Neural Progenitor Cell Distribution and White Matter Reorganization after Traumatic Brain Injury Measured by MRI and Histology

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INTRODUCTION: Neural progenitor cell (NPC) treatment of traumatic brain injury (TBI) promotes brain remodeling and functional recovery. Although investigations into the mechanisms involved in neurorestorative treatment of TBI have focused primarily on angiogenesis and neurogenesis,5-7 white matter reorganization is important for functional recovery after TBI and may be influenced by NPC distribution. We evaluated the effects of NPC treatment on white matter reorganization using MRI. We found that NPCs co-localized with regions of axonal reorganization and that MRI fractional anisotropy (FA) identified white matter reorganization as evidenced by well merged axonal bundles. However, FA failed to detect white matter remodeling in the region with crossing axons detected by orientation distribution function (ODF) on q-ball DTI.

MATERIALS AND METHODS: Male Wistar rats (n = 15) were subjected to controlled cortical impact models of TBI without (n = 7) or with scaffolds-MSC (collagen scaffolds impregnated with bone marrow stromal cells, MScs). MScs were labeled with superparamagnetic particles using ferrumoxide-protamine sulfate complex. MRI was performed 2 days after TBI and then once a week for 6-7 weeks, using a 7 T BRUKE MRI system. T1, T2, 3D, FA, radial (λr) and axial (λa) diffusivity, and fiber orientation were used to characterize biophysical changes in white matter reorganization and labeled cell distribution after TBI. T1 was measured using a Look-Locker (L-L) sequence. Q-ball reconstructions were run on data from a spherical acquisition scheme with 128 diffusion directions. To detect labeled cells and white matter reorganization, brain sections were immunostained for iron using Prussian blue staining and for white matter reorganization using Bielschowsky (axons; black) and Luxol fast blue (myelin staining; blue).

RESULTS: The labeled MScs selectively migrated toward injured boundary regions (Fig 1) where white matter reorganization was detected (Fig 2) on MRI and immunoreactive staining. White matter reorganization was established by an increase in axons (C-G, black) and myelination (C-G, blue) and coincided with increases in FA (p < 0.05, FA and D, red arrowheads) in the TBI boundary compared to the core in both treated and control groups. The treated group exhibited an early and large increase in FA (p < 0.05) in the TBI boundary at 5 and 6 weeks after TBI. Regions of white matter reorganization measured by immunoreactive staining closely matched areas of increased FA where the fiber orientation map showed more single rather than crossing fibers. However, FA did not correspond well to the region of white matter remodeling, as more crossing fibers were detected on the q-ball orientation map (Fig 2B, q-ball FD) and immunostaining at the core (histology) compared to the lesion (yellow arrows in Fig 2D). White matter reorganization after MSC treatment was observed primarily in the extended area of the corpus callosum (arrows in Fig 2B-FA and Fig 2D). The DTI fiber tracking map (Fig 2B, FT) revealed connections between regions of reorganized white matter separated by the lesion (circular colored lines, arrowheads), and these connections corresponded visually to the area of reorganized white matter on the ex vivo coronal FA map (Fig 2B, ex vivo coronal FA, arrowheads). The Gaussian DTI fiber orientation map (B, Gaussian FD) did not provide any information about crossing fibers. The diffusivity maps of the white matter remodeling were complementary, exhibiting decreased radial diffusivity (B, λr, arrowheads) and increased axial diffusivity (B, λa, arrowheads).

DISCUSSION: Our data suggest that after NPC treatment of TBI, MRI can detect migration and distribution of labeled cells and white matter reorganization and connectivity. White matter reorganization is located primarily in the extended area of the corpus callosum. Although FA shows promise in differentiating reorganized white matter from other TBI damaged tissues, it can lead to error if crossing fibers predominate. Characterization of white matter remodeling needs to be investigated further.

REFERENCES:

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