COREL-06919; No of Pages 18

Journal of Controlled Release xxx (2013) xxx–xxx

Contents lists available at ScienceDirect

Journal of Controlled Release

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

Review

Multifunctional nanoparticles for targeted delivery of immune activating and cancer therapeutic agents

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ARTICLE INFO

Article history:
Received 7 August 2013
Accepted 9 October 2013
Available online xxxx

Keywords:
Multifunctional
Nanoparticles
Immune activation
Anticancer drug delivery
Theranostics

ABSTRACT

Nanoparticles (NPs) have been extensively investigated for applications in both experimental and clinical settings to improve delivery efficiency of therapeutic and diagnostic agents. Most recently, novel multifunctional nanoparticles have attracted much attention because of their ability to carry diverse functionalities to achieve effective synergistic therapeutic treatments. Multifunctional NPs have been designed to co-deliver multiple components, target the delivery of drugs by surface functionalization, and realize therapy and diagnosis simultaneously. In this review, various materials of diverse chemistries for fabricating multifunctional NPs with distinctive architectures are discussed and compared. Recent progress involving multifunctional NPs for immune activation, anticancer drug delivery, and synergistic theranostics is the focus of this review. Overall, this comprehensive review demonstrates that multifunctional NPs have distinctive properties that make them highly suitable for targeted therapeutic delivery in these areas.

Contents

1. Introduction

Pharmaceutical carriers have been widely investigated in both laboratory and clinical settings to improve the efficiency of delivering

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0168-3659/$ – see front matter © 2013 Published by Elsevier B.V.
http://dx.doi.org/10.1016/j.jconrel.2013.10.012

therapeutic and diagnostic agents via different administration routes [1–3]. Advances in nanotechnology have provided powerful tools and techniques for rational design of these carriers [4–7]. In particular, nanoparticles (NPs) have attracted tremendous interest in the design of drug delivery vehicles in recent decades [8–13] and provide significant advantages. First, by using nano-scale carriers, the *in vivo* solubility and stability of active pharmaceutical agents (APIs) can be improved, paving the way for the use of different administration routes for enhanced and efficacious delivery [14,15]. Secondly, the small size of the vehicles can be exploited to carry payload across the cellular membrane that cannot be achieved by conventional methods [16,17]. Third, the large surface area/volume ratio afforded by NPs provides the capability to load large amounts of payload and opportunities for engineering the particle surface to achieve targeted delivery [18–21]. And finally, unlike conventional administration, in which the drug concentration in blood plasma increases rapidly and decays exponentially during drug metabolism [22], NP based drug delivery systems can realize controlled target delivery of payload [23]. Controlled release can further improve the effectiveness of the therapies by reducing both the under-dosing and overdosing issues that are often observed in conventional drug administration protocols [24–27].

Beyond the conventional methods of conferring individual functionality, such as delivery of a single type of pharmaceutical compound, multifunctional NPs have been designed to carry out diverse functions [28–31]. In contrast to conventional (i.e., mono-functional) NPs, multifunctional NPs simultaneously achieve co-delivery of multiple therapeutic agents, and provide target delivery by appropriate surface modification of the carriers' surface [32,33]. In this regard, numerous types of multifunctional NPs fabricated with different materials have emerged, including polymer NPs, mesoporous NPs, magnetic NPs, gold NPs and others [34].

Multifunctional NPs also provide unique advantages for the treatment of specific diseases [35–38]. For example, in cancer treatment, a number of research efforts have been devoted to designing multifunctional NPs to achieve co-delivery of therapeutic agents including proteins, small molecules drugs, and genes (DNA and siRNA) [12,35,39]. Multifunctional NPs (e.g., with cell penetrating peptides on their surface) can cross cancer cell barriers and become preferably retained within target cells via the endowed permeability and retention (EPR) effect [40–43], which provides the capability to deliver high quantities of drug to cancer cells. In addition, by co-loading imaging agents or molecules, the NPs can also provide diagnostic capabilities such as optical imaging or magnetic resonance imaging [44–47]. Moreover, the NP surface can be functionalized with ligands that can specifically target receptors on the cell surface for preferential or targeted drug delivery, which is especially critical in cancer treatment [48–50]. Furthermore, NPs can be tailored to deliver payloads across a number of biological barriers, such as the blood–brain barrier (BBB) which consist of tightly packed layer of endothelial cells surrounding the brain [51,52].

In this review, we will discuss the numerous types of materials used for fabricating multifunctional NPs and summarize recent progress in the use of multifunctional NPs. Fig. 1 shows a cartoon representation of a theranostic NP. Therapeutic drugs can be loaded within the NP carriers functionalized with specific targeting molecules on the surface. More than one type of drug molecule or imaging agent can be co-encapsulated within the carrier devices for multiple application purposes. Previous reviews on multifunctional nanoparticles for drug delivery have been mainly focused on a single type of material such as polymeric micelles, mesoporous silica nanoparticles, or gold nanoparticles for fabricating multifunctional NPs [39,44,53–56] or on specific applications such as drug or gene delivery and bioimaging [34,47,50,57]. A comprehensive critical analysis of different types of nanoparticle fabrication and their corresponding biomedical applications is needed to provide useful comparisons and broader perspectives to fulfill the potential of multifunctional nanoparticles in drug delivery and bioimaging applications. The objective of this review is to summarize and provide critical analysis of the recent synthesis and fabrication techniques of multifunctional NPs and their corresponding therapeutic and imaging applications. We will discuss (1) multifunctional NP synthesis and fabrication using different types of materials and (2) applications for immunotherapy, cancer therapy, as well as synergistic therapy with biomedical imaging (i.e., theranostics).

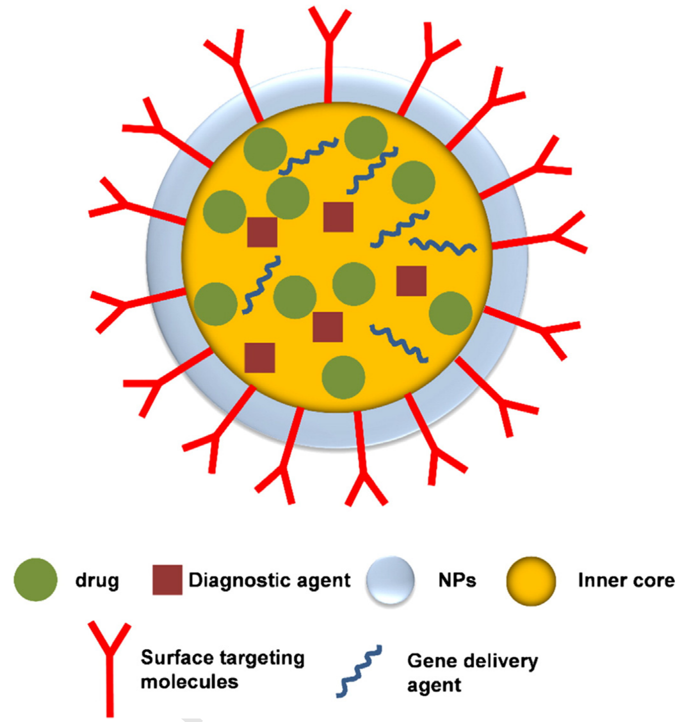

Fig. 1. Sch. of multifunctional NPs with targeted drug delivery and bioimaging functionalities.

2. Design and fabrication of multifunctional NPs

Over the past decade, numerous nano-scale platforms of drug delivery, cellular targeting, and biomedical imaging have emerged and provided synergistic therapeutic outcomes [58–62]. Multifunctional NPs fabricated using various chemistries with distinctive architectures have been designed and evaluated for potential drug delivery applications [63,64]. In general, NPs can be classified as organic/polymeric and inorganic as shown in Fig. 2, which summarizes the specific types of materials under each category. Polymers provide more flexibility in terms of chemistry and structure for fabricating nanoparticles in contrast to inorganic materials. In organic-based nanomaterials, polymeric NPs, micelles, and liposomes primarily consist of amphiphilic copolymers with biocompatibility, while crosslinked nanogels provide a network with highly porous structure, and dendrimers have tree-like branched structures [65,66]. Inorganic nanocarriers such as mesoporous silica, magnetic nanoparticles, gold nanoparticles, and quantum dots have unique properties and provide capabilities for tracking, while their rigid surfaces are amenable to functionalization [67]. Appropriate NPs need to be designed rationally according to specific situations and needs. The structure and fabrication of the different types of multifunctional NPs shown in Fig. 2 that have been developed for drug delivery, cellular targeting, and biomedical imaging will be discussed in the following section.

2.1. Multifunctional organic NPs

Organic or polymeric NPs have been widely used in designing drug delivery vehicles and have shown tremendous promise in biomedical

Please cite this article as: F. Jia, et al., Multifunctional nanoparticles for targeted delivery of immune activating and cancer therapeutic agents, J. Control. Release (2013), http://dx.doi.org/10.1016/j.jconrel.2013.10.012