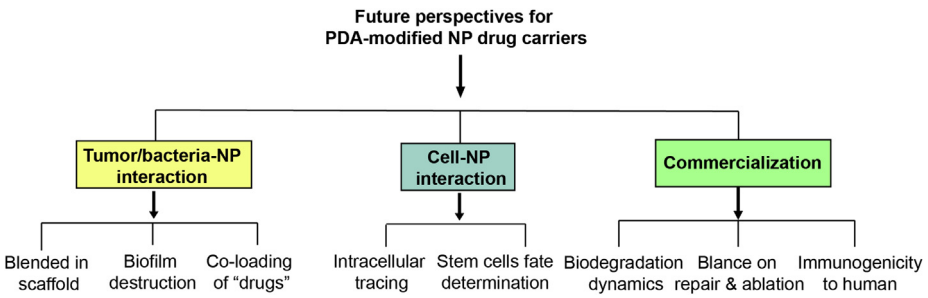

Fig. 12. Future perspectives for research on PDA-modified nanoparticle drug carriers.

attention in cancer therapy, antibiosis, prevention of inflammation, theranostics, vaccine delivery and adjuvant, tissue repair and implant materials due to the unique roles that PDA modification plays in the drug system. Although some problems in PDA modification still exist and there is yet a long way to go for their clinical applications, it can be expected that PDA will be one of the most powerful tools for nanoparticle modification and PDA-modified nanoparticle drug carriers will be applied in more and more biomedical fields.

Author contributions

A.J. and Y·W wrote the manuscript. K.L. and L.J. conceived the concept of this review. All authors discussed and commented on the manuscript.

Declaration of competing interest

The authors declare no conflict of interest.

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