Mineralized Nanoparticles as a Contrast Agent for Ultrasound and Magnetic Resonance Imaging

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Abstract : To date, imaging techniques have attracted much attention in medicine because the detection of diseases at an early stage provides greater opportunities for successful treatment. Consequently, over the past few decades, diverse imaging modalities including magnetic resonance (MR), positron emission tomography, computed tomography, and ultrasound (US) have been developed and applied widely in the field of clinical diagnosis. However, each of the above-mentioned imaging modalities possesses unique strengths and intrinsic weaknesses, which limit their abilities to provide accurate information. Therefore, multimodal imaging systems may be a solution that can provide improved diagnostic performance. Among the current medical imaging modalities, US is a widely available real-time imaging modality. It has many advantages including safety, low cost and easy access for patients. However, its low spatial resolution precludes accurate discrimination of diseased region such as cancer sites. In contrast, MR has no tissue-penetrating limit and can provide images possessing exquisite soft tissue contrast and high spatial resolution. However, it cannot offer real-time images and needs a comparatively long imaging time. The characteristics of these imaging modalities may be considered complementary, and the modalities have been frequently combined for the clinical diagnostic process. Biominerals such as calcium carbonate (CaCO3) and calcium phosphate (CaP) exhibit pH-dependent dissolution behavior. They demonstrate pH-controlled drug release due to the dissolution of minerals in acidic pH conditions. In particular, the application of this mineralization technique to a US contrast agent has been reported recently. The CaCO3 mineral reacts with acids and decomposes to generate calcium dioxide (CO2) gas in an acidic environment. These gas-generating mineralized nanoparticles generated CO2 bubbles in the acidic environment of the tumor, thereby allowing for strong echogenic US imaging of tumor tissues. On the basis of this previous work, it was hypothesized that the loading of MR contrast agents into the CaCO3 mineralized nanoparticles may be a novel strategy in designing a contrast agent for dual imaging. Herein, CaCO3 mineralized nanoparticles that were capable of generating CO2 bubbles to trigger the release of entrapped MR contrast agents in response to tumoral acidic pH were developed for the purposes of US and MR dual-modality imaging of tumors. Gd2O3 nanoparticles were selected as an MR contrast agent. A key strategy employed in this study was to prepare Gd2O3 nanoparticle-loaded mineralized nanoparticles (Gd2O3-MNPs) using block copolymer-templated CaCO3 mineralization in the presence of calcium cations (Ca2+), carbonate anions (CO32-) and positively charged Gd2O3 nanoparticles. The CaCO3 core was considered suitable because it may effectively shield Gd2O3 nanoparticles from water molecules in the blood (pH 7.4) before decomposing to generate CO2 gas, triggering the release of Gd2O3 nanoparticles in tumor tissues (pH 6.4~7.4). The kinetics of CaCO3 dissolution and CO2 generation from the Gd2O3-MNPs were examined as a function of pH and pH-dependent in vitro magnetic relaxation; additionally, the echogenic properties were estimated to demonstrate the potential of the particles for the tumor-specific US and MR imaging.

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