Development of a mucin4-targeting SPIO contrast agent for effective detection of pancreatic tumor cells in vitro and in vivo

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Abstract

In search of a unique contrast agent targeting pancreatic adenocarcinoma, new multifunctional nanoparticles (MnMEIO-silane-NH_2-(MUC4)-mPEG NPs) were successfully developed in this study. Mucin4-expression levels were determined through different imaging studies of pancreatic tumors. *In vitro* MR imaging study in HPAC and Panc-1 tumors treated with NPs showed - 89.1 ± 5.7% and - 0.9 ± 0.2% contrast enhancement. In *in vivo* study, it is found to be - 81.5 ± 4.5% versus - 19.6 ± 5.2% respectively. The MR and optical imaging studies revealed that the novel contrast agent can specifically and effectively target to mucin4-expressing tumors in nude mice. Hence, it is suggested that the contrast agents are able to provide an efficiently targeted delivery of MUC4 antibodies to mucin4-expressing pancreatic tumors.

Introduction

Pancreatic cancer is very difficult to diagnose and is the most deadly of cancers with a 5% 5 year survival rate [1]. Recent studies show that mucin4 is abundantly expressed in pancreatic tumors [2]. Therefore, mucin4 is a potential biomarker for pancreatic cancer detection. Herein, we report MR-optical contrast agents for early and specific detection of pancreatic cancer.

Materials and Methods

All cell lines (HPAC, BxPC3, and Panc-1) were incubated with contrast agents for 4 hrs at 37 °C. The cells were observed using a confocal imaging system. MR imaging was performed on a 7.0 T MRI system (TR/TE = 3,000/90). Images were acquired at pre- and post-injection. Optical imaging was acquired at pre- and post-injection using an IVIS system (ex / em = 745 nm / 820 nm).

Results and Discussion

MUC4 antibodies were functionalized and conjugated to the surface of MnMEIO-silane-NH_2-mPEG NPs to achieve preferential receptor mediated targeting to pancreatic tumors (Figure 1 (A)). The Figure 1 (B) was shown the maximum fluorescence intensity was observed in HPAC cells and the minimum in Panc-1 cells, reflecting the mucin4 expressing levels. The optical and MR images (Figure 1 (C)) of nude mice bearing subcutaneous tumor xenografts of HPAC, and Panc-1 cell lines, respectively, treated with contrast agents show that significant intensity was observed in HPAC tumor. The results of MR images were shown the negative contrast enhancements of HPAC and Panc-1 tumor cells were about - 81.5 ± 4.5% and - 19.6 ± 5.2%, respectively.

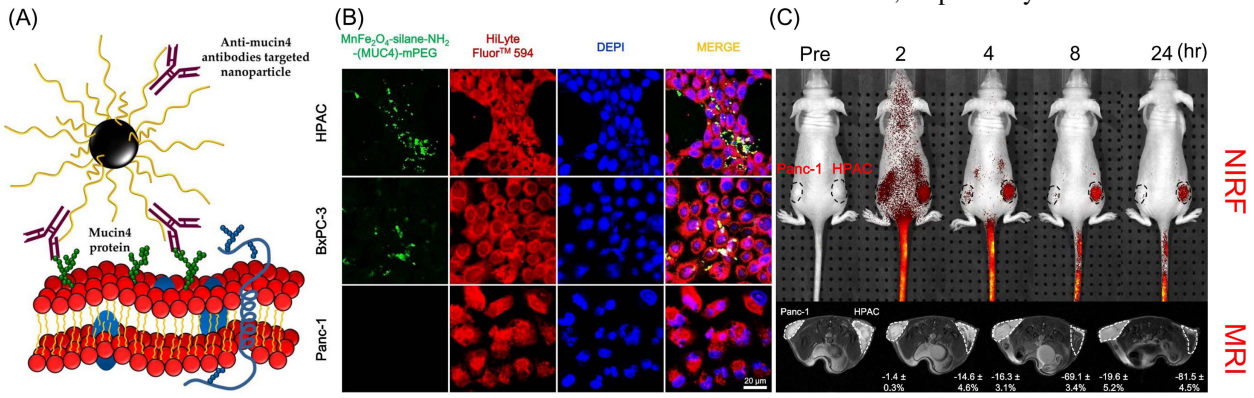

Figure 1. (A) The illustration of MnMEIO-silane-NH_2-(MUC4)-mPEG NPs and specific targeting efficacy by masking positive charges on the NPs. (B) Confocal microscopy images of negative control cell lines incubated with MnMEIO-silane-NH_2-(MUC4)-mPEG NPs (10 μg/mL) for 4 hrs at 37 °C. Cytoplasm (stained with HiLyte FluorTM 594 in red), nuclei (stained with DEPI in blue). (C) The near-infrared and T_2-weighted MR images (7.0 T) of nude mice bearing subcutaneous tumor xenografts of HPAC (right) and Panc-1 (left) tumor cells before and after injection of MnMEIO-silane-NH_2-(MUC4)-mPEG (10 mg/kg).

Conclusion

In summary, we have successfully developed the nanoparticles, MnMEIO-silane-NH_2-(MUC4)-mPEG NPs, as a unique dual-modality MR-optical imaging contrast agent. This contrast agent possessed the ability to specifically target the mucin4-expressing tumors. In this study, we have demonstrated that this contrast agent can specifically target pancreatic tumor cells. We believe our results may provide an ideal MR-optical imaging contrast agent for early diagnosis of human pancreatic tumors.

References

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