Synthesis and Evaluation of Triphenylphosphonium Conjugated ^{18}F-Labeled Silica Nanoparticles for PET Imaging Agent

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Triphenylphosphonium (TPP) is accumulated several hundredfold into intracellular fluid from the extracellular space by the plasma membrane potential. In cancer cell, the plasma membrane potential is higher than in normal cell. And silica nanoparticles (SNPs) use widely developed for biomedical use, including optical imaging, cancer therapy, targeted drug delivery. In this study, we modified different amounts of TPP on surface of silica nanoparticles. In order to evaluate the tumor uptake of TPP-SNPs, ^{18}F was labeled on the surface of silica nanoparticles. By measuring the zeta potential, it was confirmed that the high level of TPP layer on surface of silica nanoparticles was showed with higher positive charge (+31.5 mV). The uptake value of high positive charge silica nanoparticles (+31.5 mV) was higher in tumor than that of others. The difference uptake value of tumor in vivo according to the difference amount of charge on the surface of the nanoparticles was confirmed.

I. INTRODUCTION

TPP is composed of a positively charged phosphorus atom begird with three phenyl groups, giving it an extended hydrophobic surface despite the positive charge of the phosphorus atom. The positive charge enables them to infiltrate lipid bilayers easily and to accumulate 100- to 500-fold into intracellular fluid, because of the plasma membrane potential (-30 to -60 mV, negative inside).[1] In cancer cell, the plasma membrane potential is reported to be higher than in normal cell. Therefore, this cell should accumulate more TPP than normal cell.[2] Here, we report the design and synthesis of triphenylphosphonium-conjugated silica nanoparticles. SNPs possess remarkable properties, such as monodispersity, large surface area, high drug loading efficiency, and potential for hybridization with other organic/inorganic materials. In addition, SNPs are applied for several biomedical applications due to their potential as drug carriers, diagnostic and therapeutic agents.[3]

I.A. Experimental

I.A.1. Synthesis of ^{18}F labeled TPP-SNPs

Synthesis of TPP-SNPs: Different amounts of (3-carboxypropyl)triphenylphosphonium (30, 90, 150, 210 μmol) in 20 mL of DMF were mixed with N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide, N-hydroxysuccinimide and triethylamine (1:1.2:1.2:2, molar ratio). 50 mg of Amine-modified SNPs were added in each mixture and the mixtures were stirred at room temperature for 24 h. TPP modified SNPs were collected by centrifugation and washed extensively with DMF, D.W and ethanol. TPP modified SNPs (TPP-SNPs) were dried at room temperature for 24 h before use.

^{18}F labeling of TPP-SNPs: 1 mg of TPP-SNPs were suspended in 100 μL of acetonitrile, and 20 mCi of ^{18}F was introduced to the suspension upon stirring at 100℃ for 1 h. TFA was added in mixture and stirred at 100℃ for 1 h. ^{18}F-Labeled TPP-SNPs were collected by centrifugation and washed with saline.

I.A.2. Zeta potential of TPP-SNPs

TPP-SNPs, modified with different amounts of TPP, suspensions in D.W (0.1 mg/mL) were prepared for measuring zeta potential. Suspensions were treated with ultrasonication for 5 m. Zeta potential of TPP-SNPs suspensions was measured by Zeta-sizer.

I.A.3. Animal PET study

In vivo study was carried out in colon cancer cell (CT-26) xenografted Balb/c mice weighing about 20 g. ^{18}F-Labeled TPP-SNPs were intravenously injected in mice at 10 μCi/mouse. PET images were measured after 5, 15, 30, 60, 120 m of injection.

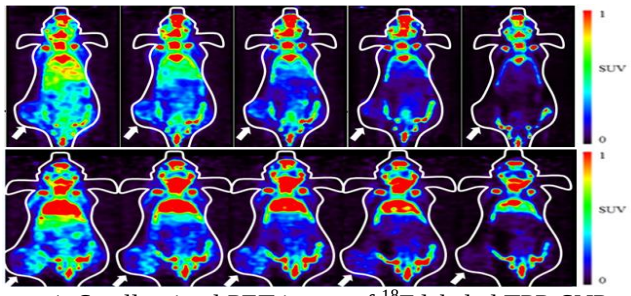

Figure 1. Small-animal PET image of ^{18}F labeled TPP-SNPs

Table 1. Surface charge values with triphenylphosphonium

Entry	SNP-NH_2	TPP	Zeta potential
2	50 mg	90 μmol	+27.2 mV
⋮		↓	
4	50 mg	210 μmol	+31.5 mV

I.A.4. Results and Discussions

The radiochemical yield of ^{18}F-Labeled TPP-SNPs were about 9%. By measuring the zeta potential, it was confirmed that the high level of TPP layer on surface of silica nanoparticles was showed with higher positive charge (+31.5 mV). PET images of ^{18}F-Labeled TPP-SNPs were obtained in CT-26 xenografted Balb/c mice at 5, 15, 30, 60, 120 m. After 5 m post intravenously injection, uptake in the tumor is pronounced for ^{18}F-Labeled TPP-SNPs. In particularly, the uptake value of high positive charge silica nanoparticles (+31.5 mV) was higher in tumor site than that of others (Fig. 1).

II. CONCLUSIONS

The conclusion was that the surface of nanoparticles could be modified positive charge using TPP, and we synthesized ^{18}F-Labeled TPP-SNPs. In PET study, we confirmed that the difference uptake value of tumor in vivo according to the difference amount of charge on the surface of the nanoparticles was confirmed.

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