Supplementary Methods

Animals and grouping methods

Adult male C57BL/6 mice (aged 12 wk, weighing 20-25 g) were purchased from the Chinese Academy of Military Science (Beijing, China). The mice were quarantined and housed for one week before being randomly divided into 4 groups: Sham, TBI, TBI+SC75741, and TBI+MCC950. The treatment was first administered at 1 h post-injury. Briefly, *SC75741* (Selleckchem, Houston, TX, USA), the *NF-κB* selective inhibitor, was applied to the mice (15 mg/ml, intraperitoneal injection) every 2 days till 14 days post-injury (DPI) according to the manufacture's instructions. *MCC950* (Selleckchem), the specific inhibitor of pyroptosis initiating receptor *NLRP3*, was dosed in the mice (10 mg/kg, intraperitoneal injection) daily for the first 3 days after injury, and then every other day till 14 DPI.

Controlled cortical impact (CCI) mouse model

The CCI mouse model used in this study can result in injury to the cerebral cortex and hippocampus, and is associated with vestibulomotor deficits and long-term neurocognitive dysfunctions. Although animals do lose body weight, they rapidly regain spontaneous ventilation, righting reflex, and the ability to ambulate. Briefly, the mice were anesthetized with 10% chloride hydrate (3.0 mL/kg body weight, intraperitoneal injection). They were then positioned in a stereotaxic device using ear bars. Following a midline scalp incision, a 3.0-mm craniotomy was performed centrally over the right parietal bone. The impounder tip of the injury device (eCCI model 6.3, American Instruments, Richmond, VA, USA) was then extended to its full impact distance, positioned on the surface of the exposed dura mater, and reset to impact its surface. To induce moderate brain injury, the impact parameters were set as: 4.5-m/s velocity, 2.0-mm depth, and 200-ms dwell time. After the impact, the craniotomy was closed with bone wax, and the scalp was sutured. The mice were placed in a

well-ventilated cage at 37 ℃ until they regained consciousness. Sham-operated mice underwent the same procedures except for the cortical impact.

RDW and Plt count determination

The mice were anesthetized with 10% chloride hydrate by intraperitoneal injection at 1 and 3 DPI. Whole blood samples were then collected via cardiac puncture, and were anticoagulated with heparin. RDW and Plt count determination were obtained using Sysmex XN-2000 automated Hematology Analyzer (Kobe, Hyogo, Japan)

ELISA assay

Brain extracts from cerebral cortex of the mice were collected at 3 DPI. ELISA assay of the inflammatory mediators, including TNF-α, IL-1β, and IL-10 were determined referring to the manufacture's instructions (Cat# MTA00B, MLB00C, M1000B; R&D, Minneapolis, MN, USA).

Modified Neurological Severity Score (mNSS) test

The mNSS test includes motor, sensory, reflex, and balance evaluations. It was conducted pre-injury and at 1, 3, 7, and 14 days post-CCI by an observer who was blinded to the experimental conditions and treatments.

Morris Water Maze (MWM) test

For the spatial acquisition trial, the mice were placed in a pool (105 cm diameter) filled with room temperature water, and allowed up to 90 s to locate a submerged platform. The mice performed 4 trials a day with a 30-min inter-trial interval for 4 consecutive days (14-17 DPI). They were introduced in varying quadrants (northwest, northeast, southwest, and southeast) of the pool for each trial, but the location of the platform was fixed. The latency-time to reach the platform was recorded, and the 4 trials were averaged. For the probe trial conducted at 18 DPI (24 h after the last spatial acquisition trial), the mice were allowed to swim freely without the platform for 60 s. The

percentage of the time spent in goal quadrant was measured. In addition, *SC75741* and *MCC950* treatment were not administered during the test.

Novel Object Recognition (NOR) test

The NOR test was carried out to evaluate cognitive function of TBI mice at 14 DPI as reported. Briefly, the mice were administered to freely explore a 40 × 40 × 50 cm open-field box for 10 min at the beginning. In the familiarization session, the mice were allowed to explore two similar objects. A stopwatch with two channels was used to record the time spent exploring each object until 20 seconds of total exploration time or 10 min of the session time has been reached. In the test session conducted 6 h later, one of the two objects was replaced by a novel object, and the mice were allowed to explore them for 10 min. The amount of time that the mice spent on exploring each object was recorded, and the index of exploring time on the novel object over the total exploring time was calculated.