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

Supramolecular dendritic polymers for diagnostic and theranostic applications

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ABSTRACT Supramolecular dendritic polymers (SDPs) provide a new opportunity for the precision diagnosis and treatment of diseases. SDPs are a novel class of non-covalently bonded macromolecules with highly branched structure and three-dimensional globular topology, which exhibit dynamic/reversible features and unique physical/chemical properties (e.g., high solubility, low viscosity, and numerous functional terminal groups). The reversibility of non-covalent interactions endows SDPs with the ability of facile preparation, smart responsiveness, and simple metabolism. These special characteristics determine the properties of SDPs, which are the key points for theranostic applications, including diagnosis, therapy, and theranostics. In this review, we briefly summarize the design and synthesis of SDPs with aimed structures, properties, functions as well as their present diagnostic and theranostic applications. These developments on the preparation and applications of SDPs for diagnostic and theranostic purpose promote interdisciplinary research fields of chemistry, material and biomedical science.

Keywords: dendritic polymers, supramolecular polymers, diagnosis, therapy, theranostics

INTRODUCTION

The diagnosis and therapy of various diseases have attracted more and more attention in recent years. To realize an efficient treatment, biocompatible and biodegradable polymers are frequently used as carriers, probes or therapeutic agents because of their macromolecular scale and smart responsiveness. Comparing to the traditional linear polymers, dendritic polymers exhibit tree-like topological structures, a high density of terminal

groups, and precise spatial control [1–3]. Therefore, dendritic polymers show great potential in various biomedical fields, especially for the diagnosis and therapy. However, there are still several obstacles for their diagnostic and theranostic applications: (1) multiple and complicated synthetic and purification steps of dendritic polymers result in ill-defined structure, low scalability and high cost; (2) uncontrollability of the ratio of diagnostic probes and therapeutic agents in dendritic polymers induces the poor reproducibility; (3) inconclusive bio-safety of dendritic polymers due to their potential toxicity, unpredicted bioelimination and long-term *in-vivo* effect limits their clinical transformation [4,5].

The appearance of supramolecular dendritic polymers (SDPs) provides a new opportunity for solving the abovementioned problems. As an elegant bridge to combine supramolecular chemistry and dendritic polymer, SDPs show dynamic/reversible features and unique physical/chemical properties [6]. Owing to the introduction of non-covalent interactions into polymeric backbone, SDPs are endowed with several particular advantages: facile synthesis and purification, switchable structures and shapes, and smart stimuli-responsiveness [7–9]. Different from conventional dendritic polymers, SDPs have a large number of complementary binding sites for building blocks because of their topological structures, which influences their morphology and functions. The highly branched three-dimensional architectures of SDPs result in attractive properties such as little molecular entanglement, low viscosity, high solubility, and a lot of functional terminal groups. Usually, hydrogen bonding, host-guest interaction, metal-ligand

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coordination, and π - π stacking are applied to construct SDPs. Nowadays, SDPs have been widely used in biomedical fields. Although many elegant reviews on SDPs have been published [6–13], to the best of our knowledge, a systematic review on the synthesis and theranostic applications of SDPs has not yet been published.

Herein, we summarize several design and synthesis strategies of SDPs, together with the diagnostic and theranostic-related properties derived from SDPs' structures and highlight the latest theranostic applications. We try to outline these exciting achievements of SDPs for diagnosis, therapy and theranostics, and hope to inspire continuous endeavors in this emerging research field.

DESIGN AND SYNTHESIS

Viewing from the regularity of branching structure, SDPs systems could be generally divided into supramolecular dendrimers (SDs) [14–18] and supramolecular hyperbranched polymers (SHPs) [19,20]. We will briefly summarize the difference in design strategy for SDs and SHPs, highlighting the methodology in synthesis. As increasing demands and interests in supramolecular hybrids, we will also give some discussion on supramolecular hybrid dendritic polymers [21–27] in the end of this section.

Supramolecular dendrimers (SDs)

In order to achieve regular and highly branched architecture, it usually needs multiple steps and sophisticated design of building blocks to fabricate SDs. Generally, the synthesis methods include template-directed approach and nontemplated approach.

In template-directed approach, branched structures are usually applied as core or subunits, acting as branching template. Zhang and coworkers utilized a three-fold β -cyclodextrin (CD_3) as the branching template, linking oligo(ethylene glycol) (OEG) chains *via* host-guest interaction (Fig. 1). A second-generation supramolecular dendrimer was obtained through dendritic design of the OEG guests [28].

In nontemplated approach, the accuracy of the dendritic structure relies on well-designed, smaller dendritic subunits as building block. The saturability and directionality guarantees the building of polymer in a controllable way. Percec and co-workers have reported various monodendrons by nontemplated approach [29]. Recently, they reported a library of six dendritic monomers containing 12-4EO-PMA and related dendronized polymethacrylates and polyacrylates which were self-assembled with methacrylate or acrylate apex *via* single-

Figure 1 Building blocks and synthesis route for template-directed approach. Reprinted with permission from Ref. [28]. Copyright 2012, Wiley-VCH.

electron transfer living radical polymerization. Zimmerman and coworkers synthesized a dendrimer with complementary donor-donor-acceptor and acceptor-acceptor-donor *via* hydrogen bonding. They got disk-shaped particles with very good stability [30].

Supramolecular hyperbranched polymers (SHPs)

Different from SDs, irregular branched structure is the key factor for SHPs. Feasible synthesis method, such as one-step fabrication, is usually used to fabricate SHPs, resulting in efficient structure-property regulation and various application explorations [31,32]. Single monomer strategy and double-monomer strategy are typical methods for SHPs fabrication.

In single monomer strategy, one heterotropic monomer (AB_n type monomer, $n \geq 2$) are used to construct SHPs [33]. Huang and coworkers designed a AB_2 monomer containing a bis(*m*-phenylene)-32-crown-10 core and two pendant paraquat arms, driving it to self-recognition to obtain a new SHP [34] (Fig. 2A). In double-monomer strategy, heterocomplementary monomers A_n and B_m ($n \geq 2$, $m \geq 3$) are usually used to obtain SHPs. For example, we reported an A_2/B_3 type SHP through host-guest interaction between an azobenzene (Azo) dimer and a β -CD trimer (Fig. 2B). Benefiting from the light-responsive building blocks, this SHP is photoreversible between polymerized and depolymerized states under ultraviolet (UV) and visible-light irradiation [35].

Figure 2 (a) Preparation of AB_2 -type SHPs through self-recognition. Reprinted with permission from Ref. [34]. Copyright 2004, American Chemical Society. (b) Preparation of photoreversible A_2/B_3 -type SHPs. Reprinted with permission from Ref. [35]. Copyright 2011, Royal Society of Chemistry.

Supramolecular hybrid dendritic polymers (SHDPs)

Supramolecular hybrid dendritic polymers (SHDPs) have drawn significant attention in various fields, due to their combination of multiple advantages. Topologically, some SDPs hybridize both advantages of dendritic and linear polymers, forming head-tail like supramolecular hybrids, star-like hybrids, and even more complicated topologic structures. Viewing from component, certain supramolecular systems combine inorganic materials with organic ones, achieving diverse functions. Among various SHDPs, supramolecular hybrid dendrimers own well-defined structure, but the synthesis route always involves multiple procedures. On the other hand, the preparation of supramolecular hybrid hyperbranched polymers is much easier at the expense of structural regularity.

Topological hybrids

A head-tail like SHDP usually employs a linear part as the tail and a dendritic part as head. Non-covalent interaction is then utilized to link the head and tail together, forming the final hybrids. With the unique topological structures, this type of supramolecular hybrids could be self-assembled into diverse morphologies, including cylinders,

Figure 3 Preparation of supramolecular topological hybrids with head-tail shape. Reprinted with permission from Ref. [22]. Copyright 2012, American Chemical Society.

fibers and so on. Zhou, Yan and coworkers [22] designed a hyperbranched polyglycerol grafted from β -CD (CD-g-HPG), and linked a long alkyl chain as tail through host-guest interaction. The resulting supramolecular hybrids self-assembled into unilamellar vesicles in aqueous solution (Fig. 3). Ji and coworkers [36] reported a novel dual-responsive SHDP by utilizing the supramolecular interaction among cucurbit[8]uril (CB[8]) and methyl viologen (MV) and indole. Then, the SHDP self-assembled into micelles and showed dual-responsive abilities when a competitive guest molecule or a reducing agent exists. Kim and Voit [37,38] fabricated a series of compounds containing calix[4]arene core moieties with dendritic polymers on them. These calixarene cores could be recognized by hydrophobic moieties with linear tails, so they are potential to be applied into SHDPs.

Supramolecular star-shape polymers are made of linear polymers as arms as well as a dendritic core with non-covalent linkage, which can also be regarded as a hybrid of polymers with different topology. Three or more arms with identical or distinct polymeric chains radiate from one core to form star-shape polymer. Special properties like various loading capacities and Janus shape could be achieved by novel design of supramolecular star-shape polymers [23,39–43].

Organic-inorganic hybrids

Besides certain organic molecules, inorganic materials also exhibit strong non-covalent interactions and thus form supramolecular systems [44,45]. Metal ions and ligands act with tunable coordination and strong binding strength. They provided accurate coordination number and direction, which makes organic-inorganic supramo-

Figure 4 Structure illustration of supramolecular organic-inorganic dendritic hybrid with a poly-oxometalate cluster $[\text{Gd}(\beta_2\text{-SiW}_{11}\text{O}_{39})_2]^{13-}$ as inorganic core and hyperbranched polymer (D-3) as arms. Reprinted with permission from Ref. [47]. Copyright 2017, Wiley-VCH

lecular dendritic hybrids a popular and useful system in a wide application [14,46]. Li and coworkers [47] developed a novel SDPs with inorganic gadolinium-substituted polyoxometalate as core and organic hyperbranched amphiphilic polymer as arms (Fig. 4). The core and arms could be assembled together through electrostatic interaction. Gu and coworkers [48] reported a self-assembled dual-functionalized low-generation supramolecular hybrid peptide dendrons (PDs) by coordination interactions. The PDs were functionalized with arginine for enhancing internalization and endosomal escape and the core of PDs were modified with lipoic acid (LA) for coordinating potentials.

PROPERTIES AND SELF-ASSEMBLY BEHAVIOR

Aqueous compatibility and biodegradability

In nature, most biological processes occur in aqueous system. In this case, good aqueous compatibility is a fundamental factor for SDPs for biological application. However, imaging probes and therapeutic agents are usually of high hydrophobicity. Luckily, various building blocks, such as CD, cucurbit[*n*]uril and sulfonate calixarene can recognize and include certain hydrophobic

guest species [36,49], which provide feasibility to obtain supramolecular system with good aqueous solubility [50–53]. Normally, good aqueous compatibility is basic for biocompatibility. The long-term accumulation is another safety concern in biomedical application. Most polymers lose the bio-application chances due to unbreakable conjugation and undegradable property. Supramolecular systems, however, are connected by a dynamic/reversible non-covalent interaction [54–56]. They can be spontaneously degraded or metabolized in physiological environment, exhibiting universally better biodegradability than covalently bonded polymers [57–59].

Stimuli-responsiveness

During biological use, especially in diagnosis and therapy, fast and smart stimuli-responsiveness is highly favored, because the environmental factors in living system could be altered in very limited scope. SDPs, which can respond to internal stimuli such as pH [50,51], redox [14], voltage [50] and enzyme [53], are usually exhibiting good release behavior or high contrast signals when using as delivery vehicles for drugs or imaging probes. At the same time, the ones responsive to external stimuli such as temperature [30,31,56], light [12,35,55], ultrasonic signal and magnetic field, can be fabricated into smart *in vitro* diagnosis or therapeutic devices [60–68].

Self-assembly behavior

Similar to traditional polymer systems, the main driving force for SDPs to self-assembly is hydrophobic interaction [65]. As a dynamic switching system, however, a typical SDPs self-assembly process usually involves two stages, firstly forming primary structure through supramolecular interaction then obtaining secondary structure through self-assembling [66]. Both of the above stages rely on non-covalent interactions. In order to achieve clear and stable primary structure as well as secondary structure, stronger interactions are usually employed in supramolecular stage. Through sophisticated design of the supramolecular system, diverse morphologies can be achieved including spherical micelles, cylindrical micelles, fibers, nano-rings and tubular vesicles [15–18,22,36,37,67].

BIOMEDICAL APPLICATIONS

Combining both advantages of dendritic polymers and supramolecular polymers, SDPs have shown great potential in biomedical application. With a three-dimensional globular topological structures, SDP own plenty of inner cavities and terminal groups, and therefore their

loading capacity and surface functions can be easily regulated. Favored functions in biomedical application, such as imaging probe loading, drug loading, targeted surface and stimuli-response, can be designed and integrated into one SDP [23]. Benefitting from the dynamic/tunable nature of non-covalent interactions, SDPs can undergo reversible switching of morphology, structures and functions. In this section, we will introduce several eye-catching studies to indicate new trends of biomedical application of SDPs in bio-imaging and diagnostic, therapeutic and theranostic applications [69–71].

Bio-imaging and diagnosis

Benefitting from the topological structures, SDPs are able to load various imaging probes, which provide safe and favored imaging environment *in vitro* and *in vivo*. Up to now, plenty of types of imaging probes, including fluorescent probes [42], ultrasound [72] and magnetic resonance imaging (MRI) contrast agents [73–75], and NIR imaging probes [74], have been successfully integrated in SDPs for bio-imaging and diagnosis.

Wu and coworkers reported a novel SDP for *in vivo* MRI imaging [75]. An inorganic metal-oxide nanocluster polyoxometalate (POM) was utilized as both Gd ligand and template. Tri(ethylene glycol) monomethyl ether (TEG) terminal groups in two generation was used to encapsulate Gd-POM through electrostatic interaction, which provides *in vivo* stability as well as good water permeation for higher relaxivity of Gd, resulting in enhanced *in vivo* imaging capacity (Fig. 5).

Therapeutic application

Controllable release of loading therapeutics is an ultimate goal for drug delivery system, and therefore an integrated delivery system is favored. Covalent conjugation based systems, however, naturally possess low degradation behavior, which causes the poor permeation into biological barriers and low release rate of therapeutics [77–79]. Benefitting from the dynamic/reversible feature, SDPs have been regarded as a promising platform for therapeutics delivery.

A large number of SDPs have been applied to load pharmaceutical agents, including chemo-drugs [80,81] and photosensitizers [82], resulting in optimized delivery and releasing behaviors like prolonged circulation time, accumulation in tumor sites, controlled drug release and reduced side effects. A significant reason for above phenomenon is that SDPs are built *via* non-covalent interaction and able to rapidly respond to environmental

Figure 5 (a) Structure illustration of MRI contrast agent Gd-loaded SDPs with hydrophobic core and hydrophilic arms. (b) T1-weighted images (i) and columnar plots of mean MRI enhancement efficiency (ii) of at liver after post intravenous injection of SDPs. Reprinted with permission from Ref. [75]. Copyright 2017, Royal Society of Chemistry.

changes.

Other than drug delivery, gene delivery is equally important in treating diseases, and non-viral delivery systems based on cationic materials have gained much attention [83,84]. Cationic materials based on covalent interaction always suffer from several disadvantages, including tedious synthesis and lack of responsiveness [85–87]. SDPs offer new opportunities for novel gene delivery vehicles, with dynamic cationic structure and tunable performance. Up to now, different kinds of genetic therapeutics, including DNA [88], siRNA [89] and interfering RNA [90] have been successfully compacted with SDPs, showing comparable gene transfection efficiency with covalent systems.

Our group has developed a facile approach for charge-

Figure 6 (a) Structure illustration of cationic SDPs with controllable amine type and charge density. (b) Luciferase expression of cationic SDPs in COS-7 cell line. Reprinted with permission from Ref. [43]. Copyright 2011, Royal Society of Chemistry.

tunable cationic SDPs for gene delivery. This system is composed of adamantane-modified hyperbranched polyglycerol (HPG), primary-amine- and tertiary-amine-modified β -CD derivatives (Fig. 6). By regulation of feed ratio of two cationic β -CD building blocks, controllable amino types and controllable charge density could be achieved, which further influenced the DNA condensation capability and buffer capacity, together with gene transfection efficiency [43].

Theranostic application

Theranostic system combining diagnosis with therapy together, is a favored approach in clinical application. These two factors can coordinate with each other, providing integrated information on disease location, drug release profile and treatment feedbacks, all of which are suggestive for further treatment.

SDP-based theranostic system is an elegant combination of supramolecular chemistry, topo-chemical science, imaging science and pharmaceutical science. SDPs are usually constructed from multiple non-covalent interactions, providing diverse and suitable physical/chemical environment for imaging probes and therapeutics. A number of pilot studies has proved its high efficiency and practicability [49,78,79,83]. Gu and coworkers [76] reported a platinum-based supramolecular dendritic system for efficient delivery of chemo-drug and near-infrared (NIR) agents. Supramolecular dendritic systems were stabilized by disulfide bonds and endowed with NIR fluorescence probes. Then PEGylated platinum derivatives were coordinated onto the abundant peripheral groups of supramolecular dendritic templates to generate

pH/redox dual-responsive theranostic supramolecular PEGylated dendritic systems (Fig. 7).

CONCLUSIONS

In this review, we have summarized the current progress in the preparation and theranostic applications of SDPs. From structural perspective, both non-covalent interactions and three-dimensional topological structures play an important role in the physicochemical properties of SDPs. Owing to the introduction of non-covalent interaction into dendritic polymeric backbone, the SDPs not only display dynamic regulation of specific structures and functions when exposed to external stimuli, but also keep the advantages of dendritic polymers. Correspondingly, SDPs exhibit the abilities of facile synthesis, good biocompatibility, inherent biodegradability, smart responsiveness, simple metabolism, and scaled preparation, which are very attractive for biomedical science. Therefore, SDPs have become an excellent platform for the diagnostic and theranostic applications.

Although great progress has been made in the field of SDPs for diagnostic and theranostic applications, this research field is still far away from sufficient and continuous efforts are particularly required. For example, the construction methods of SDPs are quite limited and current SDPs are simple and monotone. The excretory and metabolic pathways of SDPs in cells and body are not reported and the molecular interactions between SDPs and cells is unclear. More importantly, all SDPs investigations focus on the cell evaluation and mice experiments. To meet the requirements of clinical trial, the design of biocompatible and biodegradable SDPs with

Figure 7 (a) Schematic illustrations for molecular and supramolecular engineering of theranostic supramolecular PEGylated dendritic systems. (b) *In vivo* and *ex vivo* NIR imaging of nude mice bearing A549 tumor xenografts and their organs before and after 24 hours intravenous injection of saline and TSPDSs. (c) Pharmacokinetic profiles of TSPDSs and cisplatin and distribution of platinum in kidney and tumor after intravenous injection, respectively. (d) Blood urea nitrogen (BUN) and creatinine level with different administrations after a treatment course of 21 days. Reprinted with permission from Ref. [76]. Copyright 2016, Ivyspring International Publisher.

precise structures have become very urgent and important. Frankly speaking, the process of paving SDPs into diagnostic and theranostic clinical applications will be long and full of difficulties. Nevertheless, we believe that with the rapid development in this research field, the present problems will be resolved in the near future.

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超分子枝状聚合物用于疾病诊断与治疗

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摘要 超分子枝状聚合物(SDP)为疾病的诊断与治疗提供了新的方法. 这种聚合物具有非共价链接的大分子与枝状结构以及三维管状结构. 这种结构形成了动态可逆的理化特性(如高溶解性, 粘度低以及富含大量的功能团端基). 可逆的非共价相互作用使得SDP易于制备, 具有智能响应以及良好的代谢性. 这些特性决定了SDP在疾病诊断与治疗中起到关键性作用. 本综述简要总结了具有特定结构、性质和功能的SPD分子的合成与设计. SPD在诊断治疗中的应用促进了化学、材料科学以及生物医学的交叉研究.