Multi-Functional Imaging Agents for Site-Specific Detection of Prostate Cancer

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Objective: Prostate cancer is the most common cancer and second leading cause of cancer death among American men. Development of novel and non-toxic site-specific imaging agents will improve clinical outcomes in diagnosis and treatment of prostate cancer, especially in early stage prostate cancer patients. In this project, we aim to synthesize and characterize a magnetofluorescent nanoparticle for prostate cancer imaging in vivo.

Method: The designed nanoparticles consist of three components: a biocompatible super-paramagnetic iron oxide (SPIO) core, surface conjugated bombesin (BBN[7-14]) peptides, and a near-infrared fluorescent molecule (AlexaFluo-750). The magnetofluorescent nanomaterials were synthesized and purified according to previous procedures with modifications (1,2). The compound was characterized and evaluated for its binding affinity and specificity to gastrin releasing peptide receptor (GRPR) in a human prostate cancer PC-3 cell line and a severely compromised immunodeficient (SCID) mouse model bearing PC-3 xenografts.

Results: [AF750-BBN(7-14)]n-SPIO nanoparticles showed significantly higher binding to the PC-3 cells surface than AF-750-SPIO nanoparticles. In vitro 3-D confocal microscopic imaging showed that [AF750-BBN(7-14)]n-SPIO was internalized to cytoplasm with increased fluorescent intensity compared to that of AF750-BBN in PC-3 cells. The cellular binding and internalization was clearly inhibited by presaturation of GRPR sites with control BBN (Fig. 1). IC50 (the half maximal inhibitory concentration) value was 1.42 ± 0.13 μg/mL demonstrating high binding affinity of [AF750-BBN(7-14)]n-SPIO to GRPR in PC-3 cell line. After intravenous injection of [AF750-BBN(7-14)]n-SPIO in prostate cancer bearing SCID mice, serial in vivo optical imaging and MRI were performed. In vivo near infrared images clearly showed that [AF750-BBN(7-14)]n-SPIO exhibited higher near-infrared signal in the tumor tissue compared to the AF750-SPIO nanoparticles, and the tumor accumulation of [AF750-BBN(7-14)]n-SPIO nanoparticles was clearly reduced by co-injection of BBN (Fig. 2). In vitro MRI images showed [AF750-BBN(7-14)]n-SPIO nanoparticles were well uptaken in the PC3 cells, and presaturating GRPR with BBN significantly reduced the cellular uptake of the nanoparticles. Delayed signal decrease in tumor tissues in the T2* weighted MRI image were observed after [AF750-BBN(7-14)]n-SPIO nanoparticles injection. No signal decrease was observed in tumor on MRI acquired after AF-750-SPIO nanoparticles injection.

Conclusion: These results demonstrate that the BBN[7-14] conjugated AF750-SPIO nanoparticle improves their tumor accumulation in PC-3 bearing mouse model in comparison to nanoparticles without BBN, suggesting that [AF750-BBN(7-14)]n-SPIO nanoparticles may be useful for prostate cancer imaging. Funding support: DOD prostate cancer research program.

Reference:

Fig. 1. In vitro uptake of [(AF750-BBN)n-SPIO nanoparticle in PC-3 cancer cells. (A) [(AF750-BBN)n-SPIO binding , and (B) blocked binding with BBN, red is AF750 and blue is Hoechst bluestained nucleus. (C) Cellular Prussian staining of [(AF750-BBN)n-SPIO.

Fig. 2. In vivo fluorescence images and MRI in prostate cancer bearing SCID mice. Upper panel: images acquired after nanoparticles injection. Lower panel: after co-injection of the compound and unlabeled BBN.