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Stimuli-responsive dendrimers in drug delivery

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Abstract

Dendrimers have shown great promise as carriers in drug delivery due to their unique structures and superior properties. However, the precise control of payload release from a dendrimer matrix still presents a great challenge. Stimuli-responsive dendrimers that release payloads in response to a specific trigger could offer distinct clinical advantages over those dendrimers release payloads passively. These smart polymers are designed to specifically release their payloads at targeted regions or at constant release profiles for specific therapies. They represent an attractive alternative to targeted dendrimers and enable dendrimer-based therapeutics to be more effective, more convenient, and much safer. The wide range of stimuli, either endogenous (acid, enzyme, and redox potentials) or exogenous (light, ultrasound, and temperature change), allows great flexibility in the design of stimuli-responsive dendrimers. In this review article, we will highlight recent advances and opportunities in the development of stimuli-responsive dendrimers for the treatment of various diseases, with emphasis on cancer. Specifically, the applications of stimuli-responsive dendrimers in drug delivery as well as their mechanisms are intensively reviewed.

1. Introduction

Dendrimers are a class of synthetic macromolecules with a tree-like structure [1-3]. They have well-defined nanostructures with globular shapes, high density of surface functionality, limited immunogenicity, excellent monodispersity and solubility [4-6]. Compared with traditional linear and branched polymers, dendrimers possess the following advantages for biomedical applications: (1) the excellent monodispersity of dendrimer allows reproducible pharmacodynamic (PD) and pharmacokinetic (PK) behaviors, while the polydispersity of traditional polymers causes serious restrictions in PD and PK aspects in clinical trials [7]; (2) the well-defined size, structure, and molecular weight of dendrimers satisfies various applications, researchers just need to choose proper dendrimer generation [8]; (3) the high density of surface functional groups on dendrimers ensures synergistic/multivalent binding in ligand/receptor recognition [9]; (4) the globular architecture of dendrimers with controllable sizes allows them to mimic proteins without immunogenicity [10]; (5) the rapid and exciting progress in dendrimer synthesis such as click chemistry brings out a lot of interesting, aesthetic, and versatile dendrimers, providing great flexibility in the construction of dendrimer-based therapeutics [11, 12]; (6) dendrimers with excellent solubility and high reactivity can be modified with various ligands such as targeting moieties, imaging probes and biocompatible ligands for specific therapies [13]. Owing to these unique properties, dendrimers are of great interest to researchers in drug and gene delivery [14-18]. For drug delivery, the interior pockets of dendrimers can encapsulate drug molecules via non-covalent interactions such as electrostatic, hydrophobic, and

hydrogen-bond interactions, while the surface functionalities of dendrimers can be conjugated with drugs via covalent linkages [5, 19-23]. For gene delivery, the cationic dendrimers with a multivalent display of cationic groups on the surface can efficiently condense nucleic acids into nanoparticles (dendriplexes), which is beneficial for efficient cell endocytosis [16, 17]. In addition, the abundant tertiary amine groups within dendrimers such as polyamidoamine (PAMAM) and poly(prophylenimine) (PPI) can promote the endosomal escape of dendriplexes through a "proton-sponge" effect [8, 24, 25]. Besides these features, the dendrimer surface can be easily modified with various functional moieties for targeted diagnosis and therapy [13, 26]. The hyperbranched structure of dendrimers offers unique interfacial and functional performance advantages [27].

However, the performance of dendrimer-based delivery systems is usually impeded by non-specific drug or gene release, which results in limited therapeutic efficacy and undesired adverse effects [28]. Though targeted dendrimers can improve the polymer concentration at specific tissues, it is still difficult to precisely control the release of drug at the target site [29]. For example, anticancer drugs loaded within folic acid-targeted dendrimers via non-covalent interactions show a burst release profile before the accumulation of dendrimers at tumor site [30], while drugs conjugated to targeted dendrimers via ester bonds are too stable to archive the minimum effective concentration to kill cancer cells. A solution to this problem is to develop responsive systems that mimic the responsiveness of living organisms [31]. These stimuli-responsive delivery systems are actuated by an internal trigger such as tumor

acidity, redox potential, enzyme and hypoxia, and offer distinct advantages over those that release payloads passively [29, 31-33]. The drug release profiles can be easily tailored to achieve on-demand therapy. For delivery systems that are sensitive to remote triggers such as light, ultrasound and magnetic field, the payload release kinetics show a spatially and temporally controlled manner, which is beneficial for local drug delivery [34]. Among the developed systems, stimuli-responsive dendrimers have shown great promise in drug delivery [4, 31, 33, 35-39]. This review article will highlight novel strategies in the design of stimuli-responsive dendrimers, with emphasis on research in the past five years. Strategies adopted in the design of stimuli-responsive dendrimers in this review include (1) construction of dendrimer-payload conjugates with stimuli-cleavable linkages, (2) preparation of responsive micelles consisted of amphiphilic dendrimers or dendritic polymers for payload encapsulation, (3) synthesis of self-immolative dendrimers that degrade into small molecules upon exposure to a specific trigger, and (4) conjugation of dendrimers with responsive ligands which are able to activate dendrimer internalization or targeting after stimulation. The review will be organized depending on the widely used stimuli including acid, reduction potential, enzyme, light, and temperature. The concept and features of each type of stimuli-responsive dendrimers will be discussed.

2. Stimuli-responsive dendrimers in drug delivery

2.1. Acid-responsive dendrimers

Acid-responsive delivery systems are the most widely investigated stimuli-responsive

systems, especially in cancer therapy [40, 41]. Aerobic glycolysis is a recognized hallmark of malignant cancers. The cancer cells show increased glucose uptake and elevated lactic acid production under aerobic glycolysis, a phenomenon termed the Warburg effect [42]. As a result, the pH value of the extracellular environment of solid tumors (pH 6.5-6.8) is slightly lower than that of normal tissues (pH 7.2-7.4) [43]. The weakly acidic feature of tumor extracellular environment can trigger the release of payloads from acid-responsive materials in the tumor region [44]. Alternatively, the tumor extracellular acidity activates the cellular uptake of charge-reversal materials [45, 46]. Compared to traditional cancer biomarkers such as EGFR, Her/neu and PSMA, tumor extracellular acidity is independent of tumor phenotype [43, 47]. Therefore, tumor extracellular acidity has been widely used as a stimulus in the design of stimuli-responsive drug delivery systems for cancer therapy. Besides tumor extracellular acidity, the acidity of organelles such as endosomes and lysosomes (pH 5.0-6.0) within cancer cells can be used as a trigger to actuate payload release [48].

Dendrimer-drug conjugates via acid-labile bonds. Hydrazone linkage was widely used in the synthesis of dendrimer-doxorubicin prodrugs (**Fig. 1a**) [49-53]. The linkage is stable against hydrolysis at pH 7.4, but is cleavable under acidic conditions. Therefore, the prodrug remains non-toxic during blood circulation. After reaching tumors, the cleavage of doxorubicin from the dendrimer matrix is turned on by tumor extracellular acidity (pH 6.5-6.8), and the doxorubicin release rate is accelerated after endocytosis of the prodrug by cancer cells (pH 5.0-6.0). Besides doxorubicin, the hydrazone linkage is applicable for other drugs containing a ketone or aldehyde group

[35].

Boronate ester bond was recently employed to develop bortezomib prodrugs [54, 55]. Bortezomib is an anticancer drug for the treatment of multiple myeloma. Systematic administration of bortezomib was reported with high risk of adverse effects such as cardiotoxicity and thrombocytopenia. When bortezomib was conjugated to a catechol-modified PAMAM dendrimer via boronate ester bond (**Fig. 1b**), the yielding prodrug is stable at physiological pH and exhibits fast drug release under tumor extracellular acidity (pH 6.5) [44]. Since the prodrug is scarcely internalized by cells due to its neutral surface, the bortezomib release will not be triggered by lysosomal acidity, which reduces bortezomib cytotoxicity to normal cells. As a result, the prodrug is non-toxic to several cells at pH 7.4 (up to 1000 nM), but can efficiently kill cancer cells at pH 6.5 (IC_{50}=120 nM for HeLa cells and 194 nM for MDA-MB-231 cells). This "off-on" drug release behavior can improve the therapeutic efficacy and minimize the adverse effects of bortezomib. Similarly, PAMAM dendrons with a salicyl hydroxamate core were attached to boronic acid-modified proteins via acid-labile boronic acid/salicyl hydroxamate ligation (**Fig. 1c**) [56]. The cationic dendrimers can successfully deliver attached protein drugs into cells and efficiently release the proteins under endolysosomal acidity (pH 5.0). Besides, platinum-based anticancer drug diaminocyclohexyl platinum (II) (DACHPt) was conjugated to a peptide dendrimer via *N*,*O*-chelate coordination (**Fig. 1d**) [57]. The platinum prodrug is relatively stable under pH 7.4 but undergoes rapid drug release at pH 5.0. Due to the acid-responsive behavior, the prodrug shows superior anticancer activity and minimal

adverse effects to oxaliplatin in ovarian cancer therapy.

Dendrimers conjugated with acid-activable ligands. When dendrimers were modified with acid-responsive ligands, endocytosis of the dendrimers can be activated under acidic conditions. pH (low) insertion peptide (pHLIP) is an acid-responsive peptide. At neutral pH, pHLIP binds weakly to cell membranes, whereas at acidic microenvironments (pH 6.5) it inserts across the cell membrane and forms a transmembrane α-helix [58]. pHLIP can translocate a drug, imaging probe, nucleic acid, or nanoparticle into a cell under tumor extracellular acidity [59-63]. pHLIP-conjugated polylysine dendrimer shows an interesting pH-responsive gene expression behavior (**Fig. 1e**), and facilitates gene internalization into cancer cells under acidic microenvironments. Besides, the dendrimer inhibits tumor growth via improved expression of plasmid encoding short interfering RNA (siRNA) targeting vascular endothelial growth factor [64]. In a separate study, cationic PAMAM dendrimers were modified with maleyl groups via acid-labile amides (**Fig. 1f**) [65]. This modification deactivates the primary amine groups of dendrimer to negatively charged amides, which are further converted to cationic dendrimers after reaching acidic vesicles such as lysosomes. This charge-reversal strategy is essential for endosomal escape and nuclear entry of the loaded drugs.

Assembled dendrimers with acid-responsive property. Acid-responsive dendrimers can also be designed by pH-driven assembly-disassembly. Amphiphilic dendrimers are assembled into micelles under specific pH

conditions, and the assembled structures trend to disassemble into monomolecules or reorganize into structures with a distinct conformation due to altered hydrophilic-lipophilic balance (HLB). The disassembly of dendrimer-based polymeric micelles can be driven by protonation, deprotonation, and acid cleavage of acetal (**Fig. 2a**) or boronate ester bonds (**Fig. 2b**) [66-73]. As a result, the loaded drugs within the polymeric micelles may undergo pH-responsive release. These acid-responsive dendrimers facilitate the specific delivery of drugs with improved delivery efficacy and reduced adverse effects.

It is worth noting that acidity of organelles such as endosomes and lysosomes in normal cells may also activate the release of anticancer drugs from acid-responsive dendrimers after its cell internalization. This may cause non-negligible adverse effects and poor therapeutic outcomes. To avoid the triggered release of anticancer drugs by acidic vesicles in normal cells, the dendrimer surface should be modified with ligands to reduce non-specific cell internalization. Alternatively, a targeting ligand should be conjugated to dendrimer surface to deliver the responsive dendrimers to specific tumors.

2.2. Reduction-responsive dendrimers

It is reported that reducing thiols such as glutathione (GSH) are abundant in cells. The concentration of intracellular GSH (0.5-10 mM) is about 2-3 orders of magnitude higher than that of extracellular GSH (2-10 μM) [31]. Cancer cells are under oxidative stress associated with elevated reactive oxygen species (ROS) [74]. They adapt to

oxidative stress by upregulating reducing GSH to counteract the ROS [74]. As a result, the GSH concentration in cancer cells is several-fold higher than in normal cells [75]. The significant difference between intracellular and extracellular GSH concentrations especially in cancer cells has motivated the researchers to design GSH-responsive delivery systems for efficient drug delivery.

Dendrimer-drug conjugates via reduction-labile bonds. Disulfide bond is a bioreducible linkage that can be rapidly cleaved by reducing agents such as GSH via reduction or thiol-disulfide exchange reactions [76-78]. If a drug molecule is conjugated to dendrimer via a disulfide containing linker, its release can be triggered by abundant intracellular GSH. *N*-acetyl cysteine (NAC) is an antioxidant and anti-inflammatory drug. The thiol group in NAC is easily reacted with plasma proteins through forming disulfide bond. Due to the poor bioavailability and stability of NAC, it requires repeated high dosing in clinical trials, which leads to serious adverse effects. Conjugation of NAC to a dendrimer via disulfide bond can efficiently protect the drug from plasma protein binding and enable specific intracellular drug release (**Fig. 3a**) [79-83]. Similarly, the disulfide bond is adopted to construct GSH-responsive dendrimer-drug conjugates such as valproic acid, doxorubicin and paclitaxel prodrugs (**Fig. 3a**) [81, 84-87]. These prodrugs show significantly reduced adverse effects and improved therapeutic index compared to free drugs and offer promise for intracellular drug delivery.

Dendrimers and assembled dendrimers with reduction-responsive property. Reduction-responsive dendrimers can also be designed by introducing disulfide bond

in dendrimer core (**Fig. 3b**) [88], dendrimer shell (**Fig. 3c**) [89-93], spacer between dendrimer and shielding ligands such as poly(ethylene glycol) (PEG) (**Fig. 3d**) [94], and cross-linking ligands among dendrimers [95-97]. For dendrimer-based gene vectors, there is usually a dilemma: low generation dendrimers have minimal toxicity but poor transfection efficacy, while high generation ones have relatively high transfection efficacy but severe toxicity. To break down this "malignant" correlation between transfection efficacy and toxicity, low generation PAMAM dendrimers were cross-linked into nanoclusters using disulfide-containing linkers (**Fig. 4a**) [95]. After internalization by the cells, intracellular GSH can trigger the degradation of disulfide cross-linked nanoparticles into low generation dendrimers and release the bound DNA into cytoplasm. This strategy can achieve both high transfection efficacy and low cytotoxicity in gene delivery. Similarly, high efficient and low cytotoxic gene vectors can be designed by introducing disulfide bonds into the backbone of dendronized polymers (**Fig. 4b**) [98, 99].

Dendrimer-encapsulated gold nanoparticles (DEGNPs) with reduction-responsive property. Gold-thiol (Au-S) bond is another GSH-responsive linkage. Monodisperse gold nanoparticles can be synthesized using dendrimers as the template. The yielding DEGNPs can be used to load thiol containing drugs such as captopril and 6-mercaptopurine or thiolated doxorubicin and cisplatin via the Au-S bond (**Fig. 5**) [28]. The loaded drugs exhibit an "Off-On" release behavior in responsive to GSH and other reducing agents such as dithiothreitol, and the activity of drug-loaded DEGNPs can be activated by increasing intracellular GSH concentration.

The DEGNPs can be developed as a versatile drug carrier with the GSH-responsive property.

2.3 Enzyme-responsive dendrimers

Enzymes play essential roles in all biological processes. Up-regulation of enzyme expression or activity is associated with many diseases [100]. For example, matrix metalloproteinases (MMP) and cathepsin B are over-expressed in the microenvironment of various tumors. Tumor progression, invasion and metastasis are closely related to abnormal expressions of these proteases [101-103]. These proteases can sensitively cleave peptides with specific sequences, e.g. Gly-Phe-Leu-Gly oligopeptide (GFLG) is cleavable by abundant cathepsin B under physiological conditions, and collagen peptide is degradable in the presence of MMP-9. Based on these rationales, enzymes are promising triggers in the design of stimuli-responsive dendrimers.

Dendrimer-drug conjugates via enzyme-labile bonds. When anticancer drugs such as doxorubicin are conjugated to dendrimers via the specific peptide linkers like GFLG (**Fig. 6a**) and collagen (**Fig. 6b**), the yielding enzyme-responsive prodrugs can specifically deliver the drugs to tumors, efficiently kill the cancer cells and inhibit tumor growth [104-107]. Azoreductase, an enzyme responsive for azo bond cleavage, is abundant in the colon. If the anti-inflammatory drug 5-aminosalicylic acid was conjugated to PAMAM dendrimer via an azo-containing linker (**Fig. 6c**), the yielding prodrug is stable in stomach and small intestine, but exhibits fast drug release in the colon tissues [108].

Assembled dendrimers with enzyme-responsive property. Enzyme-induced HLB disruption is another strategy to design enzyme-responsive materials [17, 36, 109, 110]. Amphiphilic block copolymers composed of PEG and enzyme-responsive dendron are able to self-assemble into micelles that disassemble upon enzymatic activation (**Fig. 6d**) [111, 112]. During this process, the encapsulated cargo within the micelles exhibits quick release kinetics. Considering that the enzyme cleavable units are usually located in the hydrophobic dendron region and that the enzyme molecules are too large to penetrate into the hydrophobic core of the assembled micelles, an equilibrium between the assembled micelle and unimeric copolymer must be involved in these systems [17].

Self-immolative dendrimers with enzyme-responsive property. Though the above described enzyme-responsive dendrimers exhibit promising features in drug delivery, the main disadvantage of these materials is that the dendrimer matrixes such as PAMAM and PPI dendrimers are not degradable upon enzyme cleavage. This may generate safety problems during in vivo drug delivery. A solution to this issue is to develop enzyme-responsive self-immolative dendrimers [113-117]. The dendritic structure of these materials can entirely degrade into building monomers by a single enzymatic trigger such as 38C2 antibody, penicillin-G-amidase and β-galactosidase. Self-immolative dendritic prodrugs such as camptothecin, doxorubicin, etoposide, naproxen and monomethylauristatin E programmed to release multiple drug molecules after a single enzymatic activation [118, 119]. For example, the camptothecin prodrug is 2-3 orders of magnitude less toxic than free camptothecin, but approaches

the activity of free drug in the presence of penicillin-G-amidase [120]. In a separate study, two types of anticancer drugs including camptothecin and doxorubicin were conjugated to a single self-immolative dendrimer (**Fig. 7**) [121]. An enzymatic trigger antibody 38C2 simultaneously triggered the release of all the three drugs, which is beneficial for synergistic combinational therapy.

2.4 Light-responsive dendrimers

Light can serve as a promising external trigger in the design of stimuli-responsive materials due to its non-invasiveness and the possibility of remote spatiotemporal control [29]. The employed light triggers can be classified into ultraviolet (UV), visible or near-infrared (NIR) light according to their wavelengths.

Dendrimer-drug conjugates via light-labile bonds. Ortho-nitrobenzyl (ONB) is a light cleavable group that is widely used in the design of light-responsive materials. It is rapidly cleaved by UV lights within the wavelength range of 254 nm to 365 nm [35]. Anticancer drugs such as doxorubicin can be conjugated to dendrimers via ONB linkers (**Fig. 8a**) [122-124]. The conjugates show minimal toxicity on cells in the dark. Upon UV light irradiation, the cleavage of ONB linkage between the dendrimer and doxorubicin initiates, followed by the burst release of doxorubicin.

Dendrimers with photochemical internalization effect. Dendrimers with a porphyrin core are mainly localized on the endosomal membrane after cellular uptake [125, 126]. Upon UV irradiation, the dendrimers can generate ROS, which is responsive for endosomal membrane disruption. This property can be used to facilitate cytoplasmic delivery of drugs and genes via a photochemical internalization effect

(**Fig. 8b**). For example, the gene transfection efficacy of a ternary complex containing porphyrin-cored polyether dendrimer, DNA and cationic peptide can be dramatically improved (two orders of magnitude) after laser exposure [126]. This light-responsive system can specifically induce gene expressions in laser-irradiated regions *in vivo*, e.g. conjunctiva tissue or tumor [125, 126]. Moreover, porphyrin-conjugated PAMAM dendrimers and porphyrin-cored polylysine dendrimers also exhibit a light-responsive gene expression behavior on different cell lines [127-130].

Self-immolative dendrimers with light-responsive property. Visible light-responsive dendritic polymers can be designed by capping a visible light cleavable perylen-3-yl methanol group to the core of a self-immolative dendritic polymer (**Fig. 8c**) [37]. For example, blue light (460 nm) exposure efficiently triggered the depolymerization of the dendritic polymer and the fast release of conjugated anticancer drugs such as doxorubicin at the periphery. As a result, the dendritic prodrug shows minimal toxicity on cells without the light trigger, but comparable activity to free doxorubicin upon blue light exposure.

Though UV and visible light-triggered systems show great promise in drug and gene delivery as described above, they are hardly to be applied for in vivo applications due to their poor ability to penetrate deeply in the tissues and possible phototoxicity concerns. The light penetration limitation can be addressed by using (1) two-photon excitation which has a deeper penetration range [35], (2) upconversion nanoparticles, which can covert adsorbed NIR light to UV irradiation [131]), and (3) NIR-responsive materials [132]. Unlike UV and visible light, NIR light can penetrate

deep into tissues, enabling light-triggered delivery in large animals [34]. In addition, NIR light shows minimal phototoxicity, which will not cause damage to surrounding tissues. Diazonaphthoquinone, a hydrophobic ligand, can be converted into hydrophilic 3-indenecarboxylic acid via Wolff rearrangement upon NIR light irradiation [124]. The diazonaphthoquinone-modified amphiphilic PAMAM dendrimers are assembled into micelles in aqueous solutions. NIR light exposure will induce an HLB change in the system, which leads to the disassembly of the micelles and fast release of loaded anticancer drugs (**Fig. 8d**) [132]. Gold nanorods can strongly absorb NIR light and convert the light into heat. Gold nanorod-modified dendrimers can achieve NIR light enhanced gene delivery by a possible photochemical internalization mechanism [133]. These light-responsive delivery systems allow us to control the dose, timing, and duration of drug/gene release for specific therapy [34].

2.5 Thermo-responsive dendrimers

Interest in thermo-responsive dendrimers has steadily grown during the past decade. The temperature-sensitive dendrimers usually exhibit a phase transition above a cloud point, usually termed lower critical solution temperature (LCST) [134]. At LCST, the hydrophilicity of the dendrimers dramatically decreases, and this property is useful to develop thermo-sensitive drug delivery systems [134]. Generally, temperature-responsive dendrimers can be synthesized by several strategies: (1) directly introducing temperature-sensitive polymers such as poly(N-isopropylacrylamide) (pNIPAM) to dendrimer core or dendrimer surface [36, 135-138] (2) conjugating small compounds such as isobutyl amide [139-141], NIPAM [142],

oligo(ethylene glycol) (OEG) [143], phenylalanine [144] and peptides [145, 146] to dendrimer surface, and (3) constructing dendrimers or dendrons using amphiphilic components such as OEG [147] and β-aminoester [148] (**Fig.9 and Fig.10**). Cellular uptake of the thermo-responsive dendrimers can be significantly increased by changing the cell incubation temperature above the LCST of related dendrimers [143]. For isobutyl amide-terminated dendron bearing lipids, these temperature-sensitive materials are able to assemble into capsules, and the assembled capsules are covered into rod-like micelles or fused vesicles by heating the solution to a temperature above LCST [139]. These behaviors indicate that we can tailor the intracellular drug delivery efficacy of the dendrimers by tailoring environmental temperature.

Despite numerous temperature-sensitive dendrimers are reported, few of them were developed for responsive drug delivery. This is probably due to the poor solubility of temperature-sensitive polymers above LCST, which may generate safety concerns for in vivo applications. In addition, the drug release rate from the dendrimer is not well to control during the phase transition process. Besides, it is a challenge to heat localized tissues without hurting normal ones. A possible solution is embedding NIR light absorbing nanostructures within the dendrimer structure, and further heating the thermo-responsive dendrimer to trigger the payload release by using a NIR laser.

2.6 Multistimuli-responsive dendrimers

Generally, multistimuli-responsive delivery systems should be more sensitive in drug delivery than those only respond to a single type of stimulus [149, 150]. Considering the coexistence of acidity, hypoxia microenvironment and enzymes such as MMP in

tumors, these internal triggers can be used in combination [29]. The inherent hypoxia-targeting ability of macrophages can be used to facilitate the delivery of nanoparticles and anticancer drugs to hypoxic areas in the tumor [151, 152]. For example, PAMAM dendrimers were conjugated to macrophages via acid-responsive hydrazone linkages and the macrophages can efficiently deliver the drug-loaded dendrimers to hypoxic tumor microenvironments, followed by the release of dendrimers and anticancer drugs under tumor acidity [153]. Similarly, collagen-modified dendrimer that conjugated doxorubicin via hydrazone linkages shows both acid- and enzyme-responsive behaviors [107]. Internal triggers can also be combined with external triggers such as magnetic field, light and heat to design multistimuli-responsive dendrimers [138, 148]. Magnetic Fe_3O_4 nanoparticles grafted with a layer of dendrimer-doxorubicin conjugates can be targeted to tumors by a magnetic field [154, 155]. The release of doxorubicin molecules conjugated on dendrimer via a hydrazone linkage can be further triggered by tumor extracellular acidity [156-158]. Besides, thermo-responsive dendrimers can be endowed with light-responsive property by introducing a photothermal agent to the dendrimer. For example, thermo-responsive elastin-mimetic dendrimers encapsulated with gold nanoparticles show both thermo- and light-responsive behaviors [159].

3. Conclusions and perspectives

Stimuli-responsive dendrimers that release drugs in response to a stimulus or multistimuli are increasingly important in recent years. These smart polymers allow us

to deliver a payload in spatial-, temporal- and dosage-controlled fashions for specific therapy. There are several strategies usually adopted in the design of responsive dendrimers. First, the payloads can be conjugated to a dendrimer via stimuli-cleavable linkages, such as acid-labile bonds (hydrazone bond and boronate ester bond), thiol-responsive bonds (disulfide bond and Au-S bond), enzyme cleavable peptides, and light-degradable ONB bond. Second, the payloads can be loaded within responsive micelles consisted of amphiphilic dendrimers or dendritic polymers. The disassembly of the micelles can be triggered by a specific stimulus, followed by burst release of loaded payloads. Third, payloads can be conjugated to self-immolative dendrimers that respond to specific triggers such as enzyme, reducing agent, light and ROS. Fourth, dendrimers can be modified with responsive ligands which may activate the endocytosis, penetration, or targeting of dendrimers by a specific trigger. The flexible strategies available in the design of stimuli-responsive dendrimers and the wide range of internal and external stimuli together make responsive dendrimers a good choice to improve therapeutic outcomes and reduce adverse effects. Despite the described advantages of responsive dendrimers, most of them are limited to proof-of-concept, and a long road lies ahead to actual biomedical applications. Before the translation of stimuli-responsive dendrimers into clinical applications, the complexity of in vivo environments cannot be ignored. For example, tumors are characteristically heterogeneous in several aspects, e.g. cancer cells are abundant in both ROS and GSH [74, 75]. The heterogeneous microenvironment of tumors may lead to unexpected payload release behavior from the responsive dendrimers.

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Figures and Captions

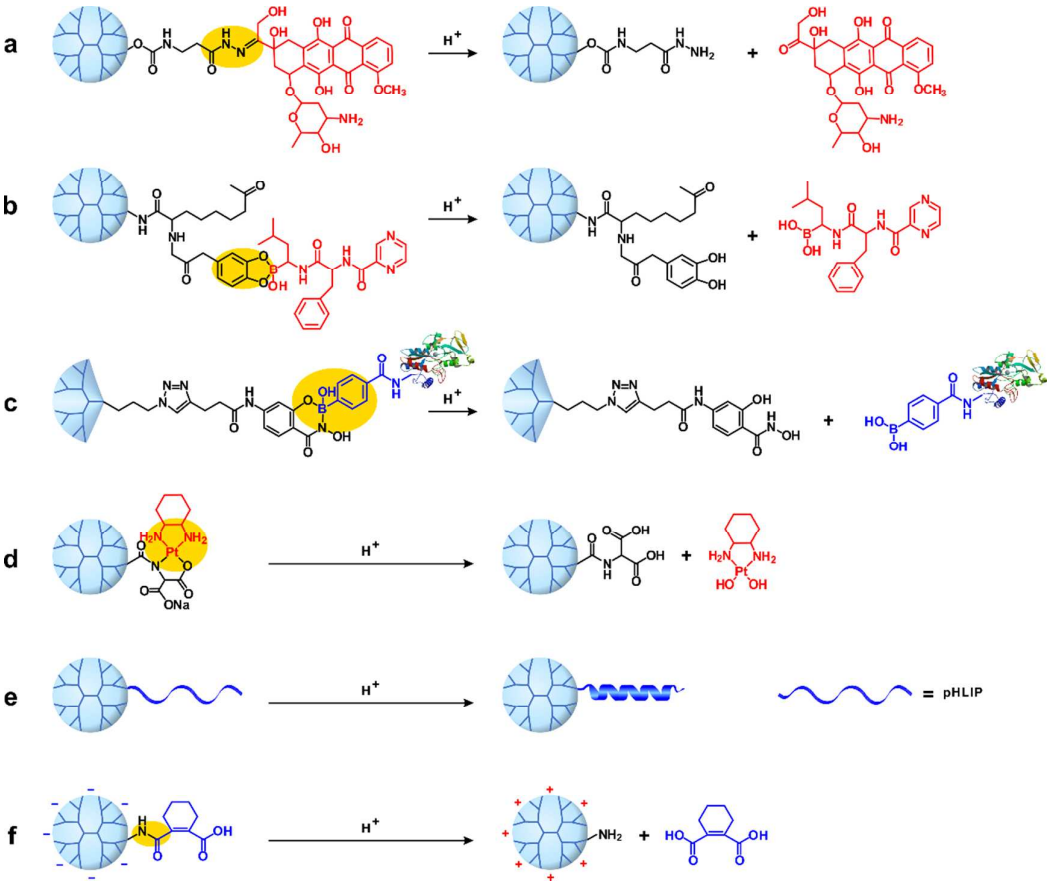

Fig. 1 Acid-responsive dendrimer-drug conjugates (a-d) and acid-activatable dendrimers (e and f). (a) Dendrimer-doxorubicin conjugate by hydrazone linkage. (b, c) Dendrimer-bortezomib (b) and dendrimer-protein (c) conjugates by boronate ester bond. (d) dendrimer-platinum conjugate by *N*,*O*-chelate coordination. (e) pHLIP-conjugated dendrimer. (f) Charge-reversal dendrimer.

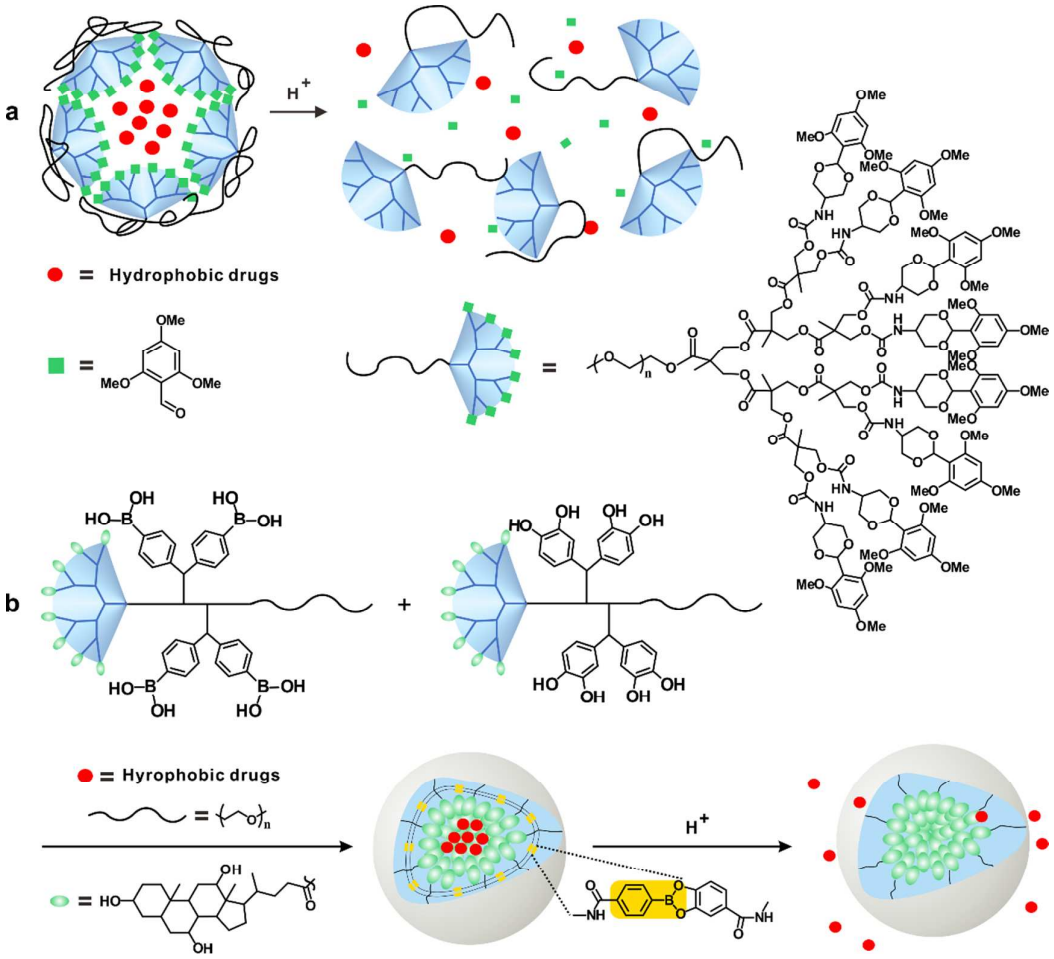

Fig. 2 Acid-triggered release of payloads from micelles consisted of amphiphilic dendrimers. Acid-responsive cleavage of acetyl groups (a) or boronate ester bond (b) on amphiphilic dendrimers, followed by micelle disassembly or changed micelle conformation, and burst release of encapsulated payloads.

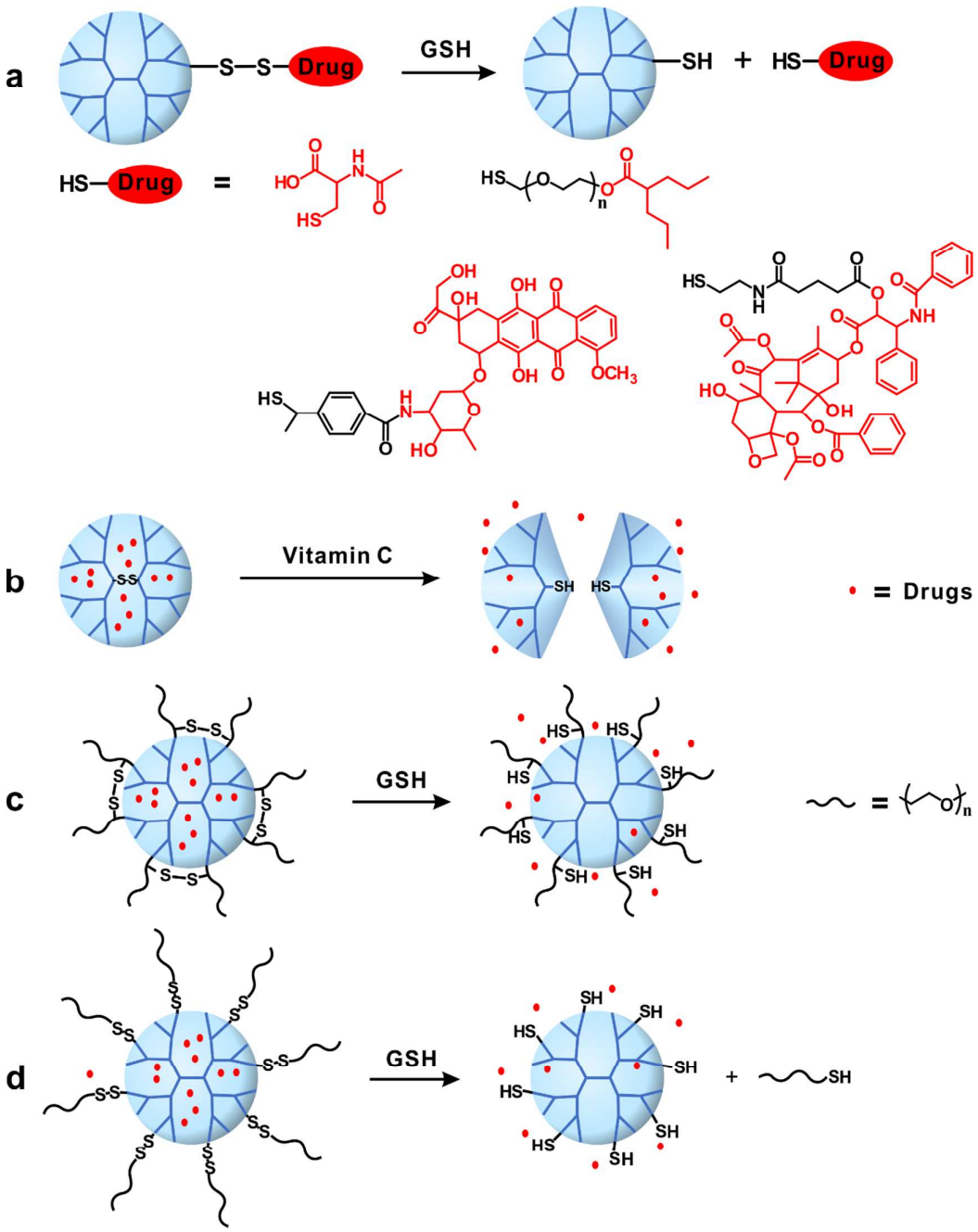

Fig. 3 Reduction-responsive dendrimers and dendrimer-drug conjugates. (a) dendrimer-drug conjugates by disulfide bond. The drugs include NAC, valproic acid, doxorubicin and paclitaxel. (b-d) Reduction-responsive dendrimers constructed by introducing disulfide bond in dendrimer core (b), dendrimer shell (c) and spacer between dendrimer and PEG (d).

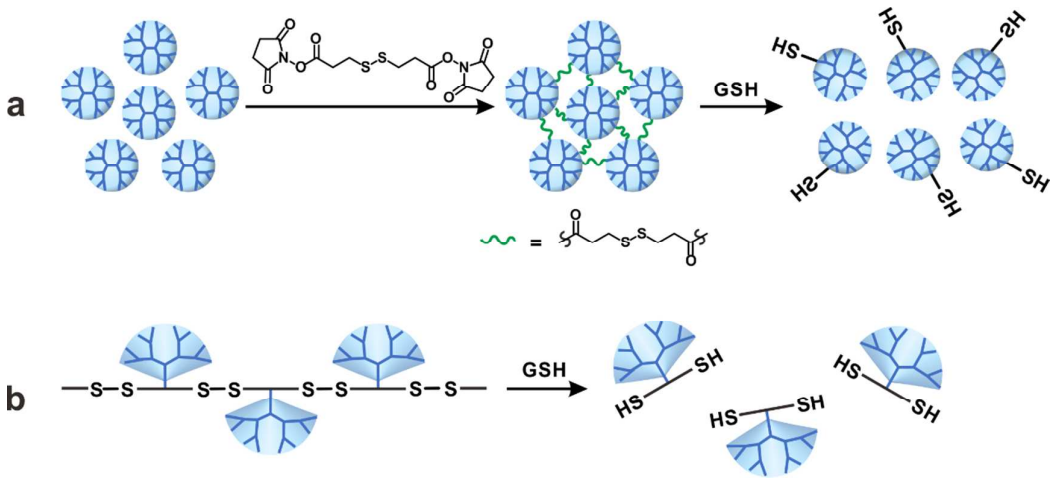

Fig. 4 Reduction-responsive dendrimers for gene delivery. (a) Clustering low generation PAMAM dendrimers into nanoclusters using disulfide-containing linkers and (b) Introducing disulfide bond to the backbone of dendronized polymers for efficient gene delivery.

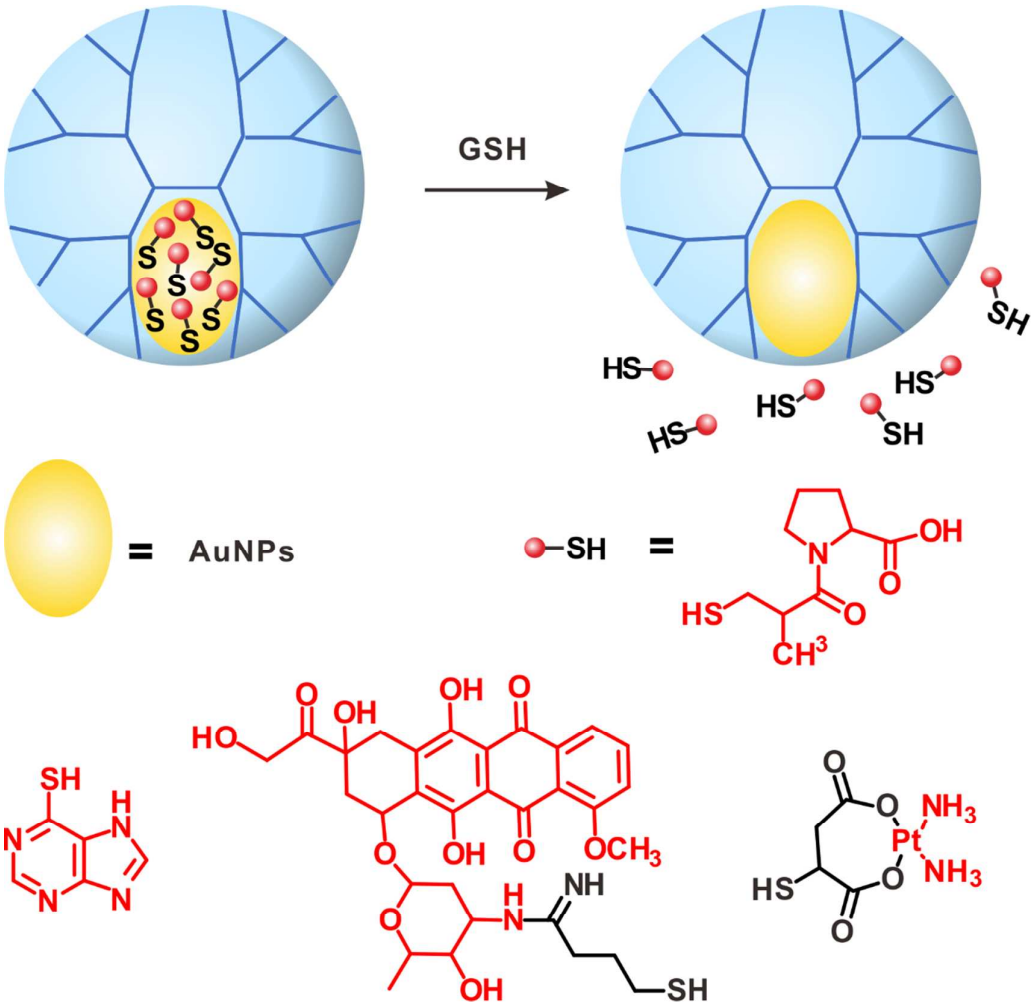

Fig. 5 GSH-responsive DEGNPs for the delivery of multiple drugs. Thiol containing drugs such as captopril and 6-mercaptopurine or thiolated doxorubicin and cisplatin were loaded to DEGNPs via Au-S bond.

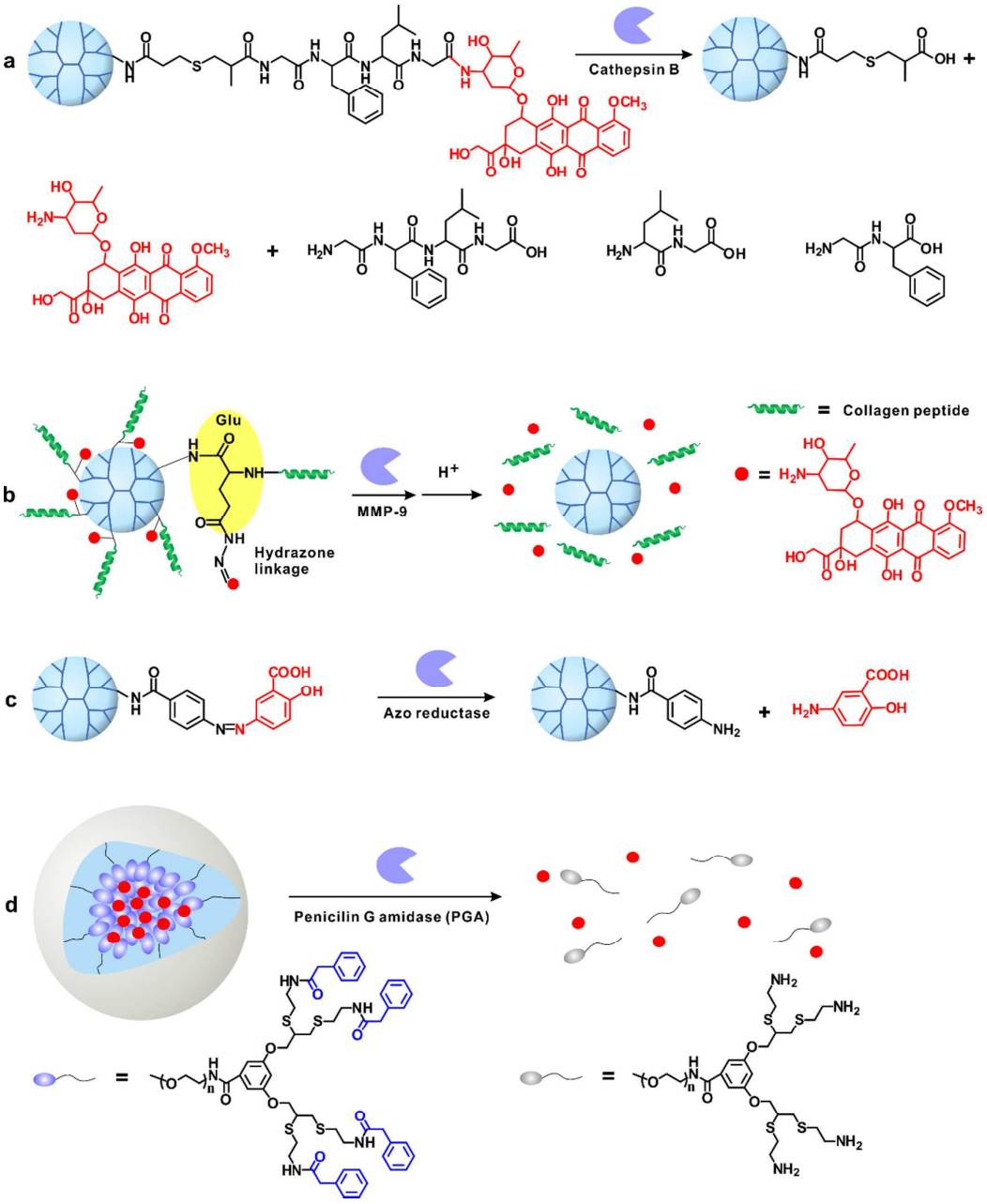

Fig. 6 Enzyme-responsive dendrimers in drug delivery. (a, b) Dendrimer-doxorubicin conjugates via GFLG (a) or collagen (b) peptide. (c) Dendrimer-5-aminosalicylic acid conjugate via an azo-containing linker. (d) Enzyme-triggered the disassembly of micelles consisted of amphiphilic dendrimers.

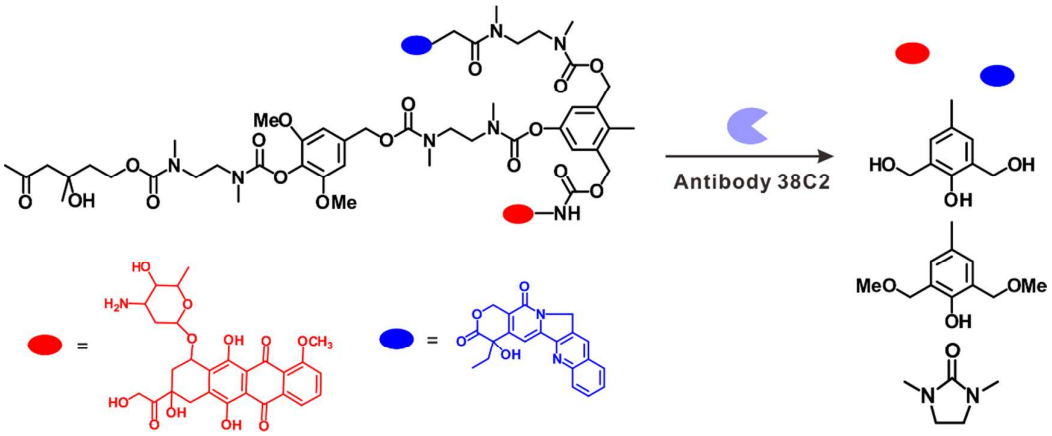

Fig. 7 Enzyme-triggered simultaneous delivery of three anticancer drugs from a self-immolative dendrimer.

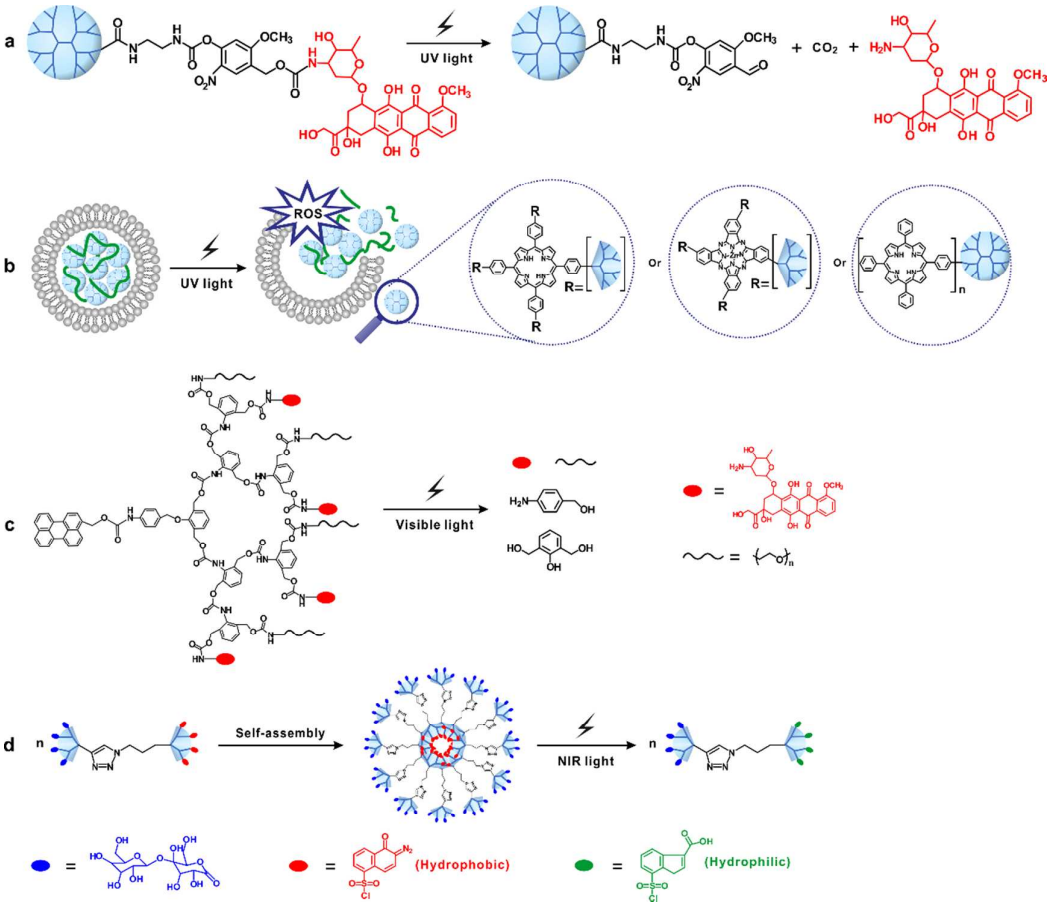

Fig. 8 Light-responsive dendrimers and dendrimer-drug conjugates. (a) Dendrimer-doxorubicin conjugate via an ONB linker is cleavable upon UV light irradiation. (b) Porphyrin-cored or porphyrin-conjugated dendrimers generate ROS upon UV light irradiation, which facilitates the cytoplasmic delivery of drugs and genes by a photochemical internalization effect. (c) Visible light triggered the degradation of a self-immolative dendritic polymer, followed by the release of conjugated anticancer drugs. (d) NIR light coverts hydrophobic diazonaphthoquinone to hydrophilic 3-indenecarboxylic acid via Wolff rearrangement, which leads to the disassembly of micelles consisted of amphiphilic dendrimers.

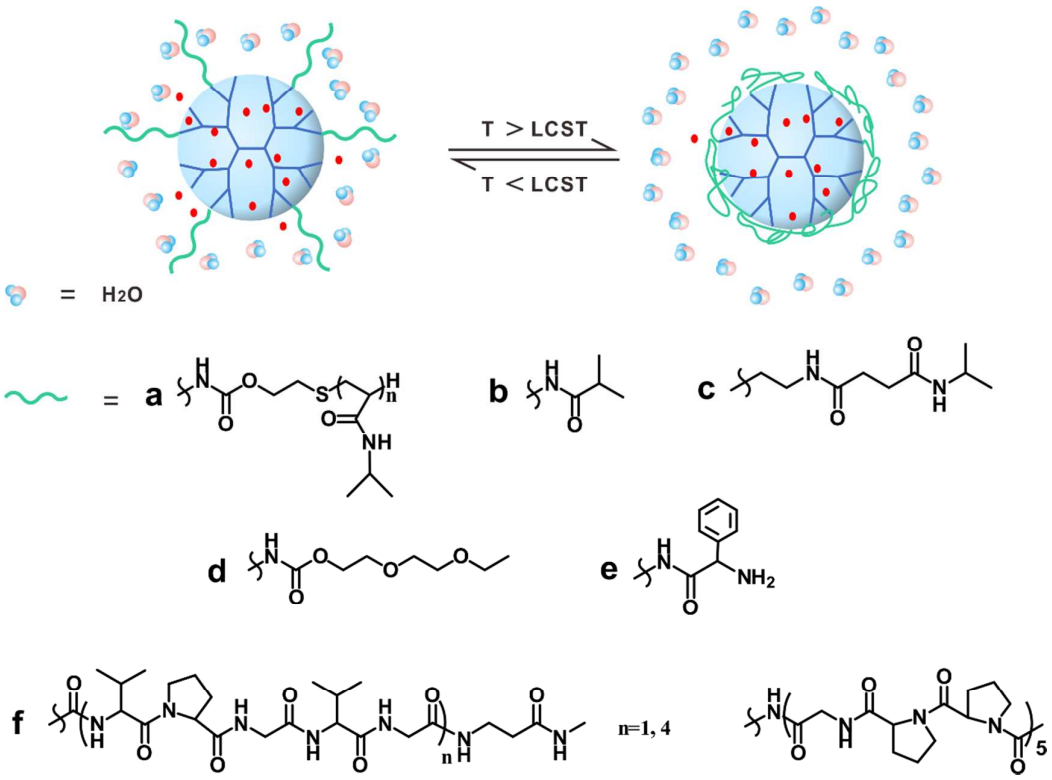

Fig. 9 Thermo-responsive dendrimers. (a) Dendrimer grafted with pNIPAM. (b) Isobutyl amide-terminated dendrimer. (c) NIPAM-terminated dendrimer. (d) OEG-terminated dendrimer. (e) Phenylalanine-modified dendrimer. (f) Collagen peptide-modified dendrimer.

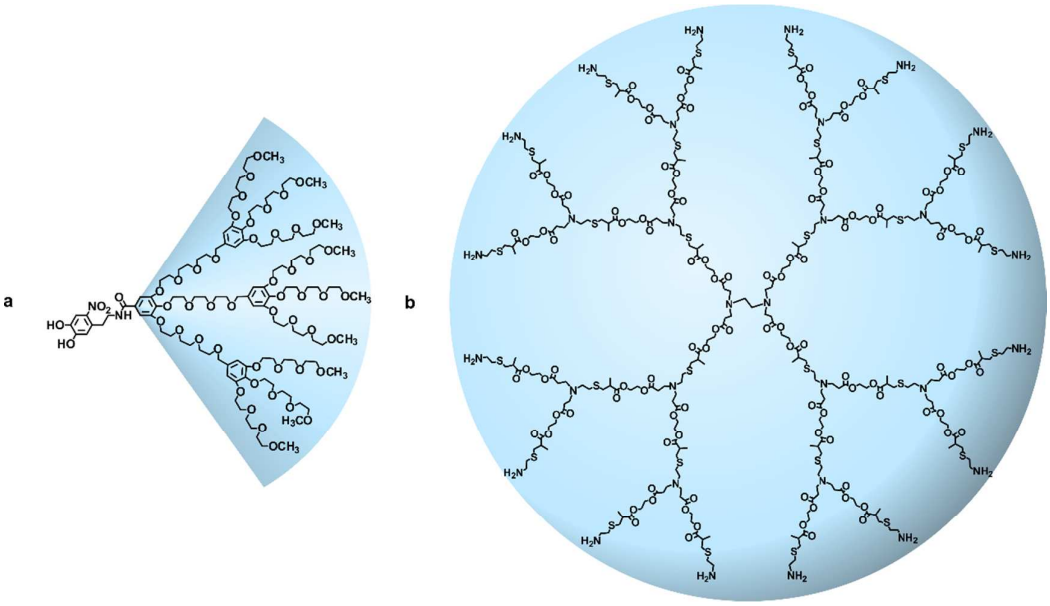

Fig. 10 Thermo-responsive dendrimers composed of OEG (a) or β-aminoester (b).