Development of multifunctional magnetic nanoparticles for specific and early diagnosis of pancreatic cancer

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Abstract

The present study is aimed at designed and development of MR-optical imaging contrast agent for early and specific detection of pancreatic cancer. A highly sensitive and specific dual modality T_2 weighted MR-optical imaging agents (SPIO-mAb-Cy777 NPs) has been synthesized. The SPIO NPs and Cy777 serves as MR enhancer and NIR optical imaging dye respectively. The anti-MUC4 mAb has been used as targeting moiety to target MUC4 receptor which is exclusively expressed in pancreatic cancer. An ex-vitro and in vitro experiments shows significant negative contrast enhancement in MUC4 positive cell line, on the contrary contrast enhancement was not observed in MUC4 negatively expressed cell. Therefore, we can conclude that the SPIO-mAb-Cy777 NPs can specifically target MUC 4 receptor and can be potentially used as tool for the detection of pancreatic cancer with high specificity and sensitivity.

Introduction

Pancreatic cancer (PC) is one of the most lethal malignancies and exhibits rapid metastasis. The five-year survival rate of pancreatic cancer is 6%[2]. Having known through extensive clinical experience, it is widely accepted that early diagnosis may lead to cure or at least offer extended life to the cancer patients. One of the major clinical hindrance in the detection of pancreatic cancer is symptomatological similarity between pancreatic cancer and chronic pancreatic. Recent studies have shown that membrane mucin MUC4 (human) receptor is not expressed in case of chronic pancreatic. On the contrary the membrane mucin MUC4 (human) is abundantly expressed in case of pancreatic cancer. Therefore, MUC4 receptor can potentially serve as biomarker for pancreatic cancer. Herein, we report MR-optical imaging agent (SPIO-mAb-Cy777-mPEG NPs) for early and specific detection of pancreatic cancer.

Materials and Methods

The monodisperse SPIO-nanoparticles were obtained by thermal decomposition method. Post-synthesis ligand exchange reaction was carried out to replace hydrophobic oleic acid and oleylamine surfactants with mPEG-NH_2-silane in order to transform hydrophobic SPIO nanoparticles into hydrophilic ones. *In vitro* MR imaging was carried out using two MUC4 positive cell lines (HPAC and BxPC-3) with low express of MUC4 negative cell Panc 1 as control group. All cell lines were incubated with SPIO-mAb-y777-mPEG NPs (0.5 mM Fe), washed by PBS buffer and scanned by 3.0 T MRI.

Results and Discussion

The monodisperse SPIO-nanoparticles were synthesize by thermal decomposition method. The hydrodynamic diameter and relaxivity values of SPIO NPs are shown in Table 1. The mPEG-NH_2-silane coated SPIO NPs have a relatively narrow size distribution with mean size of 39.3 ± 2.2 nm which was increased 55.9 ± 5.6 nm upon conjugating anti-MUC4 mAb, and Cy777. The relaxivity values (r_1 and r_2) of the SPIO-mAb-Cy777-mPEG NPs measured at 20 MHz were 35.7 ± 1.5 and 216.1 ± 4.4 $mM^{-1}s^{-1}$, respectively. Figure 1a shows ex vitro MR Resovist™ and synthesized SPIO. The synthesized SPIO NPs shows significant higher contrast enhancement compare to that of clinically use Resovist™ at different concentration (0.5, 0.25, 0.125 and 0.00625 mM). In addition, significantly high negative contrast enhancement can be observed at glance in the cell line (BxPC-3 and HPAC) positively expressing MUC4 receptor compare to that of non MUC4 receptor expressing cell lines (Panc 1), as shown in Figure 1 b. These results demonstrate that SPIO-mAb-Cy777-mPEG NPs can be potentially use for detection of pancreatic cancer.

Table 1. Hydrodynamic diameter and relaxivity values of SPIO NPs

Compound[a]	Size (nm)	r_1 ($mM^{-1}s^{-1}$)	r_2 ($mM^{-1}s^{-1}$)	r_2/r_1
SPIO-mPEG	39.3 ± 2.2	30.1 ± 1.3	239.7 ± 15.9	7.9
SPIO-mPEG-Dye	41.6 ± 8.2	33.5 ± 0.6	209.5 ± 7.8	6.3
SPIO-mPEG-mAb-Dye-mPEG	55.9 ± 5.6	35.7 ± 1.5	216.1 ± 4.4	5.7
SPIO-Cys-Dye-mPEG	42.7 ± 4.3	34.3 ± 0.8	210.0 ± 5.4	6.1

[a]Dye = Cy777 ; linker = N-succinimidyl-3-maleimidopropionate (NSMP) ; mAb = Anti-MUC4 antibody ; Cys = cysteine。

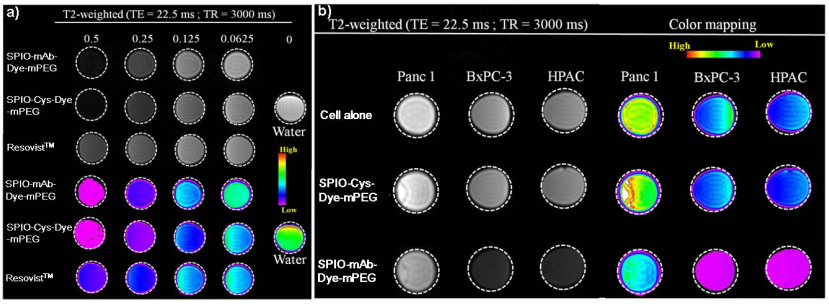

Figure 1. *In vitro* T2-weighted MR images of SPIO-Cys-Dye-mPEG、SPIO-mAb-Cy777-mPEG and Resovist™ at different concentration mM of Fe. a) was show that compare the SPIO-mAb-Cy777-mPEG and Resovist™. b) was show that analysis of specifically targeted on Panc 1、BxPC-3 and HPAC cell lines.

Conclusion

In summary, we successfully synthesized SPIO-mAb-Cy777 nanoparticles for MR and optical imaging. The *In vitro* results confirming that the nanoparticles can specifically targeted to MUC4 receptor expressing of cells. Thus, the SPIO-mAb-Cy777 nanoparticles could be potentially used as contrast agents for molecular MR imaging and reducing the off-targeted. Therefore, we further anticipated that this approach could be exploited for pancreatic cancer therapy.

References

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