Bacterial Gene Provides Cellular Contrast for MRI

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Introduction To enhance cell contrast for molecular MRI, we have examined the potential of iron regulatory proteins to act as contrast agents. Magnetotactic bacteria, for example, derive their magnetic properties from magnetosomes: membrane-bound, intracellular structures that form iron biominerals in response to the coordinated activity of approximately 20 genes (1). Similar to SPIO particles in size and composition, magnetosomes respond comparably to magnetic fields. We have investigated the ability of mammalian cells to produce magnetosome-like particles by expressing the *MagA* gene from *Magnetospirillum* sp. AMB-1 (2).

Methods N2A cells were stably transfected with *MagA* cDNA, cloned into the Enhanced Green Fluorescent Protein (GFP) vector, pEGFP-C3, at EcoR1. Cell populations were cultured under selection in the presence or absence of 250 μM ferric nitrate. 3D MRI was acquired at 11T with a dual echo: spin echo at TE=5 ms and a gradient echo at TE=15 ms, TR=1000 ms, 128 x 128 x 8 with 8 averages, 137 minutes, 65x65x75 μm resolution. In figure 1, the gradient echo image in C was subtracted from the spin echo image in E to produce the positive contrast image in D.

Results Overexpression of GFP-MagA fusion protein increases cellular contrast in neuroblastoma cells (Figure 1). Correlation of gradient echo and positive contrast images confirms that signal voids are due to cells. In serial planes, MagA expression allows detection of cells in adjacent layers, resolving cellular detail from a mixed population of cells.

Discussion The bacterial iron transporter, MagA, may be used to enhance contrast in mammalian cells. By combining genetic engineering and MRI, we have developed a gene expression system that harnesses the ability of cells to form iron biominerals, and thus, acts as a contrast agent for non-invasive imaging. These studies will enable long-term tracking of cells and molecular events, including reporter gene activity for MRI.

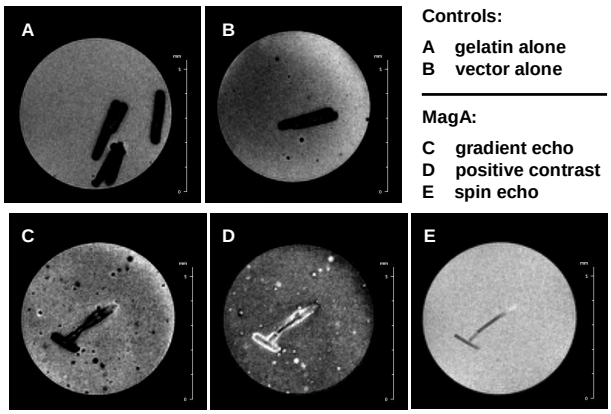

Figure 1. Molecular MRI of MagA Expression in Mouse Neuroblastoma Cells. MagA was expressed in N2A cells and cultured under selection. Media was supplemented with iron for 7 days prior to mounting live cells in gelatin/phosphate buffered saline pH 7.4 and imaging by MRI at 11 Tesla. Panels A and B are gradient echo images showing an axial cross section through the gelatin phantom and gelatin containing 10^6 cells expressing vector alone, respectively. The plane of focus is marked by human hair. Panels C-E are gradient echo, positive contrast (difference) and spin echo images of a single, axial cross section through gelatin containing 10^6 MagA-expressing cell.

References

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2. Nakamura, C. *et al*. (1995) J. Biol. Chem. **270**, 28392-28396.