NLRP3-ASC inflammasomes contributes to sustained glial reactivity and cognitive impairment after TBI

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Background:

This study aimed to investigate the roles of ASC and NLRP3 inflammasome complexes in neuroinflammation and cognitive outcomes following traumatic brain injury (TBI), using both closed-head injury (CHI) and controlled cortical impact (CCI) models.

Materials and Methods:

We analyzed single-cell RNA sequencing data to assess Pycard (Asc) and other inflammasome related genes expression in microglia after CHI. The persistence of inflammasome-related protein upregulation was evaluated in wild-type and Asc-deficient mice, alongside behavioral assessment of cognitive impairment. In CCI models, we examined the effects of genetic deletion of Nlrp3 and pharmacological inhibition with NLRP3-specific compounds on microglial activation, ASC aggregation, and neurological recovery. Intravital imaging was employed to visualize microglial responses post-injury.

Results:

Pycard (Asc) was predominantly expressed in microglia after CHI, with sustained upregulation of inflammasome proteins for weeks post-injury. Asc-deficient mice showed markedly reduced inflammasome activation and were protected against CHI-induced mild cognitive impairment. In CCI models, NLRP3 inflammasome activation was identified as a key mediator of early neuroinflammation and microglial activation. Both genetic deletion of Nlrp3 and oral administration of NLRP3 inhibitors preserved microglial homeostasis, reduced ASC aggregation, and significantly improved neurological and cognitive recovery. Intravital imaging confirmed that NLRP3 inhibition prevented microglial activation after TBI.

Conclusion:

ASC and NLRP3 inflammasome complexes play pivotal roles in sustaining neuroinflammation and mediating cognitive deficits following mild brain trauma. Targeting the NLRP3-ASC inflammasome axis represents a promising therapeutic strategy to reduce long-term neurocognitive decline and the risk of neurodegeneration after TBI.