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Review

Development of self-immolative dendrimers for drug delivery and sensing

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ABSTRACT

Traditional dendrimers possess unique cascade-branched structural properties that allow for multivalent modifications with drug cargos, targeting/delivery agents and imaging tools. In addition to multivalency, the dendrimer's macromolecular size also brings about the enhanced permeability and retention (EPR) effect, which makes it an attracting agent for drug delivery and biosensing. Similar to other macromolecules, therapeutic application of dendrimers in the human body faces practical challenges such as target specificity and toxicity. The latter represents a substantial issue due to the dendrimer's unnatural chemical structure and relatively large size, which prohibit its *in vivo* degradation and excretion from the body. To date, a class of self-immolative dendrimers has been developed to overcome these obstacles, which takes advantage of its unique structural backbone to allow for cascade decompositions upon a simple triggering event. The specific drug release can be achieved through a careful design of the trigger, and as a result of the fragmentation, the generated small molecules are either biodegradable or easily excreted from the body. Though still at a preliminary stage, the development of this novel approach represents an important direction in nanoparticle-mediated drug delivery and sensor design, thereby opening up an insightful frontier of dendrimer based applications.

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Contents

1. Introduction

Dendrimers are branched tree-like macromolecules [1] with multiple end-groups that can be functionalized for applications in imaging [2–4], gene therapy [5–7], and drug delivery [8–11]. In traditional approaches of dendrimer-based drug delivery, the biologically active substances are covalently attached to termini and thereby require independent cleavages for their release, whereas recently, an emerging class of dendrimers has been built that allows for the simultaneous release of all end-groups upon a single triggering event [12, 13]. As illustrated in Fig. 1, a triggering unit is connected to the branched skeleton composed of adaptor units. The repetitive growth of branches creates

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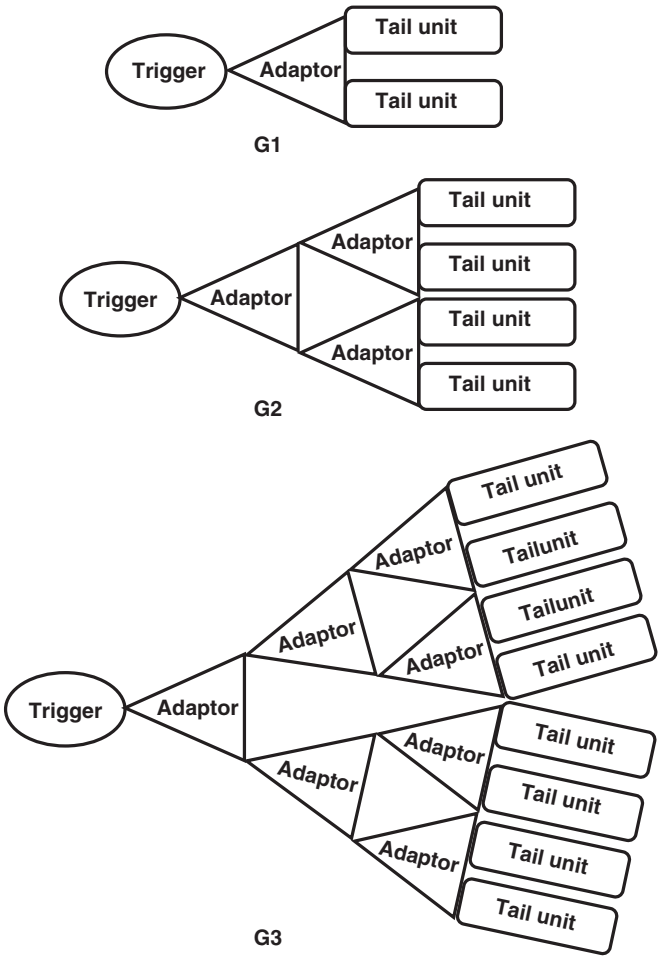

Fig. 1. Representative models of self-immolative dendrimers. "Trigger" is the head unit connected to the branched skeleton comprised of "Adaptor" units. "Tail units" can be drugs or signaling molecules that are attached to the adaptors at the end of skeleton. "G1", "G2", and "G3" are the generation of dendrimers that measures the repetitive growth of branches. A signal stimuli received by the trigger would lead to its cleavage from the skeleton, which initiates a cascade of disassembly of adaptors, followed by the final release of tail units.

a spherical periphery that can be attached with drugs or other agents as tail units. The extent of branches has been precisely defined by generation number (G), for which the first generation (G1) has only one adaptor branch, and the second generation (G2) has two additional adaptors, etc. The higher generation number a dendrimer has, the more tail units it can carry.

In the event of controlled release, an initial stimulus is recognized by the trigger, which undergoes subsequent cleavage and triggers rapid disassembly of the branched skeleton, breaking it down to separate building blocks and finally inducing the consequent release of all tail-units. This self-exploding multiple-release system was termed "Cascade-release" [12], "Self-immolative" [13], or "Dendritic amplification" [14] by different authors. This concept was initially introduced by De Groot et al. [12] and Amir et al. [13] at the same time, and a similar discovery was later on also reported by Szalai et al. [14]. Over the past decade, crucial progress has been continuously achieved in the field of self-immolative drug delivery and sensing. Herein, we comprehensively summarized the recent developments of self-immolative dendrimers in terms of trigger, adaptor, and tail unit. The intriguing designs and approaches presented here may shed a light on future research in dendrimer based therapeutics and diagnostics, thereby impacting the whole community.

2. Basic design of the scaffold

2.1. Adaptor design

In early studies, based on the finding that a 4-aminocinnamyl alcohol linker can undergo a 1, 8-elimination to release its end-groups, branching was introduced to make it a double-release linker. For G2, the second generation self-immolative platform, double-release linkers were connected through carbamate linkages to the core nitrodiol (**1**) (Fig. 2). Once the trigger nitro group was reduced to amine, the resulting dendrimer can have a cascade of self-eliminations, leading to its complete disassembly (see electron pushing mechanism of (**1**) in Fig. 2) [12]. The aromaticity of resulting intermediates can be regenerated by simple water hydrolysis, which consequently led to a second self-elimination. Eventually all the tail units were released and the dendrimer was completely decomposed to aminodiol building blocks [12]. Meanwhile, 2, 6-bis(hydroxymethyl)-*p*-cresol was also reported as a basic building block to construct the skeleton of the dendrimer (**2**). The two hydroxybenzyl groups can be attached with drugs through a carbamate linkage, while the phenol group can be connected through an N, N′-dimethylethylenediamine spacer to the hydroxybenzyl group of another building block to create multiple generations (Fig. 2). The final phenol functionality in the core was connected to a trigger, whose removal initiated spontaneous cyclization of the spacer, and consequently a sequence of self-eliminations [13]. Similar to the branched 4-aminocinnamyl alcohol based dendrimer, the intermediate (1,4-quinone methide) here can also have its aromaticity regenerated by water [13]. Afterwards, a dendrimer (**3**) based on 2,4-bis(hydroxymethyl)phenol was also

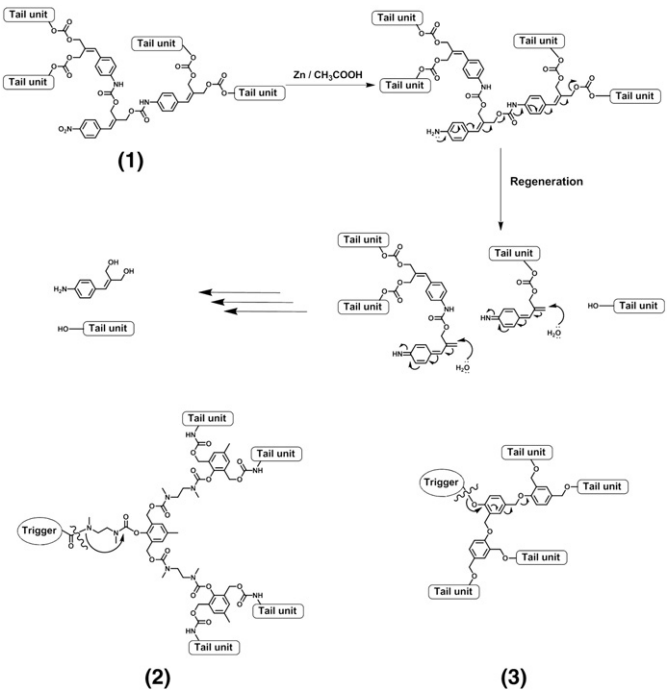

Fig. 2. Initially developed self-immolative dendrimers based on different fragmentation mechanisms. Dendrimer (**1**) was built on branched 4-aminocinnamyl alcohol based adaptors, and was dissembled through a 1, 8-elimination, following the reduction of the nitro group in the trigger by zinc/acetic acid. The intermediate can be regenerated by nucleophiles such as water, to initiate another round of elimination. Eventually all the tail units were released, and the dendrimer was completely decomposed. Dendrimer (**2**) on the bottom left was developed based on adaptor 2, 6-bis(hydroxymethyl)-*p*-cresol, the skeleton of which was connected with the trigger by a N, N′-dimethylethylenediamine linker that underwent 1,5-intra-cyclization to transmit the cleavage signal. Dendrimer (**3**) on the bottom right was prepared by adaptor 2, 4-bis(hydroxymethyl)phenol that was subjected to 1, 4- and 1, 6-eliminations during self-immolation.