The Effects of Elongation Strain on Human Choroid Plexus Epithelial Cells as a Model of Traumatic Brain Injury (TBI)

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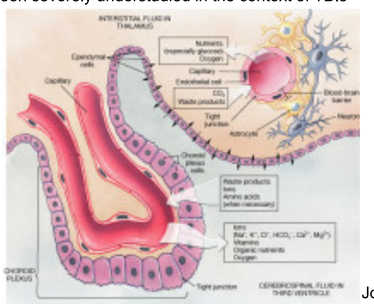
Background

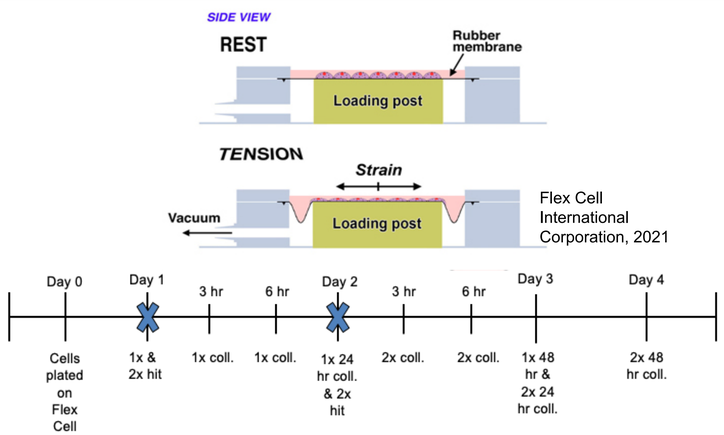
- In the U.S., there are ~1.5 million reported traumatic brain injuries (TBI) per year with varying degrees of severity that inflict injury at the cellular level
- The Choroid Plexus (CP) plays a significant role in brain homeostasis
- The CP has also been severely understudied in the context of TBIs



John Leiff, MD

Objective

Elucidate the extent of structural and neurochemical changes that occur in human choroid plexus epithelial cells (HuCPECs) in response to physical trauma



Flex Cell International Corporation, 2021

Methods

The FlexCell tension system was used to induce mechanical stimulation and elongation strain to the HuCPECs. HuCPEC's structural integrity was analyzed using immunohistochemistry for tight junction proteins. Microarrays were used to analyze cytokine production and glutamate secretion.

Elongation Strain Causes 48-hour Increase in Inflammatory Cytokines

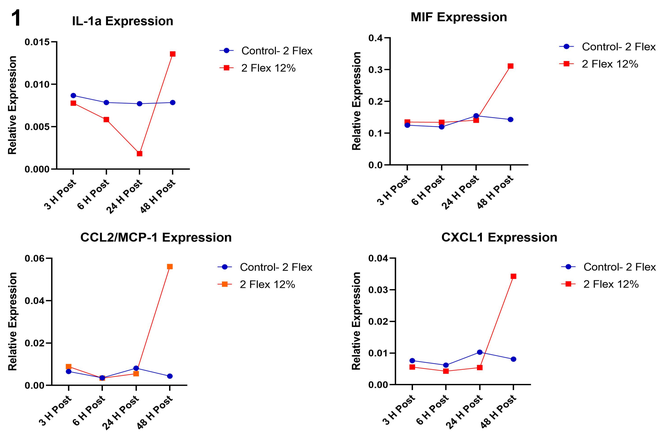


Figure 1: Line graphs show the quantified change in production of 4 pro-inflammatory cytokines over time in the 2 hit vs 2 hit control conditions. Data shows exceptional increase in cytokine production across: IL-1a, MIF, CCL2, and CXCL2. Most specifically, significant increases are observed between 24-48 hours post-injury in the 2 hit condition. These results corroborate with the delayed symptomatic presentation seen in TBI.

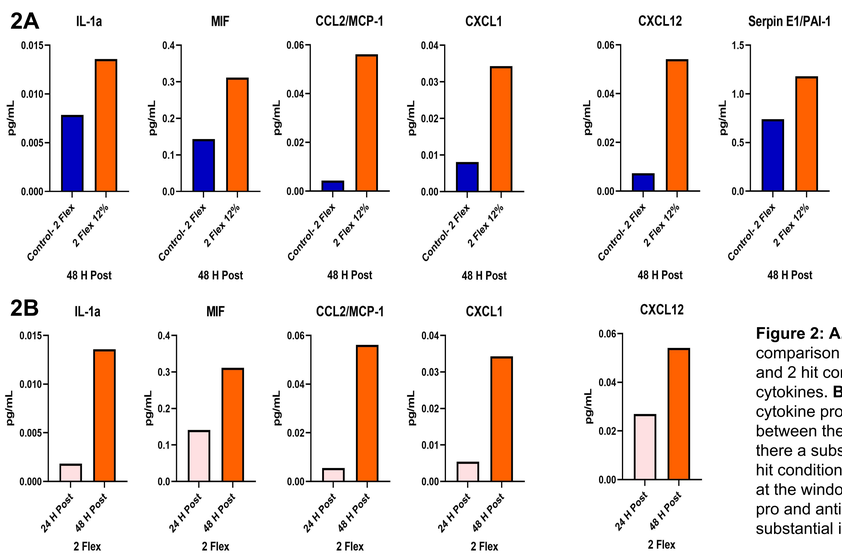


Figure 2: A. Bar graphs show the overall comparison of cytokine production between 2 hit and 2 hit control across pro & anti-inflammatory cytokines. **B.** Bar graphs comparing the change in cytokine production within the 2 hit condition between the 24 and 48 hour time points. Not only is there a substantial increase across the board for 2x hit conditions in general (A), the most noteworthy is at the window of 1-2 days post injury where both pro and anti-inflammatory cytokines exhibit substantial increases in production (B).

Conclusions

- This project offers support to the documented clinical manifestations of a delayed symptom presentation seen with head injury
- There is a significant inflammatory cellular response to mild head injury, most notably @ 48 hours post hit
- The data sheds light on the inflammatory role that the Choroid Plexus can invariably inflict during head injury
- From our study, it is evident that choroid plexus epithelial cells are susceptible to injury from head trauma and that these subtle changes can be deleterious both structurally and functionally
- Our protocol serves as a valid model for other cell types to further explore the trauma response seen with TBIs and better understand the consequences of secondary inflammatory insults

Future Directions

- Cytokine array: measuring *new* cytokine production across each time point in addition to total production
- Longer time points – how persistent is the inflammatory response?
- Increase Flex Cell hit magnitude and parameters to better model TBI vs mild head injury
- Collecting supernatant between the 1st and 2nd hits for the 2 hit condition as a means to compare the difference during the incubation period

Acknowledgements

Dr. William Thompson, IUSM

MUCOM Research Committee