In vivo monitoring of transplanted human embryonic stem cell-derived oligodendroglial progenitors in a mouse model of multiple sclerosis

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Introduction: Cell therapy is an effective treatment method for neurodegenerative disease. Studies have shown that transplanted neural precursor cells can attenuate the disease symptoms of experimental autoimmune encephalomyelitis, an animal model of multiple sclerosis. Once transplanted, little is known about the i*n vivo* migration and distribution patterns of cells within the host brain. We have transplanted Feridex-labeled human embryonic stem cell (hESC)-derived oligodendroglial progenitors (OPs) into the brain of mice with EAE and followed their overall distribution within the brain parenchyma using serial MRI.

Materials and Methods: Female C57Bl/6 mice were immunized with MOG35-55 peptide in Freund's adjuvant containing H37RA. Prior to transplantation, the hESC-derived OPs were incubated with a mixture of Feridex and PLL for magnetic labeling. Three different experimental groups were used: 1) mice receiving live Feridex-labeled cells (n=5); 2) mice receiving dead Feridex-labeled cells (n=5); and 3) mice receiving live unlabeled cells (n=5). Cells were injected into the right cerebral ventricle at seven days post EAE induction. MRI was performed in vivo on individual mice at 1, 5, 15, and 30 days post tx using a 400 MHz (9.4 tesla) horizontal bore NMR system (Bruker) and 50 mm volume coil with the following parameters: 3D rapid acquisition with relaxation enhancement; TR= 400 ms; TE=15.6 ms; RARE factor = 4; FOV=1.4x1.4x1.2 cm; resolution=109x109x375 µm; average=1.

Results: The clinical scores of both live groups were lower compared to the Feridex-labeled dead cell group after transplantation (Fig. 1). At day 1 post tx, hypointense MRI signals were detected mainly in the ventricle and ventricular zone (Fig. 2A, circles). These signals were also detected on days 5 (Fig. 2B), 15 (Fig. 2C), and 30 PT (Fig. 2D), and occasionally detected in the subarachnoid space (arrows), cerebral cortex, thalamus, and hypothalamus. The area of hypointensity signal in the ventricles between Bregma 0 ± 0.375 mm and Bregma -3.37 ± 0.375 mm at day 30 PT was significantly decreased ($p<0.05$), compared to the 1, 5, and 15 days post tx (Fig. 3). There were no significant differences between days 1, 5, and 15.

Conclusion: We conclude that magnetic labeling does not impair the therapeutic benefit of hESC-derived OPs for *in vivo* applications reducing the disease burden of EAE. We postulate that cell migration mainly occurs through the ventricular system to the parenchyma at 15 -30 days post tx.

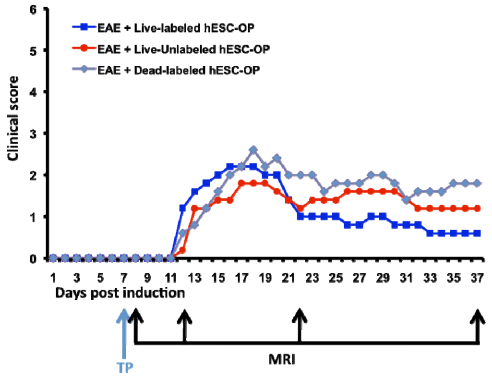

Figure 1. The clinical course of EAE after transplantaion of hESC-derived OPs.

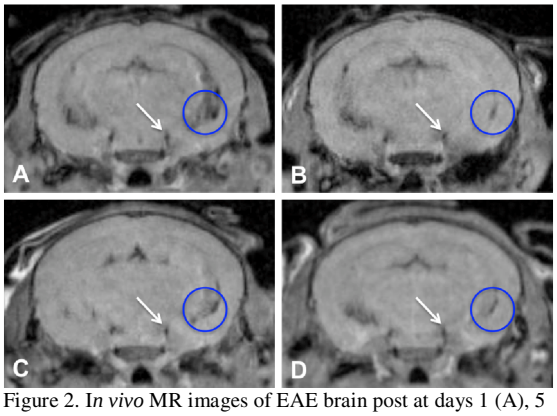

Figure 2. I*n vivo* MR images of EAE brain post at days 1 (A), 5 (B), 15 (C), and 30 (D) post transplantation. Imaging parameters: TR = 1400 ms, TE = 15.6, matrix = 128 x 128 x 32, FOV = 1.4 x 1.4 x 1.2, acquisition time 24 min.

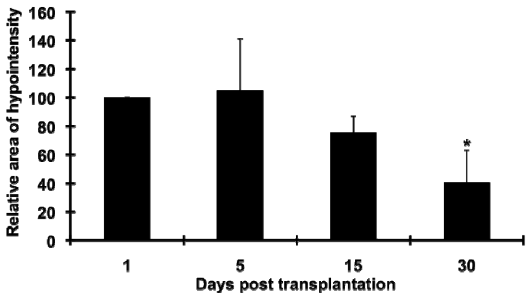

Figure 3. The quantitative analysis of the area of hypointensity in the ventricles of mice (n =5) after transplantation. *$p<0.05$, compared to post transplantation 1, 5, and 15 days.