Multicomponent T1 Targeted Contrast Agent for MR Imaging of HER-2/neu Receptors

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Abstract

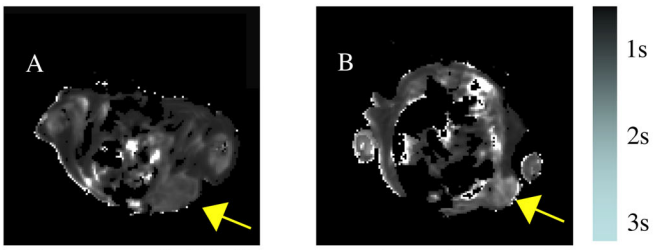
Recently we demonstrated the use of MRI in detecting HER-2/neu receptor expression in an animal breast cancer model using a novel two-step avidin-biotin system. We have extended this concept to a three-step approach to increase sensitivity of detection. MRI studies were performed with a HER-2/neu expressing human breast cancer cell line. HER-2/neu receptors were pre-targeted with biotinylated anti-HER-2/neu mAb, Herceptin. After 24h, mAb were chased by avidin that (i) cleared circulating mAb from the vasculature and (ii) labeled mAb attached to the tumor receptors. Pre-labeled receptors were imaged with biotinylated albumin-GdDTPA contrast agent (CA) using quantitative T1 MRI. Specific accumulation of the contrast agent in HER-2/neu expressing tumors pre-targeted with the specific biotinylated antibody was demonstrated. Pharmacokinetics of the antibody was also monitored with micro-SPECT imaging using [^{125}I]-Herceptin. This three-step approach can be extended to other biotinylated imaging platforms with higher T1 or T2 relaxivity.

Materials and methods

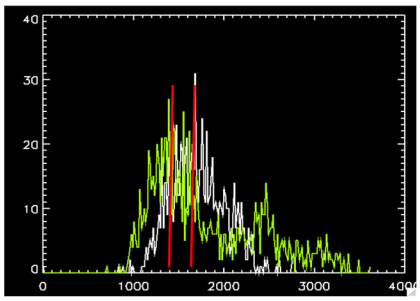
BT-474 human mammary carcinoma cells were grown to 80% confluency and HER-2/neu expression was determined by FACS using FITC-labeled Herceptin. Two to three millions BT-474 cells were inoculated in the mammary fat pad of female SCID mice and a slow release 17β-estradiol pellet (0.18 mg/60-day release, half a tablet, Innovative Research of America) was inoculated in the opposite flank. Tumors were grown for 12-16 weeks. Multicomponent MR agent consisted of biotinylated anti-HER-2/*neu* humanized mAb, Herceptin, Genentech; purified avidin (Rockland, PA) used for the chase step, and biotin$_4$-albumin(GdDTPA)$_{19}$ conjugate. MRI studies were performed on a Bruker Biospec 4.7T spectrometer equipped with a home-built mouse volume coil. Quantitative T1 MR imaging was used using saturation recovery multi-slice spin-echo pulse sequence. Mouse SPECT/CT imaging was performed with X-Spect, Gamma Medica, Inc. with radiolabeled [^{125}I]-Herceptin.

Results

Quantitative T1 maps of BT-474 tumors acquired 10h after injection of biotin-albumin-GdDTPA contrast are shown in a figure for two animals. The first animal was treated with biotinylated Herceptin (0.5mg, i.v.) followed after 12h by avidin (0.5mg, i.v.) and after 4h delays by biotin-albumin-GdDTPA (0.5mg/g, i.v.). The control animal was treated with the same protocol, except non-biotinylated Herceptin was used for prelabeling. Pooled histograms for distribution of relaxation rates in treated and control animals (3 animals per group) are also shown in the figure. Density of the accessible receptors was estimated from the shift in the T1 histogram between the control and treated tumors $\Delta(1/T_1)$ = 0.11 $s^{-1}$and relaxivity of the CA R_1 ~ 200 $(s \bullet mM)^{-1}$as D ~ 3.7E5 receptors/cell. Micro SPECT imaging performed 24h post administration of [^{125}I]-Herceptin (215-259 μCi i.v.) before and 4h after chase with cold avidin confirmed an efficient clearance of the unbound antibody by the avidin chase.



T1 maps of BT-474 tumors imaged with (a) biotinylated and (b) non-biotinylated Herceptin. Tumors are indicated by arrows.



T_1 (ms)

Discussion

Experiments demonstrated significantly different retention of the contrast agent in tumors treated with biotinylated vs non-biotinylated mAb. Quantitative T_1 maps allow determination of the accessible receptor density that can be an important parameter for planning anti-cancer therapy.

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