Acta Biomaterialia 8 (2012) 3005–3013

Contents lists available at SciVerse ScienceDirect

Acta Biomaterialia

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

Folate–PEG–superparamagnetic iron oxide nanoparticles for lung cancer imaging

Mi-Kyong Yoo [a,b,1], In-Kyu Park [c,1], Hwang-Tae Lim [d], Sang-Joon Lee [c], Hu-Lin Jiang [d], You-Kyoung Kim [a], Yun-Jaie Choi [a], Myung-Haing Cho [d,e,f,*], Chong-Su Cho [a,*]

[a] Department of Agricultural Biotechnology and Research Institute for Agriculture and Life Sciences, Seoul National University, Seoul 151-921, South Korea
[b] Department of Advanced Material Engineering for Information and Electronics, Kyung Hee University, Yongin 446-701, South Korea
[c] Department of Biomedical Science, Chonnam National University Medical School and Center for Biomedical Human Resources (BK-21 program), Gwangju 501-746, South Korea
[d] Laboratory of Toxicology, College of Veterinary Medicine, Seoul National University, Seoul 151-742, South Korea
[e] Department of Nano Science and Technology, Graduate School of Convergence Science and Technology, Advanced Institute of Convergence Technology, Seoul National University, Suwon 443-270, South Korea
[f] Graduate Group of Tumor Biology, Seoul National University, Seoul 151-742, South Korea

ARTICLE INFO

Article history:
Received 1 December 2011
Received in revised form 23 March 2012
Accepted 17 April 2012
Available online 24 April 2012

Keywords:
Magnetic nanoparticles
Folate
Poly(ethylene glycol)
Lung cancer
Imaging

ABSTRACT

While superparamagnetic iron oxide nanoparticles (SPIONs) have been widely used in biomedical applications, rapid blood clearance, instability and active targeting of the SPIONs limit their availability for clinical trials. This work was aimed at developing stable and lung cancer targeted SPIONs. For this purpose firstly folic acid (FA)-conjugated poly(ethylene glycol) (FA–PEG) was synthesized, and FA–PEG–SPIONs were subsequently prepared by the reaction of FA–PEG with aminosilane-immobilized SPIONs. FA-PEG-SPIONs were labeled with Cy5.5 for optical imaging. The intracellular uptake of FA–PEG–SPIONs–Cy5.5 was evaluated in KB cells and lung cancer model mice to confirm active targeting. The sizes of the FA–PEG–SPIONs were little changed after up to 8 weeks at 4 °C, suggestive of very stable particle sizes. The results of fluorescent flow cytometry and confocal laser scanning microscopy suggest that the intracellular uptake of FA–PEG–SPIONs–Cy5.5 was greatly inhibited by pre-treatment with free folic acid, indicative of receptor-mediated endocytosis. Stronger optical imaging was observed in the lung cancer model mice for FA–PEG–SPIONs–Cy5.5 than PEG–SPIONs–Cy5.5 6 and 24 h post-injection through the tail vein, due to receptor-mediated endocytosis.

1. Introduction

Nanoparticles have attracted much attention owing to their unusual electronic [1], optical [2], and magnetic [3] properties. Especially, nanoparticles have been used for various biomedical applications, such as diagnostics and therapeutics, due to their unique capabilities and their few side-effects. Among nanoparticles, superparamagnetic iron oxide nanoparticles (SPIONs) offer high potential for several biomedical applications, such as magnetic resonance imaging [4], tissue repair [5], hyperthermia treatment [6] and as drug delivery systems (DDSs) [7], owing to their biocompatibility, appropriate surface architecture, and easy conjugation with targeting ligands [8]. In particular, drug-loaded SPIONs can be directed to the desired target site by an external magnetic field while simultaneously tracking the distribution of SPIONs in the body [9]. Application of SPIONs as DDSs requires that the SPIONs be stable under physiological conditions and that the circulation half-lives of the SPIONs in vivo should be long, as they are mainly captured by the reticuloendothelial system (RES) [10]. Many researchers have used poly(ethylene glycol) (PEG) to stabilize SPIONs, because a PEG shell on nanoparticles (NPs) facilitates their steric stabilization [11,12] and increases their circulation time in the bloodstream, because PEG minimizes protein adsorption and recognition by macrophages of the mononuclear phagocyte system [13,14].

The introduction of a targeting moiety onto SPIONs is aimed at increasing selective cellular binding and internalization through receptor-mediated endocytosis [15]. Folate receptors (FARs) on the cell membrane are a potential molecular target for tumor imaging because the FAR is highly expressed in a number of epithelial carcinomas [16] and the FAR provide highly selective sites that differentiate tumor cells from normal cells [17]. FARs are often present in large numbers on cancer cells with their limited expression on normal cells [18]. FARs are also over-expressed on activated and non-resting macrophages, although functional FARs are not expressed on resting macrophages or normal epithelial cells, which helps in targeting genetically altered cells [19].

* Corresponding authors. Address: Laboratory of Toxicology, College of Veterinary Medicine, Seoul National University, Seoul 151-742, South Korea. Tel.: +82 2 880 1276; fax: +82 2 875 8842 (M.-H. Cho), Department of Agricultural Biotechnology and Research Institute for Agriculture and Life Sciences, Seoul National University, Seoul 151-921, South Korea. tel.: +82 2 880 4636; fax: +82 2 875 2494 (C.-S. Cho).
E-mail addresses: mchotox@snu.ac.kr (M.-H. Cho), chocs@plaza.snu.ac.kr (C.-S. Cho).
[1] The first two authors contributed equally to this work.

1742-7061/$ - see front matter © 2012 Acta Materialia Inc. Published by Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.actbio.2012.04.029