Targeted Herceptin-Dextran nanoparticles for noninvasive imaging of Her2/neu receptor by MRI

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Abstract

The surface of superparamagnetic iron oxide nanoparticles (SPIO) were modified with dextran and Herceptin to improve their dispersion and ability to target specific receptors. The signal intensity of positive-cell tumor was significantly lower than that of negative-cell tumor from precontrast to postcontrast images of the tumor. Internalization of CLIO-Herceptin into targeted cells were observed by in vitro and in vivo MR imaging studies.

Introduction

Molecular Imaging has recently been developed very rapidly and extensively in biotechnology [1]. Tumor-targeted drug delivery can enhance the effectiveness of chemotherapeutics while decreasing the systemic toxicity of these drugs. Iron oxide nanoparticles for MR imaging are often coated with dextran, which itself has been frequently used as a drug carrier because of its biocompatibility, water solubility and their ability to escape capture by macrophages. There are some reports that macromolecules conjugated with Herceptin, were successfully recognized by Her2/neu receptor and internalized into cells via Her2/neu receptor-mediated endocytosis [2]. In this study, we synthesized a new T_2-weighted agent which has nanometer-size, hydrophilic, long-circulating dextran-coated and characterized CLIO particles that were tethered to Herceptin.

Methods

We tested various cell lines with different levels of HER2/neu overexpression: SKBR-3, BT-474, MCF-7 and MDA-MB-231. In addition, we had chosen KB cells as negative cell for control which lacks Her2/neu receptors. All cells were incubated with CLIO-Herceptin (0.3 mM Fe), washed by PBS buffer and scanned by 3.0 T MRI. Five nude female mice were injected with SKBR-3 and KB cells into the left and right lateral thigh of mice and produced a high yield of tumor into the lateral thigh of nude mice after one to two weeks. MR imaging studies were performed with a 3.0 T MR imager and a high-resolution animal coil.

Results and Discussion

The CLIO-Herceptin were synthesized and characterized by TEM, SQUID, and FT-IR. Moreover, TEM analysis showed the well-dispersed nanoparticles which coated with dextran. The detection of saturation magnetization by SQUID magnetometry demonstrated that CLIO-Herceptin has zero remanance on the magnetization loop, high saturation magnetization (80 emu/g) and small coercivity (about 3 G). The internalization of CLIO-Herceptin nanoparticles into positive cells were confirmed by in vitro MR imaging study (Fig 1.). With the CLIO-Herceptin conjugates, the detection of the BT-474 cell line (which have a relative high HER2/neu expression level) occurred with a noticeable MR contrast (T2-weighted MR images). As the relative HER2/neu expression level increased, the MR contrast increased consistently. The enhancement of signal intensity were 75 %, 70 %, 40 % and 25 % for the BT-474, SKBR-3, MCF-7 and MDA-MB-231cell lines, respectively. The signal intensity of positive cells in the present of CLIO-Herceptin is significantly lower than that of positive cells only. No signal intensity change was observed for the negative cells in the presence and absence of CLIO-Herceptin. The internalization of CLIO-Herceptin into SKBR-3 cell tumor was also confirmed by in vivo study. Figure 2 shows the T2-weighted fast spin echo images of a tumor-bearing mice before (Fig. 2, left) and 1 h after (Fig. 2, right) intravenous administration of CLIO-Herceptin. The signal intensity of SKBR-3 cell tumor on the left was significantly lower than that of KB cell tumor. In other words, the nanoparticles were readily internalized into Her2/neu receptor-expressing tumor cells.

Conclusion

We have successfully prepared and characterized CLIO-Herceptin, which was shown high saturation magnetization, well-dispersed and low uptake by macrophage. Moreover, CLIO-Herceptin had ability to target the positive cells proved by in vitro and in vivo MR imaging studies.

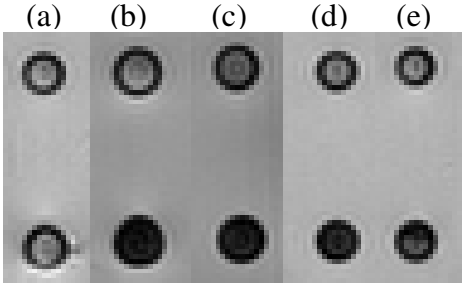

Fig 1. *T*2-weighted images of positive and negative cells after the treatment with or without 0.3 mM CLIO-Herceptin. (a) KB cells (b) BT-474 cells (c) SKBR-3 cells (d) MCF-7 cells (e) MDA-MB-231 cells. Upper: cells treatment without contrast agent. Lower: cells treatment with contrast agent.

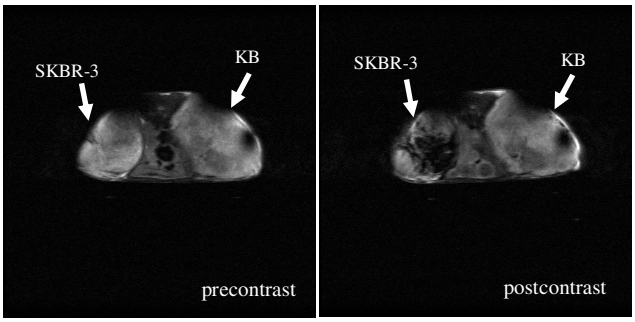

Fig 2. *T*2-weighted in vivo images of pre- and post-injection of CLIO-Herceptin.

References

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