Synthesis and Functional Evaluation of Gadolinium Oxide Nanoparticles as a PA-MR Dual Imaging Probe for Theranostics

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Nanomaterials have been studied as delivery vehicles of drugs and imaging agents, and could be functionalized to have specificity, efficacy, and safety.[1] "*Theranostics*" as a new concept, which combines diagnostic and therapeutic capabilities in one dose, has attracted much attention in medicinal chemistry. We have already succeeded in developing water-dispersible, size-controlled, and biocompatible Gd_2O_3 nanoparticles (Gd NPs) as a highly effective dual imaging probe for both photoacoustic (PA) and magnetic resonance (MR) imaging to realize diagnostic accuracy as well as early detection of "tumors".[2] In this study, clinically-used anticancer reagent, doxorubicin (DOX), were conjugated into gelatin-coated Gd NPs (Gelatin-DOX-Gd NPs) through strong electrostatic interaction to develop a novel theranostics probe.

The functional evaluation of Gelatin-DOX-Gd NPs was carried out as follows. Dynamic light scattering (DLS) measurements showed that the hydrodynamic diameter of water-dispersed Gd NPs without modification increased monotonically for 3 days. In sharp contrast, no aggregation of Gelatin-Gd NPs and Gelatin-DOX-Gd NPs were observed during 3 days. These results indicated that the gelatin inhibited the aggregation of Gd NPs because of its capability to form protective colloids. Electrophoresis Light Scattering (ELS) measurement showed that the surface potential of Gd NPs changed from positive to negative after coating with gelatin. These results clearly showed that Gd NPs were coated by gelatin properly.

As for MRI, longitudinal relaxivity (r_1) of Gelatin-DOX-Gd NPs was much larger than that of clinically used Gd-DTPA (Magnevist®). These results clearly showed that Gelatin-DOX-Gd NPs are effective as a positive contrast agent for MRI. In addition, *in vitro* release of DOX from Gelatin-DOX-Gd NPs occurred in the presence of matrix metalloproteinase-2 (MMP-2) located around tumors, and Gelatin-DOX-Gd NPs showed apparent cytotoxicity toward HeLa cells (human cervix epithelial adenocarcinoma), which were secreting MMP-2. Consequently, Gelatin-DOX-Gd NPs were expected as a new theranostics probe for treatment of cancer as well as PA and MR imaging agent.

1) Aminolroayaei F.; Shahbazi-Gahrouei D. *et al. IET Nanobiotechnology.* **2021**, 15(3), 247-256.
2) Kimura, Y.; Kondo, T. e*t al. Adv. Healthcare Mater.* **2012**, 1, 657-660.