An EDB fibronectin specific contrast agent for molecular imaging of cancer metastasis

Zheng Han[1], Zhuxian Zhou[1], Maneesh Gujrati[1], and Zheng-Rong Lu[1]
[1]*Department of Biomedical Engineering, Case Western Reserve University, Cleveland, Ohio, United States*

Purpose

The purpose of the study is to develop targeted MRI contrast agent for molecular imaging of breast cancer metastases. Metastasis, the spread of cancer from primary tumor sites to distant organs, account for 90% of deaths among breast cancer patients[1]. The current diagnostic method of gadolinium-enhanced MRI is sensitive only to large tumors, thus necessitating the development of molecular imaging agent that could facilitate early detection and accurate evaluation of metastases. We have developed a peptide targeted MRI contrast agent specific to extradomain B fibronectin (EDB-FN), which is highly expressed in the extracellular matrix of aggressive tumors. Up-regulation of EDB-FN is evident in early metastases due to epithelial-to-mesenchymal transition (EMT), which enables small metastases to be detected by EDB-FN targeting MRI contrast agent.

Methods

Phage display technique was used to develop EDB-FN targeting peptide. The resulting 7-amino acid peptide, ZD2, was synthesized in solid phase. The imaging agent, ZD2-(HP-DO3A), was synthesized by conjugating Gd-(HP-DO3A) to the peptide using click chemistry. MRI images of MDA-MB-231 flank tumors were acquired using a 2D T1-weighted gradient fat suppression sequence three weeks after tumor injection. After six weeks, primary tumors were removed and metastatic tumors were evaluated with MRI using a 3D T1-weighted gradient echo sequence. A commercial clinical MRI contrast agent, Prohance®, was used as control in all MRI studies. For both contrast agents, a dose of 0.1mmol/kg was administered via tail vein. Parameters of MRI sequences were described before[2].

Results

The structure of targeted MRI contrast agent, ZD2-(HP-DO3A), is illustrated in Fig.1A. The contrast agent has relaxivities of r_1=5.29mM^{-1}s^{-1} and r_2=6.213mM^{-1}s^{-1}. MR imaging of MDA-MB-231 primary tumors indicated the preferential binding of ZD2-DO3A in tumor, resulting in high contrast-to-noise ratio (CNR) in tumor region compared with Prohance®, as shown in Fig.1B and Fig.1C. Small metastases in colon region (orange arrow) and on the leg (green arrow) as located in bioluminescence imaging (BLI) can also be detected with ZD2-DO3A in vivo using MRI. On the contrary, Prohance® failed for detection of these two metastatic tumors, as shown in Fig.1D.

Discussion and Conclusion

We developed a targeted MRI contrast agent for molecular imaging of breast cancer metastases. Our result showed that both primary tumor and small metastases were enhanced by the EDB-FN targeting contrast agent. Further comprehensive evaluation of the targeted contrast agent in different tumor models is on-going to validate the accuracy and sensitivity of detection of micrometastasis with MRI and ZD2-(HP-DO3A).

References

1. Marx V. Tracking metastasis and tricking cancer. Nature. 2013; 494: 133-136.
2. Zhou Z, et al. Peptide targeted tripod macrocyclic Gd(III) chelates for cancer molecular MRI. Biomaterials. 2013; 34: 7683-7693.

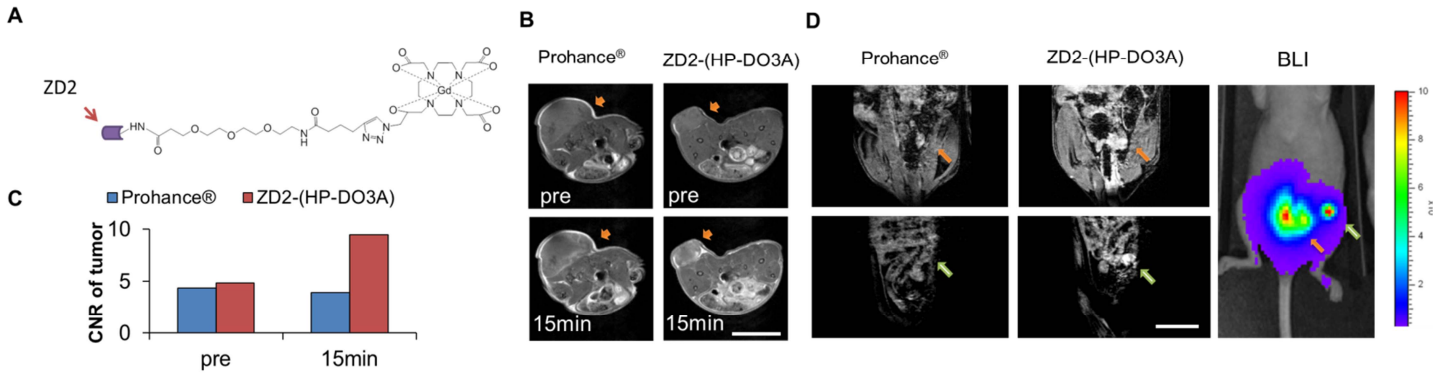

Fig.1 A. The structure of ZD2-(HP-DO3A). B. Axial MRI images of MDA-MB-231 flank tumors enhanced by ZD2-(HP-DO3A) and Prohance® at a dose of 0.1mmol/kg before injection (pre) and 15min after injection. C. CNR analysis of flank tumor region from before injection and 15min after injection with Prohance® or ZD2-(HP-DO3A). D. Coronal MRI images of mice with MDA-MB-231 metastatic tumors 15min after injection of Prohance® or ZD2-(HP-DO3A). Bioluminescence image of the same mouse was used as a reference. Scale bar: 1cm.