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Deletion of Myeloid Pannexin-1 Channels decrease Chemokine's expression and improves Cognitive function after Brain trauma

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by

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ABSTRACT

Mild traumatic brain injury (mTBI) has diverse short-term and long-term neurobehavioral impairments and neurological consequences. Neuroinflammation is an especially significant secondary injury of mTBI that leads to cognitive dysfunction and impairment of locomotor activity. During mTBI, there is an activation of microglial and glial cells, blood-brain barrier (BBB) disruption, and infiltration of leukocytes to the injury site. Pannexin1(Panx1) channels are important conduits of Adenosine 5 Triphosphate (ATP) release, and this ATP release is associated with leukocyte infiltration and damage severity after brain trauma. However, the molecular mechanisms that cause neuroinflammatory injury after mTBI are unknown. Our lab reported that pharmacological blockage of Panx1 channels in mice after mTBI is neuroprotective and anti-inflammatory. Recently our lab also published findings that indicate deletion of Panx1 in myeloid cells of mice improves motor coordination, cognitive function, and blood-brain barrier (BBB) leakage 6 days post-mTBI. This study examined the long-term effects of myeloid Panx1 channels on the neurobehavioral and structural changes in the brain after mTBI. It found that myeloid panx1 KO mice displayed improved memory and cognition outcomes and locomotor activity at 6 weeks post-mTBI, and it showed a reduction in wound herniation and stagnant BBB leakage compared to injured control mice. Subsequent studies focused on the short-term effects of deleting Panx1 channels in myeloid cells of mice, which significantly reduced infiltration of all leukocytes to the injury site 3 days post-mTBI. Additionally, the myeloid Panx1 KO mice displayed lower expression of various chemokines that were upregulated in control mice after brain trauma. Furthermore, caspase

activation and cleavage of Panx1 channels could be a potential mechanism of activation of Panx1 channels in TBI. These findings are significant because they suggest that activation of myeloid Panx1 channels mediates infiltration of leukocytes via activation of chemotaxis signaling and deletion of myeloid panx1 channels in long-term has neuroprotective effects. Overall, our study indicates that Panx1 channels could serve as a therapeutic target for neuroinflammation and neuroprotection after mTBI.