Future Perspectives of Radionanomedicine Using the Novel Micelle-Encapsulation Method for Surface Modification

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Abstract The emerging radionanomedicine has multifunctional and theranostic purposes. For these purposes, radionanomedicine should achieve the efficient and specific delivery of therapeutic agents by multifunctional characteristics, using low amounts of nanomaterials in vivo. Recent research on radiolabeled micelle-encapsulated nanomaterials has been made on the their efficacy and safety using a one-step surface modification method (Jeong's method). This one-step multifunctional approach to the nanoparticle can be the important challenge in producing effective nanoplatforms for cancer imaging and therapy.

Keywords Radionanomedicine · Nanomedicine · Radioisotope · Nano-materials · Surface-modification

Research using radiolabeled nanoparticles can be termed as 'radionanomedicine' [1, 2]. A focus of the emerging nanomedicine has been on the development of multifunctional nanoplatforms to improve the efficiency of therapy or

theranosis (both therapy and diagnosis) [3, 4]. Such multifunctional radionanomedicines can deliver multiple cancer-targeting ligands (for improvement of target specificity), therapeutic radionuclides or therapeutic drugs (for therapy) and diagnostic radionuclides (for diagnosis) simultaneously. Indeed, the development of multifunctional radionanomedicine has become a possible state-of-the-art in nanomedicine research [5, 6]. We will focus on the recent achievements of multifunctional radionanomedicine and its future perspectives.

The primary concept of radionanomedicine is the labeling of radionuclides onto the nanomaterials. Highly sensitive radioisotope tagging can reduce the amount of nanomaterials used in vivo, because it is easy to evaluate where the nanoparticles locate in vivo by nuclear medicine modalities. Commonly used radioisotopes are diagnostic radionuclides (generator-produced ⁶⁸Ga [7], cyclotron-produced ⁶⁴Cu [8, 9] or ⁸⁹Zr [10]), and therapeutic radionuclides (reactor-produced ¹⁷⁷Lu [11, 12], generator or reactor-produced ⁹⁰Y [13], and generator-produced ¹⁸⁸Re [14, 15]). The labeling of nanomaterials with radionuclides can be accomplished intrinsically and extrinsically. Intrinsically radiolabeled nanoparticles have been prepared by various methods, such as mixing the cold precursor with a radioisotope to make the core, trapping radioisotope specifically on the surface of nanomaterials, and using neutron or proton beam activation after core preparation [16, 17]. Extrinsically radiolabeled nanoparticles have been functionalized with chelators bound to the surface of nanomaterials [18]. Chelators used for extrinsically radiolabeling nanoparticles are DOTA (1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid), NOTA (1,4,7-triazacyclononane-1,4,7-triacetic acid), DTPA (diethylene triamine pentaacetic acid), TETA (1,4,8,11-tetraazacyclotetradecane-1,4,8,11-tetraacetic acid), DFO (desferrioxamine B), etc. [19].

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The important issue of radionanomedicine is the use of trace amounts of radiolabeled nanomaterials for in vivo theranosis. This requires increased specific delivery of nanoparticles to target tissues or decreased nonspecific binding to normal tissues, which was proven to be difficult to achieve in practice. In a previous study, a multispecific nanoparticle that has two or more different types of targeting ligands enabled specific and effective agent delivery [20].

The biological properties of nanoparticles depend on the ligands attached to their surfaces, and polyethylene glycol (PEG) molecules are often used to reduce nonspecific normal-tissue uptake [21]. However, the conventional method, which is a multistep and step-by-step approach for surface modification of nanoparticles, has many difficulties. First of all, the multistep chemical reactions can cause decreasing total yield of modified nanoparticles. In addition, in each reaction step, we have to consider the reaction time, temperature, pH, impurities, solvents, reagent concentrations, etc. Sometimes, a complicated situation can be induced by the conjugation of two or more ligands.

Recently, Lee et al. [22] developed a modified encapsulation method (Jeong's method) to produce multifunctional nanoparticles (Fig. 1). This method could be the solution to the challenge for the preparation or radiolabeling of multifunctional nanomaterials. Jeong's micelle-encapsulation method proposed a quick and easy method to prepare multifunctional nanomaterial in one-step under mild conditions, which could preserve ligand integrity. This method was inspired by the hydrophilization method used for quantum dots [23, 24], surface-enhanced Raman scattering (SERS) dots [25], quantum-dot-embedded silica nanoparticles [26], and gold or iron oxide nanomaterials [27, 28]. Jeong's method contributes to achieving surface multifunctionality and hydrophilicity of nanoparticles by the use of combined multiple amphiphiles with different functional groups

simultaneously, and can result in homogeneous multifunctional nanoparticles. One-step functionalization of all ligands, the chelator, and PEGs, followed by radiolabeling and purification will be an indispensable solution to the problems of conventional methods for surface modification. Another important issue of radionanomedicine is quality control of the nanoparticles. This concern can also be solved by Jeong's method, which can provide monodisperse nanoparticles even after the multifunctional surface modification [29]. Although Jeong's method has great feasibility and a future in radionanomedicine, we have to thoroughly evaluate the unexpected toxicity from lipid contents used for encapsulation and also develop the quantification method of functional groups encapsulated on their nanoplatforms.

The multifunctional nanoparticle can be used for multiradioisotope labeling or a multitargeting strategy. Here, we can suggest the use of this multifunctional nanoparticle for theranosis ($^{68}\text{Ga}/^{64}\text{Cu}$ and ^{177}Lu) or dual-energy combined internal therapy using (^{177}Lu and ^{90}Y) dual radioisotope tagging (Fig. 2a, b). Further suggestion of multifunctional nanoparticles for clinical application can be expected by multiple ligands for efficient tumor targeting {e.g., prostate-specific membrane antigen (PSMA) [30], Arg-Gly-Asp (RGD) [31], etc.}, and ^{64}Cu for biologic effective dose (BED) prediction and validation, and ^{177}Lu for radionuclide therapy (Fig. 2c).

In conclusion, the advantage of multifunctional radionanomedicine for in vivo application is that the amount of nanomaterials can be decreased as low as possible. And multifunctional radionanomedicine can eliminate the concerns about the possible hazards of pharmacologic amount of nanomaterials administered, and be used for a multiradioisotope or multitargeting approach. Finally, the trace technology behind radionanomedicine using multifunctional radionanomaterials will help the progress of the translation of nanomedicine.

Fig. 1 Schematic figure of the surface modification of nanostructures with long alkyl tail and hydrophilic ligand head, which enable multifunctionality on nanoparticles in one step

Fig. 2 Expected usage of multifunctional nanoparticles using dual radiotracers, and the suggestion for effective treatment of cancer **(a)** prediction and validation of biological effective dose (BED) using therapeutic ^{177}Lu and diagnostic $^{68}\text{Ga}/^{64}\text{Cu}$, **(b)** dual-energy combined internal radiotherapy using therapeutic ^{177}Lu and ^{90}Y , and **(c)** multiple ligands can be used for efficient tumor targeting (e.g., PSMA, RGD, etc.), and ^{64}Cu for BED prediction and validation, and ^{177}Lu can be used for radionuclide therapy

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Conflict of Interest Yung-Sang Lee, Yong-il Kim, and Dong Soo Lee declare that they have no conflicts of interest.

Ethical statement This article does not contain any studies with human participants or animals performed by any of the authors. The manuscript has not been published before or is not under consideration for publication anywhere else and has been approved by all co-authors.

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