Development of Functional Nanocarriers via Surface Engineering of Dendrimers

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Abstract

Dendrimers are highly branched and well-defined synthetic polymers. Owing to their unique structures, versatile bioactive molecules can be modified onto their end groups and/or encapsulated within dendrimers. Therefore, dendrimers are highly potential as nanocarriers for drug delivery systems (DDS). We have investigated various surface engineered dendrimers to achieve biocompatible and stimuli-responsive functions. For instance, polyethylene glycol (PEG)-grafted polyamidoamine (PAMAM) dendrimers could encapsulate anticancer drugs, photosensitizers, gold nanoparticles and other molecules. PEG-grafted dendrimers, which exhibit prolonged blood retention and accumulation in tumor sites via the enhanced permeability and retention (EPR) effect and could attenuate the anti-PEG immune response. We found the tumor accumulation property is related to their hydration states, which represents a new criterion for designing tumor-targeting nanocarriers. Besides, peptide- and amino acid-modified PAMAM dendrimers have been developed as artificial proteins as well as pH- and thermo-responsive nanoparticles, which could be applicable as dual-responsive DDS and sensing systems. We have also studied dendrimers with anionic terminal groups for specific delivery to lymph nodes. Although various anionic terminal dendrimers accumulated in lymph nodes after intradermal injection, their association with immune cells differed depending on the terminal structures. We successfully achieved delivery to lymph node–resident T cells using anionic terminal phenylalanine (Phe)-modified dendrimers. This review summarizes the potential of dendrimers as functional nanoparticles for DDS and highlights the significance of surface engineering in controlling dendrimers' biological properties.

Keywords: drug delivery system, dendrimer, surface engineering, stimuli-responsive materials, immune cells, lymph node, cancer therapy

1. Introduction

Dendrimers are synthetic polymers with highly branched and well-defined structures, and extensive research efforts have been devoted to their utilization as functional materials across a wide range of scientific and technological fields.

Dendrimers are synthetic polymers possessing highly branched architectures and have been extensively studied as functional materials across various fields. Unlike conventional synthetic polymers formed through chain-growth or step-growth polymerization, dendrimers are synthesized through stepwise growth from a central core, enabling precise control over molecular weight and the number of terminal functional groups. These structural features allow dendrimers to incorporate a wide range of bioactive molecules either through covalent bonding or non-covalent interactions, endowing them high potential as drug carriers (Fig. 1).[1)–4)]

While other nanocarriers such as liposomes and polymeric micelles have also been widely investigated, these systems are molecular assemblies. In contrast, dendrimers are single-molecule nanoparticles with sizes of a few nanometers, comparable to those of proteins. This unique size and structural definition suggests that dendrimers can exhibit distinct functionalities compared to other delivery systems.

This review summarizes our research on the development of dendrimer-based functional nanocarriers synthesized through various surface engineering approaches of dendrimers.

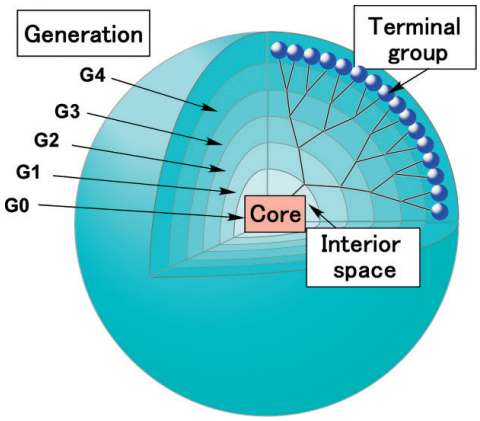

Fig.1 Design capabilities of dendrimer structures

2. Modification of Functional Molecules into Dendrimers

Poly(amidoamine) (PAMAM) dendrimers are commercially available and among the most extensively studied dendrimer systems.[1)–4)] Polyethylene glycol (PEG), known for its excellent water solubility and biocompatibility, is

widely used for the surface modifications of nanocarrier.

We synthesized PEG (molecular weight 2 kDa) grafted PAMAM dendrimers encapsulating various drugs and bioactive molecules (Fig. 2).[4)–8)] To evaluate their loading capacities, it is necessary to separate and quantify the loaded molecules. For the purification of covalently conjugated small molecules, dialysis or ultrafiltration can be adopted due to the clear molecular weight differences between modified dendrimers and unreacted small molecules. For non-covalent encapsulation, their separation relies on the solubility of the loaded molecules. For instance, when hydrophobic drugs are encapsulated, PEG-grafted dendrimers remain water-soluble, allowing the indirect quantification via ultraviolet-visible (UV-Vis) spectroscopy. Calibration curves based on absorbance versus drug concentration were made in advance. The concentration of the drug in the loaded dendrimer solution is determined from absorbance values, enabling calculation of the number of drug molecules per dendrimer. It is essential to confirm that drug absorption spectra remain unchanged upon loading and that they do not overlap with dendrimers' intrinsic absorption spectra. If there's any overlapping, dendrimer's absorbance should be subtracted for the calculation.

Alternatively, high-performance liquid chromatography (HPLC) can be used, in the cases of dendrimers with non-covalently modified molecules. As shown in Fig. 3, the HPLC analysis of the concentration of anticancer drug paclitaxel, calibration curves relating concentration to peak area enable accurate determination of drug loading capacity.

Due to the presence of tertiary amines within PAMAM dendrimers, anionic compounds can be efficiently encapsulated via electrostatic interactions. After loading PTX into dendrimers in methanol, the solvent is removed, followed by the addition of deionized water. The soluble fraction is analyzed by HPLC to estimate the concentration of drug loaded into dendrimers, and the number of drug molecules per dendrimer is calculated. In the case of PAMAM dendrimers, tertiary amino groups inside the structure are proved to allow efficient loading of anionic molecules (Fig. 2).[4)]

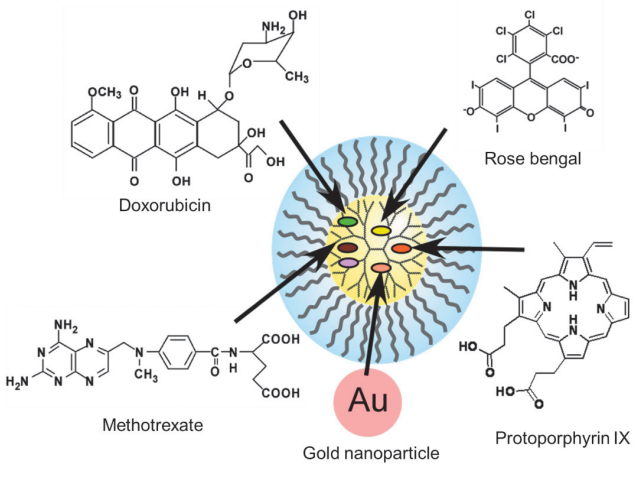

Fig.2 Encapsulation of various molecules in PEG-grafted dendrimers.

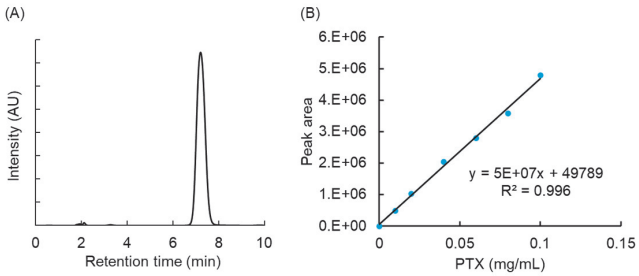

Fig.3 HPLC analysis of PTX. (A) A typical chromatogram, (B) A calibration curve. (mobile phase: methanol/H_2O = 7/3 (v/v), flow rate: 1.0 mL/min, detection at 230 nm).

To achieve effective drug delivery systems (DDS), loaded drugs must be released from dendrimers after their delivery to the target site. In the case of covalent conjugated drugs, dendrimers have been designed to incorporate mechanisms that enable intracellular drug release triggered via cleavable linkers such as acid-sensitive hydrazone bonds or enzyme-degradable linkers. Hydrazone bonds can be cleaved in the acidic environment of endosomes after dendrimers are internalized into cells via endocytosis, thereby allowing intracellular drug release.[8)] In addition, by employing linkers that are degraded by cathepsin B, which is overexpressed in cancer cells, it is possible to achieve drug release specifically within cancer cells.[8)]

In contrast, when drugs are loaded through non-covalent interactions, it is essential that they are stably retained within the dendrimer core. Anionic compounds can be encapsulated via electrostatic interactions with the tertiary amine groups inside PAMAM dendrimers. However, under physiological conditions, the high ionic strength weakens these electrostatic interactions, leading to the rapid release of hydrophilic anionic compounds.[5)] Therefore, strategies such as disulfide conjugated networks or hydrophobic shells have been employed to enhance the loading capacity of encapsulated drugs.[10), 11)]

Gold nanoparticles (AuNPs) can scatter X-rays and are therefore applicable as contrast agents for X-ray computed tomography (CT). In addition, due to their localized surface plasmon resonance (LSPR), AuNPs exhibit a characteristic optical absorption around 520 nm, enabling their potential applications for colorimetric sensing and photothermal therapy. Furthermore, their intrinsic catalytic activity also allows their applications as nanozymes.

We fabricated AuNPs-dendrimers by using various dendrimers as nanoreactors to encapsulate AuNPs within their cores.[7), 12), 13)] Specifically, 55 equivalents of chloroauric acid were added to PAMAM dendrimers generation 4 (G4), which possess 62 internal tertiary amine groups, allowing the formation of ion pairs within the dendrimer interior. Subsequently, reduction with sodium borohydride yielded AuNPs inside. The formation of AuNPs can be confirmed by UV-Vis absorption spectroscopy. Moreover, given that particle size influences the absorption properties of AuNPs, changes in the UV-Vis spectrum can also be used to monitor variations in their nanoparticle sizes.

Notably, when dendrimers are used as nanoreactors, the resulting AuNPs are typically very small (～2 nm), and therefore do not exhibit a distinct absorption near 520 nm. Instead, a broad spectrum gradually decreasing from 400 to 600 nm can be observed.

The formation of AuNPs was further confirmed by transmission electron microscopy (TEM). Besides, their surface analyses using cryogenic TEM (cryo-TEM) and X-ray photoelectron spectroscopy (XPS) verified that the AuNPs were generated within the interior of the dendrimers.[14]

3. PEG-grafted Dendrimers for Drug Delivery Systems

Owning to the more permeable vascular walls of neovasculature formed in tumors than that of normal blood vessels; consequently, intravenously administered PEGylated nanoparticles tends to accumulate in tumor tissue via the enhanced permeability and retention (EPR) effect. Therefore, PEGylated nanoparticles are widely used as drug carriers for cancer therapy.

In PEGylated nanoparticles, both the chain length and grafting density of PEG on the surface significantly influence their tumor accumulation behaviors. Therefore, PEG-grafted dendrimers with varying PEG chain lengths, grafting densities, and dendrimer generations were synthesized. Their blood retention properties and tumor accumulation behaviors were systematically studied.[15)–17)] We found that PEG with a molecular weight of 1 kDa did not confer tumor accumulation, instead leading to the accumulation in liver, indicating that PEG with a molecular weight of at least 2 kDa is required. Furthermore, insufficient PEG grafting density also resulted in preferential liver accumulation rather than tumor sites, suggesting that a minimum grafting density for PEG-grafted dendrimers. Thus, in the development of such drug delivery systems, it is necessary to prepare a variety of PEGylated nanoparticles and optimize PEG chain length and grafting density through the results of animal experiments. However, from the perspective of animal welfare, there is a strong demand to minimize animal experiments.

In recent years, the relationship between hydration states and interactions with biological systems has been elucidated, leading to the proposal of the intermediate water theory. According to such theory, in addition to nonfreezing water (which does not freeze even at −100 ℃) and free water (which melts at 0 ℃), a third category—intermediate water, which melts below 0 ℃—is defined. This intermediate water is found to function as a barrier layer that suppresses nonspecific adsorption.[18)]

In our recent research, we investigated the relationship between intermediate water amount and in-vivo accumulation behavior for PEG-grafted dendrimers with various structures. The results demonstrated a clear correlation between intermediate water amount and the tumor-to-liver accumulation ratio (Fig. 4).[17)] These findings suggest that intermediate water amount can serve as a predictive parameter for in-vivo biodistribution, offering the potential to optimize nanocarrier design through quantitative hydration analysis without relying on extreme amount of animal experiments.

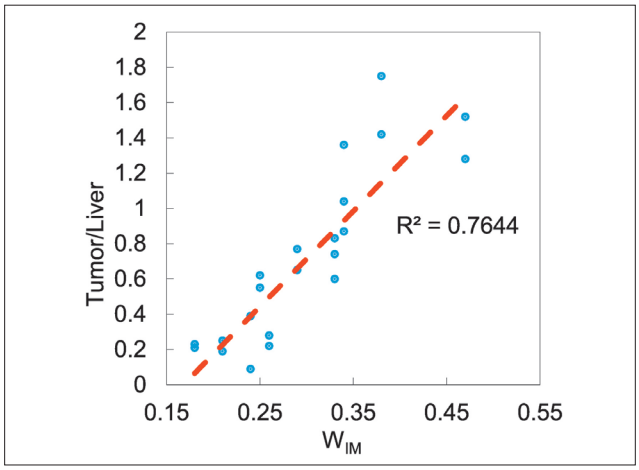

Fig.4 Relation between intermediate water amount and tumor accumulation in PEG-grafted dendrimers.

Currently, similar studies are being extended to dendrimers grafted with other biocompatible polymers, such as zwitterionic polymers, to further explore the correlation between intermediate water amount and biodistribution.

In recent years, it has become evident that repeated administration of PEGylated nanoparticles, such as PEGylated liposomes, leads to a significant reduction in blood retention, a phenomenon known as accelerated blood clearance (ABC). This occurs because anti-PEG antibodies are generated after the first administration, resulting in rapid recognition and clearance by the immune system upon subsequent doses.19 Since anticancer drugs are typically administered multiple times with low dosage, avoiding the ABC phenomenon is essential for the effective design of PEGylated nanocarriers.

It has been demonstrated that PEG-grafted dendrimers, which possess smaller particle sizes and higher PEG grafting densities than PEGylated liposomes, can effectively circumvent the ABC phenomenon.[20)] Our current research focus are on the elucidation of the underlying mechanisms of anti-PEG immune suppression, as well as the relationships among dendrimer structure, hydration states and anti-PEG immune responses.

4. Stimuli-responsive Dendrimers

Stimuli-responsive drug carriers can be utilized to construct delivery systems that enable the accumulation of carriers at diseased sites and the selective release of drugs in those regions. Although our body temperature is approximately 37 ℃, localized heating of diseased region can be achieved through hyperthermia therapy, which has greatly motivated the development of thermo-responsive drug carriers. In addition, pH-responsive drug delivery systems have also been extensively investigated, owning to the pH variation across physiological environments and intracellular compartments. Representative examples include enhanced drug release in acidic endo-

somal compartments following endocytosis, as well as targeting strategies that exploit the slightly acidic tumor microenvironment.[21)]

Focusing on elastin, a thermos-responsive protein, we developed elastin-modified dendrimers by conjugating peptides containing the repeating sequence of an elastin-like peptide (ELP), valine–proline–glycine–valine–glycine (VPGVG) to the end groups of dendrimers. Elastin-modified dendrimers were synthesized by modifying different generations of PAMAM dendrimers with VPGVG and $(VPGVG)_2$ (denoted as ELP1 and ELP2). Besides, the effects of peptide chain length and dendrimer generation on the thermos-responsive behavior were investigated by temperature-dependent turbidity measurements. The temperature was set to increase from 20 ℃ at a rate of 1 ℃/min, and the transmittance of aqueous elastin-modified dendrimer solutions (1 mg/mL) was monitored at 500 nm, where dendrimers exhibit no intrinsic absorption. A decrease in transmittance at elevated temperatures indicated a phase transition behavior. Furthermore, dendrimers conjugated with ELP1 exhibited a transition around 50 ℃, whereas those with ELP2 showed a transition near physiological temperature, indicating the elongation of peptide chain lowered the phase transition temperature.

In addition, circular dichroism spectra were measured using dilute elastin-modified dendrimer solutions (0.05 mg/mL) that did not undergo phase transition upon heating. The spectra results revealed an increase in the β-turn structure–associated peak at 218 nm and a decrease in the random coil–associated peak at 196 nm with increasing temperature, indicating a conformational transition from a random coil to a β-turn structure, similar to natural elastin proteins (Fig. 5). The aforementioned results suggest that elastin-modified dendrimer exhibit elastin-like behavior, where temperature-induced secondary structural changes of surface peptides increased the hydrophobicity, leading to the aggregation and phase transition.[22)]

Next, by incorporating gold nanoparticles (AuNPs) with photothermal conversion properties into elastin-modified dendrimer, we constructed dual stimuli-responsive nanoparticles exhibiting both thermal and photo-responsiveness. When applied to cancer cells, these nanoparticles enabled greater cellular uptake of AuNPs compared

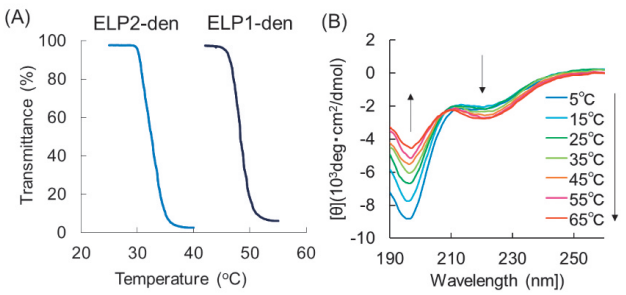

Fig. 5 Thermoresponsive properties of elastin dendrimers.
(A) Temperature-dependent turbidity measurements of ELP1- and ELP2-modified dendrimers,[22)]
(B) Temperature-dependent CD spectra of ELP2-modified dendrimer.[13)]

to PEG-grafted dendrimers containing AuNPs, resulting in an enhanced photothermal cytotoxicity.[13)] While it is difficult to incorporate AuNPs into natural elastin proteins, the use of elastin-modified dendrimer as an artificial protein-mimicking material allows the design of multifunctional systems combining thermos- and photo-responsiveness.

PAMAM dendrimers exhibit pH responsiveness due to the presence of amino groups both internally and on their surface. We synthesized phenylalanine (Phe)-modified PAMAM dendrimers with different terminal structures and found that they exhibited distinct thermo- and pH-responsiveness depending on their terminal functional groups.

Specifically, amine-terminated Phe-modified dendrimers exhibited lower critical solution temperature (LCST)-type phase transition behavior upon heating under basic conditions,[23)] whereas carboxyl-terminated Phe-modified dendrimers exhibited upper critical solution temperature (UCST)-type phase transition behavior upon cooling under weakly acidic conditions.[24)] Moreover, a dendrimer sequentially modified with Phe and succinic anhydride (den-Phe-Suc) displayed a UCST-type thermoresponsiveness at pH 5.5 and LCST-type behavior at pH 4 (Fig. 6).[25)] By loading AuNPs into this type of dendrimer, a colorimetric sensor responsive to both pH and temperature was developed. At pH 5, changes in both the absorption spectrum and solution color were observed above 40 ℃ , whereas no such changes occurred at pH 5.5 after heating (Fig. 6).[26)] This phenomenon was attributed to irreversible changes in the sizes of AuNPs under acidic and high-temperature conditions. Therefore, these nanoparticles are expected to have great potential as sensing materials capable of detecting thermal history through visible color changes.

Lymph nodes serve as reservoirs of immune cells and act as sites of immune responses, while also being common sites for metastatic cancer cell accumulation. Therefore, delivery to lymph nodes is of great significance for cancer therapy and diagnosis. In recent cancer immunotherapy studies, immune cells within lymph nodes proximal to tumors play critical roles, and the development of delivery systems targeting these immune cells is highly desirable to enhance therapeutic efficacy.

It is reported that molecules with molecular weights below approximately 70 kDa can efficiently diffuse within lymph nodes, thus, dendrimers with small particle sizes are well suited for lymph node delivery.[27), 28)] We demonstrated that the aforementioned anionic Phe-modified dendrimers could be delivered to lymph nodes following intradermal administration.[29)]Furthermore, dendrimers modified with hydrophobic cyclohexanedicarboxylic acid (CHex) and Phe were found to be taken up by immune cells within lymph nodes, including T cells, and that their uptake by T cells was enhanced under weakly acidic conditions (pH 6.5), corresponding to the characteristic of the tumor microenvironmen.[30)]

In cancer immunotherapy, T cells in tumor-draining lymph nodes play a crucial role in mediating immune

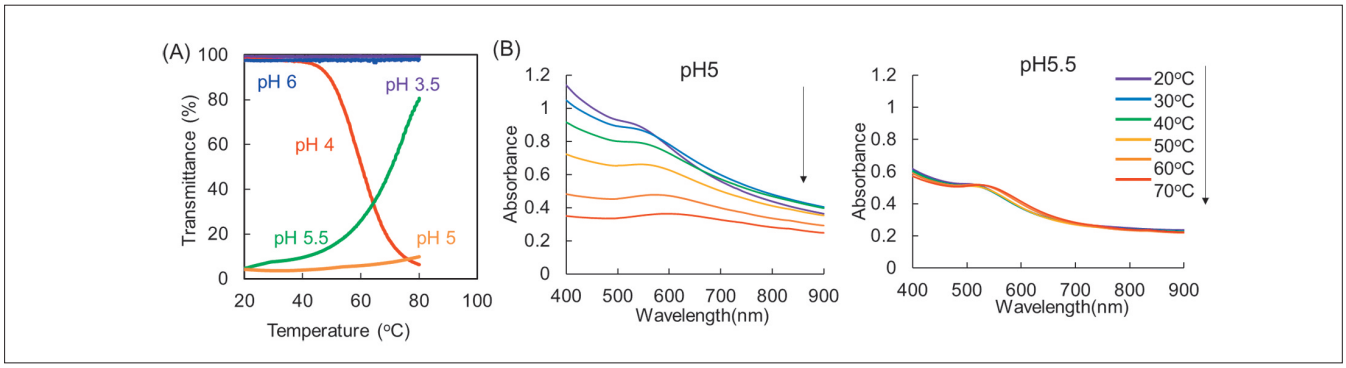

Fig.6 Thermo- and pH- responsive properties of den-Phe-Suc. (A) Temperature-dependent turbidity measurements at different pH;[25] (B) Temperature-dependent spectra of AuNPs-loaded den-Phe-Suc at different pH.[26]

responses. However, unlike delivery to phagocytic cells such as macrophages and dendritic cells, intracellular delivery into T cells is particularly challenging. By employing CHex- and Phe-modified dendrimers, we demonstrated that various molecules could be delivered into T cells, which was difficult to achieve using conventional methods. Currently, this dendrimer system is being further explored for the delivery of model drugs and nucleic acids into T cells.[31)–33)]

5. Conclusion

In this review, we presented some of our representative research with a focus on functional nanoparticles developed via surface engineering of dendrimers. By leveraging the small particle size and high density of terminal functional groups inherent to dendrimers, we demonstrated that it is possible to achieve delivery capabilities and biological functions that are difficult to realize with conventional methods.

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The HPLC analysis shown in Fig. 3, as well as the various spectroscopic measurements and temperature-dependent experiments presented in Figs. 5 and 6, were carried out using instruments provided by JASCO Corporation. We would also like to thank the staff of the Osaka and Yokohama offices of JASCO Corporation for their great support in instrument maintenance and relocation.

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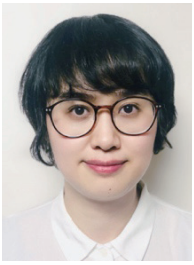
Current Research Interests: Development of nanomedicine and biomaterials with a focus on dendrimer-based systems.



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Current Research Interests: Development of functional polymeric materials and biomedical devices with a focus on functional elastomers and shape memory polymers.