Acta Biomaterialia 35 (2016) 1–11

Contents lists available at ScienceDirect

Acta Biomaterialia

journal homepage: www.elsevier.com/locate/actabiomat

Review article

Tailoring the dendrimer core for efficient gene delivery

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ARTICLE INFO

Article history:
Received 11 November 2015
Received in revised form 16 January 2016
Accepted 22 February 2016
Available online 23 February 2016

Keywords:
Dendrimer
Core effect
Gene delivery
Flexibility
Hydrophobicity

ABSTRACT

Dendrimers have been widely used as non-viral gene vectors due to well-defined chemical structures, high density of cationic charges and ease of surface modification. Although a large number of studies have reported the important roles of dendrimer architecture, component, generation and surface functionality in gene delivery, the effect of dendrimer core on this issue still remains unclear. Recent literatures suggest that a slight alternation in dendrimer core has a profound effect in the transfection efficacy and biocompatibility. In this review, we will discuss the transfection mechanism of dendrimers with different types of cores in respect of flexibility, hydrophobicity and functionality. We hope to open a possibility of designing efficient dendrimers for gene delivery by choosing a proper dendrimer core.

Statement of Significance

As a branch of researches on dendrimers and dendritic polymers, the design of biocompatible and high efficient polymeric gene carriers has attracted increasing attentions during these years. Although the effect of dendrimer generation, species, architecture and surface functionality on gene delivery have been widely reported, the effect of dendrimer core on this issue still remains unclear. Recent literatures suggest that a minor variation on the dendrimer core has a profound effect in the transfection efficacy and biocompatibility. This critical review summarized the dendrimers with different types of cores and discussed the transfection mechanism with particular focus on the flexibility, hydrophobicity, and functionality. It is hoped to provide a new insight to design efficient and safe dendrimer-based gene vectors by choosing a proper core.
To the best of our knowledge, this is the first review on the effect of dendrimer core on gene delivery. The findings obtained in this filed are of central importance in the design of efficient polymeric gene vectors. This article will appeal a wide readership such as physical chemist, dendrimer chemist, biological chemist, pharmaceutical scientist, and biomaterial researchers. We hope that this review article can be published by *Acta Biomaterialia*, a top journal that publishes important reviews in the field of biomaterials science.

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http://dx.doi.org/10.1016/j.actbio.2016.02.031
1742-7061/

1. Introduction

Dendrimers are a class of synthetic polymers with tree-like topological structures, well-defined architectures, monodispersity, a high density of terminal groups, and good solubility [1–3]. They are typically comprised of three parts: a central core, repeated units, and terminal groups (Fig. 1) [4–6]. Dendrimers are synthesized in a step-wise manner. The repeated units are organized around a central core in concentric layers by successive reactions [7]. Each reaction step leads to an additional generation of branching and the number of layers is defined as dendrimer generation (denoted as G, Fig. 1) [8]. The terminal groups are located on the dendrimer surface. The number of terminal groups, molecular weight and size of a dendrimer are related with its generation and can be precisely controlled during synthesis [8]. Because of the unique structures, dendrimers have been widely used in biomedical applications, such as drug delivery, gene delivery, cancer diagnosis, hydrogels, bio-sensors and tissue engineering [9–17]. Among these applications, the use of dendrimers as gene vectors has attracted increasing interest [18–22].

Dendrimers have grown in popularity in gene delivery mainly due to well-defined chemical structures, high density of terminal groups and ease of surface modification [8,23,24]. Compared to liposome-based gene vectors, these have several unique features in gene delivery, e.g. facile manufacturing, stable formulation, ease of modification with functional ligands, and high permeability [25]. The terminal groups of dendrimers can be easily converted to amine groups with positive charges. Cationic dendrimers can efficiently condense nucleic acids (DNA and RNA) through multivalent electrostatic interactions and protect them from enzymatic degradation. The formed dendriplexes can be internalized by cells via different endocytosis pathways (Fig. 2). In addition, some of the dendrimers such as polyamidoamine (PAMAM), poly(prophylenimine) (PPI) and poly(ether imine) (PETIM) possess a high density of tertiary amine groups in the dendrimer scaffold. These tertiary amine groups are protonable under endolysosomal pH conditions (pH 5.0–7.4). This pH buffering behavior may promote the endosomal escape of dendriplexes through a possible "proton sponge" effect (Fig. 2) [19].

Though dendrimers have shown great promise in gene delivery, they were not specially designed for gene delivery [26]. These materials are usually criticized by relatively low transfection efficacy (compared to lipid-based vectors and viral vectors) and non-negligible toxicity (generation- and concentration-dependent). The 'critical nanoscale design parameters' (CNDPs) including size, shape, flexibility/rigidity, architecture, elemental composition, and surface chemistry of polymers should be carefully optimized to achieve efficient gene delivery [1]. During the past decade, the effects of dendrimer generation (G1 to G10), dendrimer species (PAMAM, PPI, PETIM, polylysine, triazine, phosphorus, carbosilane and viologen), dendrimer architecture (symmetrical dendrimer, dendron, lipid-bearing dendron, Janus dendrimer), and surface functionality (primary amine groups, lipids, amino acids, fluorous compounds, saccharides, proteins and peptides) on gene delivery efficacy and cytotoxicity have been intensively investigated (Fig. 3) [18,19,27–29]. All these parameters play important roles in dendrimer-mediated gene delivery. By choosing proper generation, species, architecture, surface functionality, or using supramolecular strategies [24], the performance of a dendrimer can be optimized to meet the need for higher efficacy and lower cytotoxicity [18,19]. Besides these well-known parameters, several recent studies demonstrated that dendrimer core also has a profound effect in gene delivery [30–34]. The central core of a dendrimer directly determines number of terminal groups, molecular size, shape and conformation (Fig. 4) [8]. It may significantly influence the physic-chemical properties (hydrophobicity, flexibility, host-guest behavior and functionality) of a dendrimer [35]. A slight alternation in dendrimer core may dramatically influence the transfection efficacy and biocompatibility. In this short review article, we will discuss how the dendrimer core influences its performances in gene delivery.

2. Effect of dendrimer core on gene delivery

2.1. Core tailors the flexibility of a dendrimer

The transfection efficacy of a polymer depends on several parameters such as nucleic acid condensation, cellular uptake, endosomal escape, intracellular nucleic acid release, and nuclear entry (Fig. 2) [26,36–40]. Effective condensation of DNA or RNA into stable and small dendriplexes is the prerequisite of efficient gene delivery. Otherwise, the nucleic acids might be degraded by cellular extracts with nuclease activity and large dendriplexes are not beneficial for efficient endocytosis by the cells [26,36]. Polymer with a greater flexibility is responsive for better nucleic acid condensation. However, most of intact dendrimers have a globular shape with a relatively rigid structure. Szoka Fc and coworkers found that partially degraded PAMAM dendrimers (fractured dendrimers) with more open and flexible structures have significantly improved transfection efficacy (>50-fold) than the intact ones [41].

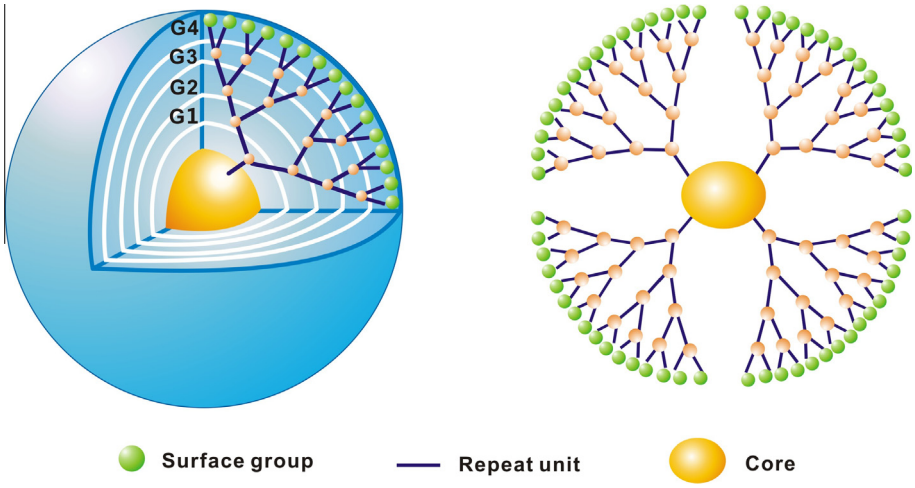

Fig. 1. Structure of a typical dendrimer. The dendrimer is comprised of three topological parts: a central core, branched units and terminal groups.