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博 士 学 位 论 文

功能纳米颗粒的设计合成及其肿瘤诊断治疗应用研究

Design and preparation of functional nanoparticles and their application in cancer diagnosis and therapy

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摘　要

功能化无机纳米材料具有良好的生物兼容性、优异理化性质、易于表面修饰以及尺寸、形貌易于调控等优势，被广泛应用于生物医学领域。其中，磁共振成像造影剂和抗肿瘤药物运载系统，以其能有效提高肿瘤诊断的准确性和治疗的效果，已经成为该域中最富有活力的分支，受到广大科研工作者的关注。鉴于发展新型高效的磁共振造影剂和无机纳米抗肿瘤药物运载系统具有重要的现实意义，本博士论文设计合成了多种功能性无机纳米材料，并对其肿瘤诊断和治疗的能力进行了系统性的考察。主要研究内容概括如下：

第一章：简要综述了功能化无机纳米材料在磁共成像振造影剂和抗肿瘤药物运载系统方面的研究进展，并阐明博士论文的选题依据和研究内容。

第二章：基于高有效半径的磁性纳米材料可以产生更强的T2造影效果，我们通过引入氯离子，成功合成了尺寸可控的内凹形Fe3O4纳米颗粒。对其磁共振造影性能的研究表明，较传统球形纳米颗粒，该内凹形的Fe3O4纳米颗粒具有更大的有效半径，从而表现出更强的地缩短水质子T2弛豫时间的能力。活体研究表明，该内凹形Fe3O4纳米颗粒非常适合于对肝脏和肝癌组织进行高效T2磁共振造影成像。

第三章：在氯离子作用下，我们通过形貌控制合成，得到了Fe3O4纳米六方片。结构研究表明，该片状Fe3O4纳米材料的基面为四氧化三铁的{111}晶面并裸露出大量的铁原子核。研究发现，片状Fe3O4纳米材料的{111}晶面裸露出的大量铁原子，大大提高了铁原子核与水质子进行化学交换的几率，使得该片状Fe3O4纳米材料的T1造影成像能力远远高于传统球形Fe3O4纳米材料。

第四章：基于大有效半径和高饱和磁化强度的磁性纳米材料可以产生更强的T2造影效果这一理论，我们通过阳离子交换反应，在保持原有Fe3O4纳米颗粒形貌不发生改变的条件下，成功合成了多种形貌的锰和锌掺杂Fe3O4纳米颗粒。基于其大的有效半径和高饱和磁化强度，该纳米颗粒表现出超高的T2磁共振造影成像能力，使得其能够非常灵敏的对肝脏、原位肝癌和转移肝癌进行T2造影成像，为肿瘤的准确诊断提供重要依据。

第五章：设计合成了一种基于氧化铁纳米材料的智能纳米药物运载系统。该智能纳

米药物能够通过亚胺键将抗癌药物阿霉素偶联到氧化铁纳米材料表面，具有磁性可控、主动靶向和酸性药物释放的特点。实验结果表明，这些特点使得该智能纳米药物能够更有效地杀死肿瘤细胞，提高了阿霉素的抗癌药效。

第六章：设计合成了以空心二氧化硅纳米材料作为载体，运载三氧化二砷抗癌药物的智能纳米药物运载系统。基于其理想的尺寸、酸响应药物释放能力和主动靶向能力，该智能纳米药物运载系统能有效提高三氧化二砷对肿瘤细胞的药效，更好的促进肿瘤细胞的分化，还能对肿瘤细胞的迁移进行更有效地抑制。更重要的是，活体实验表明，该智能药物能在无毒副作用的前提下对实体瘤的生长进行有效地抑制。

第七章：设计合成了一种集药物释放检测，肿瘤诊断和肿瘤治疗为一体的多功能纳米药物。在酸性条件下，该多功能纳米药物能够同时释放出锰离子和砷离子。由于释放出的锰离子能有效提高T1磁共振信号，该多功能纳米药物能够对砷离子在小鼠体内的的释放过程进行实时监测。更重要的是，活体实验表明，该智能药物能在无毒副作用的前提下对实体瘤进行准确的检测并对其生长进行有效地抑制。

关键词：氧化铁纳米颗粒；智能纳米药物；肿瘤诊断；肿瘤治疗

Abstract

Functional inorganic nanomaterials with good biocompatible, excellent physical and chemical properties, easy modification, and tunable size and morphology have been widely used in biomedical. Since magnetic resonance imaging (MRI) contrast agent and inorganic drug delivery systems can improve the accuracy and efficiency in cancer diagnosis and therapy, development of new and effient inorganic nanomaterials in drug delivery and MRI contrast agent are highly desirable and important. In this dissertation, we have developed kinds of functional inorganic nanomaterials to achieve accurate diognosis and effective therapy to tumor. The main investigations are summarized as follows:

Chapter 1. Recent research progress of functional inorganic nanomaterials in MRI contrast agent and drug delivery systems have been briefly reviewed. Besides, we also demonstrated the research significance and content in this thesis.

Chapter 2. We report a new strategy to achieve extremely high transverse relaxivity by controlling the morphology of Fe3O4 nanoparticles. We successfully fabricate size-controllable octapod Fe3O4 nanoparticles by introducing chloride anions. The octapod Fe3O4 nanoparticles (edge length of 30 nm) exhibit an ultrahigh r2 value, indicating that these octapod Fe3O4 nanoparticles are much more effective T2 contrast agents for in vivo MRI and small tumor detection comparing to conventional iron oxide nanoparticles, which holds great promise for highly sensitive, early stage and accurate detection of cancer in the clinic.

Chapter 3. We have demonstrated hexagonal Fe3O4 nanosheets can be prepared by introducing of chloride anions. The prepared Fe3O4 nanosheets are enclosed by (111) facets. We demonstrate that the main contribution of the T1 contrast of magnetic nanoparticles is the chemical exchange between photon and iron ion on the surface of nanoparticles. Since the (111) facet is an iron-rich facet, the T1 contrast ability of Fe3O4 nanosheets is significantly higher than the

traditional spherical Fe_3O_4 nanoparticles.

Chapter 4. We demonstrate that cation exchange can engineer the composition of iron oxide nanocrystals to significantly improve the magnetic resonance contrast ability in molecular imaging. We successfully construct manganese or zinc doped iron oxide nanoparticles with diverse shapes (sphere, cube, and octapod) by facile cation exchange reactions. The engineered shaped-anisotropic iron oxide nanoparticles exhibit both high saturated magnetization values and large effective boundary radii, which ensures the extremely high r2 values. The engineered iron oxide nanoparticles with ultrahigh relaxivity serve as high-performance T2 contrast agents for in vivo imaging, early tumor detection, and high-sensitive metastatic tumor diagnosis, particularly hepatic carcinomas.

Chapter 5. We describe a smart and targeted magnetic nanocarriers to control the delivery and release of anticancer drug doxorubicin (DOX) in vitro. The conjugation of targeted magnetite nanoparticles and DOX molecule via acid-labile imine bonds endows the nanocarriers with three advanced features: magnetically controllable, specific targeting, and pH-responsive. These advantages endow the intelligent drug delivery system to improve the chemotherapeutic efficacy and reduce the side effects, which has great potential to become a favorable strategy for delivery of drugs to the desired sites in patients.

Chapter 6. We report a facile strategy to achieve high anticancer activity of arsenic trioxide by loading the nanoparticulate prodrug into hollow silica inorganic nanoparticles. Because of the appropriate size, pH sensitivity, and surface targeted modification, this smart nanosized drug delivery system can deliver arsenic trioxide into cancer cells efficiently and exhibit much higher cytotoxicity to a variety of cancer cells than free arsenic trioxide. Moreover, this nanomedicine can further promote the differentiation and inhibit the migration of cancer cells. In vivo results suggest that this drug delivery system can significantly inhibit the growth of solid tumors without adverse side effects.

Chapter 7. We reported an ATO-based multifunctional drug delivery system that efficiently delivers ATO to treat tumors and allows real-time monitoring of ATO release by activatable T1 imaging. Acidic stimuli triggered the simultaneous release of manganese ions and ATO, which dramatically increase the T1 signal (bright signal) and enabled real-time visualization and monitoring of ATO release and delivery. Moreover, this smart multifunctional drug delivery system significantly improve ATO efficacy and strongly inhibit the growth of solid tumors without adverse side effects.

Keywords: iron oxide nanoparticles;intellegent drug delivery systems;cancer diagnosis;cancer therapy

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