Immunomodulation and magnetic resonance tracking of transplanted human glial-restricted precursor cells in a mouse model of multiple sclerosis

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Introduction: Multiple sclerosis (MS) is a demyelinating disease of the central nervous system. Multiple lesions with local of inflammatory cells infiltrations and demyelination have been demonstrated in the MS, and inhibition of this process is the primary therapeutic target. Stem cell therapy is an attractive application for the treatment of MS, because transplanted cells possess two major benefits, immunomodulation and cell replacement. Human glial-restricted precursor (hGRP) cells are an attractive cell source for cell therapy in MS, because they have been shown to generate myelin in hypomyelinated Shiverer mice. We have transplanted labeled hGRP cells into the brain of mice with experimental autoimmune encephalomyelitis (EAE), an animal model of MS, and followed their viability and overall distribution within in the brain.

Materials and Methods: Female C57Bl/6 mice were immunized with MOG35-55 peptide in Freund's adjuvant containing H37RA, and were observed daily for clinical signs of EAE. At 14 days post-immunization, mice were intra-cerebro-ventricularly injected with $5x10^5$ hGRP cells that were magnetically labeled with contrast agent (Molday ion, Biopal; catalogue #: CL-50Q02-6A-50), and transfected with the bioluminescent gene luciferase, while control mice received only PBS. After transplantation, mice were monitored to determine the primary migration route and viability of transplanted cells in the brain using MRI, and BLI, respectively, and spleens were obtained from both groups to evaluate the immunomodulatory effect of transplanted cells on the antigen-specific T cell proliferation.

Results: The severity of EAE paralysis in the hGRP cell-transplanted groups was significantly suppressed (Fig. 1). In MRI at day 1 post-transplantation (PT), hypointense MRI signals were detected mainly in the ventricles, and most of these signals remained in the ventricles on days 5, 10, 20, and 30 PT (Fig. 2). Bioluminescence signal was detected on day 1 PT, and it greatly declined on day 5 PT (Fig. 3). At day 10 PT, bioluminescence signal was at a very low level, and was completely lost on day 20 PT (Fig. 3). At days 10 (Fig. 4A) and 20 PT (Fig. 4B), hGRP cell-treated mice showed a significant decrease in antigen-specific T cell proliferations in response to MOG and concanavalin A, compared to control mice.

Conclusion: We conclude that intracerebroventricular administration of hGRP cells has an immunomodulation effect, but does not result in cell replacement, at least in this current study. Our findings suggest the signals generated from transplanted hGRP cells in the ventricle modulate the systemic immune response.

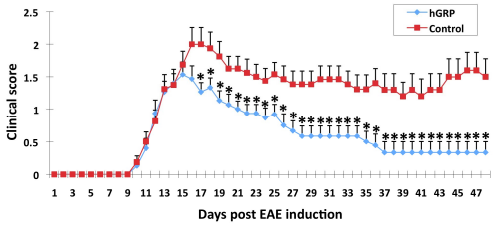

Figure 1. Effect of transplanted hGRP cells on the clinical course of EAE. The clinical severity of EAE was attenuated in hGRP-transplanted mice compared with control mice. *p<0.05, compared to controls.

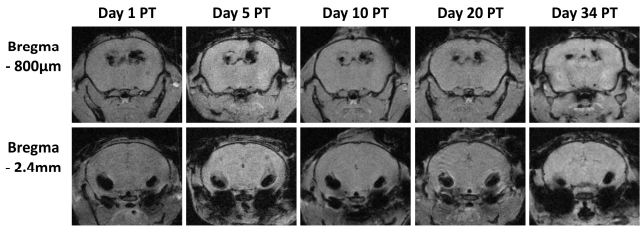

Figure 2. Serial *in vivo* MR tracking of labeled hGRP following intracerebroventricular delivery at day 14 post-EAE induction. Imaging parameters: FLASH; TR=316.5 ms; TE=3.49 ms; FOV=1.2x1.2 cm; average=6; slice thickness=400µm.

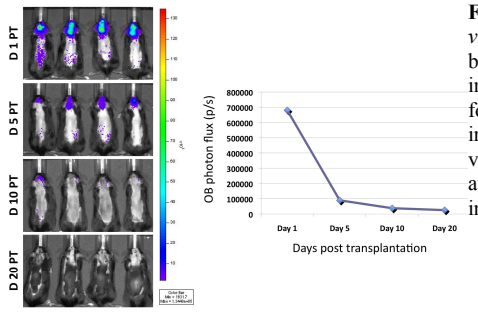

Figure 3. Serial *in vivo* bioluminescence imaging of hGRP following intracerebrolateral ventriclar delivery at day 14 post-EAE induction.

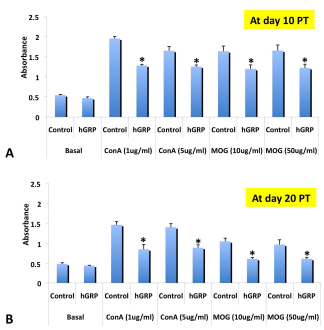

Figure 4. Effect of transplanted-hGRP cells on antigen-reactive T cell proliferation at days 10 (A), and 20 (B) post-transplantation. *p<0.05, compared to controls.