Therapeutic approaches to target inflammation following TBI through inhibition of the p38α MAPK

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Background: Closed head traumatic brain injury (TBI) triggers an acute inflammation response that involves resident glia and other immune cells. Neurologic outcome is dependent on the essential balance between restoration of tissue homeostasis after the initial injury and resolution of the injury-induced innate immune response. Natural resolution of the injury-induced proinflammatory cytokine response such that neurologic sequelae are attenuated is generally not successful.

Purpose/Hypothesis: Therapeutic interventions during critical dosing time windows are needed in order to reduce the dysregulated inflammation that is causally linked to the neuropathologic sequelae. Previous work has generated a causal link between the p38α mitogen-activated protein kinase (MAPK) mediated intracellular signaling pathway and the injurious proinflammatory cytokine response in neurodegenerative animal models of disease. The recent availability of highly specific molecular probes for p38α inhibition allow a more refined in vivo analysis of this intracellular signaling pathway and its link to dysregulated glia function and neuroinflammation in TBI with its more rapid pathology progression kinetics.

Methods: We have recently explored these processes in TBI through the combined use of these in vivo p38α dynamic molecular probes and genetics based in vivo tools, such as targeted knockdown of p38α in specific inflammatory cell types.

Results: We found that genetic suppression of p38α in myeloid cells resulted in less TBI induced deficits in a running wheel behavioral task and cognitive deficits as measured by the radial arm water maze. Suppression of p38α activity through selective pharmacological action or through reduction of p38α protein levels generated reduction of injury induced cytokine levels in the brain.

Conclusions: The congruence of outcomes from genetic and pharmacological approaches provides a unique battery of outcomes consistent with p38α as a potential therapeutic target in TBI.