Progress in Polymer Science xxx (2014) xxx–xxx

Contents lists available at ScienceDirect

Progress in Polymer Science

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

Dendrimer-based molecular imaging contrast agents

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ARTICLE INFO

Article history:
Received 30 December 2013
Accepted 22 August 2014
Available online xxx

Keywords:
Dendrimers
Molecular imaging
Contrast agents
Organic/inorganic nanohybrids
Radionuclide-based imaging
Cancer diagnosis

ABSTRACT

This review reports recent advances on the use of dendrimer nanotechnology to build up various contrast agents for different single-mode or dual-mode molecular imaging applications. The versatile dendrimer scaffolds with 3-dimensional spherical shape, highly branched internal cavity, and tunable surface conjugation chemistry enable the facile modification of dendrimer surface with different imaging agents (*e.g.*, fluorescent dyes, traditional small molecular contrast agents, or metal ion/chelator complexes) and targeting ligands, and convenient entrapment, stabilization, and self-assembly to form various organic or organic/inorganic hybrid nanoparticles that can be used as multifunctional contrast agents for both non-radionuclide- and radionuclide-based molecular imaging applications. In particular, strategies used to generate multifunctional nanoprobes for different modes of targeted molecular imaging of cancer are discussed in detail.

Contents

Abbreviations: 3D, 3-dimensional; ACPPD, ACPPs conjugated dendrimers; ACPPs, activatable cell-penetrating peptides; Ag DENPs, dendrimer-entrapped Ag NPs; Ag DSNPs, dendrimer-stabilized Ag NPs; Au DENPs, dendrimer-entrapped Au NPs; Au DSNPs, dendrimer-stabilized Au NPs; CT, computed tomography; DANPs, dendrimer-assembled nanoparticles; DENPs, dendrimer-entrapped NPs; DMAA-IPA, 3-N-[(N',N'-dimethylaminoacetyl) amino]-α-ethyl-2,4,6-triiodo-benzenepropanoic acid; DNCs, dendrimer nanoclusters; DOTA, tetraazacyclododecane tetraacetic acid; DPTA, diethylenetriaminepentaacetic acid; DSNPs, dendrimer-stabilized NPs; DTA, diatrizoic acid; EDC, 1-ethyl-3-(3-dimethyl aminopropyl) carbodiimidehydrochloride; EPR, enhanced permeability and retention; FA, folic acid; FAR, FA receptors; FI, fluorescein isothiocyanate; G5.NH_2, amine-terminated generation 5 PAMAM dendrimers; HuTac, humanized anti-Tac IgG; *m*PEG, PEG monomethyl ether; MR, magnetic resonance; NCPs, nanocomposite particles; NIR, near infrared; NPs, nanoparticles; NSF, nephrogenic systemic fibrosis; OEG, oligoethylene glycol; PAMAM, poly(amidoamine); PBS, phosphate buffered saline; PEG, polyethylene glycol; PET, positron emission tomography; PGA, poly(glutamic acid); PLL, poly(L-lysine); PPI, poly(propylene imine); QDs, quantum dots; RGD, arginine-glycine-aspartate; SCIO, shell-crosslinked iron oxide; SCN-Bz-DTPA, 2-(p-isothiocyanatobenzyl) diethylenetriaminepentaacetic acid; SPECT, single photon emission computed tomography.

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http://dx.doi.org/10.1016/j.progpolymsci.2014.08.002
0079-6700/

1. Introduction

Nanomedicine, the integration of nanotechnology with biology [1], chemistry [2], and medicine [3], is an emerging and very fascinating research field with extensive applications, including but not limited to temporal and spatial site-specific drug delivery [4,5], local therapy [6,7], and diagnosis [3,8,9]. As a remarkable progress in nanomedicine, molecular imaging [10,11] has been widely explored since it allows real-time visualization of cellular functions of living organisms and related molecular interactions [12]. The diagnosis and recognition of disease has evolved considerably by means of the modern imaging technologies, such as fluorescence imaging [13,14], computed tomography (CT) [15,16], magnetic resonance (MR) imaging [17–23], positron emission tomography (PET) [24–26], and single photon emission computed tomography (SPECT) [27,28]. In the conventional sense, different imaging techniques have been used to detect and visualize the ultimate effects of a disease rather than the early-stage of the disease [29]. However, for efficient therapy and improved patient care, current nanomedicine involving many different disciplines has been dealing with new molecular imaging technologies for probing fundamental molecular processes that cause the disease [30,31]. Although different kinds of bodily tissues can exhibit contrast *via* different imaging technologies, it can be challenging to image and identify the interface between two adjacent tissues or soft tissues in contrast with blood or other physiological fluids [32]. Likewise, conventionally used contrast agents are often small molecular compounds, which share the common severe disadvantages, such as short imaging time due to the fast metabolism process, renal toxicity at a relatively high concentration, and lack of tissue/organ specificity [33]. Therefore, to meet the challenges required for precise disease diagnosis with improved imaging quality and specificity, it is essential to develop various contrast agents in either laboratory or clinical settings [34,35].

Recent advances in nanotechnology have enabled the development of various nanomaterials that can be used as contrast agents for different molecular imaging applications [3,4,24,32,36–38]. Among the used nanomaterials, dendrimers [39–45], a class of highly branched, monodispersed, synthetic macromolecules with well-defined tree-like three-dimensional (3D) architecture and composition, have attracted a great deal of attention. The structures of several commonly used dendrimers are shown in Fig. 1 [46]. The unique features of dendrimers with highly branched interior, 3D spherical shape, and well-defined surface functional groups enable many different modifications or constructions of functional nanoparticles (NPs) for various biomedical applications [46–53]. In particular for molecular imaging applications, dendrimers can be functionalized with multiple targeting ligands to afford enhanced specific cellular uptake *via* polyvalent binding [54,55] to improve the imaging specificity. The abundant terminal groups of dendrimers enable dendrimer periphery to be functionalized with multiple imaging elements to have dual- or multi-mode imaging functionalities [33]. Likewise, the generation-dependent physical size of dendrimers may be used to tune their excretion behavior and imaging time, to optimize the payloads of different imaging elements, and to tune the passive targeting behavior through enhanced permeability and retention (EPR) effect [56–58]. Lastly, appropriate surface modification of dendrimers is able to render the dendrimers with improved biocompatibility [59,60]. These properties of dendrimers enable the dendrimer-based nanoscale contrast agents to overcome the drawbacks of conventional contrast agents that are based on small molecular compounds. There are many approaches to using dendrimers to construct various nanoscale contrast agents. For instance, dendrimers can be linked with fluorescent molecules, iodinated small molecular CT contrast agent, gadolinium (Gd) or radionuclide chelators for fluorescence [61–65], CT [66–68], MR [57,58,69,70], or radionuclide-based imaging [71–74], respectively. Simultaneously, dendrimers can be used as templates or stabilizer to form dendrimer-entrapped metal NPs (DENPs) or dendrimer-stabilized metal or other inorganic NPs (DSNPs) for CT [48] or MR [75,76] imaging applications. In addition, functionalized dendrimers can be assembled onto preformed NPs for

Please cite this article in press as: Qiao Z, Shi X. Dendrimer-based molecular imaging contrast agents. Prog Polym Sci (2014), http://dx.doi.org/10.1016/j.progpolymsci.2014.08.002