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Bisphosphonate-functionalized coordination polymer nanoparticles for the treatment of bone metastatic breast cancer

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ABSTRACT

Bone is the most common organ affected by metastatic breast cancer. Targeting cancers within the bone remains a great challenge due to the inefficient delivery of therapeutic to bone. In this study, a polyethylene glycol (PEG) coated nanoparticles (NPs) made of a Zn^{2+} coordination polymer was linked with a bone seeking moiety, alendronate (ALN), to deliver cisplatin prodrug (DSP) to the bone. The particle sizes of this novel system, DSP-Zn@PEG-ALN NPs, were regulated by adjusting the volume ratio of water phase to oil phase in microemulsion. It was small enough (about 55 nm) to extravasate through the clefts (80 nm) of the bone's sinusoidal capillaries and localize into metastatic bones. DSP-Zn@PEG-ALN NPs showed much higher affinity for hydroxyapatite *in vitro* and bone *in vivo* than non-targeted DSP-Zn@PEG NPs and cisplatin. In addition, the *in vivo* biodistribution studies demonstrated that about 4-fold of platinum was delivered to the bone metastatic lesions than that in healthy bones by DSP-Zn@PEG-ALN NPs intravenously. Finally, DSP-Zn@PEG-ALN NPs not only inhibited the tumor growth efficiently but also reduced the osteocalastic bone destruction. Besides, DSP-Zn@PEG-ALN NPs showed significantly reduced toxicity of cisplatin. These results indicate that the DSP-Zn@PEG-ALN NPs have a great potential in enhancing chemotherapeutic efficacy for the treatment of bone metastatic breast cancer.

1. Introduction

Breast cancer is the most common cancer and the second leading cause of cancer-related deaths among women all over the world [1]. Breast cancer has a predilection to metastasize to other organs, especially to the bone. More than 80% of women who die from breast cancer show evidence of bone metastasis [2]. Once the bone metastasis occurs, the chance of survival [3] and quality of the life for the patients decrease significantly, with a clinical result including bone pain, pathological fracture, nerve compression and hypercalcemia [4–6].

The present approaches for treating bone metastasis are mainly concentrated on surgical resection, radiotherapy and chemotherapy [7]. However, their efficacies are greatly limited due to the low permeability in the bone tissue and poor selectivity to the multiple bone metastatic nodules [8,9]. Therefore, novel approaches for treating metastatic breast cancer are clearly needed.

Great efforts have been made to achieve bone targeting using nanoparticle-based targeted drug delivery systems, including silica nanoparticles [10,11], polymer micelle/nanoparticles [12–14], and liposomes [15,16]. Among them, liposomes have attracted considerable attention due to their inherent biocompatibility [17]. However, for a systemically administered system to target the bone mineralized tissue, it has to cross the blood-bone marrow barrier including the clefts of bone marrow sinusoidal capillaries with diameter about 80–100 nm [18–20]. Therefore, nanoparticles with diameters smaller than 80 nm were used in this study. Polymer nanoparticles have attracted the interest of many research groups and various functional polymer nanoparticles have been widely used in the last decades [21–23]. Coordination polymer nanoparticles (CPNs) are a class of burgeoning materials which are self-assembled from metal ions and organic bridging ligands. CPNs have shown a great potential in drug delivery systems, because of their tunable compositions, sizes, and shapes; biological compatibility; stability in physiological environments; and intrinsic biodegradability [24]. Herein, CPNs were used for enhancing the targeting efficiency of nanoparticles by regulating its sizes.

To achieve active targeted drug delivery to the bone, there are well-known functional ligands including bisphosphonates, tetracyclines, and acidic oligopeptides [25]. Among them, bisphosphonates (*e.g.*, alendronate (ALN), risedronate, etidronate) are often used due to their high affinity to bone and therapeutic effects on bone diseases [26].

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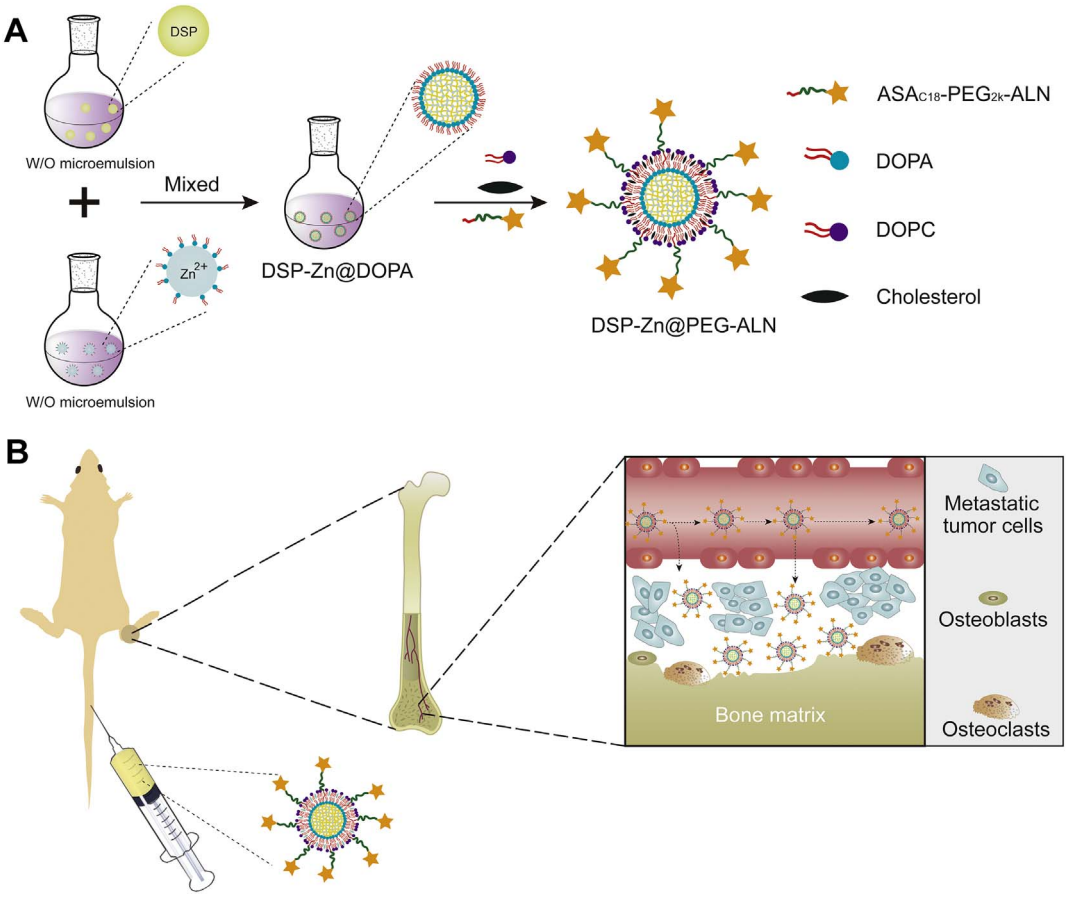

Scheme 1. (A) Preparation of DSP-Zn@PEG-ALN NPs. (B) Illustration of bone targeting delivery system, DSP-Zn@PEG-ALN NPs.

Additionally, an important feature of bisphosphonates is that its uptake in bone metastatic lesions is 10–20–fold higher than in healthy bone tissues [8,14,26–28].

In this study, ultrasmall CPNs (about 55 nm) were constructed by chelating prodrug of cisplatin, cis,cis,trans-diamminedichlorodisuccinato-platinum (DSP), with Zn^{2+} metal ions in water-in-oil (W/O) microemulsion to form nanoparticles which were stabilized by coating phospholipids. To preferentially deliver DSP to the bone tissues, ALN, a bone seeking moiety, was linked to a fatty acid modified polyethylene glycols (PEG). The formed targeting moiety was intercalated into the phospholipids of the nanoparticles. As shown in Scheme 1, the bisphosphonate functionalized CPNs contain three main components: (I) DSP-Zn NPs, a biodegradable CPNs, to form an rigid inner core; (II) PEG, a layer of stealth, to prolong blood circulation time; and (III) ALN, which is a bisphosphonate, a targeting moiety to selectively bind to bone.

We hypothesized that DSP-Zn@PEG-ALN NPs could effectively cross the blood-bone marrow barrier with proper size and preferentially accumulate in the bone metastatic lesions under the guidance of ALN. Then, DSP was quickly released from DSP-Zn@PEG-ALN NPs in the lower pH microenvironment of bone metastatic lesions and thus, killing the metastatic cancer cells and preventing bone loss. Simultaneously, during the release of DSP, DSP-Zn@PEG-ALN NPs can gradually be degraded to avoid accumulation toxicity. Though DSP-Zn@PEG-ALN NPs have been well constructed, further efforts should be paid to the industrial production of the nanoparticles for its clinical transformation.

2. Materials and methods

2.1. Materials

Octadecylsuccinic anhydride (ASA_{C18}, > 95%) and ALN sodium were purchased from TCI (Tokyo, Japan). Cisplatin (CDDP, 99.99%), succinic anhydride (SA, 99%), 4-dimethylaminopyridine (DMAP, 99%), 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (EDC, 98%), *N*-hydroxysuccinimide (NHS, 98%), and triethylamine (TEA, 99%) were purchased from Aladdin Industrial Corporation (Shanghai, China). Hydroxyapatite (HA), 2-morpholinoethanesulfonic acid (MES, BioUltra), 3-(4,5-dimethyl-2-thiazolyl)-2,5-diphenyl-2-H-tetrazolium bromide (MTT), and polyethylene glycol 2000 (PEG_{2k}, Mw = 2000, BioUltra) were purchased from Sigma-Aldrich (St. Louis, USA). Roswell Park Memorial Institute (RPMI) 1640 medium, pancreatic enzymes and fetal bovine serum (FBS) were purchased from Gibco. Ultrapure water (18.2 Ω) was obtained from an Ultra Bio Mk2 ultrapure system (Elga, UK). Dioleoylphosphatidic acid (DOPA), cholesterol, and 1,2-dioleoyl-sn-glycero-3-phosphocholine (DOPC) were purchased from Avanti Polar Lipids, Inc. (Alabaster, USA). All other reagents were purchased as analytical reagent grade and used as received.

MCF-7 cells and MDA-MB-231 cells were purchased from the Laboratory Animal Center of Sun Yat-sen University. Sprague–Dawley rats (200 ± 20 g), Kunming mice (20 ± 2 g), and BALB/C-nu/nu mice (6 weeks old) were supplied by the Laboratory Animal Center of Sun Yat-sen University. All experimental procedures were approved and supervised by the Institutional Animal Care and Use Committee of Sun Yat-sen University.