Synthesis and Characterization of Ultrasmall Superparamagnetic Iron Oxide Nanoparticles-Encapsulated Liposomes as a Novel pH-Responsive T1-Weighted MRI Contrast Agent for Cancer Diagnosis

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Statement of Purpose: Magnetic resonance imaging (MRI) has been increasingly used in clinical diagnosis of a variety of disorders including cancer owing to its excellent spatial resolution, soft tissue contrast, and unlimited tissue penetration which enable it to provide exquisite anatomical and functional information. To improve the sensitivity of MRI and thus enhance the visibility of neoplastic lesions within the body, exogeneous contrast agents (CAs) are often administered to patients prior to MRI examination. However, current magnetic resonance imaging (MRI) contrast agents, dominated by Gadolinium (Gd)-based chelates, suffer from low sensitivity, non-specificity, rapid clearance, and potential toxicity which often result in suboptimal cancer diagnosis. To address this issue, stimuli-responsive MRI contrast agents based on superparamagnetic iron oxide nanoparticles (SPIONs) have received particular interest owing to their good sensitivity, tumor selectivity, and higher biocompatibility in comparison to the conventional Gd-based agents. To this regard, in this study, pH-responsive ultrasmall SPIONs-encapsulated liposomes (SPIONs-Lips) were developed as a novel contrast agent able to release encapsulated SPIONs and subsequently generate distinguishable T1 MRI signal in response to the cancer acidic microenvironment.

Methods: Hydrophilic ultrasmall SPIONs were synthesized through co-precipitation process and subsequently SPIONs-Lips were prepared according to the thin film hydration method. SPIONs and SPIONs-Lips were characterized in terms of size, polydispersity index (PDI), ζ-potential, and X-ray diffraction. Encapsulation efficiency of SPIONs-Lips was determined, and their pH-responsiveness was evaluated by MRI after incubation in buffers having various pH (7.4, 6.5, 5). In addition, cytotoxicity of SPIONs and SPIONs-Lips were evaluated by MTT assay against CHO cells and PC3 cancer cells.

Results: The synthesized SPIONs and SPIONs-Lips had average hydrodynamic size of 9.3 nm with PDI < 0.2 and 105.7 nm with PDI <0.1, respectively. SPIONs-Lips showed an encapsulation efficiency of 27.3 %. In vitro MRI studies demonstrated brighter images and considerable increase in r1 values in response to the acidity of the buffers which validated the release of SPIONs from liposomes and consequently their higher interactions with protons in the acidic microenvironment. Moreover, cytotoxicity studies demonstrated >80 % viability of both CHO and PC3 cells after 72 h incubation at the Fe concentration of 0−200 μg/mL which confirm the high biocompatibility of the proposed nanostructure.

Conclusion: This work proposed a novel SPION-based T1-weighted MRI contrast agent with a sensitive response to acidic microenvironment and higher biocompatibility in comparison to the current MRI contrast agents. The disruption of the synthesized nanostructure in the acidic tumor microenvironment, subsequent release of SPIONs and increase in their r1 value can facilitate effective cancer diagnosis.