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Alendronate conjugated nanoparticles for calcification targeting

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ABSTRACT

In this article, the synthesis of a novel calcification-targeting nanoparticle (NP) is reported, which is realized through dopamine self-polymerization on the poly(lactic-co-glycolic acid) (PLGA) particle surface and subsequent alendronate conjugation. Cell viability and proliferation tests confirmed that such particle has low cytotoxicity and good biocompatibility. Experiments were designed to observe whether the synthesized NPs can pass through an obstructive hydrogel and directly bind themselves to hydroxyapatite (HA) NPs (mimicking calcified spots) and HA porous scaffolds (mimicking calcified tissues); and the result was positive, indicating ingenious targeting of NPs on calcifications. The calcification-targeting NPs are expected to be with promising applications on calcification-related disease diagnoses and therapies.

1. Introduction

As a kind of pathologic bone metastases, calcification can happen in normal tissues like vascular, nervous, mammary tissues or cartilage, which is not easy to be detected. *In vivo* calcification is a result of calcium deposition, which is similar to embryonic osteogenesis [1–3]. Calcification may include both osteogenic and chondrogenic differentiation of cells [3]. In calcified tissues, many bone matrix proteins and growth factors are expressed, such as bone morphogenetic protein-2 (BMP-2) [4], osteoprotegerin (OPG) [5] and osteopontin [6], indicating the calcification progress similar to bone formation and thus hydroxyapatite (HA) plays a role as the major ingredient of calcified tissues. General impression about calcification is that it indicates a benign lesion, which will not cause too serious consequences threatening life. But researches demonstrated that calcification is a distinguishing feature of cancers such as human breast cancer [7] and prostate cancer [8]. Under this consideration, diagnosis delay may lead to patients' condition worsened and even endanger their lives. Traditional methods on calcification detection mainly include magnetic resonance imaging (MRI)[9] and *in vivo* micro-computed tomography (CT) via electron beam [10] or X-ray [11]. However, these methods usually come with obvious drawbacks like low resolution and the images may be illegible against diagnoses.

In recent years, nuclear medicine and fluorescence labelling have been widely studied on in vivo imaging. For instance, Montet et al. [12] used nanoparticles (NPs) bound with RGD peptides to detect integrins on BT-20 tumor cells, while gold nanoparticles were employed in-cell protein detection by Cognet et al [13]. In these cases, nanoparticles with homing ability can be considered ideal tools to be labelled for disease diagnosis and even therapy. Generally, nanoparticles have been exploited as effective drug carriers for decades. As for cancer treatment, anticancer drugs can be more effectively transported to tumor tissues after being conjugated to NPs, in compare with oral administration or directly injection [14–16]. Accordingly, NPs as anticancer-drug carriers are able to promote drug distribution in carcinoma tissues and simultaneously reduce side effects in normal tissues.

As a matter of fact, due to the lack of functional groups, many material surfaces cannot be modified directly by fluorescent molecules or drugs. Motivated by adhesive proteins in mussels, Lee et al. [17] presented polydopamine (PDA) as an excellent coating material which can apply to a large amount of materials including metals, inorganic materials and polymers. This method is quite facile to be realized through merely immersing substrates into an alkaline buffer solution containing dopamine for hours. After being modified by dopamine, various molecules can be easily immobilized or conjugated onto the modified surfaces of materials. According to a study of Jiang et al. [18], heparin was immobilized onto a hydrophobic polyethylene (PE) porous membrane through coupling with a reactive PDA layer, which modified the membrane surface in advance. Results showed platelet adhesion and anticoagulation abilities of the PE porous membrane

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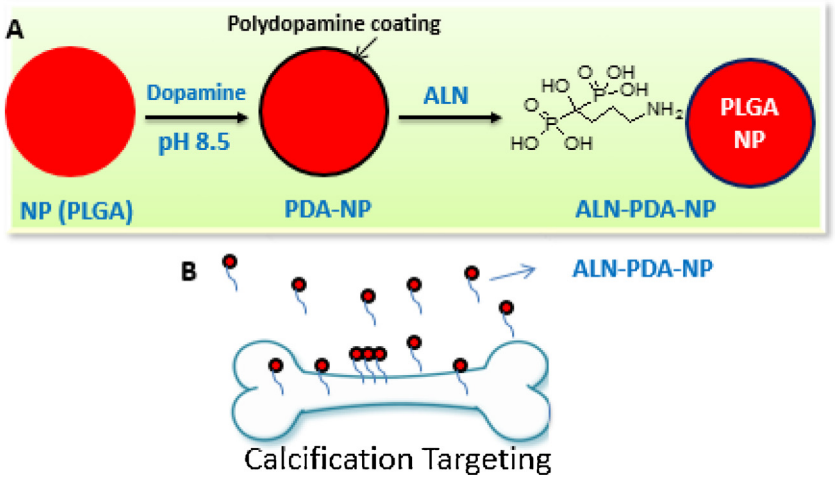

Fig. 1. Schematic diagrams of alendronate grafting on the surface PLGA nanoparticles through dopamine polymerization (A) and bone targeting of ALN-PDA-NP (B).

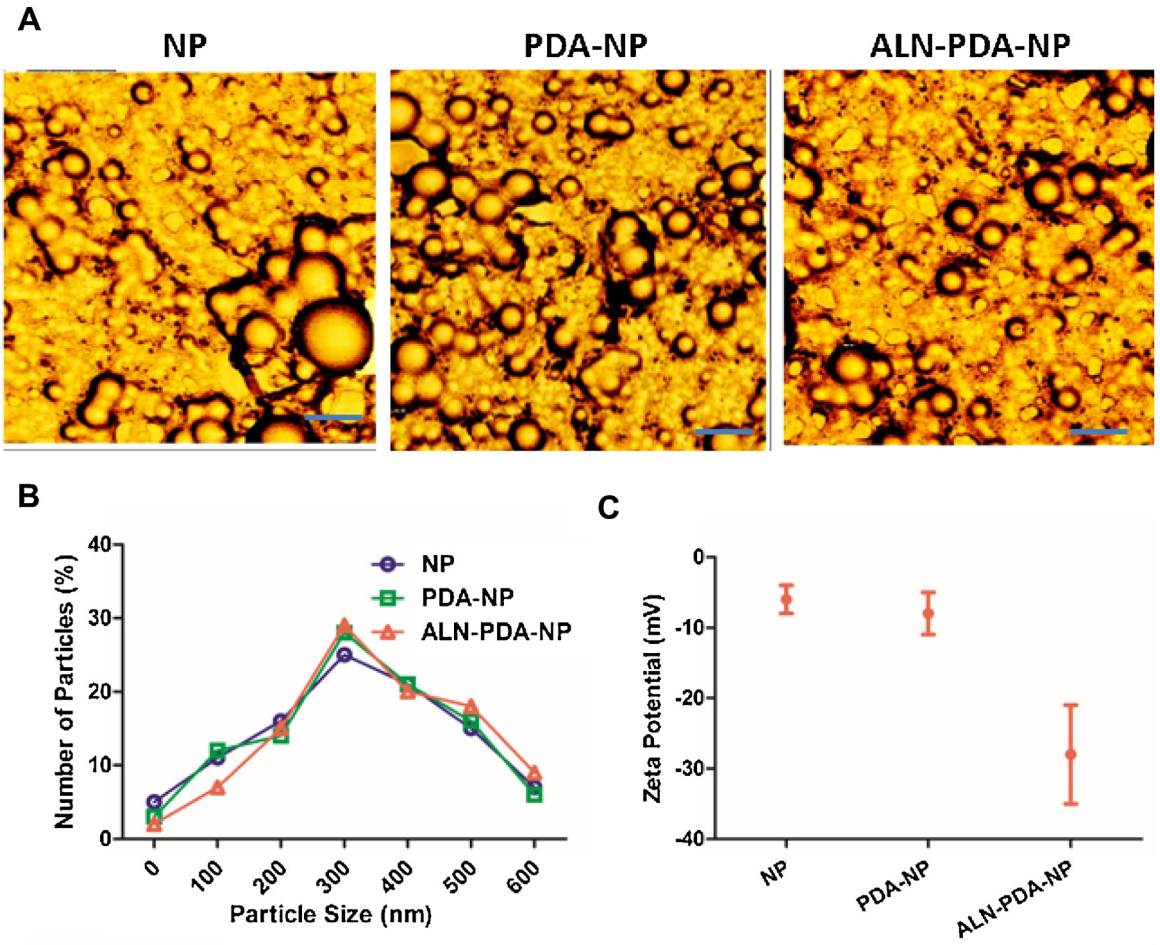

Fig. 2. (A) Atomic force micrographs (scale bar: 500 nm); (B) Particle size distribution graph; (C) Zeta potential graph of the three different particles.

were enhanced, indicating heparin was conjugated well with the PDA layer. Via attaching initiator on PDA coating carbon nanotubes (CNTs), polydimethylamino-ethyl methacrylate (PDMAEMA) brushes were formed by atom transfer radical polymerization on the CNT surface [19]. Liu et al. [20] synthesized core-shell Fe_3O_4-PDA NPs as drug carriers, and anticancer drug bortezomib (BTZ) was successfully bound to the particles, exhibiting great control release properties. Through surface modification with PDA, materials with great biocompatibility and biodegradability, such as poly(lactide-co-glycolide acid) (PLGA), obtain the ability to overcome the lack of reactive groups and can therefore carry functional molecules for better medical applications. In this work, we designed a novel calcification-targeting nanoparticle through coating the PLGA NP with PDA and subsequently combining it with alendronate, which has been formerly researched as a bone-targeting reagent for its impressive ability of HA orientation [21]. In vivo experiments had