SPECIAL ISSUE: Diagnostic and Theranostic Platforms Based on Dendrimers and Hyperbranched Polymers

Dendrimer-based strategies for cancer therapy: Recent advances and future perspectives

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ABSTRACT This review reports some recent advances on the use of dendrimer-based systems for cancer therapy. Dendrimers are emerging as promising carriers or stabilizers for drugs and nanoparticles (NPs) due to their highly branched 3-dimensional globular shape, internal hydrophobic cavity and multiple peripheral functional groups. The fabricated nano-platforms loaded with therapeutic agents such as drugs, siRNAs or NPs can be further modified to have targeting specificity, antifouling properties and good biocompatibility. In particular, recent advances in the surface modifications of dendrimers and the application of dendrimers as versatile platforms for different therapeutic treatments to cancer including chemotherapy, radiotherapy, photothermal therapy, photodynamic therapy, gene therapy, and combination therapy will be introduced in detail.

Keywords: dendrimer-based systems, cancer therapy, drug, nanoparticles, therapeutic agents

INTRODUCTION

Dendrimers with “onion skin-like” branched layers and a precise number of functional groups can act as a mono-dispersed platform for various biomedical applications. The word “dendrimer” originated from the Greek word “dendrons” with the literal meaning of tree or branches [1]. Typically starting from a core, the dendrimer grows to have emanated branches step by step to form different generations, having particular size, terminal functional group and defined molecular weight. The most major ways to synthesize dendrimers are the divergent method and convergent growth, which was developed by Tomalia [2], and Hawker and Frechet [3], respectively. Of course, some less well-explored strategies have also been in-

troduced by other researchers, such as double exponential growth [4], hypercore and branched monomer growth [5], click chemistry [6] and lego chemistry [7].

Owing to its special 3-dimensional (3D) structure, perfect water solubility, low immunogenicity and easiness of functionalization, the dendrimer-based system has become one of the most promising and efficient platforms for cancer therapy [8]. Since the first ever dendrimers were described by Vögtle in 1978, a variety of different dendrimer types have been developed and used, such as poly(amidoamine) (PAMAM) dendrimer [9–13], poly(propyleneimine) (PPI) dendrimer [14,15], polylysine (PLL) dendrimer [16] and phosphorus dendrimer [17], providing versatile dendrimer-based systems for cancer treatment.

PAMAM dendrimers with ethylenediamine core and branch cell multiplicity are usually synthesized by the “divergent” method (Fig. 1). They are the first complete dendrimer family to be synthesized, characterized and commercialized [2,18] and often referred to as “artificial proteins” (Fig. 2) [8]. These outstanding features afford their wide uses as globular protein replacements for different applications. PPI dendrimers were firstly reported by Buhleier *et al.* [19] in 1978. They usually have a core of 1,4-diaminobutane and are synthesized with a divergent method (Fig. 3) [20,21]. PLL dendrimers containing L-lysine in their branching units are one kind of peptide-based dendrimers [22,23]. Phosphorous dendrimers with phosphorus atoms at each branching unit [24,25] are considered to be particularly suitable for biomedical applications due to the phosphorus element, which is essential for life [7,26].

The unique characteristics of dendrimers distinguish

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Figure 1 Synthesis of tetra-functional poly(amidoamine) (PAMAM) dendrimers: exhaustive Michael addition of amine groups with methyl acrylate, followed by amidation of the resulting esters with ethylenediamine. Reproduced with permission from Ref. [8], Copyright 2001, Elsevier.

Figure 2 A dimensionally scaled comparison of a series of poly(amidoamine) (PAMAM) dendrimers (NH_2 core; $G=4-7$) with a variety of proteins, a typical lipid-bilayer membrane and DNA, indicating the closely matched size and contours of important proteins and bioassemblies. Reproduced with permission from Ref. [8], Copyright 2001, Elsevier.

them from conventional linear polymers [27–29] and endow dendrimers with advantages for many delivery applications [30]. The globular shape and the defined periphery functional groups of dendrimers endow them with an ability to not only encapsulate drug molecules within their interior or conjugate drug molecules on their periphery, but also be modified with a range of functional agents. The globular shape of dendrimers, as opposed to the random coil-structured linear polymers, could affect their biological properties and thus lead to the discovery of many interesting effects [31]. Studies have shown that PAMAM dendrimer-based drug delivery system has lower half-maximal inhibitory concentration (IC_{50}) of drugs and more cellular uptake than linear PEG-based

Figure 3 Synthesis of different generations (3.0G, 4.0G and 5.0G) of PPI dendrimers. Reproduced with permission from Ref. [21], Copyright 2014, Elsevier.

system [32]. Due to the great monodispersity that is close to that of protein and the controlled architecture, nano-size, and shape, dendrimers are often considered to be one of the most promising vehicles for the delivery of drugs, proteins, and other therapeutic agents [27,33–35].

For desired biomedical applications, surface modification of dendrimers is necessary. For instance, PEGylation endows the system with good biocompatibility, stability and elongated blood circulation time. For nanomedicinal applications, dendrimers have been used as platforms to physically load drugs by electrostatic interaction or by hydrophobic interaction, covalently link drug molecules on the dendrimer periphery, compress genetic materials (e.g., short-interfering RNA, siRNA) *via* electrostatic interaction, entrap inorganic NPs within the dendrimer interior, or stabilize inorganic NPs. These strategies allow for the generation of various dendrimer-based nano-platforms for different treatments of cancer including chemotherapy, radiotherapy, photothermal therapy (PTT), photodynamic therapy (PDT), gene therapy, or

combination therapy. Since some of the related research in the field has been reviewed earlier [36–38], in this review, we mainly report the recent advances (from 2013 till now) in the applications of different dendrimer-based strategies for cancer therapy. This review starts with a brief introduction, followed by detailed discussion of the related research in the field, and ends with conclusion and future perspectives. It should be noted that this review does not intend to give a comprehensive overview of the whole literature database, but rather discusses some key developments and advances in the field in the last several years.

DENDRIMER SURFACE DECORATION AND FUNCTIONALIZATION

The toxicity of dendrimers impedes their biological applications due to the characteristics, which is related to the chemistry of the core and mainly to the surface end groups [39]. Amine-terminated dendrimers have high positive charge that strongly interacts with negatively charged cell membranes to result in cell lysis [40]. Therefore, the surface decoration of dendrimers is necessary (Table 1). In addition, the properties of non-specific cell membrane binding and specific targeting can also be gained through surface functionalization.

PEGylation

Polyethylene glycol (PEG) modification is the dominating way to increase the biocompatibility of dendrimers, to prolong the blood circulation time of dendrimers *in vivo* and to enable tumor accumulation through the enhanced permeability and retention (EPR) effect [41]. In a previous report, Peng *et al.* [42] reported that generation 5 (G5) PAMAM dendrimers with PEG modification had enlarged surface periphery, enabling enhanced entrapment of Au NPs to form stable dendrimer-entrapped gold nanoparticles (Au DENPs) after acetylation of the remaining dendrimer terminal amines. The PEGylated Au DENPs have improved cytocompatibility, longer half-decay time (31.76 h) than that of Au nanorods (12.5 h). Furthermore, PEG is also commonly used as a spacer between dendrimers and targeting or other functional agents. For instance, Shrikant *et al.* [43] studied the influence of PEG spacer chain length on the targeting efficiency of folate (FA)-modified PPI dendrimers. In that work, PEG with different M_w (1,000, 4,000, 6,000, or 7,500) was used to connect FA and PPI, followed by docetaxel loading. The results show that PPI modified with PEG ($M_w=7,500$) has lowest drug release rate and all the PEGylated PPI dendrimers have better blood compatibility than PPI dendrimers without PEGylation. Due

Table 1 Examples of dendrimer surface decoration and functionalization

Dendrimer type	Surface modification agent	Function	Reference
PAMAM	PEG	Reducing cytotoxicity	[42]
	Phosphorylcholine		[44]
	CBAA		[45,46]
	Acetyl		[42,46–48]
	CBAA		[45,46]
	RGD		[49–53]
	pAb antibody		[54]
	Lactobionic acid		[55]
	Fluorescein isothiocyanate	Fluorescence imaging	[55]
	Fluorochrome Cy5.5		[50]
PPI	PEG	Reducing cytotoxicity	[43,56]
	Maltotriose		[57–59]
	Anti-EGFRvIII scFV	Targeting property	[60]
	FA		[61]
PLL	Histidine, pyridine, piperazine	Buffering capacity property	[62]
	PEG	Reducing cytotoxicity	[63]
	FA	Targeting property	[64]
Phosphorous dendrimers	Azabisphosphonate	Targeting property	[65]
	8-Anilino-1-naphthalenesulfonate	Fluorescence imaging	[66]

to the optimized steric hindrances of PEGs with M_w of 4,000, the designed multifunctional PPI device enables the highest cellular uptake, which is desired for drug delivery applications.

Zwitterion modification

In general, NPs suffer quick clearance by reticuloendothelial system (RES) within organs, such as the liver, spleen, and lung after intravenous injection [67–69]. For highly efficient cancer therapy, it is critical to make the drugs effectively delivered to the tumor region. Hence, it is important to design a drug delivery system having good antifouling properties (protein resistance ability), extended blood circulation time, and limited macrophage cellular uptake by the RES. Studies have shown that NPs modified with zwitterionic molecules of cysteine display good antifouling properties, extended blood circulation time and enhanced tumor penetration and retention [70,71]. The special structure of zwitterionic molecules consists of an equal molar ratio of positive and negative charges in close proximity. Each ion pair of positive and negative groups can hold a large quantity of water molecules around and form a protective layer of water on the surface of materials, thus shielding the hydrophobic interactions between the pollutants and the material surface [46]. Jia *et al.* [44] used acryloyloxethyl phosphorylcholine (APC) to modify G5 PAMAM dendrimers and about 50 APCs were connected to each G5 PAMAM dendrimer as confirmed by ^1H NMR and potentiometric titration. The results showed that the zwitterionic “lipid-like” molecules can reduce the cytotoxicity of dendrimers but at the same time retain their cell uptake ability. Wang *et al.* [45] reported the modification of carboxybetaine acrylamide (CBAA) onto G5 PAMAM dendrimers. The CBAA-modified dendrimers showed excellent compatibility with protein and cells, and in particular, the CBAA-modified dendrimers could exist and keep their conformation in the presence of fibrinogen in aqueous solution and the hydrodynamic size of the dendrimers did not change, confirming their excellent antifouling properties. Recently, our group [46] used G5 PAMAM dendrimer modified with different degrees of CBAA as templates to entrap Au NPs. Compared with the control group $\{(\text{Au}^0)_{100}\text{-G5-NHAc-}m\text{PEG}_{20}\}$, the CBAA-modified one showed better antifouling properties and higher degree of CBAA modification resulting in much less macrophage cellular uptake, longer half-delay time (44.54 h), and enhanced computed tomography (CT) imaging of rat blood pool, rabbit lymph nodes and mouse tumors after intravenous injection.

Glycosylation

The decoration of carbohydrate ligands to dendrimers renders them with nearly neutral charges [35], improved biocompatibility *in vitro* and *in vivo* [49], which hence may be used to substitute PEGylation to achieve the same goals [72,73]. The most commonly utilized carbohydrate ligands include glucose, maltose, maltotriose, mannose and lactose, meanwhile the intermediate enamine of dendrimers can be reduced to form secondary and tertiary amines bearing the desired carbohydrate units [74]. The glycosylated dendrimers are widely applied as drug delivery systems, therapeutics and diagnostics for neurodegenerative diseases. Ida *et al.* [57] studied the maltotriose residue-modified PPI dendrimers with DNA-damaging agent fludarabine for chronic lymphocytic leukemia therapy. The addition of PPI-G4-OS-Mal-III and PPI-G4-DS-Mal-III dendrimers to B-CLL cells significantly induced the cell apoptosis within these lymphocytes. Moreover the glycosylated PPI dendrimers can even be used as antiamyloidogenic and antiprion agents. Klementieva *et al.* [58] found that PPI glycodendrimers of the fourth and fifth generations with neutrally charged maltose shell can reduce the toxicity of the brain extracts of Alzheimer's disease to SH-SY5Y cells, a neuroblastoma cell line. The neutrally charged or cationic maltose shell-modified PPI dendrimers were able to penetrate the cytoplasm of cells and reach the brain when administered intranasally. Besides reducing the cytotoxicity and endowing the dendrimers with the ability to cross the blood brain barrier, glycosylation can also be used to improve the r_1 relaxivity of dendrimers-based magnetic resonance (MR) imaging contrast agents. The PPI-MAL DS-DOTA (Gd) complexes with an r_1 relaxivity of $10.2 \text{ mmol}^{-1} \text{ L s}^{-1}$ much higher than that of commercial DTPA(Gd) agent ($3.4 \text{ mmol}^{-1} \text{ L s}^{-1}$) enabled enhanced MR imaging of mouse blood pool and organs. The modification of maltose leads to a longer global rotational correlation time due to the increased molecular dimension of the dendrimers/Gd (III) complexes, and a longer exchange lifetime of the coordinated water molecules resulting from H-bond between hydroxy of maltose and other ligand units [59].

Targeting agent modification

Although dendrimers can passively target tumor tissues by EPR effect due to the hyper permeability of tumor vasculature [75,76], the low specificity-resulted dose-dependent side effects still impede the biological applications of dendrimers. Fortunately, periphery groups of dendrimers enabled covalent conjugation of various tar-

geting moieties including monoclonal antibodies, peptides/proteins, vitamins, glycosylation, or other ligands for active targeting of cancer cells *via* a receptor-mediated pathway [55,60,62,65,77–79]. Here we introduce several typical targeting agents such as Arg–Gly–Asp (RGD) peptide, FA and anti-human myoglobin detection antibody (pAb) for dendrimer surface modifications. RGD, a tripeptide, has a high affinity to cancer cells over-expressing $\alpha_v\beta_3$ integrins. The RGD peptide is usually conjugated with PEG through amide bond or thiol-maleimide coupling, followed by reacting the other PEG carboxyl end group with the terminal amine of dendrimers [49,50]. For instance, our group used RGD to modify PAMAM dendrimers of different generations for gene and drug delivery, as well as PTT of tumors [51–53]. FA can specially connect with FA receptors, which are overexpressed in many types of human carcinomas [80,81]. Kesharwani *et al.* [61] investigated the potential to use FA-anchored and drug melphalan-loaded PPI dendrimers with different generations (PPI3, PPI4 and PPI5) for targeted therapy of cancer cells. The authors showed that IC_{50} values of MP-FPPI3, MP-FPPI4, MP-FPPI5, and free melphalan were 8 ± 0.15 , 0.9 ± 0.02 , 0.2 ± 0.01 and $10\pm0.17\ \mu\text{mol L}^{-1}$, respectively for MCF-7 cells (a human breast cancer cell line), while for CASKI cells (a human uterine cancer cell line), the corresponding IC_{50} values were 3.11 ± 0.04 , 0.93 ± 0.06 , 0.75 ± 0.02 and $2.17\pm0.11\ \mu\text{mol L}^{-1}$, respectively. Hence, the FA-mediated targeting efficacy showed a generation-dependent behavior with a higher cancer cell targeting efficiency for higher generation dendrimers. In another work, Zhang *et al.* [54] reported the bioconjugation of gold nanoparticle (AuNP)-PAMAM with pAb antibody by mixing the NPs and antibody followed by centrifugation to move the excess antibodies. The electrochemical characteristics of the immunosensor assay indicated that pAb-AuNP-PAMAM could be specifically adsorbed to mAb-modified glassy carbon electrode in the presence of target myoglobin, exhibiting high specificity and good precision toward target myoglobin.

Others

Apart from the four types of decoration and functionalization discussed above, lots of other modification strategies have been performed to endow the dendrimers with good biocompatibility and desired functionality [62]. Zhang *et al.* [48] investigated the influence of different functional groups on the release of anticancer drug doxorubicin (DOX) from PAMAM dendrimers. The terminal amines of G5 PAMAM dendrimers were firstly

converted to acetyl (G5.NHAc), glycidol hydroxyl (G5.NGlyOH), and succinamic acid (G5.SAH), respectively, followed by physical encapsulation of DOX. The NMR results showed that interactions between G5.NHAc or G5.NGlyOH dendrimers with DOX were much stronger than that between G5.SAH dendrimers and DOX, hence DOX released quickly from the G5.SAH dendrimers. In addition, acetylation is a widely used way to reduce the cytotoxicity of dendrimers to neutralize the dendrimer terminal amines, which is proven to be toxic to cells at a relatively high concentration [64]. At the dendrimer concentration above $1\ \text{mmol L}^{-1}$, the fully acetylated generations 2 and 4 PAMAM dendrimers were nontoxic, while the cell viability for 50% acetylated PAMAM dendrimer was 70% at $1\ \text{mmol L}^{-1}$ for Caco-2 cells [47]. Interestingly, 50% acetylation of dendrimers endowed them with the highest permeability coefficient of $3.0\times10^{-6}\ \text{cm s}^{-1}$, but the fully acetylated dendrimers and the unmodified dendrimers had almost the same membrane permeability (2.1×10^{-6} versus $1.7\times10^{-6}\ \text{cm s}^{-1}$). Furthermore the dendrimer peripheral groups can be modified with other functional agents such as DOTA or dye for imaging element chelating or for fluorescence imaging [50,66,82,83]. For example, the dendrimer-DOTA [59] can be used for chelating agent such Gd (III) ions for MR imaging, and dendrimer-FITC conjugates [46] are usually applied in cellular tracking of the materials *in vitro* or fluorescence imaging *in vivo*.

CANCER THERAPY

With the unique structural characteristics, globular shape, and abundant terminal groups [84,85], dendrimers have been widely used for drug delivery [36], as well as for the development of various nanoplatforms for different types of cancer therapy such as chemotherapy, radiotherapy, PTT, PDT, gene therapy and the combination therapy (Table 2).

Dendrimer-based drug delivery systems

The dendrimer-based platform can be used to load anticancer drugs either through physical encapsulation or through covalent conjugation. According to the combination form of dendrimers and drugs (Fig. 4), the dendrimer-based drug delivery system can be divided into two main types: (1) dendrimer/drug complexes and (2) dendrimer/drug conjugates.

Dendrimer/drug complexes

Diverse drugs can be encapsulated within the hydrophobic interior of dendrimers or connected to the den-

Table 2 Examples of dendrimer-based cancer therapy

Cancer therapy type	Dendrimer type	Functional agents	Reference
Chemotherapy	PAMAM	DOX	[86]
		2-ME	[87]
		GEM	[88]
		α -TOS	[53,89]
		DOX	[90]
Radiotherapy	PPI	MTX	[43]
	PLL	MTX	[43]
	PAMAM	^{131}I	[91,92]
		^{177}Lu	[93,94]
PTT	PAMAM	GNRs	[95]
		ICG	[96]
		MoS ₂	[97]
		CuS	[98]
		Au NSs	[51]
PDT	PAMAM	Ce6	[99]
	PPI	Phthalocyanines	[100]
	Phosphorus dendrimers	Methylene blue	[101]
		Rose bengal	[101,102]
		Rose bengal	[101,102]
Gene therapy	PAMAM	Luciferase-targeted siRNA or Bcl-2 siRNA	[103]
		Bcl-2 siRNA	[51,97,104–107]
		siBcl-xl, siBcl-2, siMcl-1 siRNAs and a siScrambled sequence	[108]
	PPI	Bcl-2 siRNA	[109]
		Luciferase-targeted siRNA	[60]
		pDNA	[56,62]
	Phosphorus dendrimers	siBcl-xl, siBcl-2, siMcl-1 siRNAs and a siScrambled sequence	[108]

Figure 4 Dendrimer-based drug delivery systems of different types: (a) Drugs physically entrapped inside the dendrimers; (b) drugs adsorbed on the surface of the dendrimers through different intermolecular interaction forces; (c) drugs conjugated to the dendrimers. Reproduced with permission from Ref. [37]. Copyright 2013, the Royal Society of Chemistry.

dendrimer surface through hydrogen bonding, van der Waals interactions, and electrostatic interactions [110]. The formation of dendrimer/drug complexes not only increases the solubility of hydrophobic anticancer drug, but also renders the drug to be released in a sustained manner. In this case, the molecular structure of drugs has not been changed, and hence the therapeutic activity of the

drugs is well maintained. A range of hydrophobic anticancer drugs such as DOX, 2-methoxyestradiol (2-ME) and methotrexate (MTX) have been physically complexed with dendrimers. In our earlier work, we showed that the surface functional groups of G5 PAMAM dendrimers significantly influenced the therapeutic activity of 2-ME after it was encapsulated within the dendrimers. 2-ME encapsulated within G5 dendrimers with succinamic acid termini did not exhibit anticancer activity to KB cells (a human epithelial carcinoma cell line), while once encapsulated within G5 dendrimers functionalized with glycidol hydroxyl and acetamide groups, the complexes were able to deliver 2-ME to inhibit cancer cell growth [87]. In another study, generation 4 PPI-grafted nanocrystalline cellulose (NCC) was modified with FA to load DOX and the DOX release under different pHs was tested. At pH 7.4 and pH 5.3, the NCC without FA showed a higher cumulative DOX release when compared to the FA-conjugated systems, primarily due to the steric hindrance of the conjugated FA. Meanwhile under a lower

pH, the DOX release rate from both FA-targeted NCC and non-targeted NCC increased [90].

Dendrimer/drug conjugates

Dendrimer/drug conjugates are formed through covalent conjugation of chemotherapeutic drugs with the dendrimer periphery *via* covalent bond. The drug should be released after the spacer between dendrimers and drugs are broken up. Therefore, the drug release kinetics is generally related to the types of the connecting bond. The most used linkers include hydrazone, imine, ester, carbamate, amide, disulfide, and enzyme-cleavable peptide sequence [111,112]. For instance, DOX was conjugated to the G4 PAMAM dendrimers through an acid-labile-hydrazone linkage, which is endo/lysosomal pH-sensitive [86]. The *in vitro* drug release measurement showed that 11.5% of DOX was released after 60 h incubation at pH 7.4, and 67.6% and 88.2% drug released within 25 and 60 h, respectively at pH 5.0. Zhang *et al.* [88] showed that the glycyl phenylalanyl leucyl glycine tetra-peptide, an enzyme-cleavable linker, could be used to conjugate gemcitabine (GEM) and lysine peptide dendrimer. Owing to the presence of Cathepsin B enzyme in tumor cellular environments, GEM was quickly released from the particles. *In vivo* assay data demonstrated that PEGylated lysine peptide dendrimer-GEM conjugates could inhibit the tumor growth (90%) 2-fold better than free GEM.

Chemotherapy

Chemotherapy of cancer is based on the use of chemical drugs to prevent the proliferation, invasion and metastasis of cancer cells. Generally cancer chemotherapy faces lots of challenges including low specificity resulting in dose-dependent side effects, short blood circulation time and high drug tolerance [41,113]. While the dendrimer/drug complexes or conjugates can overcome these defects well: 1) the multiple modification of terminal agent of dendrimers can endow them with targeting specificity to cancer cells; 2) the special dendritic platform efficiently retards the release rate of drugs and elongates the blood circulation time to have improved pharmacokinetics; 3) the introduction of particular drugs or agents can restrain the drug tolerance [114]. Previously, Zhu *et al.* [53] reported a way to covalently connect dendrimer and α -tocopheryl succinate (α -TOS), which could kill cancer cells even when combined with dendrimers. The formed Au-TOS-RGD DENPs or Au-TOS-FA DENPs were used for targeted chemotherapy and computed tomography (CT) imaging of cancer cells. For Au-TOS-RGD DENPs, the IC_{50} of α -TOS was $18.2 \mu\text{mol L}^{-1}$, which is much lower

Figure 5 Schematic illustration of the synthesis of the Au-TOS-FA DENPs (a), growth of U87MG xenografted tumors after various treatments (b) and the body weight of U87MG tumor-bearing mice after various treatments (c). The relative tumor volumes and body weight were normalized according to their initial weights (Mean $\pm$ SD, $n=6$). Reproduced with permission from Ref. [89]. Copyright 2015, Elsevier.

than that of free α -TOS ($33.8 \mu\text{mol L}^{-1}$) for treatment of U87MG cells (a human glioblastoma cancer cell line). As for Au-TOS-FA DENPs (Fig. 5), the IC_{50} of α -TOS was $19.2 \mu\text{mol L}^{-1}$, slightly higher than that of Au-TOS-RGD DENPs [89], presumably resulting from the different targeting modification. *In vivo* antitumor efficacy assay showed that the tumor inhibition effect of Au-TOS DENP-treated group (6.65 ± 1.00 times tumor growth) was lower than that of Au-TOS-FA DENP-treated group (5.23 ± 0.72 times tumor growth), but greater than that of free α -TOS (7.37 ± 0.65 times tumor growth) at the same dose of α -TOS, suggesting the efficiency of targeting property and the advantage of dendrimer-drug nanoconjugates. In another study, D- α -tocopherol polyethylene glycol succinate (TPGS) was conjugated with docetaxel (DTX) and paclitaxel (PTX), respectively to render the drugs with enhanced solubility and cellular toxicity. All the nanoformulations displayed enhanced water solubility of DTX

and PTX. Cytotoxicity studies of DTX, Dendrimer-DTX (DB), DTX-loaded dendrimer-TPGS mixed micelles (DD), PTX, Dendrimer-PTX (PB) and PTX-loaded dendrimer-TPGS mixed micelles (PD) in A549, MCF-7 and CHO cells were conducted. In the studied concentration range, dendrimer-drug formulations showed better anticancer therapeutic efficacy than pure or free DTX and PTX for both lung and breast cancer cells. While the TPGS modified DD and PD were more cytotoxic than the corresponding plain dendrimer formulations (DB and PB). What's more, the dendrimer-drug formulations showed low toxicity to the CHO cells, possibly resulting from the facts that the take-up way through endocytosis and the altered physiology processes of nanoformulations for cancer cells differed from those for normal cells [114].

Radiotherapy

Cytotoxic levels of radiation can be delivered to the tumor site by radionuclides labeled onto the dendrimer scaffold. A number of radionuclides such as ^{131}I [84], yttrium-90 (^{90}Y) [115], Lutetium-177 (^{177}Lu) [94], rhenium-188 (^{188}Re) [116] and strontium-89 (^{89}Sr) [117] have been used for radiotherapy in the clinic. Among these radionuclides, ^{131}I and ^{177}Lu have been labeled onto dendrimers for radiotherapy of cancer. ^{131}I has relatively long half-life ($t_{1/2}=8.01$ days), appropriate radiation energy (0.606 MeV, 89.9%), and convenient labeling methods. At the same time, it has the ability for simultaneous single-photon emission computed tomography (SPECT) imaging and radiotherapy [118]. ^{177}Lu is a β - and γ -emitting radionuclide with a physical half-life of 162 hours (6.73 days) [119,120]. Recently, we successfully labeled G5 PAMAM dendrimer with ^{131}I by the linked 3-(4'-hydroxyphenyl) propionic acid-OSu (HAPAO). In addition, the dendrimer periphery was modified with various targeting agents including FA [91], chlorotoxin (CTX) (Fig. 6) [91], and *Buthus martensii* Karsch chlorotoxin [92] for theranostics of tumors. Our studies showed that the ^{131}I -labeled PAMAM dendrimers exhibited good targeting specificity and excellent radiotherapy efficacy to xenografted tumor models [91,92]. In another study, ^{177}Lu was labeled to the dendrimer surface by chelating with S-2-(4-Isothiocyanatobenzyl)-1,4,7,10-tetraazacyclododecane tetraacetic acid [93]. Similarly, Héctor *et al.* [94] synthesized ^{177}Lu -DOTA-dendrimer-FA-bombesin with Au NPs entrapped within the dendrimers to investigate the radiopharmaceutical potential for targeted radiotherapy and the simultaneous detection of FA receptors and gastrin-releasing peptide receptors overexpressed in T47D breast cancer cells. ^{177}Lu -De-

Figure 6 The structure of chlorotoxin-conjugated multifunctional dendrimers labeled with radionuclide ^{131}I (a), the SPECT images of *ex vivo* tumors (b) and the tumor volume (c) of C6 tumor-bearing mice after various treatments (mean $\pm$ SD, $n=5$). Reproduced with permission from Ref. [91]. Copyright 2015, American Chemical Society.

nAuNP-FA-bombesin was obtained with a radiochemical purity of >95% as determined by size exclusion radio high-performance liquid chromatography. The results of the cell viability indicated that ^{177}Lu -DenAuNP-FA-bombesin was about 4 times more lethal than that of ^{177}Lu -DenAuNP without FA, indicating the targeted radiotherapeutic efficiency of ^{177}Lu -DenAuNP-FA-bombesin.

PTT

PTT uses the heat between 41 and 45°C induced by PTT agents that are able to transform near-infrared (NIR) laser light to thermal energy to ablate tumor cells [121]. In order to achieve the PTT treatment of tumors, PTT agents have been modified with dendrimers to form functional nanohybrids. The PTT agents such as Au NPs with different morphologies (Au nanorods [95], Au nanosheets [122] and Au nanostars [51]), copper sulfide (CuS) [98] and molybdenum sulfide (MoS_2) [97] are able to be functionalized with dendrimers as templates or stabilizers. Li *et al.* [95] investigated a new type of hybrid dendrimers with a core of a gold nanorod (GNR) and a shell of PEG-modified PAMAM (PEG-PAMAM) (Fig. 7). Different generations of PEG-modified cystamine-cored PAMAM (G2-G4) dendrimers were firstly synthesized and then used to stabilize the GNRs. The addition of PEG-PAMAM dendrimer did not affect the morphology of GNR. Stability test showed that PEG-PAMAM G4 dendrimer-GNR hybrids aggregated in an aqueous solution, while other generations of PEG-PAMAM enabled the formation of stable hybrids, especially the PEG-PAMAM G3 dendrimer-GNR hybrids. The following assay proved that GNR-cored PEG-PAMAM G3 dendrimers

Figure 7 Schematic illustration of pH-sensitive PEGylated PAMAM dendrimer-DOX conjugate-hybridized gold nanorod (PEG-DOX-PAMAM-AuNR) for combined photothermal-chemotherapy. Reproduced with permission from Ref. [95]. Copyright 2014, the Royal Society of Chemistry.

also exhibited excellent photothermal property that can be used to ablate HeLa cells and xenografted mouse tumor model under an 808 nm NIR laser irradiation.

In another work, Zan *et al.* [96] developed a kind of nanogel (NG) encapsulated with β -cyclodextrin (β -CD)-functionalized PAMAM dendrimer. Through electrostatic interaction between PAMAM and drugs, the DOX or indocyanine green (ICG) can be stably encapsulated within the NGs (DINGs). Assays of NIR light-triggered NG dissociation and drug release showed that the temperature of DINGs increased more rapidly than free ICG, presumably due to the fact that the maximum absorption peak of free ICG was at 780 nm, while that of DINGs was at 795 nm, quite close to the irradiation wavelength of 805 nm. The NIR irradiation could apparently decrease the IC_{50} of DOX from 33 to 7 $\mu\text{g mL}^{-1}$, showing efficient synergistic effect of combined photothermal-chemotherapy and NIR light-triggered drug release. The *in vivo* antitumor efficacy assay showed that the tumor growth was largely suppressed when treated with DINGs and NIR irradiation, and the tumor volume even decreased to a very small size within 16 days.

PDT

PDT is a useful method to destroy cancer cells by reactive oxygen species (ROS) and singlet oxygen that are produced by photosensitizers (PS) when exposed to visible or NIR laser light. The PS/dendrimers nanoformulations can be formed by covalent binding [99,123,124], physical encapsulation [100,125,126], electrostatic interaction [101,102] between PS and dendrimers. Meanwhile the PS can be used as branch unit to synthesize PS-based dendrimers for photodynamic treatment of cancer [127]. Bastien *et al.* [99] synthesized a conjugate using the photosensitizer chlorin e6 (Ce6) and PAMAM G4.5 dendrimers (Fig. 8). Although the singlet oxygen quan-

tum yield of the PAMAM G4.5-Ce6 conjugate was 2.1 times lower than that of free Ce6, the IC_{50} of G4.5-Ce6 conjugate was 7 times lower ($0.1 \mu\text{g mL}^{-1}$) than that of free Ce6 ($0.7 \mu\text{g mL}^{-1}$) due to the higher cellular uptake of G4.5-Ce6 conjugate. Phthalocyanines (Pc) derivative with promising potential for fluorescence imaging and PDT for tumors was also encapsulated within the cavity of G4 PPI dendrimers [100]. The drug encapsulation efficiency could be up to 20% due to hydrophobic linker of Pc, and the formed nanocarrier has a particular NIR absorption at 700 nm. Cytotoxicity assay data showed that the formulation had efficient phototoxicity ($IC_{50} = 0.9 \mu\text{g mL}^{-1}$) after exposure to a 670 nm laser and low dark cytotoxicity ($IC_{50} = 28 \mu\text{g mL}^{-1}$) to the cancer cells.

As for phosphorus dendrimers, the most used way to form PS/dendrimer formulation is electrostatic interaction. For example, the anionic phosphorus dendrimers were used to load positively charged methylene blue, and

Figure 8 (a) Synthesis of mono-(PcSi(OH)(mob), 2) and disubstituted (PcSi(mob)₂, 3) derivatives of the silicon phthalocyanine (PcSi(OH)₂, 1). (b) Schematic representation of tumor targeted theranostic platform based on phthalocyanine-loaded dendrimer (Pc-Luteinizing Hormone Releasing Hormone). Reproduced with permission from Ref. [100]. Copyright 2013, American Chemical Society.

the cationic phosphorus dendrimers were used to encapsulate negatively charged rose bengal (RB) both through electrostatic interaction [101]. The RB-phosphorus dendrimer complex processed cationic charges. RB and dendrimer showed no “dark” toxicity in three cancer cell lines (ASZ, BSZ, and CSZ, respectively). When being irradiated, RB decreased the cell viability only to 53% in CSZ cells at the concentration of $0.75 \mu\text{mol L}^{-1}$, while the complex exhibited almost 85%–95% phototoxicity against all three cell lines at the concentration of $0.5 \mu\text{mol L}^{-1}$, indicating the efficient PDT property of rose bengal–phosphorus dendrimer complex [102].

Gene therapy

Anionic nucleic acid can be easily condensed by cationic dendrimers with plenty of amine groups by electrostatic compression. The formed nucleic acid/dendrimer polyplexes can be surface modified to have different functionalities and the compressed nucleic acid can be protected from enzymatic degradation. What's more, some dendrimers including PAMAM, PPI and poly(ether imine) with a plenty of tertiary amine groups can exert a “proton sponge” effect to help polyplexes escape from lysosomes. Therefore, the nucleic acid can be well protected and efficiently released to the cytoplasm and expressed [128]. Among these dendrimers, PAMAM dendrimer [88,129,130], phosphorus dendrimer [108] and PPI dendrimer [109,57] have been mostly used. A range of modification strategies have been adopted to reduce the cytotoxicity of dendrimers such as dodecylation [103,131], arginine-modification [132], or PEGylation. Chang *et al.* [103] used dodecylated G2, G3 and G4 PAMAM dendrimers to deliver luciferase (Luc)-targeted siRNA or Bcl-2 siRNA to HeLa cells and MDA-MB231 cells for gene silencing. Compared with unmodified G2, G3 and G4 PAMAM dendrimers, dodecylated G2, G3 and G4 showed significantly higher gene silencing efficacy. Especially, 84.6% of Luc gene was knocked down by dodecylated G4 dendrimers, meanwhile more than 90% of cells survived, showing the best delivery efficiency.

Interestingly, some studies have shown that after entrapment of Au NPs within the interiors of dendrimers, the 3D spherical shape of dendrimers are well reserved, consequently featuring much more binding sites with DNA than dendrimers without Au cores [104]. So the capability of dendrimers to compact pDNA was significantly improved, which is essential for improved gene delivery [105,106]. Hou *et al.* [107] designed a vector of Au DENPs partially modified with *m*PEG for non-viral pDNA/siRNA delivery. The pDNA encoding Luc or en-

hanced green fluorescent protein and the Bcl-2 siRNA were successfully packaged, respectively, by the partially PEGylated Au DENPs for effective delivery to HeLa cells to express the related proteins or to silence the expression of Bcl-2 protein. Three different cationic dendrimers (PAMAM, phosphorus and carbosilane) with anticancer siBcl-xl, siBcl-2, siMcl-1 siRNAs and a siScrambled sequence were investigated by Ionov *et al.* [108] to study the mechanisms of interaction. Circular dichroism spectroscopy showed that the general shape of the siRNA spectra was unaltered by dendrimers after their interaction. Through gel electrophoresis, it was proven that the dendrimer/siRNA polyplexes well protected the siRNA from RNase degradation and only the addition of heparin led to its release from the polyplexes.

Studies have shown that fluorinated dendrimers can improve the transfection efficacy and decrease the cytotoxicity for gene delivery applications [109,133]. Wang *et al.* [133] synthesized the perfluoro acid-modified G5 PAMAM dendrimers, which are able to achieve excellent gene transfection efficacy in several cell lines (higher than 90% in HEK293 and HeLa cells) at extremely low N/P ratios. In addition, the fluorinated dendrimer shows excellent serum resistance and exhibits high gene transfection efficacy even in medium containing 50% fetal bovine serum. Apart from PAMAM dendrimers, different generations of PPI dendrimers were also studied as gene vectors. In order to improve the transfection efficacy and decrease the cytotoxicity of PPI dendrimers, Liu *et al.* [109] prepared a series of fluorinated PPI dendrimers including G3, G4, and G5 PPI dendrimers. The studied fluorinated PPI dendrimers showed comparable or superior transfection efficiency to that of Lipofectamine 2000, jetPEI, branched poly(ethyleneimine), SuperFect, PolyFect, as well as arginine-modified dendrimers in HEK293, HeLa cells and 3D multicellular spheroids.

Combination therapy

The commonly used chemotherapeutic agents often have limited therapeutic effectiveness because of undesirable side effects, multidrug resistance and poor drug delivery efficiency to the interior of the solid tumor due to the abnormal vessel and anoxic microenvironment of tumors [134]. Each mode of radiotherapy, PTT, PDT and gene therapy has its own disadvantages and limitations. Therefore, combination therapy seems to be necessary to improve the therapeutic effect [51,97,135]. For instance, the combination of PTT and chemotherapy (photothermal-chemotherapy) has been proven to be more effective than the respective monotherapy because additive

or synergistic effects can be realized [136–138]. Dendrimers can also act as a valuable platform for combination cancer therapy. Li *et al.* [86] prepared G4 PAMAM dendrimer-stabilized GNRs to conjugate DOX with a pH-sensitive linker for combined cancer photothermal-chemotherapy under *in vitro* and *in vivo* conditions. Both *in vitro* cytotoxicity and live cell staining assays validated the synergistic photothermal-chemotherapy effect of PEG-DOX-PAMAM-AuNR on HeLa cells. The *in vivo* studies of the PEG-DOX-PAMAM-AuNR (irradiation +) group exhibited remarkable tumor growth delay on day 16, underscoring the great potential of PEG-DOX-PAMAM-AuNR for combination cancer therapy. For combination radiotherapeutic-photothermal therapy, the dendrimer nanoplatfrom has been designed to label with radioisotopes and entrap or stabilize some nanoparticulate PTT agents, such as Au NPs [126]. Besides these two types of combination described above, there are other combination therapy strategies including PTT-PDT [123,139,140], genetic-chemotherapy [134,135], genetic-PDT [141] and genetic-PTT [51,97].

Gene therapy are often used as a complementary therapy to combine with other approaches. For instance, Shi's group developed two different nanoplatfroms for combination gene and PTT of tumors based on PAMAM dendrimer-stabilized Au nanostars (NSs) [51] or MoS₂ nanoflakes [97]. In their study, RGD-modified dendrimer-stabilized Au NSs (RGD-Au DSNs) with a mean diameter of 52.2±14.2 nm for the Au NSs exhibited an apparent surface plasmon resonance (SPR) peak at around 800 nm. The RGD-Au DSNs were used to compact Bcl-2 siRNA for targeted PTT and gene therapy of cancer cells *in vitro* and the xenografted tumor model *in vivo* under the irradiation of an 808 nm laser (Fig. 9) [51]. Different from the Au NSs, MoS₂ nanoflakes displayed strong NIR absorption in a wide spectral range. Combinational PTT and gene silencing of cancer cells *in vitro* showed that the cell inhibition efficacy followed the order of G5-MoS₂/siRNA polyplexes+laser (21.0%) > G5-MoS₂+laser (45.8%) > G5-MoS₂/siRNA polyplexes (68.7%), demonstrating significant enhanced cancer cell inhibition efficacy [97].

CONCLUSIONS AND FUTURE PERSPECTIVES

In summary, this review has described the recent advances of different dendrimer-based platforms for various strategies developed for cancer therapy. The periphery of dendrimers can be diversely functionalized with PEG, zwitterions, glycosyl, and targeting agents to improve the

Figure 9 Schematic illustration of the formation of the RGD-Au DSNs for CT/thermal imaging and combinational therapy of tumors. Reproduced with permission from Ref. [51]. Copyright 2016, WILEY-VCH.

therapeutic efficacy. The unique structural properties of dendrimer platform enable the drug to be physically loaded within the dendrimer interior *via* hydrophobic interactions or covalently conjugated onto the dendrimer surface *via* covalent reaction. Meanwhile radioisotopes and other chemical agents can be introduced to the dendrimer surface for radiotherapy, photothermal and photodynamic therapy. Apart from the photosensitive materials like ICG and IR-780, a range of inorganic NPs such as CuS NPs, Au NSs and MoS₂ nanoflakes have been integrated with dendrimers *via* entrapment or stabilization strategy for PTT of tumors. The inherent surface cationic amines of dendrimers not only enable the diverse modification but also make it possible to condense nucleic acid materials for gene delivery. More importantly, the dendrimers can also serve as a platform for combination cancer therapy to induce combined or synergistic therapeutic efficacy. Therefore, dendrimers have been truly demonstrated as a unique platform for construction of different multifunctional nanoplatfroms for cancer therapy applications.

Although many studies have been focused on the improvement and optimization of dendrimer-based platform for cancer therapy, dendrimer-based systems with higher biocompatibility, enhanced efficacy of treatment and metabolism mechanism still remain to be explored. For example, zwitterion-modified dendrimers with anti-fouling properties have shown to be protein-resistant [45] and antifouling dendrimer-entrapped gold nanoparticles can be used for enhanced CT imaging of blood pool and tumors [46]; however the antifouling dendrimer-based drug delivery or theranostic platforms have not been re-

ported in the literature. Furthermore, apart from ^{131}I and ^{77}Lu , there are few other radionuclides have been introduced to dendrimers for radiotherapy. X-ray and gamma-ray radiation by irradiator have been reported to be effective for radiotherapy with radiosensitizer for radiation enhancement effect [142,143]; however this radiotherapy mode has not been combined with dendrimer-based nanodevices. In addition, by combination of dendrimers with other vectors such as carbon nanotubes [144] and laponite [145], more advantages for cancer therapy can be endowed. For instance, dendrimer-modified carbon nanotubes enabled high drug payload and encapsulation efficiency both up to 97.8% and can be used for targeted and pH-responsive delivery of DOX into cancer cells [144]. However, these studies need to be further explored for *in vivo* tumor model investigations.

Although the dendrimer-based strategies for antitumor therapy have been well studied, much room remains to be explored and addressed to improve their efficacy of treatment and find out their metabolic mechanism of safety concerns. The clinical translation of dendrimers has not yet been achieved. Currently, DEP® cabazitaxel has received regulatory and ethics approval to commence its phase I/II clinical trial. It is the second product from Starpharma's DEP® platform to enter the clinic following the DEP® docetaxel, which delivered positive phase I clinical results in 2017 and recently progressed to phase II. The reproducible benefits observed for DEP® docetaxel and DEP® cabazitaxel in preclinical models include decreased bone marrow toxicity and enhanced efficacy, and in both cases DEP® has also allowed for a detergent-free formulation resulting in significant additional benefits for patients (<http://www.starpharma.com>). Hence, there is still long way to go for the effective development of dendrimer-based nanomedicine. Improvements can be made through deep understanding the tumor micro-environment, tumor metabolism, and tumor metastasis to further design suitable multifunctional dendrimer-based platforms for enhanced therapy.

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基于树状大分子的癌症治疗策略: 最新进展和未来展望

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摘要 本文综述了一些基于树状大分子体系应用于癌症治疗的研究进展。树状大分子拥有高度支化的三维球状结构、内部疏水空腔以及多种表面功能基团, 因而可以作为药物和纳米颗粒的载体或者稳定剂。装载了治疗试剂(如药物、siRNA或者纳米颗粒)的纳米平台可进一步被修饰而获得靶向特异性、抗污性能和良好的生物相容性。本文详细介绍了树状大分子表面修饰并作为多功能平台应用于对癌症的不同治疗手段的进展, 包括: 化疗、放疗、光热治疗、光动力治疗、基因治疗以及联合治疗。