Mini Review Article

Traumatic brain injury-related inflammatory projection: beyond local inflammatory responses

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Acute neuroinflammation induced by microglial activation is key for repair and recovery after traumatic brain injury (TBI) and could be necessary for the clearance of harmful substances, such as cell debris. However, recent clinical and preclinical data have shown that TBI causes chronic neuroinflammation, lasting many years in some cases, and leading to chronic neurodegeneration, dementia, and encephalopathy. To evaluate neuroinflammation *in vivo*, positron-emission tomography has been used to target translocator protein, which is upregulated in activated glial cells. Such studies have suggested that remote neuroinflammation induced by regional microglia persists even after reduced inflammatory responses at the injury site. Furthermore, unregulated inflammatory responses are associated with neurodegeneration. Therefore, elucidation of the role of neuroinflammation in TBI pathology is essential for developing new therapeutic targets for TBI. Treatment of associated progressive disorders requires a deeper understanding of how inflammatory responses to injury are triggered, sustained, and resolved and how they impact neuronal function. In this review, we provide a general overview of the dynamics of immune responses to TBI, from acute to chronic neuroinflammation. We discuss the clinical significance of remote ongoing neuroinflammation, termed "brain injury-related inflammatory projection". We also highlight positron-emission tomography imaging as a promising approach needing further development to facilitate an understanding of post-TBI inflammatory and neurodegenerative processes and to monitor the clinical effects of corresponding new therapeutic strategies.

Key words: Microglia, neurodegeneration, neuroimaging, neuroinflammation, traumatic brain injury

INTRODUCTION

RESEARCH ON NEUROINFLAMMATION has expanded our knowledge of both acute and chronic inflammation in the central nervous system (CNS). Common etiological factors involve CNS injury, infections, toxins, and autoimmunity. Although transient inflammatory responses are protective and facilitative of tissue repair following injury, acute neuroinflammation could cause secondary injury after traumatic brain injury (TBI).[1,2] By contrast, chronic neuroinflammation is associated with the progression of neurodegenerative diseases, including Alzheimer's disease, Parkinson's disease, and chronic traumatic encephalopathy.[3–5]

In the CNS, inflammatory reactions occur through innate and acquired immune system mechanisms induced by glial cells, particularly microglia. Sensing disturbances in the brain, these cells rapidly activate and accumulate locally in response to neuronal cell injury or foreign entry in the brain. Microglial activation plays a central and differential role in regulating neuroinflammation. Immediately after a TBI, they assume both pro-inflammatory functions, resulting in neurotoxicity, and anti-inflammatory roles, fostering neuroprotection.[6–8] Evidence suggests that prolonged neuroinflammatory responses mediated by microglia after CNS injury are detrimental,[8] as they are linked with an increased risk of chronic neurodegenerative diseases.[3–5] Moreover, inflammation does not resolve immediately and tends to persist chronically after injury.[9]

Positron-emission tomography (PET) has been used to identify and diagnose CNS disorders and drug monitoring.[10] To evaluate neuroinflammation *in vivo*, PET studies have been used to identify translocator protein (TSPO) structures, which are upregulated in activated microglial cells.[11] The

strength of the ongoing inflammation detected during these exams is evaluated using the standardized uptake value (Fig. 1). Using this approach, a more detailed characterization of neuroinflammation after focal TBI has been reported (Fig. 2), which suggested that remote neuroinflammation could be induced by regional microglia in the subacute phase and could persist even after a reduction of inflammatory responses at the injury site.[12] These findings provided strong evidence that injury-induced inflammation migrates to remote sites along neuronal projections. The term "brain injury-related inflammatory projection" (BIRIP) was therefore coined to describe tract-related chronic neuroinflammatory pathology (Fig. 3). Most previous research has investigated neuroinflammation in the peri-injury area. This is often of limited value when attempting to treat the remote inflammation. In this review, we provide a general overview of the dynamics of the immune response to TBI, from acute to chronic neuroinflammation, and discuss the clinical significance of BIRIP. We also highlight PET imaging as a promising approach that could improve interpretation of inflammatory processes and neurodegeneration after TBI, as well as monitor the clinical effects of new therapeutic strategies.

ACUTE NEUROINFLAMMATION AFTER TBI: WHAT IS NEUROINFLAMMATION?

TRAUMATIC BRAIN INJURY-ASSOCIATED brain damage can occur across two main phases: (i) a primary damage phase occurring at the moment of insult, involving contusions, diffuse axonal injury, and/or intracranial hemorrhage, and invariably resulting in immediate cell death; (ii) a secondary phase involving herniation, brain edema, and intracranial pressure elevation.[13] Particularly in cases of moderate and severe injuries, these biological reactions from both phases could persist over a much longer period than previously believed, lasting a few days to a number of weeks.[14] These injuries trigger various cellular and molecular responses that characterize inflammation, in order to restore the cellular homeostasis of the damaged tissue. Unregulated inflammatory processes often lead to exacerbation of the primary damage and delay in cell death. Therefore, neuroinflammation is considered to be a major contributor to secondary injury and, in many cases, TBI-induced neuroinflammation could be more detrimental to pathological progression than the primary injury itself.[15]
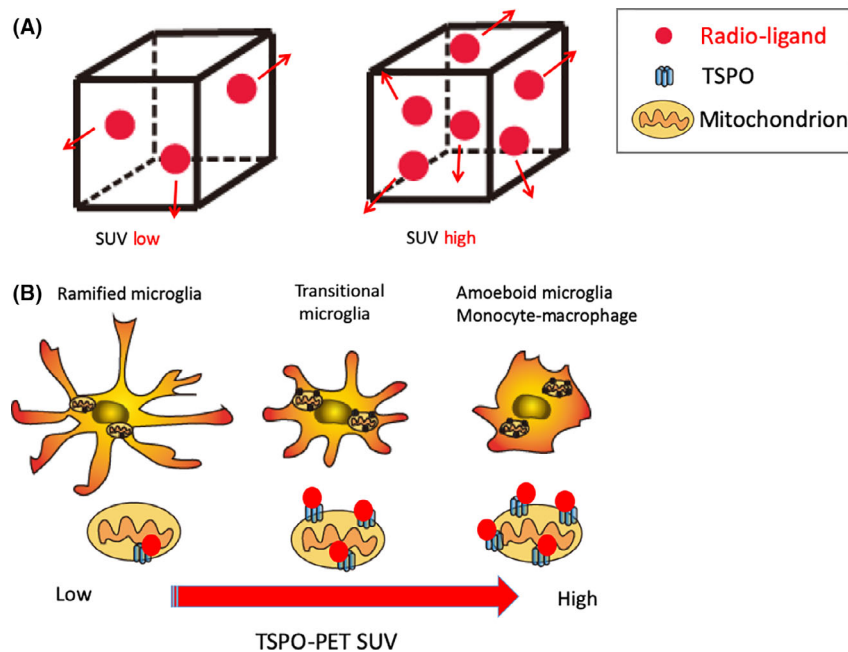

Fig. 1. Transformation of microglia is consistent with standardized uptake value (SUV) mapping. A, The SUV is a dimensionless ratio used historically by nuclear medicine professionals to distinguish between "normal" and "abnormal" levels of uptake. The higher the density of tracer molecules labeled with positron-emitting isotopes, the higher the SUV. B, The transition of microglia from a normal resting state to an activated state is associated with increased expression of translocator protein (TSPO) on the surface of mitochondria. PET, positron-emission tomography.
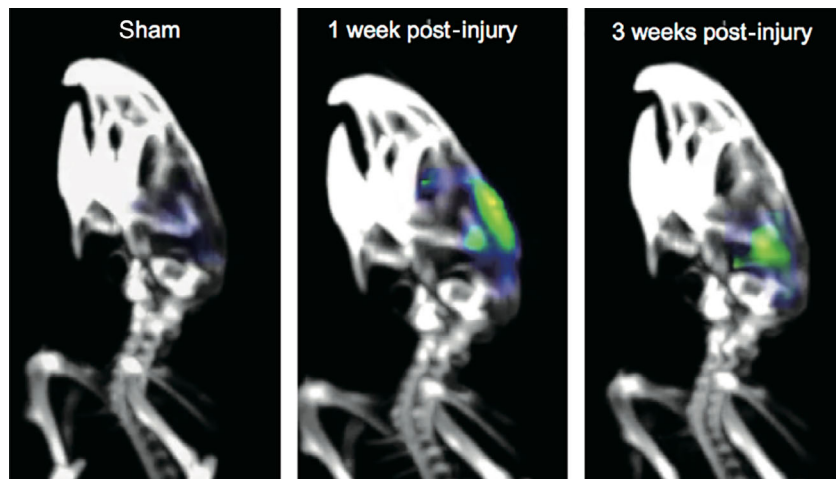
Fig. 2. Positron-emission tomography/computed tomography imaging of migratory inflammation after controlled cortical injury. Multiplanar reconstruction images over the whole skull illustrate additional translocator protein uptake detected around the ipsilateral thalamus, remote from the primary injury site, suggesting that remote neuroinflammation induced by regional microglia persists even after inflammatory responses have diminished at the injury site. Left, sham (1 week post-operation); middle, 1 week post-injury; right, 3 weeks post-injury.
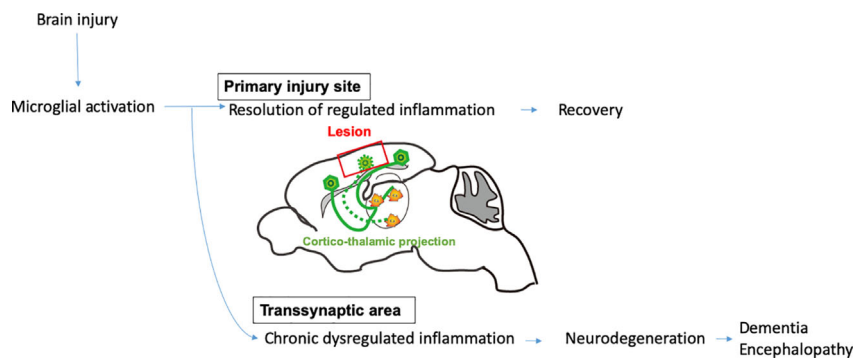

Fig. 3. Brain injury-related inflammatory projection (BIRIP). Neuronal damage provokes local inflammatory responses, mainly induced by microglia, propagating transsynaptic neuroinflammation and neurodegeneration. In light of the association of this mechanism with neuronal tracts, this was termed BIRIP.

ACUTE NEUROINFLAMMATION AFTER TBI: CELLULAR RESPONSES

UNTIL RECENTLY, THE brain was considered an immune-privileged site. However, inflammation after TBI is now recognized to involve a robust and complex interaction between central and peripheral cells, which occurs by way of the blood-brain barrier that becomes disrupted due to injury.[13] Acute neuroinflammation starts by early resident microglial activation. Chemoattractants released from pro-inflammatory microglia promote peripheral immune cell infiltration into the injury site. Anti-inflammatory microglia simultaneously contribute to the restoration of tissue homeostasis by clearing debris, sealing defective barriers, and producing neurotrophic factors.[6] Immediately after TBI, neutrophil recruitment is initiated from peripheral circulation, followed by infiltration of lymphocytes and monocyte-derived macrophages.[13] Additionally, infiltration of myeloid-derived suppressor cells, a heterogeneous population of immature suppressor cells generated due to aberrant myelopoiesis under pathological conditions, is found to occur in the brain following focal TBI.[16] Although infiltrating monocytes or myeloid-derived suppressor cells might be a therapeutic target of the secondary inflammation in the peri-injury area, their depletion before entering the injury site is found to aggravate BIRIP.[12,16]

REMOTE NEUROINFLAMMATION INDUCED BY RESIDENT MICROGLIA AFTER FOCAL OR DIFFUSED BRAIN INJURY

ALTHOUGH THE ACUTE inflammatory response after TBI is expected to eventually resolve to baseline, some patients develop chronic neuroinflammation that can last for years after injury.[17,18] Diffuse axonal injury (DAI) causes neuronal inflammation and degeneration in large white matter tracts. An autopsy study involving patients who survived for more than 1 year after DAI revealed greater amoeboid microglia in subcortical white matter tracts (versus control tissue) associated with thinning of the corpus callosum.[19] Other neuropathological studies of preclinical and clinical DAI cases have shown that microglia activation is central in chronic white matter degeneration.[19–21] This persistent neuroinflammation might influence the spread of abnormal proteins, such as amyloid plaques and neurofibrillary tangles, and could cause neurodegeneration following DAI.[22] Although often located at sites of axonal injury, post-DAI neuroinflammation could be demonstrated in more distant brain locations over time, tracking the Wallerian degeneration of damaged axons.[23]

This is also corroborated in a study that used the controlled cortical impact mouse model for focal brain injury to demonstrate long-term neuroinflammation in the ipsilateral thalamus, remote from the initial injury site, even after the original inflammatory response had subsided.[12] Furthermore, the hypointensity on T2-weighted magnetic resonance imaging (MRI), which is causally related to the fewer fibers, was observed (Fig. 4). A study of adult patients with moderate-to-severe TBI showed diffuse binding of the TSPO ligand ^{11}C-(R)-PK11195 in areas remote to the trauma, including the thalamus, putamen, and occipital cortex, up to 17 years after injury.[17] These results reiterate that the consequences of local damage can also be seen in remote but interacting regions.[12,17]

CLINICAL INTERPRETATION OF CHRONIC INFLAMMATION

A KEY QUESTION arising from the data discussed above is whether remote TBI-responsive neuroinflammation is a clinically relevant therapeutic target.

Patients with both DAI and focal injury often have disabling problems with attention, memory, and executive function. These higher order cognitive functions require the integration of information and processes across spatially distinct brain regions. Diffuse axonal injury produces neurological impairment due to the disconnecting of brain networks.[23] Likewise, the thalamus connects different regions, including the cortex, basal ganglia, and cerebellum, and shows functional specialization, with different responses to thalamic hemorrhage or infarct seen during different cognitive tasks, such as reasoning or language-related tasks.[24] Damage to these connections and functions is observed in many neurological and psychiatric diseases and in neuronal jamming (a syndrome involving thalamic dementia, aphasia, neglect, and chronotaraxis).[24] Persistent inflammation can cause these impairments through an unregulated inflammatory response that facilitates neurodegeneration. Indeed, inflammation in the thalamus, detected by TSPO PET, is more strongly associated with severe cognitive impairments.[17]

IN VIVO IMAGING TOOLS OF NEUROINFLAMMATION

NEUROIMAGING OFFERS A wide array of non- or minimally invasive techniques to characterize
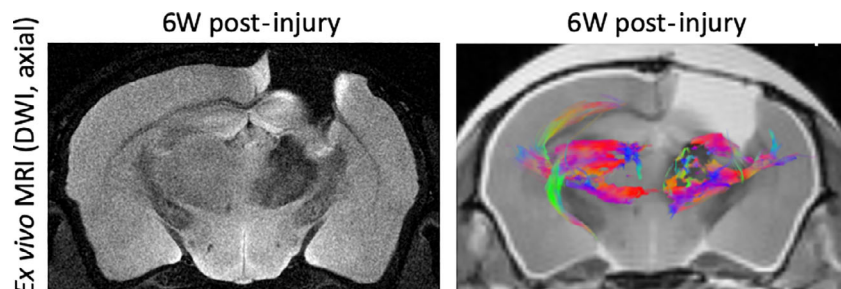

Fig. 4. Damage to the thalamic network in the chronic phase after cortical injury. Magnetic resonance imaging showing that damaged tissue in the initially injured area is cleared and replaced by cavitation at 6 weeks post-focal brain injury. Left panel, diffusion-weighted *ex vivo* magnetic resonance imaging scans from mice with traumatic brain injury at 6 weeks (6W) post-injury. Hypointensity in the ipsilateral thalamus becomes clearly defined at 6W post-injury. Right panel, *ex vivo* tractography at 6W post-injury, with the bilateral thalami as the target region. Fiber tracts could be traced in the contralateral but not in the ipsilateral thalamus. Blue, rostral-caudal; green, dorsal-ventral; red, medial-lateral. DWI, diffusion-weighted imaging.

neuroinflammatory processes. Recent technical advances in imaging techniques such as PET and MRI have encouraged their use in evaluating functional, neurochemical, and anatomical changes in the diseased brain after TBI.[25,26] These methods target the activation of CNS immunocompetent cells (e.g., imaging glial activation using TSPO tracer),[11,12] pathological consequences of neuroinflammation (e.g., imaging decreased neuronal tracts by MR tractography or altered neurochemical or functional abnormality using MR spectroscopy),[12] and CNS infiltration by circulating immune cells (e.g., tracking monocyte infiltration into brain parenchyma using iron oxide nanoparticles and MRI).[27]

As inflammation occurs prior to brain atrophy, neuroinflammation monitoring can be used as an early biomarker as opposed to diagnostic criteria for cognitive disorders, including imaging criteria for chronic conditions such as brain atrophy and ventricular enlargement. Thus, developing imaging tools for detecting neuroinflammation presents an attractive and non-invasive approach to enable prediction of long-term brain damage and cognitive outcomes, facilitate early diagnosis, track disease progression, and aid in the rational design and clinical assessment of patient responses to therapeutic interventions. Other forms of acute, focal CNS damage, such as multiple sclerosis and ischemic stroke, might also be accompanied by similar migratory neuroinflammation.[28,29] Thus, apart from TBI, the term BIRIP can also be proposed to describe other tract-related chronic neuroinflammatory pathologies. As TSPO PET cannot yet distinguish between neurotoxic and neuroprotective inflammation, future studies should explore changes in microglial phenotypes in BIRIP.

CONCLUSION

POST-TRAUMATIC INFLAMMATION CAN be beneficial and/or potentially harmful. Following a primary TBI insult, inflammatory responses are triggered at the injury site, aiming to repair the damaged tissue. However, the excessive pro-inflammatory reaction can become an important driving force for neurodegenerative diseases or cognitive disorders after TBI. To date, treatments for brain injury have mainly focused on controlling inflammation in the peri-injury area during the acute phase. However, as remote-chronic BIRIP plays a key role in post-TBI neurodegeneration, a greater understanding of such inflammatory dynamics in TBI could lead to more spatiotemporally appropriate treatments. Positron-emission tomography imaging of neuroinflammation is a promising approach requiring further development so as to improve simultaneous interpretation of inflammatory processes and neurodegeneration after TBI, and monitor the clinical effect of new therapeutic strategies.

DISCLOSURE

Approval of the research protocol: N/A.
Informed consent: N/A.
Registry and the registration no. of the study/trial: N/A.
Animal studies: All procedures were performed in accordance with the Osaka University Medical School's Guidelines for the Care and Use of Laboratory Animals, and approved by the institutional ethics committee.
Conflict of interest: None.

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