Human Neural Stem Cell Mediated Neuroprotection in Penetrating Traumatic Brain Injury (PTBI) Model is Transplant Location Dependent

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Introduction

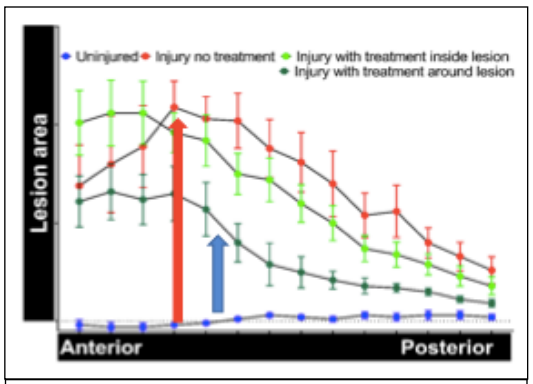
Progressive tissue loss drives disability in severe PTBI survivors. No current treatments mitigate secondary damage. Recently our lab elucidated the role of TBI induced neuroinflammation in driving tissue loss and allowing for robust durable neural stem cell (NSC) engraftment. We hypothesized that clinical trial grade human NSC (hNCS) transplant location can therefore influence the progression of secondary damage.

Methods

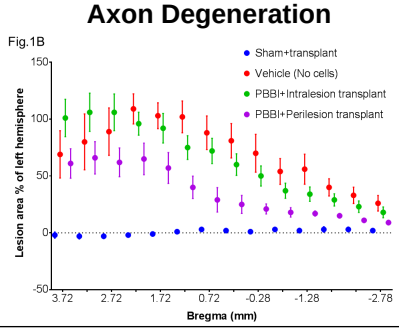
- A group of 40 rats was randomized to the following groups: (Gr1) PTBI+vehicle, (Gr2) no injury + hNCS, (Gr3) PTBI+hNSCs in lesion penumbra or (Gr4) PTBI+hNSCs intralesion.
- All injured rats had unilateral PTBI and all transplants were done 1-week post injury with a million cells and subsequent immunosuppression.
- Intralesion transplants were administered directly into the lesion and perilesion transplants were injected into 8 points in a cube around the lesion
- 12 weeks post-transplant (measure of robust durable engraftment) brain sections were stained to assess (1) lesion volume/spared tissue (progression/neuroprotection), (2) motor ability using grid walk, (3) immunohistochemsitry.

Results

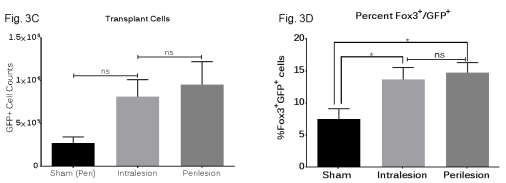
- Significant reduction of mean lesion volume, increased motor cortex sparing (P<0.0001 Gr3 vs Gr1) but not Gr4 vs Gr1.
- hNSC engraftment was significantly greater in Gr3, 4 vs Gr2.
- Transplant survival or neuronal differentiation did not differ between Gr3 and 4.
- On grid walk Gr 3 and 4 animals had significantly fewer foot faults compared to Gr1, albeit not enough to abolish injury effect (vs Gr2).



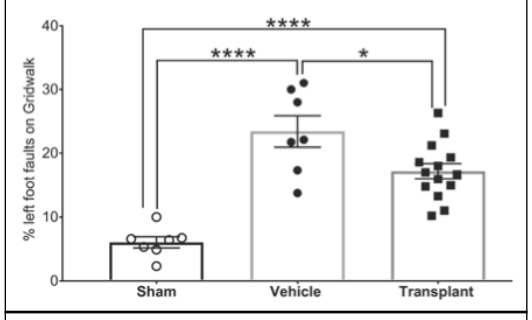
Axon Degeneration



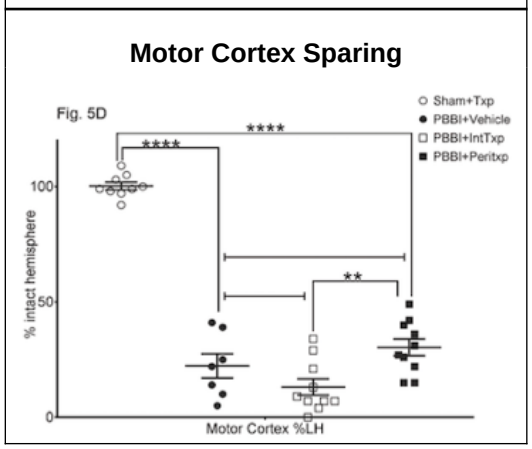
Engraftment and Differentiation



Gridwalk Test



Motor Cortex Sparing



Conclusions

At 12 weeks post-transplantation (1) hNSC mediated neuroprotective effect is location dependent whereas engraftment and differentiation weren't. (2) Motor recovery was due to neuroprotection rather than cell replacement. In aggregate with ongoing safety study data, our results suggest that neural stem cells offer an opportunity to mitigate TBI induced disability and warrants further investigation as part of a clinical trial.

Learning Objectives

1) Describe the effect of transplant location on Human neural stem cells mediated mitigation of penetrating TBI induced progressive tissue loss
2) Consider alternative uses of neural stem cell transplants
3) Understand the potential for hNSC in prevention of loss / regaining of motor ability.

References

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