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Bacteriogenic magnetic nanoparticles as magnetic resonance imaging contrast agents

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Magnetic resonance imaging (MRI), which has excellent spatial resolution and soft tissue contrast, is a commonly used imaging tool for clinical disease diagnosis. MRI contrast agents are often administered to enhance the image contrast between normal and diseased tissues because of their ability to shorten the relaxation time of the surrounding water molecules. Paramagnetic gadolinium-based metal chelates have predominantly been using as T_1 MRI contrast agents in clinic. There is another class of MRI contrast agents, superparamagnetic iron oxides (SPIOs), which, instead of altering T_1, have dominant effect on decreasing the transverse relaxation time (T_2) (1). In contrast to the T_1 contrast agents that generate brighter signals, SPIOs produce darker signals, so called negative contrast. However, SPIOs have much higher molar relaxivity and are thus widely used for molecular MRI applications such as cell tracking and molecular targeting (2,3). SPIO nanoparticles that comprise mainly magnetite, the ferric form of iron oxide, can be synthesized with high uniformity in size at varied diameters or lengths.

Intriguingly, some microbes are found to have innate ability to synthesize magnetite to form specific intracellular organelles, the magnetosomes (4). Among these microbes, magnetotactic bacteria (MTB), a group of Gram-negative bacteria have been extensively studied. The MTB magnetosome is composed of a protein-rich lipid bilayer membrane and the enclosed crystals of magnetic iron oxides (5). Individual magnetosomes are aligned in a linear chain by attaching to a cytoskeletal filament, which allow the bacterial to navigate along the geomagnetic field. The size of magnetosomes is highly uniform but varies between species. Genomic analysis of MTBs has identified a number of genes that are highly likely to be involved in regulation of magnetosome biosynthesis. These genes are responsible for encoding various membrane proteins that are essential to either maintain the structural integrity or transport iron, the building blocks of magnetosome (6,7).

Attracted by its paramagnetic property, researchers have been exploring the potential of magnetosomes as useful MRI contrast agents (8). Isolation and purification of

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magnetosomes from bacteria have previously been studied in terms of their paramagnetic relaxivity (9). In the March 2017 issue of *Biomaterials*, Boucher *et al.* have taken a further step to develop genetically modified magnetosomes with surface expression of RGD peptides, which enables MRI to monitor their specific targeting to αvβ3 integrins-overexpressing brain tumors in a mouse model of glioma (10). This study utilizes the gene construct of MamC that is known to associate with magnetosome production in *Magnetospirillum magneticum* AMB-1 strain. Genetic fusion of MamC with the RGD sequence and a yellow fluorescence reporter gene enables the AMB-1 strain to express RGD peptides at the outer surface of magnetosomes. The RGD-magnetosomes purified from the bacterial present a uniform size of 40 nm. The authors conduct both *in vitro* and *in vivo* studies showing the RGD-magnetosomes have excellent binding specificity to αvβ3 integrins-expressing tumor cells. Importantly, *in vivo* T_2*-weighted MRI provides both temporal and spatial information of intratumoral biodistribution of the RGD-targeted probe in orthotopic U87 gliomas. As presented in the article, there is initially no difference in intratumoral signal decrease on T_2*-weighted images between RGD-labeled and non-labeled magnetosomes at earlier time points post systemic administration. However, MRI clearly reveals significantly more RGD-targeted magnetosomes in glioma at 24 h, indicating their ability to bind to αvβ3 integrins-expressing tumor vascular endothelial cells and tumor cells and subsequently become internalized into the cells.

Compared to the chemically synthesized SPIOs, the transverse relaxivity r_2 (560 $mM^{-1}s^{-1}$ measured at 11T) of the magnetosomes reported in this study is notably higher, which may also contribute to improved MRI sensitivity. As presented in the MR images, SPIO, the T_2 contrast agent, generates negative contrast on T_2 or T_2*-weighted images. It is noticeable that signal loss due to SPIO shortening of T_2 relaxation time is often difficult to differentiate from those low signals induced by B0 inhomogeneity or susceptibility artifacts, occurring particularly with T_2*-weighted sequences. Longitudinal MRI measurements may provide a solution to the problem by comparing pre and post SPIO administration. To overcome this drawback, various strategies including the off-resonance imaging techniques and the “hot-spot” analysis have been exploited, aiming to generate positive contrast of SPIO (11,12). Alternatively, it is recognized that SPIOs also exhibit a high longitudinal relaxivity r_1, which may be utilized to generate positive T_1 contrast if applied with appropriate imaging sequences. Indeed, recent studies have shown that a ultrashort echo time (UTE) imaging sequence with very short echo time (TE), typically below 0.1 ms, is able to minimize T_2 effect to provide T_1-weighted signal enhancement (13).

Even though glioblastoma multiforme (GBM) is composed of highly angiogenic and leaky microvessels, it is well recognized that disruption of blood brain barrier (BBB) in GBM is heterogeneous, indicating many intratumoral regions still contain the intact BBB. Much effort has been made to improve delivery of therapeutic or imaging agents to brain tumors by penetrating the BBB. Although various strategies have been explored to improve drug permeation into brain tumors via physical or chemical means to manipulate the tumor BBB, limited success has been achieved. Integrins, the cell surface adhesion molecules that connect the extracellular matrix (ECM) to the cytoskeleton have been identified to overexpress on neovascular endothelial cells during tumor angiogenesis. In particular, αvβ3 integrin has been a well-recognized angiogenic biomarker (14,15). In addition to its vascular

expression, αvβ3 integrins are also found to present abundantly on glioma cells. Hence, a number of monoclonal antibodies, peptides, and peptidomimetic agents against αvβ3 integrin have been developed. For example, Cilengitide, a cyclic RGD-based peptide, is being tested for treatment of clinical GBM. Cyclic RGD peptides have also been used to facilitate targeted delivery of imaging contrast agents or anti-cancer therapeutics. In particular, a number of nanocarriers functionalized with surface RGD peptides have been convincingly shown to deliver therapeutic or imaging agents to brain tumor tissues (16).

Alternative to the use of magnetosomes isolated from the bacteria, several studies have introduced the magnetosome gene constructs into the mammalian cell genome (17). For example, magA, another gene identified in *Magnetospirillum magneticum* AMB-1 strain, which is known for its role on iron transportation, has been transduced into several types of mammalian cells including stem cells (17,18). Like those magnetosome-producing bacteria, these magA containing mammalian cells are able to produce intracellular magnetosomes. As one of the main applications of molecular MRI is to track the cells labeled with SPIOs, the magnetosome gene-transduced stem cells or lymphocytes seem ideal to serve for this purpose. The information obtained by non-invasive *in vivo* MRI of biodistribution of the cells will be valuable for stem cell therapy or immunotherapy.

Safety index of imaging contrast agents is critical for their *in vivo* application in preclinical studies and ultimate clinical translation. There are concerns about if introduction of magnetosomes or the magnetosome reporter gene into the mammalian cells may have adverse effects on the cells. As reported in this article and also observed by several other groups, the isolated magnetosomes are biocompatible and thus safe to use at the dose of ~200 μmol/kg. However, the authors are still cautious about its possible long term side effect. Given the bacteria-derived products, magnetosomes can trigger the host immunity. Although this is not the case in this work in which the immunocompromised mice are used, further studies in this respect will be necessary. In summary, the work by Boucher and colleagues has established genetically modified bacterial magnetosome with surface expression of tumor-targeting ligands, and successfully demonstrated its potential as a useful brain tumor-targeted imaging contrast agent for molecular MR imaging.

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