Transplantation of MPIO Labeled hMSC Aggregates in a Rodent Ischemia Model

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Introduction

Nearly 800,000 people experience stroke in the USA every year[1], resulting in significant neurological damage and potentially severe motor function inhibition. A promising technique to alleviate and treat ischemic stroke is the cerebral injection of human mesenchymal stem cells (hMSC)[2]. Here, large hMSC aggregates are labeled intracellularly with micron-sized iron oxide particles (MPIO) and transplanted directly into the lateral ventricles, or cortex, of ischemic and naïve rats. Using high resolution fast spin echo and gradient recall echo images, e*x* and *in vivo* images were acquired at 11.75 and 21.1 T to identify initial aggregate placement as well as potential dissociation and migration of individual cells.

Experimental

MPIO labeled aggregates were instituted (~40 aggregates/injection) following a transient Middle Cerebral Artery Occlusion (MCAO) of 1.5 h to induce ischemia and compared to injection in naïve rats. Aggregates were injected in the cortex and lateral ventricle of the brain. High resolution fast spin echo (FSE), gradient-recalled echo (GRE) and diffusion-weighted SE scans were acquired to identify initial placement of the aggregates, their integrity, potential migration of individual cells from the aggregates. To map temporal changes, MCAO and naïve rats were imaged *ex vivo* at day 1, 3 and 8 post-implantation, with *in vivo* imaging conducted on day 7 post implantation. *Ex vivo* MRI was performed at 11.75 T at a resolution of 100-μm isotropic for all scans. *In vivo* MRI was acquired at 21.1 T at resolutions of 50x50x300 or 100x100x300 μm for ^{1}H images.

Results and Discussion

Imaging on days 7 and 8 post-intraventricular implantation of labeled hMSC aggregates in naïve subjects indicate penetration into the contralateral and 3rd ventricle (**Fig.1**). As seen in **Fig.2**, similar penetration patterns of labeled aggregates are observed on day 3 in a MCAO rat. Additionally, migration indicated in **Fig.2b** suggests dissociation of aggregates into individual cells.

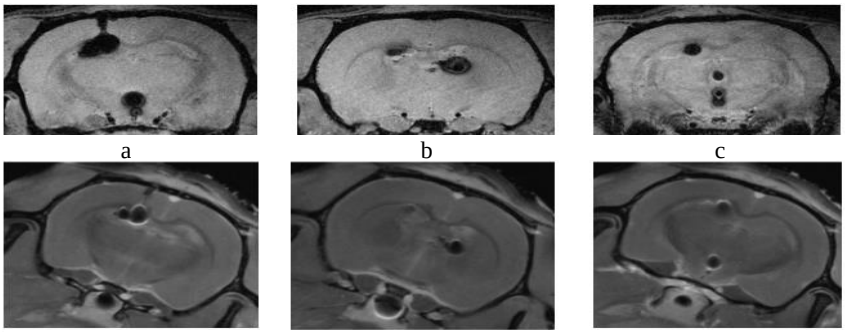

Fig.1 Aggregate implantation in lateral ventricle (a, d) of naïve rat at 7 days (a, b, c, *in vivo*) and 8 days (d, e, f, *ex vivo*) post transplantation.

Conclusions

These data demonstrate the potential for hMSC aggregates as a delivery mechanism for cell therapy applied to ischemic stroke. Aggregates penetrated the ventricular system and show potentially earlier tendency to dissociate in an ischemic condition. Preliminary data suggest that aggregates implanted by intraventricular injection experience more dynamic alterations compared to a direct cortical injection, which showed minimal dissociation and migration of cells (data not shown).

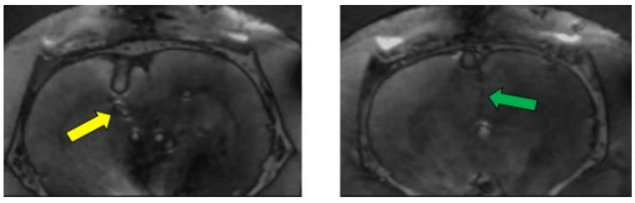

Fig.2 Implantation site (a) and axial migration (b) of aggregates in a MCAO rat, day 3 post transplantation (moving anterior to posterior, *ex vivo*).

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References

[1] U.S. Department of Health & Human Services, National Institute of Health. www.nichd.nih.gov.
[2] Sart, S., *et al*., Tissue Eng. B Rev, **20(5)**, 365-380 (2014).