Neuroprotective B Cell Therapy for Traumatic Brain Injury

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Background

Traumatic brain injury (TBI) remains a significant cause of morbidity and mortality worldwide, affecting approximately 1% of the population each year[1]. Secondary injury cascades following the initial insult play a significant role in mediating neurological dysfunction in TBI and are driven by inflammatory responses to injury. Indeed, along with axonal injury, neuroinflammation represents one of the primary drivers of lesion progression in both the acute and the chronic phases of TBI[2], becoming especially detrimental during the latter phase[3]. Despite significant medical need, there are currently no immunomodulatory therapeutic agents available for the treatment of patients with TBI[4].

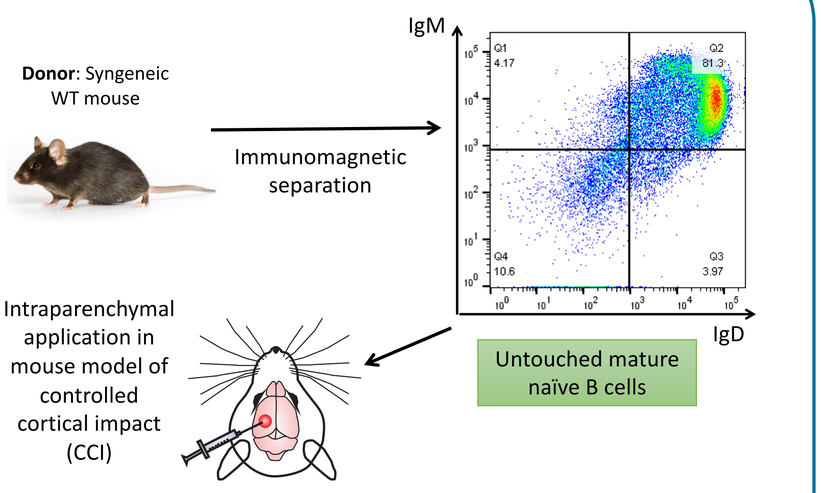
B Cell Immunotherapy for Tissue Repair

Recent studies indicate that B cells can act as powerful modulators of tissue regeneration.[5] In addition to their potential to differentiate into antibody-producing plasma cells, B cells can efficiently present antigens to T cells and modulate local immune responses through secretion of pro- and anti-inflammatory cytokines.[6] We showed previously that topically-applied mature B cells have immunomodulatory properties and strongly promote tissue regeneration, including cutaneous nerve growth, in acute and chronic skin wounds.[7,9]

Hypothesis

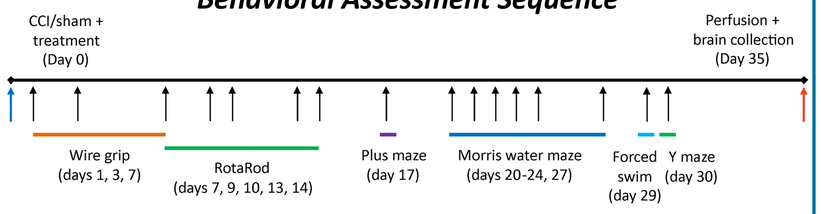
We hypothesize that the application of purified B cells directly at the site of CNS injury has a neuroprotective effect, mediated by the local immunomodulatory action of B cells on infiltrating and resident immune cells.[8,9]

Methods

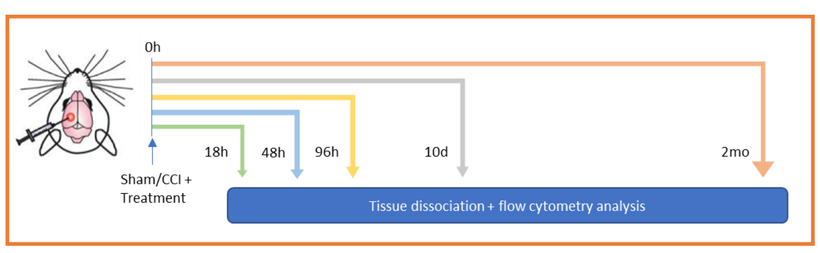


At the time of injury, mice were injected intraparenchymally at the lesion site with 2×10^6 mature naïve syngeneic splenic B cells. Control CCI mice received equal numbers of T cells or only saline, and sham-injured mice (craniotomy only) were given B cells or saline. N = 10-12 animals/treatment.

Behavioral Assessment Sequence



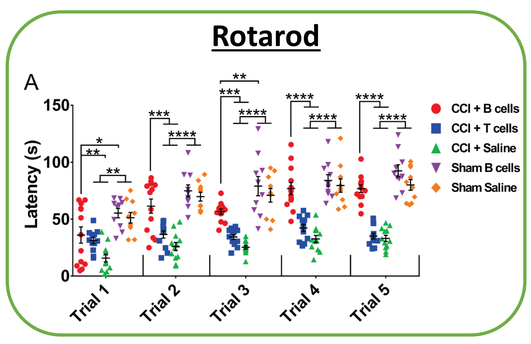
Flow Cytometry Analysis Timeline

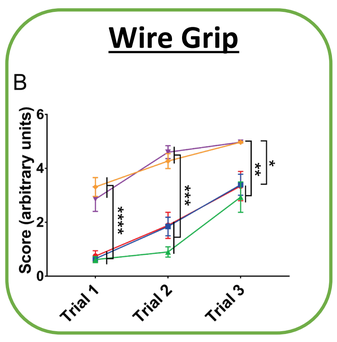


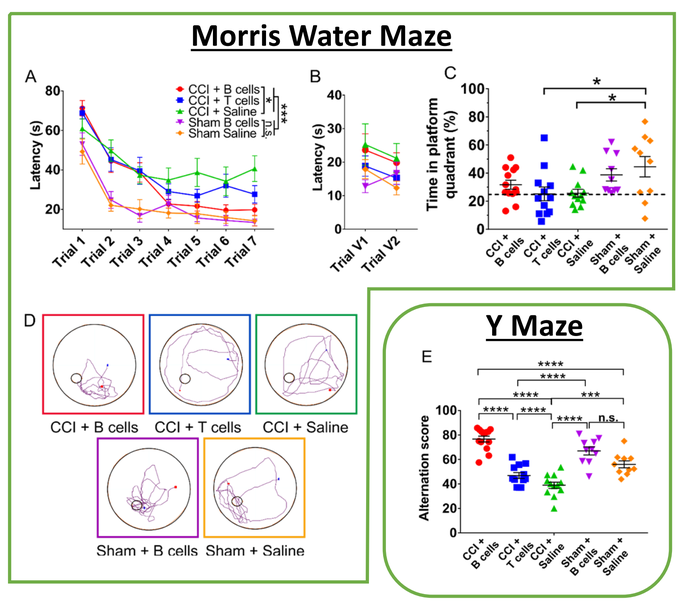
Following CCI/sham injury mice underwent behavioral assessments at multiple timepoints to evaluate motor and cognitive function. Brain samples were collected at specified intervals and processed for flow cytometry analysis to investigate cell population dynamics and cytokine production.

Results

B Cell Application Improves Motor & Cognitive Functional Recovery After CCI

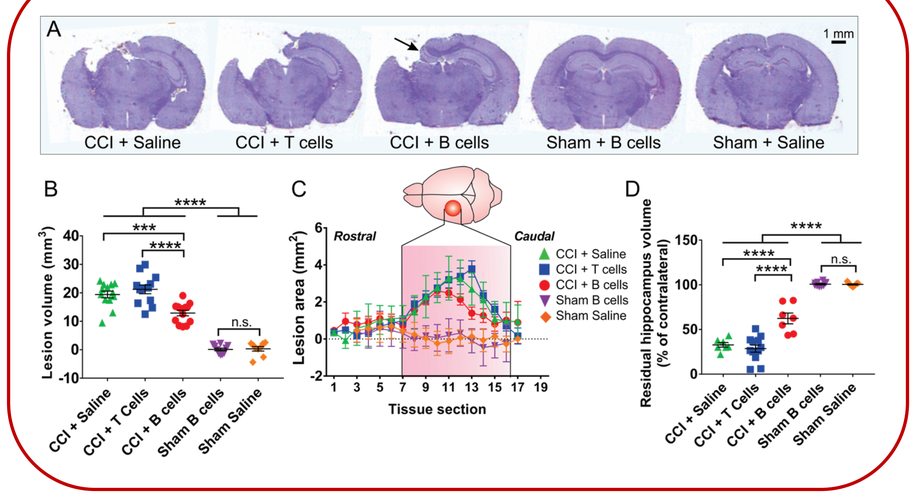




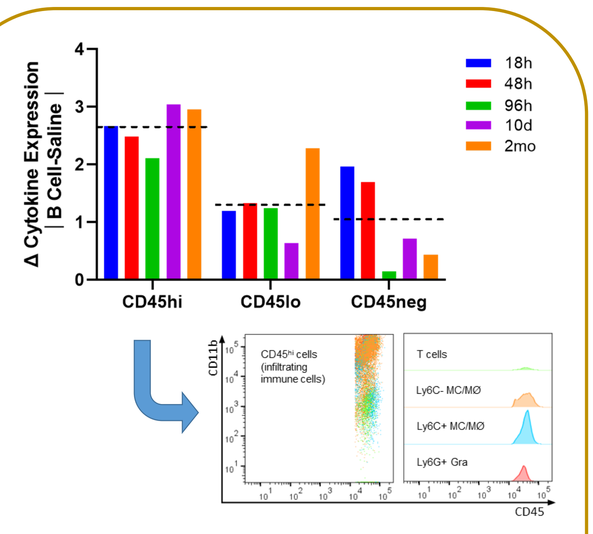


- A single application of purified mature naive B220⁺/CD19⁺/IgM⁺/IgD⁺ B cells at the time of injury improves motor and cognitive functional recovery after CCI in multiple behavioral assays.
- By contrast, control animals, treated with equivalent numbers of T cells or saline, showed significant neurobehavioral deficits.

B Cell Application Reduces Lesion Volume 35 days Post-CCI

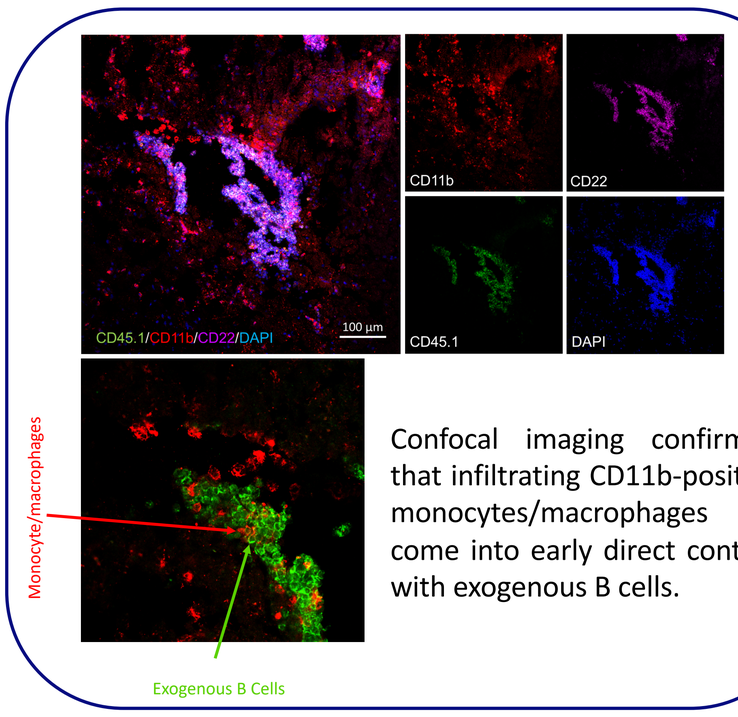


B Cell Application Impacts Global Cytokine Production



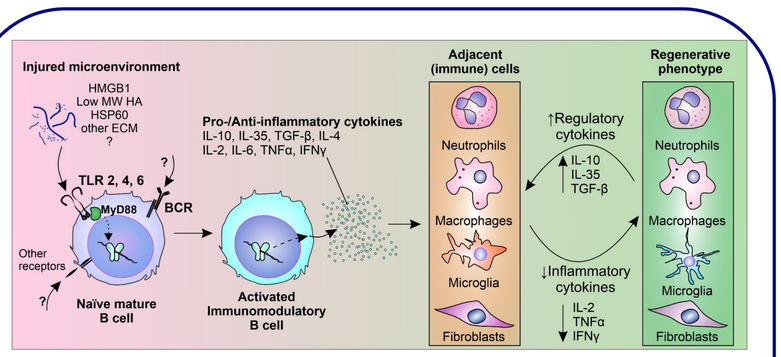
Flow cytometry analysis of the injury site showed that in the presence of B cells, populations of CD45^{high} cells, composed predominately of infiltrating peripheral myeloid cells, exhibited the greatest global change in cytokine production.

Infiltrating Monocytes/Macrophages Migrate Towards the Injury Site and Interact Closely with B Cells



Confocal imaging confirmed that infiltrating CD11b-positive monocytes/macrophages come into early direct contact with exogenous B cells.

B Cell-Mediated Immunomodulation in the Context of Injury



In the context of injury, B cells are hypothesized to adopt an immunomodulatory phenotype that modulates infiltrating immune cells through the secretion of regulatory and inflammatory cytokine expression.[9]

Conclusions

The present work describes, for the first time to our knowledge, the use of a direct application of B cells in a preclinical TBI model to modulate structural and functional outcome after injury.

We found that a single intraparenchymal delivery of purified (>95%) mature, naïve B cells at the time of CCI can significantly reduce post-injury learning and memory deficits and reduce brain tissue loss.

The previously unknown protective effects of exogenous B cells are likely mediated in part by interactions with infiltrating peripheral myeloid cells, and their immunomodulation of pro- and anti-inflammatory cytokines.

References

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Acknowledgements

This work was supported by funds from the NIH National Institute of Neurological Disorders and Stroke award R01NS117598 to R.F.S. and by a summer internship award from the Vaccine and Immunotherapy Center (VIC) at Massachusetts General Hospital (MGH), Harvard Medical School (HMS) and Edinburgh Medical School to S.M.