

行政院國家科學委員會專題研究計畫 期中進度報告

奈米材料於生物醫學上之應用(1/3) 期中進度報告(精簡版)

計畫類別：整合型
計畫編號：NSC 95-2120-M-002-009-
執行期間：95年08月01日至97年07月31日
執行單位：國立臺灣大學化學系暨研究所

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處理方式：本計畫可公開查詢

中華民國 96 年 12 月 28 日

Abstract

In this period, we emphasized on biological applications, specifically on synthesis new cell labeling materials, continued cell labeling investigation and superoxide dismutase (SOD) mimetic studies.

過去半年我們專注開發中孔洞材料在生醫方面的用途。我們合成新的細胞標籤材料及繼續研究已合成之特殊細胞標籤在活體之表現，並發展仿生材料。

Keyword: mesoporous silica nanoparticles, MRI, multifunctional, superoxide dismutase, cell labeling, human mesenchymal stem cells, hMSC

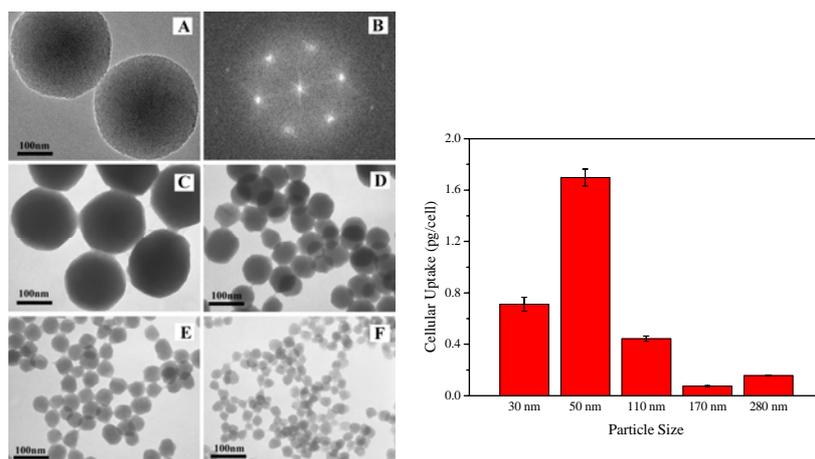
Introduction

In this report, a diverse range of the chemistry in nanospace will be discussed. This includes the applications of mesoporous silica and nanoparticles in many chemical reaction-recognition systems. In this period, we emphasized on biological applications, specifically on synthesis new cell labeling materials, continued cell labeling investigation and superoxide dismutase (SOD) mimetic studies.

Results

Synthesis of New Materials

1. Well-ordered mesoporous silica, MSNs, of various sizes were synthesized by varying the pH of the reaction mixture, sizes of 280, 170, 110, 50, and 30 nm were obtained and their cell uptake efficiency were compared. Like other nanoparticles such as nanogold, latex beads, and sugar coated quantum dots, 50 nm nanoparticles were the most efficient ones to be engulfed by cells.

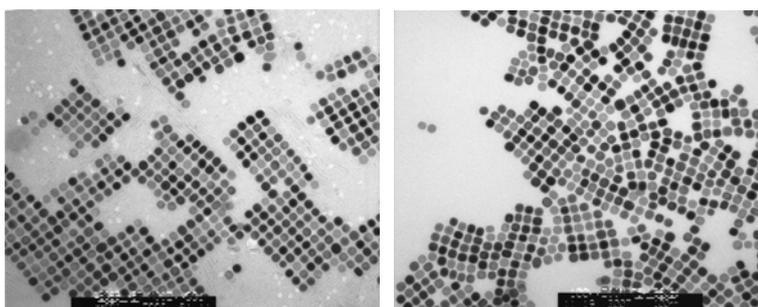


Left: MSNs of A) 280 nm, C) 170 nm, D) 110 nm, E) 50 nm, and F) 30 nm.

Right: Quantitative results on cell uptake with various sized MSNs.

2. MnO and FeMnO_x were synthesized via thermo-decomposition of the corresponding carboxylates. The resulting nanoparticles were even in size and

aligned well on the TEM grid.

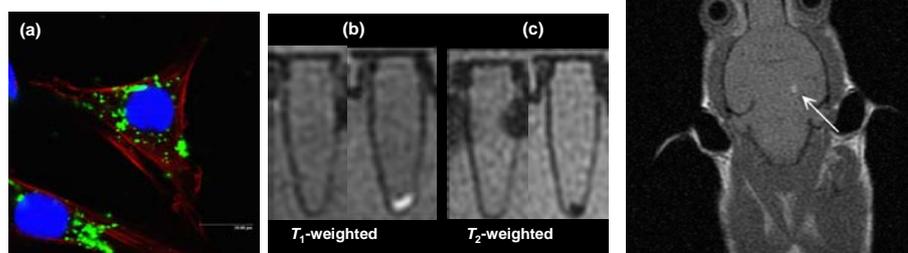
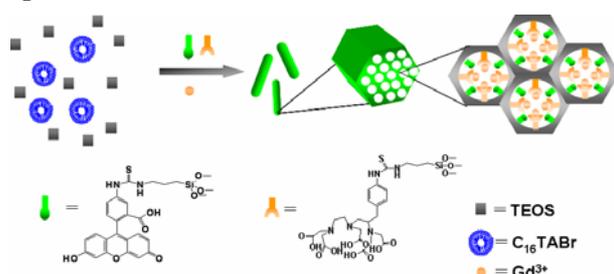


TEM of MnO

FeMnOx

Cell Labeling

1. New multifunctional paramagnetic Gd containing mesoporous silica, Gd-Dye@MSN and Gd-Dye@MSN-R, were synthesized and characterized. These nanoparticles were ~110 nm spheres and ~500x100 nm rods, respectively. Both spheres and rods can label hMSC and 3T3-L1 cells with high efficiency.

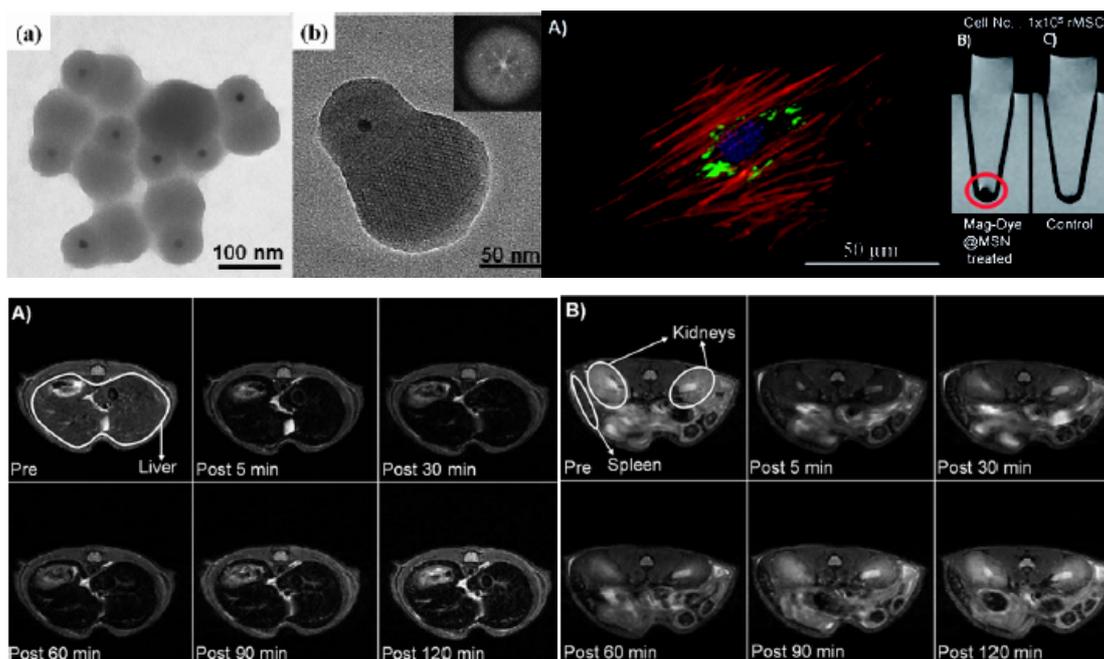


Cell uptake of Gd-Dye@MSN-R

Labeled hMSCs and 3T3-L1 were unaffected in their viability, proliferation and differentiation capabilities into adipocytes, osteocytes, and chondrocytes which can still be readily MRI-detected. MR imaging, with a clinical 1.5 T MRI system and low incubation dosage of Gd, low detection cell numbers, and short incubation time were demonstrated on both loaded –cells and hMSC injected mouse brain. This study shows that the advantages of biocompatibility, durability, high internalizing efficiency, and pore architecture make MSNs to be ideal vector of T1-agent for stem cell tracking with MRI. One paper has been accepted by “Small”, the other has been submitted to

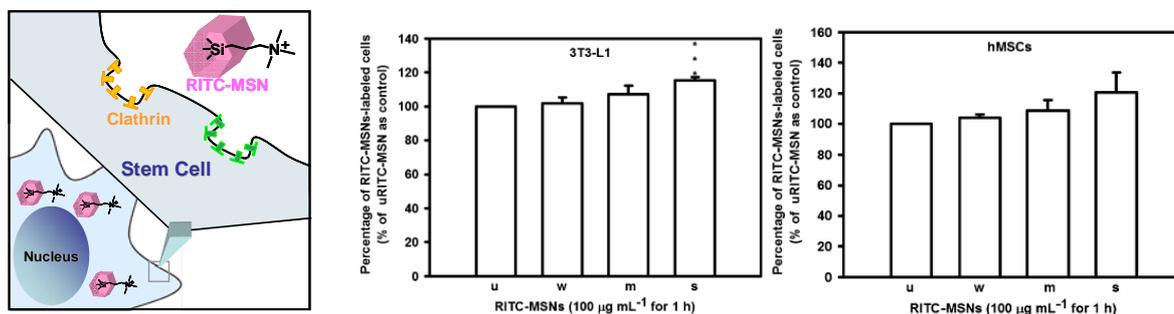
Biomaterials.

2. Multifunctional mesoporous silica nanoparticles, Mag-Dye@MSN, with MRI T2 imaging contrast enhancing and fluorescence imaging capabilities and as a drug reservoir were synthesized. Intracellular labeling and animal magnetic resonance imaging studies on Mag-Dy@MSN followed the synthesis. The utility of multifunctional Mag-Dye@MSN resides in their ability to combine organic/inorganic and diagnostic/therapeutic components within a nanoscaled size. We have demonstrated the advantage of multifunctional nanoparticles in histology samples where fluorescence can be used to detect the presence of nanoparticles directly in animal without further staining. The reported experiments are crucial to the in vivo application of Mag-Dye@MSN, they are the baseline information before the mesoporous silica nanoparticles can be used as diagnostic/therapeutic drug carriers. Published in *Chem. Mater.*, and *ChemBioChem*.



3. Demonstrated surface functionalization with different amounts of positively charged quaternary ammonium group is quite biocompatible and can enhance the uptake of MCM-41 type mesoporous silica nanoparticles for more efficient cellular labeling. However, the charge effect of cell-uptake is cell type and surface charge dependent. At low surface charge, the normal clathrin- and actin-dependent mechanisms operate, which by themselves are already quite efficient for hMSC and 3T3-L1 cells. Above a certain threshold of surface charge, a new unrevealed charge-dependent mechanism starts to be effective for hMSC. The highly

positive-charged MSNs with specific endocytosis pathways could serve as a new approach to study the uptake mechanism and to improve the application for stem cell tracking. Published in *Biomaterials*,



4. Model superoxide dismutase complexes were attached to mesoporous silica both ionically and covalently; IC₅₀'s were demonstrated to be similar to the homogeneous species. A better model complex had been identified and will be immobilized in MSNs for in vitro cell studies.

Publications

1. Tsai, C.-P., Y. Hung, Mou, C. -Y. High Contrast Paramagnetic Fluorescent Mesoporous Silica Nanorod as a Multifunctional Cell-imaging Probe, *Small*, accepted.(2007)
2. Wu, S.-H., Lin, Y.-S., Hung, Y., Chou, Y.-H., Hsu, Y.-H., Chang, C., Mou, C.-Y., "Multifunctional Mesoporous Silica Nanoparticles for Intracellular Labeling and Animal Magnetic Resonance Imaging Studies", *ChemBioChem*, online.(2007)
3. T.-H., Wu, S.-H., Yao, M., Lu, C.-W., Lin, Y.-S., Hung, Y., Mou, C.-Y., Chen, Y.-C., Huang, D.-M., "The Effect of Surface Charge on The Uptake and Biological Function of Mesoporous Silica Nanoparticles in 3T3-L1 Cells and Human Mesenchymal Stem Cells", *Biomaterials*, 2007, 28, 2959
4. Lu, C.-W., Hung, Y., Hsiao, J.-K., Yao, M., Chung, T.-H., Lin, Y.-S., Wu, S.-H., Hsu, S.-C., Liu, H.-M., Mou, C.-Y., Yang, C.-S., Huang, D.-M., Chen, Y.-C. "Bifunctional Magnetic silica Nanoparticles for Highly Efficient Human Stem Cell Labeling" *Nano Lett.* 2007, 7, 149.
5. Lin, Y.-S., Wu, S.-H., Hung, Y., Chou, Y.-H., Chang, C., Lin, M.-L., Tsai, C.-P., Mou, C.-Y. "Multifunctional Composite Nanoparticles-Magnetic, Luminescent and Mesoporous" *Chem Mater.*, 2006, 18, 5170