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Does neuroinflammation drive the relationship between tau hyperphosphorylation and dementia development following traumatic brain injury?

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Abstract

A history of traumatic brain injury (TBI) is linked to an increased risk for the later development of dementia. This encompasses a variety of neurodegenerative diseases including Alzheimer's Disease (AD) and chronic traumatic encephalopathy (CTE), with AD linked to history of moderate-severe TBI and CTE to a history of repeated concussion. Of note, both AD and CTE are characterized by the abnormal accumulation of hyperphosphorylated tau aggregates, which are thought to play an important role in the development of neurodegeneration. Hyperphosphorylation of tau leads to destabilization of microtubules, interrupting axonal transport, whilst tau aggregates are associated with synaptic dysfunction. The exact mechanisms via which TBI may promote the later tauopathy and its role in the later development of dementia are yet to be fully determined. Following TBI, it is proposed that axonal injury may provide the initial perturbation of tau, by promoting its dissociation from microtubules, facilitating its phosphorylation and aggregation. Altered tau dynamics may then be exacerbated by the chronic persistent inflammatory response that has been shown to persist for decades following the initial impact. Importantly, immune activation has been shown to play a role in accelerating disease progression in other tauopathies, with pro-inflammatory cytokines, like IL-1β, shown to activate kinases that promote tau hyperphosphorylation. Thus, targeting the inflammatory response in the sub-acute phase following TBI may represent a promising target to halt the alterations in tau dynamics that may precede overt neurodegeneration and later development of dementia.

KEYWORDS: Alzheimer’s disease; Chronic traumatic encephalopathy; Neuroinflammation; Tau; Traumatic brain injury

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