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WHITE MATTER DAMAGE AFTER TRAUMATIC BRAIN INJURY: A ROLE FOR DAMAGE ASSOCIATED MOLECULAR PATTERNS

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Abstract

Traumatic brain injury (TBI) is a leading cause of mortality and long-term morbidity worldwide. Despite decades of pre-clinical investigation, therapeutic strategies focused on acute neuroprotection failed to improve TBI outcomes. This lack of translational success has necessitated a reassessment of the optimal targets for intervention, including a heightened focus on secondary injury mechanisms. Chronic immune activation correlates with progressive neurodegeneration for decades after TBI; however, significant challenges remain in functionally and mechanistically defining immune activation after TBI. In this review, we explore the burgeoning evidence implicating the acute release of damage associated molecular patterns (DAMPs), such as adenosine 5′-triphosphate (ATP), high mobility group box protein 1 (HMGB1), S100 proteins, and hyaluronic acid in the initiation of progressive neurological injury, including white matter loss after TBI. The role that pattern recognition receptors, including toll-like receptor and purinergic receptors, play in progressive neurological injury after TBI is detailed. Finally, we provide support for the notion that resident and infiltrating macrophages are critical cellular targets linking acute DAMP release with adaptive immune responses and chronic injury after TBI. The therapeutic potential of targeting DAMPs and barriers to clinical translational, in the context of TBI patient management, are discussed.

Keywords

microglia; macrophage; white matter injury; oligodendrocyte; HMGB1; S100; Toll like receptor; T-cell; lymphocyte; leukocyte

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1. INTRODUCTION

Traumatic brain injury (TBI) is a significant public health issue, killing or debilitating more individuals than breast cancer, AIDS, multiple sclerosis, and spinal cord injury combined [1]. TBI, defined as a blow or jolt to the head that produces permanent or temporary impairments in neurological function, may affect individuals regardless of gender, ethnicity, age, and socioeconomic status. In spite of improvements in awareness and preventative safety measures, TBI contributes to nearly one-third of injury-related deaths [2] and millions of TBI survivors live with the neurological consequences of a prior TBI [3]. In contrast to other common neurological diseases, such as stroke and Alzheimer's disease, TBI is more prevalent in younger populations, resulting in substantial loss of productive years and the need for life-long assisted care. This burdens both families and health care systems that provide cognitive, emotional, physical, and psychological support for TBI survivors. Altogether, TBI places an annual $76.5 billion burden on society [4, 5].

Despite the high prevalence and poor outcomes associated with TBI, there is a lack of effective treatment options to improve outcomes. The vast majority of pre-clinical studies to date focused on achieving acute neuroprotection, largely characterized by histological measures of cell death and lesion volume. Unfortunately, many promising pre-clinical and early stage clinical findings ultimately failed to improve long-term outcomes in later phase clinical trials [6]. Given the mechanistically complex and heterogeneous nature of neurological injury, a number of factors were suggested as possible variables that contributed to the lack of translation, including suboptimal experimental models, inadequate randomization and blinding procedures, and selection of drugs with poor pharmacokinetics, limited brain penetration, and/or narrow therapeutic windows [7]. While additional attention to experimental design and target selection will undoubtedly enhance scientific discovery and future drug development, reassessment of neuroprotection as a primary therapeutic target is warranted. In this mini-review, we discuss the emerging association between innate immune activation and chronic white matter injury after TBI. We also identify molecular and cellular targets for the development of therapeutic strategies to limit progressive neurological injury after TBI.

2. CHRONIC NEURODEGENERATION AFTER TBI: IS WHITE MATTER INJURY A VIABLE THERAPEUTIC TARGET?

2.1 Primary Injury and Acute Neuroprotection

Impact and/or coup-contrecoup injuries produce immediate mechanical injury, including axonal shearing and widespread neuronal cell death throughout the cerebral cortex, hippocampus, cerebellum, and thalamus after both clinical and experimental TBI [8–16]. Cell death, ranging from immediate necrosis within the contusion core to delayed apoptosis in the surrounding tissue, is associated with poor neurological outcomes after TBI. A preponderance of experimental investigation over the past several decades focused on elucidating acute injury mechanisms, with the ultimate goal of developing neuroprotective drugs. While a thorough analysis of the shortcomings of all acute neuroprotection studies is beyond our scope herein (for review, see [7]), as just one example, an abundance of pre-

clinical literature supported a detrimental role for acute activation of NMDA-type glutamate receptors (NMDA-R) after TBI. Specifically, global NMDA-R antagonists (e.g. MK-801) potently reduced neuronal necrosis *in vitro* and in rodent models of TBI; however, clinical translational of NMDA-R antagonists were hampered by poor therapeutic windows and intolerable side effects [17]. The repeated lack of success at targeting acute neuroprotection necessitates mechanistically distinct approaches to improve outcomes after TBI. In particular, there is increased attention to defining secondary injury mechanisms, which may provide therapeutic targets that are temporally amenable to clinical intervention.

2.2 Diffuse Axonal Injury

TBI is frequently associated with coup-contrecoup injuries, which produce cerebral contusions and traumatic axonal injury. A coup injury occurs at the site of impact whereas a contrecoup injury occurs on the opposite side of impact [18]. In general, coup injuries are caused by acceleration trauma that occurs when a moving object impacts a stationary head. In contrast, contrecoup injuries are characteristic of deceleration trauma whereby the moving head strikes a stationary object [18]. In addition, cerebrospinal fluid (CSF), which is denser than brain tissue, rapidly moves towards the impact site, displacing the brain to the other side of the skull to produce contrecoup injury [19]. These injuries differentially affect grey matter and white matter and profoundly influence the care and treatment of TBI patients.

Grey matter consists of neuronal cell bodies, dendrites, glia, synapses, and capillaries. In addition, grey matter contains oligodendrocytes, a subtype of glial cell that myelinates up to sixty adjacent axonal segments [20]. Conversely, white matter is primarily comprised of interconnected myelinated axon tracts that allow rapid neurotransmission between different brain regions. In addition to producing focal damage, the differential movement of grey and white matter during acceleration-deceleration results in widespread, diffuse axonal tearing at grey-white matter junctions [21]. As diffuse axonal injury and loss of white matter integrity are strongly associated with chronic sensorimotor, cognitive, and psychiatric dysfunction in both pre-clinical and clinical TBI [22–28], therapies that limit white matter damage and enhance remyelination may profoundly improve long-term clinical outcomes.

White matter injury is undoubtedly initiated during acceleration-deceleration, yet the majority of axonal damage is ultimately not due to physical shearing at the time of TBI [29]. Rather, demyelination and delayed atrophy of white matter tracts develops for over one year post-TBI in rodents [30–33] and progresses for decades in TBI patients [34, 35]. This temporal pattern of delayed white matter injury may therefore provide an amendable therapeutic window; however, the mechanisms that occur between the initial traumatic event and the manifestation of white matter loss remain poorly defined.

3. DAMAGE ASSOCIATED MOLECULAR PATTERNS (DAMPs): MEDIATORS OF PROGRESSIVE WHITE MATTER INJURY?

A prospective study found that 47% of TBI patients exhibited large lesions within the corpus callosum, the largest white matter structure in the brain [36]. The corpus callosum is particularly susceptible to injury due to a rigid attachment to the falx cerebri, a fold of dura

mater that descends into the longitudinal fissure, and due to connections with the two independently mobile cerebral hemispheres [21]. A separate study determined that 96% of moderate-severe TBI patients showed atrophy of at least one brain region and 76.8% of TBI patients showed significant loss of corpus callosum volume [34]. Although the mechanisms remain poorly defined, white matter degradation, including a 25% reduction in corpus callosum thickness, was correlated with inflammatory activation at one-year after a single TBI [37]. Similarly, the degree of persistent thalamic inflammatory activation was closely related with thalamo-cortical white matter tract damage in moderate-severe TBI patients with diffuse axonal injury [38]. Thus, defining the regulatory mechanisms of immune activation may identify novel opportunities to affect TBI outcomes.

DAMPs are a diverse set of host molecules that are passively released after trauma or tissue injury. DAMPs, which include proteins such as high mobility group box protein 1 (HMGB1) and heat-shock proteins, extracellular matrix proteins such as hyaluronan fragments, and non-proteins such as adenosine 5′-triphosphoate (ATP), uric acid, heparin sulfate, and DNA [39–43], bind pattern recognition receptors (PRR) to initiate innate immune activation. With respect to brain injury, DAMPs induce pro-inflammatory activation in microglia, astrocytes, and neurons [44–46]. Although the predominance of studies linking DAMPs with the development of white matter injury utilized chronic neurological injury models, which may be mechanistically distinct from TBI, these studies may provide valuable insights to inform future investigations after neurotrauma. Indeed, a number of recent studies observed conserved mechanisms of immune-mediated neurovascular injury between chronic neurodegenerative diseases and TBI [47–50]. In the following subsections, we detail the emerging role for several DAMPs in the development of white matter loss, including references specific to TBI when available.

3.1 Purinergic Signaling

ATP is an essential small molecule that transports chemical energy to facilitate cellular metabolism and intracellular signaling. ATP also is released at low concentrations into the extracellular space as a mechanism of inter-cellular signaling under physiological conditions. In contrast, the passive, extracellular release of high concentrations of ATP initiates innate immune activation following traumatic or ischemic injuries [51]. ATP, a microglial chemoattractant that is rapidly released into the extracellular space from damaged neurons, is associated with poor outcomes after TBI [52, 53], yet the mechanistic and functional significance remains largely undefined. The biological actions of ATP are mediated by ubiquitously expressed purinergic receptors, which are grouped into G-protein coupled P2Y receptors, which bind ATP, ADP, UTP, UDP, and UDP-glucose, and ATP-gated cation permeable P2X receptors.

P2Y receptors are an eight-member receptor family in humans [54], although only P2Y2 and P2Y11 reportedly bind ATP [55]. The role of P2Y receptors is largely unstudied after TBI, though stimulation of ADP-binding P2Y1 receptors reduced edema, attenuated reactive astrogliosis, and enhanced neurological function after TBI [56, 57]. Furthermore, P2Y6 antagonism increased the permeability of the glial limitans and elevated parenchymal cell death following TBI [58]. GPR17, a P2Y-like receptor that mediates neurovascular

remodeling in the rodent brain, was strongly co-localized in microglia/macrophages and expressed by proliferated oligodendrocyte precursor cells of TBI patients, suggesting some P2Y family members may represent potential targets for white matter repair after neurotrauma [59, 60]; however, the functions of the ATP binding P2Y members, P2Y2 and P2Y11, remain completely undefined after TBI, providing several exciting areas for future exploration.

In contrast to P2Y, all seven P2X family members bind ATP [54, 61, 62]. Of the P2X members, only P2X7 has received attention after TBI [63–65]. We reported that global genetic or pharmacological blockade of P2X7 reduced neuroinflammation and improved neurobehavioral outcomes in a murine controlled cortical impact model of TBI [64]. This observation was subsequently extended to a weight drop TBI model, where P2X7 activation was associated with the development of post-traumatic cognitive deficits [63, 65]. Although ATP-P2X7 signaling has not been definitely implicated in white matter loss after TBI, ATP mediates reactive gliosis after axonal degeneration via a P2X mediated mechanism [66]. Moreover, ATP signaling directly induced oligodendrocyte death and ischemic white matter damage via activation of P2X7 in a rodent model of multiple sclerosis [67, 68]. Consistent with these reports, P2X7 inhibition reduced anatomic damage, reduced neuronal loss, attenuated local inflammatory responses, and improved outcomes after weight drop induced thoracic spinal cord injury in rats [69, 70]. Another report observed a decrease in P2X7 expression in cultured oligodendrocyte precursor cells after two hours of oxygen-glucose deprivation or in the cerebral cortex, subcortical white matter, and hippocampus after neonatal hypoxia-ischemia, indicative of an endogenous protective mechanism to restrict white matter damage [71]. Similarly, P2X7 inhibition prevented ischemic oligodendrocyte injury and protected myelin after ischemic stroke [72]. Thus, targeted inhibition of P2X family members, including P2X7, may limit white matter injury and improve TBI outcomes.

3.2 Toll-like receptor signaling

Toll-like receptors (TLR), a thirteen-member, evolutionarily-conserved family of single, membrane spanning receptors, initiate innate immune responses after activation by pathogen-associated molecular patterns (PAMPs) or by DAMPs. We reported that acute neuronal release of HMGB1 increased neurovascular injury after experimental TBI via a TLR4-dependent mechanism [73]. We and others also determined that acutely increased plasma or cerebrospinal fluid levels of HMGB1 independently predicted one-year mortality and unfavorable outcomes in severe TBI patients [73–76]. While these data implicate a detrimental role for early HMGB1- TLR4 signaling after TBI, release of HMGB1 from reactive astrocytes, beginning at two weeks after experimental stroke increased the accumulation of endothelial progenitor cells and enhanced peri-infarct angiogenesis within injured white matter via a mechanism that involves activation of receptor for advanced glycation endproducts (RAGE) [77, 78]. Thus, the temporal pattern of HMGB1 release and/or the molecular target of action may determine whether beneficial or detrimental outcomes occur.

Causative studies linking TLR with white matter injury are lacking, yet TLR2, TLR4, HSP70, and MyD88 were localized in macrophages/microglia in lesioned regions and in

subcortical white matter after experimental TBI [73, 79]. TLR2, TLR4, and HMGB1 also were increased in reactive glia within spinal cords of patients with amyotrophic lateral sclerosis (ALS) spinal cords [80], a neurodegenerative disorder characterized by motor neuron loss and extensive white matter injury. Although detailed studies remain to be performed after TBI, intravenous injection of the exogenous TLR4 ligand, endotoxin, induced focal periventricular white matter injury, inflammation, and release of S100β (see section 3.3.1), which served as an early biomarker of white matter injury in preterm fetal sheep [81, 82]. In addition, improvements in axonal integrity and reduced oligodendrocyte injury following ischemic preconditioning were eliminated in TLR4$^{-/-}$ mice [83]. Moreover, mice with a global genetic knockout of MyD88, an adapter molecule required for TLR4 signaling, reduced white matter loss in a neonatal hypoxic-ischemic model of brain injury [84]. In agreement with these reports, brain expression of myelination-associated proteins was attenuated in global TLR4$^{-/-}$ mice, as compared to wild-type mice, following chronic ethanol intake [85].

The aforementioned studies documented a detrimental role for TLR in white matter injury, yet a number of contrasting reports implicate TLR in white matter sparing and/or repair. TLR1, TLR2, TLR4, and TLR5 were increased after spinal cord injury, an injury characterized by acute oligodendrocyte loss with the subsequent proliferation of oligodendrocyte progenitor cell to repair damaged tissue. Interestingly, TLR4 mutant mice exhibited sustained locomotor deficits, increased demyelination, astrogliosis, and macrophage activation after SCI [86]. TLR4 activation similarly supported oligodendrocyte lineage cell sparing, long-term oligodendrocyte and oligodendrocyte progenitor replacement, and chronic functional recovery after contusive spinal cord injury [87]. Thus, TLR4 may exhibit protective effects on white matter under certain conditions. In addition to potentially protective effects of TLR4, activation of TLR2 also was associated with reduced degeneration of central myelinated fibers, whereas global TLR2$^{-/-}$ mice exhibited greater axonal injury after experimental spinal cord injury [88]. Taken together, modulation of TLRs may mediate both context-dependent demyelination and endogenous white matter repair. As such, considerable effort must be directed toward identifying endogenous TLR ligands, the temporal pattern of TLR expression/activity, and the cell type(s) mediating the divergent effects of TLR after injury.

3.3 S100 proteins

S100 proteins are a 21-member family of low molecular weight (9–13 kDa), helix E-loop-helix F (EF)-hand calcium-binding proteins [89]. Despite significant sequence and structural homology, S100 family members are implicated in a variety of diverse physiological functions, including the regulation of cellular contraction, cell motility, cellular growth and differentiation, transcription regulation, membrane organization, angiogenesis, and anti-oxidant function [90]. A number of S100 proteins, including S100β, S100A4, S100A8, S100A9, S100A12, and S100A13, are secreted in a tissue- and cell-type specific manner and function as cytokines. Although the extracellular receptors responsible for mediating the biological activity of S100 proteins remain incompletely resolved, S100β [91–93], S100A1 [94], S100A4 [95, 96], S100A5 [95], S100A6 [97], S100A7 [98], S100A8/A9 [99, 100], S100A11 [101, 102], S100A12 [92, 103], S100A13 [104], and S100P [105] reportedly

interact with RAGE. In addition, TLR4 serves as a receptor for S100A8/A9 [106], consistent with a role for S100 family members as DAMPs. The following sub-sections detail the established roles for several prominent S100 proteins after TBI and highlight fertile areas for future exploration.

3.3.1 S100β—S100β is highly expressed in the human brain, including prominent expression in astrocytes and in many neural cell types [107]. The physiological release of S100β exerts neurotrophic effects in the brain [94] and intense S100β expression also is observed within white matter tracts, including the corpus callosum [108]. CSF levels of S100β correlated with white matter injury after pneumococcal meningitis [109] and endotoxin-induced periventricular white matter injury in preterm fetal sheep was associated with higher S100β levels [81]. Reduced tissue expression of S100β was observed in the corpus callosum of schizophrenia patients [110] whereas increased serum levels of S100β directly correlated with white matter injury in schizophrenic patients [111] and in asphyxiated preterm babies [112]. In line with these findings, acutely increased serum levels of S100β were associated with patient mortality and poor acute and chronic outcomes after severe TBI [113–119] and were predictive of cognitive function at 4 months after pediatric mild TBI [120]. Increased S100β and S100β auto-antibody serum levels were also observed in football players who had experienced repeated sub-concussive events and correlated with white matter changes and cognitive decline [121]. As extracranial sources of S100β do not affect serum levels in humans [122], reduced tissue expression likely reflects increased extracellular release due to pathological conditions [111]. Functionally, S100β inhibition reduced neurodegeneration [123] and $S100\beta^{-/-}$ mice or antibody-mediated neutralization of S100β attenuated microglial reactivity and improved memory function after experimental TBI [124]. Thus, S100β may represent a predictive biomarker of outcomes and target for therapeutic development after TBI [125].

3.3.2 S100A4—In addition to S100β, prolonged upregulation of S100A4 was observed in white matter astrocytes in response to degeneration of myelinated axons after peripheral nerve or dorsal root injury [126]. Similarly, expression of S100A4 in astrocytes within the spinal cord or brain white matter was associated with white matter degeneration [127]. Moreover, extracellular application of S100A4 increased the motility of cultured astrocytes, suggesting a role in the formation of a glial scar [128, 129]. Although the functional importance is unexplored after acute neurovascular injury, S100A4 promotes tumor angiogenesis [130] and delayed S100A4 expression at three months post-TBI was linked with improved outcomes [131]. Thus, S100A4 may exert temporal- and/or cell-dependent effects to differentially regulate tissue recovery and injury.

3.3.3 S100A6—S100A6, which is highly expressed in the CNS, interacts with S100β in human astrocytoma and melanoma cells [132, 133]. Whereas the biological actions of S100A6 in the brain remain largely undefined, expression of S100A6 is increased within astrocytes in response to glutamate excitotoxicity within the axotomized hypoglossal nucleus in mice [134]. Notably, reduced S100A6 expression in the hippocampus was associated with subsequent cognitive decline after lateral head acceleration-induced TBI whereas a delayed elevation of S100A6 was associated with cognitive recovery [135]. Thus,

expression of either S100A4 or S100A6 may facilitate long-term neurological recovery after TBI.

3.4 Hyaluronic acid

Hyaluronic acid (HA), a non-sulfated glycosaminoglycan, is widely expressed within the nervous system, skin, cartilage, and eye. In addition to serving as a key component of the extracellular matrix, HA also influences tissue hemodynamics and cellular motility via activation of several cell surface receptors, including CD44 and Receptor for Hyaluronan Mediated Motility (RHAMM). Following injury, the extracellular release of HA provides a substrate for hyaluronidases, a seven-member family of enzymes that degrade HA into oligosaccharides and low molecular weight hyaluronan. HA degradation products exhibit pro-angiogenic properties [136, 137], although HA fragments also generate pro-inflammatory responses by activating TLR2 and/or TLR4 on macrophages and dendritic cells [138, 139]. Additionally, HA promotes the recruitment of inflammatory cells into damaged tissue [140].

Hypoxia induced HA production and increased the activity of hyaluronidases, a class of enzymes required for HA degradation [141]. In line with these findings, gene expression for hyaluronan synthases (HAS1) and HAS2, which catalyze the production and extracellular release of hyaluronan, was increased in the ipsilateral brain at 1–3 days post-TBI [142]. Hyaluronidase 1 (HYAL1) also was increased in the contralateral hemisphere at 1–3 days post-TBI [142] whereas expression of the HA receptor, CD44, was dramatically increased around the contusion for up to one week post-TBI [142]. Moreover, a recent genome wide sequencing study from perilesional cortex, thalamus, and hippocampus at three months post-TBI separately revealed a similar upregulation of CD44 after TBI [131], suggesting a dynamic regulation and role for HA metabolism after TBI; however, the precise functions and therapeutic potential of HA remains poorly defined after CNS injury.

Diffusion tensor imaging revealed that defined prefrontal cortical white matter lesions are associated with HA-rich regions in older individuals [143]. Similarly, white matter loss correlated with elevated HA levels following a single episode of hypoxia-ischemia injury in a preterm fetal sheep model of *in utero* hypoxemia [144]. Consistent with these studies, HA decreased the density of myelin basic protein expressing oligodendrocytes in organotypic forebrain slices from postnatal rat pups [145] and blocked oligodendrocyte lineage progression via a TLR2-dependent mechanism in chronic multiple sclerosis lesions [146, 147]. Notably, hyaluronidase treatment reduced both CD44 and TLR4 expression, attenuated leukocyte infiltration and pro-inflammatory cytokine levels, while simultaneously enhancing oligodendrocyte progenitor cell maturation, increasing myelination, and promoting neurological recovery in a rabbit model of intraventricular hemorrhage [148]. Thus, recombinant human hyaluronidase may provide a novel, efficacious therapy to limit white matter damage after TBI.

4. IS MICROGLIAL ACTIVATION THE CELLULAR LINK BETWEEN DAMP RELEASE AND WHITE MATTER INJURY?

Defining a deleterious role for DAMPs is imperative to validate clinically relevant, prognostic biomarkers and to provide a mechanistic understanding of progressive neurodegeneration after TBI; however, DAMPs are passively released from injured neurons immediately after necrotic injury. As such, strategies that directly block DAMP release likely possess low translational value due to a narrow therapeutic window, as observed with other acute neuroprotectants. In contrast, defining the molecular and cellular mechanisms, downstream from DAMP release, may provide more feasible targets for medical intervention.

Microglia, the resident macrophages of the CNS, exist in a resting state within the healthy brain. Microglia are rapidly activated following CNS injury, chronically persist within the human brain for nearly two decades after a single TBI, and as such, are regarded as a biomarker of injury after TBI [37, 149, 150], but it is unclear whether these changes reflect a causative factor in neurodegeneration or an adaptive response to progressive injury. Interestingly, microglia exhibit morphological and phenotypic changes to generate diverse functions in response to microenvironmental cues [151]. For example, activated microglia phagocytose cellular debris, produce neurotrophic factors, and release anti-inflammatory cytokines, including TGF-β and IL-10, to aid in tissue recovery [152], yet microglia also release pro-inflammatory mediators to disrupt the blood-brain barrier, to recruit peripheral leukocytes into the injured CNS, and to evoke rapid cell death in adjacent oligodendrocytes [153–155]. Moreover, dysregulated microglial activation produces chronic neuroinflammation, including the persistent release of pro-inflammatory cytokines and reactive oxygen species [156], which contribute toward evolving neurodegeneration [157]. Therefore, defining the mechanisms of DAMP-induced microglial activation may identify new opportunities to enhance neurological recovery and/or to attenuate neurodegeneration.

4.1 Microglial TLR Signaling

HMGB1 is associated with deleterious outcomes in a number of injury models, including TBI (see section 3.2). HMGB1 stimulated leukocyte chemotaxis and activation *ex vivo* [158–160] and induced microglial activation, increased neuroinflammation, and exacerbated neurocognitive deficits, at least in part, via a TLR-dependent mechanism in several non-traumatic injury models [161–163]. The passive release of HMGB1 from NMDA-injured neurons similarly increased pro-inflammatory activation in primary human and murine microglia via a TLR4-dependent mechanism [73, 164]. In addition, neuronal release of HMGB1 in and around the contusion was associated with poor outcomes after experimental TBI, at least in part, via activation of TLR4 on microglia/macrophages [73]. Functionally, anti-HMGB1 antibody therapy or glycyrrhizin, a HMGB1 release inhibitor, reduced inflammatory activation and lessened blood-brain barrier opening after lateral fluid percussion in rats [165, 166]. Similarly, BoxA mediated neutralization of HMGB1 inhibited aging-induced potentiation of microglial pro-inflammatory priming [167]. Thus, microglia are a critical cellular target of HMGB1 within the CNS after TBI.

The specific role of myeloid TLR4 activation remains unexplored after TBI; however, microglial inflammation is associated with axonal injury after experimental autoimmune encephalitis (EAE), a model of multiple sclerosis [168]. Moreover, HMGB1 and myeloid expression of TLR2/TLR4 were elevated within active inflammatory lesions in human and experimental multiple sclerosis [169]. While EAE represents a chronic neurological injury model, activation of microglial TLR4 mediated oligodendrocyte cell death *in vitro* and in the developing pericallosal white matter of immature rodents [170]. Consistent with these findings, suppression of myeloid TLR4 using CD200-Fc reduced phagocytosis of oligodendrocyte precursor cells by macrophages and enhanced endogenous recovery in a murine model of white matter ischemia [171]. Similarly, *fructus mume*, a traditional medicine in Asian countries, reduced white matter loss, attenuated both astrocytic and microglial activation and inhibited TLR4/MyD88 dependent signaling after permanent bilateral common carotid artery occlusion [172]. These findings suggest a conserved role microglial TLR4 activation in the initiation of white matter loss in both chronic and acute neurological injuries, a possibility that requires further exploration in experimental models of TBI.

The downstream molecular mediators of microglial activation by HMGB1 are poorly defined. Interestingly, HMGB1 binds to microglial macrophage antigen complex 1 (Mac1) to activate NADPH oxidase, a key enzyme involved in the generation of oxidative stress [173]. We and others observed a biphasic induction of NADPH oxidase expression and activity after TBI, with initial neuronal activity followed by a secondary peak in microglia up to four days later [15, 174, 175]. Inhibition of NADPH oxidase decreased neuronal cell death, attenuated pro-inflammatory microglial activation, reduced blood-brain barrier disruption, limited the accumulation of beta-amyloid, and improved neurocognitive outcomes in multiple experimental models of TBI [15, 174, 176–182]. Oligodendrocytes are extremely susceptible to oxidative damage due to a high metabolic rate [183, 184]. Although a functional association between microglial NADPH oxidase activity and white matter loss remains undetermined after TBI, NADPH oxidase is expressed in microglia and infiltrating macrophages in active multiple sclerosis lesions and NADPH oxidase activity is associated with demyelination, white matter damage, and tissue loss after EAE in mice [185, 186]. Importantly, activation of microglial TLR4 induced pre-oligodendrocyte injury via a NADPH oxidase mediated mechanism in a neonatal rat model of periventricular leukomalacia, which is characterized by white matter loss around the cerebral ventricles [187]. Thus, targeted inhibition of microglial NADPH oxidase may limit white matter loss and improve long-term outcomes downstream from HMGB1-TLR4 activation. This possibility requires further pre-clinical development and exploration.

4.2 Microglial purinergic signaling

ATP, a microglial chemoattractant released from damaged neurons, is associated with poor outcomes after TBI [52, 53]. Amongst the purinergic receptors, P2X1, P2X4, and P2X7 are expressed in amoeboid microglia during development and beginning at postnatal day 30, P2X7 positive microglia are observed throughout the forebrain [188, 189]. Although the functional importance of P2X receptors remain poorly defined after TBI, P2X4 was acutely localized in microglia/macrophages after experimental TBI in rats [190] whereas inhibition

of P2X4 reduced hypoxia-induced pro-inflammatory signaling in isolated microglial cells [189]. Although a mechanistic link between P2X7 and white matter injury has not been established to date, genetic or pharmacological P2X7 inhibition reduced the expression and release of the pro-inflammatory cytokine, interleukin-1β (IL-1β) and improved outcomes after TBI [63–65]. The production of IL-1β by amoeboid microglia increased oligodendrocyte injury in the periventricular white matter of rats following neonatal hypoxia [191] and perinatal IL-1β exposure induced ventricular enlargement, increased the loss of mature oligodendrocytes, and produced white matter injury in rats [192]. Neutralization of ATP, an important ligand for P2X7, during the acute injury phase reduced neurological injury after EAE, which is characterized by widespread white matter loss [193]. Consistent with these reports, administration of the selective microglial inhibitor, minocycline, attenuated microglial activation, decreased IL-1β production, protected developing oligodendrocytes, and attenuated white matter injury in neonatal rat brains [194, 195]. Similarly, inhibition of CX3CR1, a receptor involved in microglial chemotaxis, decreased microglial activation, reduced IL-1β production, attenuated white matter injury, and improved neurocognitive function in a pre-clinical model of vascular cognitive impairment [196]. While the aforementioned findings suggest a detrimental role for microglia after TBI, minocycline failed to attenuate traumatic axonal injury, tissue atrophy, neurodegeneration, or spatial learning deficits in a pediatric head trauma model [197]. Thus, additional experimentation is required to ascertain whether the effects of microglial activation are model dependent, time dependent, and/or age specific after TBI.

4.3 Macrophage infiltration: a detrimental consequence of microglia activation after TBI?

The CNS maintains an immunoprivileged status, yet a robust and sequential set of immune responses develops in the hours and days after TBI [198, 199]. In particular, activation of innate immunity, an evolutionarily conserved system of immediate, non-specific host protection, temporally correlates with widespread cellular necrosis after TBI [200]. Although the precise mechanisms remain to be determined, the rapid, local activation of microglia induces the release of powerful chemoattractants that recruit professional phagocytes, such as monocyte-derived macrophages, to sites of injury [201]. In particular, HMGB1-TLR4 signaling is implicated in leukocyte trafficking during trauma [202]. These coordinated changes facilitate the clearance of damaged cells and debris, but chronic immune activation exacerbates secondary injury and worsens outcomes [156, 203, 204]. Thus, early microglial activation after the release of DAMPs may initiate the recruitment of peripheral innate immune mediators after TBI; however, the beneficial and/or detrimental implications of macrophage trafficking into the CNS remain incompletely characterized after TBI.

Myelin is extensively degraded within the cerebrum after pre-clinical TBI [205, 206] and elevated myelin basic protein is observed in CSF of pediatric and adult TBI patients [207–210]. The presence of myelin debris after traumatic axonal injury inhibits axon regeneration and blocks the differentiation of oligodendrocyte progenitor cells, restricting intrinsic remyelination and impeding spontaneous recovery [211]. Early macrophage activation enhanced the phagocytosis of myelin debris after Wallerian degeneration [212, 213] and increased remyelination after spinal cord injury [214], supporting a beneficial effect of acute

macrophage infiltration. Conversely, chronic accumulation of pro-inflammatory macrophages within both white and grey matter temporally preceded oligodendrocyte apoptosis, widespread myelin loss, and white matter injury for weeks after experimental TBI [215, 216]. Consistent with the latter deleterious functions, macrophages accumulated within the corpus callosum of >25% patients at 1 year post-TBI and correlated with white matter loss and neurological dysfunction for over 17 years post-TBI [37, 149]. In line with these findings, TLR4 activation accelerated myelin phagocytosis after sciatic nerve lesion [217–219] and activation of myeloid TLR4 mediated oligodendrocyte injury and exacerbated white matter injury in immature rodents [170]. Thus, DAMPs may play a dual role both in myelin clearance and in mediating white matter loss.

In addition to the temporal changes, the activation status of macrophages may contribute toward white matter injury after TBI. Upon activation, macrophages polarize into distinct phenotypes based on the local microenvironment to generate context-dependent functions. Toward this end, “classically activated” (M1) macrophages exhibit a pro-inflammatory phenotype whereas “alternatively activated” (M2) macrophages release anti-inflammatory mediators to dampen immune responses [220, 221]. Consistent with a role for TLR4 in mediating M1 macrophage polarization [222] and in reprogramming M2 macrophages toward a M1 phenotype [223, 224], we reported that both $TLR4^{-/-}$ mice and C3H/HeJ mice, which contain a spontaneous inactivating point mutation in the TLR4 signaling domain, exhibited a reduction in M1 polarization over the first 72h after experimental TBI [225]. Of note, a progressive increase in the ratio of M1:M2 macrophages temporally correlated with evolving neurological injury, including white matter loss and reduced brain volume, after TBI [37, 187, 225, 226]. In line with the aforementioned studies, M1 macrophages accumulated within peri-contusional white matter, within grey matter, and within the contralateral cortex by d3 after TBI, preceding oligodendrocyte apoptosis and widespread myelin loss (hallmarks of white matter injury) over the next several weeks [215]. In contrast, M2 macrophages increased the accumulation of oligodendrocyte progenitor cells and promoted white matter recovery after TBI [215]. Consistent with these findings, conditioned media from M1 macrophages increased oligodendrocyte cell death after oxygen-glucose deprivation whereas conditioned media from alternatively activated (M2) macrophages was protective [187].

5. TRANSLATIONAL IMPLICATIONS

5.1 Model Selection

The selection of an appropriate pre-clinical animal model is essential for target validation and for the development and translation of any therapy. Given the convenience, low cost, and widespread availability of advanced transgenic animals, the majority of TBI research is performed in rodent models of controlled cortical impact, lateral fluid percussion, or weight drop-induced injury. Although each model exhibits distinct strengths and weaknesses [227], no single model fully replicates the complex and heterogeneous pathophysiological of human TBI. In addition, the rodent brain is lissencephalic, is dramatically smaller than the human brain, and is composed of ~10% white matter. Thus, despite the mechanistic benefits of using rodents to identify and screen potential therapeutic targets, such as DAMP

associated signaling pathways, lower species remain sub-optimal for the study of progressive white matter loss after TBI. Despite the higher cost and experimental complexities, large animals, such as swine, are gyrencephalic, exhibit a similar ratio of white to grey matter (60:40) to humans, and as such, may provide a more suitable model system to mimic human TBI [228, 229]. In line with possibility, a porcine model of controlled cortical impact was reproducible and clinically relevant with respect to multi-parametric neuromonitoring and histological outcomes [230, 231]. With the advent of improved genetic tools, such as CRISPR/Cas9 technology [232–235], future work will combine the genetic and mechanistic benefits of rodents with the anatomical and physiological advantages of a porcine TBI model.

5.2 Therapeutic development

Future studies will undoubtedly utilize Cre-loxP and targeted gene-silencing techniques establish whether cell-type specific deletion of DAMP receptors improves TBI outcomes. These approaches will identify the precise cellular and molecular mechanisms whereby DAMPs, which are immediately and locally released at the site of impact, contribute to delayed white matter injury spatially distant from the initial TBI; however, these studies possess little translational value beyond target validation. DAMPs are acutely and passively released from damaged cells, including necrotic neurons, immediately after brain injury [73, 236–238]. Thus, despite preclinical reports by our laboratory and others showing either direct HMGB1 neutralization or inhibition of PRR could improve acute TBI outcomes in rodents if administered within the first hours after injury [73, 165, 166, 239–243], a narrow therapeutic window makes successful clinical translation into TBI patient populations seem unlikely. Thus, elucidation of the downstream mechanisms linking DAMP release with poor outcomes is imperative for the development of efficacious approaches with a realistic window for intervention.

5.2.1 Do DAMP-activated macrophages generate adaptive immune responses after TBI?—DAMPs induce pro-inflammatory M1 polarization as a part of the innate immune response after injury. While broad operational definitions for M1/M2 polarization indicate the general inflammatory status after injury, in reality, macrophages polarize along a dynamic continuum rather than rigid, binary polarization phenotypes [244]. Thus, defining the functional implications of DAMP-induced myeloid cell activation may identify novel approaches to improve long-term outcomes after TBI.

Activated macrophages, a component of the mononuclear phagocyte system, exhibit antigen-presenting capability in draining lymph nodes during a primary immune response via a MHC class II-dependent process. The CNS was long believed to lack a classical lymphatic system, yet specialized meningeal lymphatic vessels were recently identified as a conduit for the bi-directional movement of macromolecules and immune cells between the brain and the deep cervical lymph nodes [245, 246]. Indeed, activation of T-lymphocytes occurs within deep cervical lymph nodes, rather than at the site of CNS injury [247].

DAMP-mediated activation of TLR4 increased MHC class II expression [248] and enhanced MHC Class II dependent antigen presentation [249]. Increased expression of myeloid MHC

Class II antigens was observed after experimental or clinical TBI [250–252]. Interestingly, HLA-DR, a MHC Class II antigen expressed on macrophages, bound myelin basic protein to initiate adaptive immune responses [253, 254]. As auto-antibodies against myelin basic protein induce demyelination after multiple sclerosis [255], myelin-loaded macrophages may similarly initiate progressive white matter injury after TBI. Coupled with the finding that pharmacological inhibition of MHC Class II-dependent antigen processing reduced neurodegeneration after TBI [256], activated macrophages may link acute TBI with deleterious, long-term adaptive immune responses.

5.2.2 T cell polarization is a consequence of macrophage activation after TBI

—DAMP-mediated activation of myeloid cells may, in turn, generate adaptive immune responses to mediate chronic white matter injury. Macrophage activation temporally preceded leukocytosis, brain T-lymphocyte infiltration, parenchymal inflammation, and clinical deterioration after TBI [250, 257, 258]. T-lymphocytes, mediators of adaptive immunity, are comprised of functionally diverse subsets that exert opposing effects. In particular, helper T-cells (T_H) cells augment immune responses after antigen recognition by stimulating antibody production and by releasing cytokines to potentiate activation of cytotoxic T-cells and macrophages. Although T-lymphocytes do not routinely cross the blood-brain barrier [259, 260], CNS accumulation of infiltrating macrophages and T_H cells was associated with neurodegeneration after experimental TBI and in resected brain tissue from TBI patients [256, 257, 261]. Therefore, elucidating the mechanisms of T-lymphocyte activation may provide novel opportunities for therapeutic intervention, downstream of macrophage activation.

Polarized macrophages release phenotype-specific cytokines to differentiate naïve T_H cells into T_H subtypes, such as T_H1, T_H2, and T_H17 [262], to provide long-lasting, antigen-specific immunity [249, 263–267]. We showed that monocytes isolated from the CNS after TBI stimulated T-cell proliferation and increased T_H1 and T_H17 polarization [225]. Moreover, activation of myeloid TLR4 simultaneously increased T_H1/T_H17 polarization and reduced T_{REG} production in both blood and brain for several weeks after TBI in mice [225]. While the efficacy of T_H1/T_H17 inhibition remains unexplored after TBI, T_H17 cells drove chronic microglial polarization after EAE and co-culture studies showed myelin-specific T-lymphocytes that secreted IL-17 potently activated inflammatory cytokine expression in microglia [268, 269]. Furthermore, attenuation of brain T_H17 influx reduced white matter injury, limited brain atrophy, and prevented chronic functional deficits after neonatal hypoxia-ischemic injury [270]. These findings are in line with reports showing myelin-reactive T_H17 cells induced demyelination and impaired endogenous remyelination in pre-clinical white matter injury models and in multiple sclerosis patients [271–276]. In addition, curcumin, a curry spice that we found to improve TBI outcomes [243], attenuated expression of RORγT, a transcription factor involved in T_H17 differentiation, decreased myelin basic protein-autoreactive T cells, and blocked the production of IL-17, the signature cytokine released by T_H17 cells, after EAE [277]. Curcumin also attenuated T_H17 production in ovalbumin-sensitized mice and in acute graft vs. host disease [278, 279]. As such, treatment strategies targeting T_H17 production and/or activity may provide a potential option to improve long-term outcomes.

Functionally, the M1 macrophage derived, cytokines, IL-6 and IL-23, are essential for T_H17 polarization [280–285]. We reported HMGB1 increased IL-6 production in primary human macrophages and after experimental TBI via a TLR4-dependent mechanism [73]. Similarly, the TLR4 agonist, LPS, induced IL-23 expression in peritoneal macrophages via TLR4 activation [286]. Finally, HMGB1-TLR4 signaling also increased myeloid IL-23 expression and subsequent T_H17 production/mobilization after myocardial ischemia-reperfusion [287], periodontitis [288], or neonatal hypoxia-ischemia [270], although this issues remains to be fully studied after TBI. Given the temporal delay between TBI and adaptive immune responses, blocking T_H polarization, secondary to DAMP-induced macrophage activation, may provide a feasible approach to limit long-term progressive injury. In addition, the presence of T_H1/T_H17 cells in blood may provide a prospective biomarker for patients that are susceptible for progressive white matter loss. We are actively exploring these interesting and clinically significant questions.

6. CONCLUSIONS

White matter injury is an important component of long-term neurological injury after TBI; however, the limited understanding of progressive white matter damage contributes to a lack of viable therapeutic options. The immune system is increasingly regarded as a critical, yet poorly understood, effector of neurological outcomes after TBI. Thus, defining the protective and detrimental roles of the immune system may improve the diagnosis, management, and treatment of TBI patients. Toward this end, the acute release of DAMPs may promote poor long-term neurological outcomes after TBI, yet potential delays in diagnosis and treatment coupled with narrow therapeutic windows may limit the ultimate clinical utility of DAMP/PRR inhibition. These translational barriers emphasize the need for innovative strategies to attenuate the detrimental long-term actions of acute DAMP release. For example, limiting the myeloid-lymphoid immune transition may provide an unexplored therapeutic avenue to reduce progressive white matter loss and to improve long-term clinical outcomes. Moreover, detection of myelin-directed T_H1/T_H17 cells may provide a blood biomarker to prospectively diagnose patients at risk of developing chronic neurodegeneration. Despite the inevitable challenges, improved definition of the relationship between immune activation and white matter injury will advance the clinical management and recovery of TBI patients.

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HIGHLIGHTS

- White matter injury induces long-term neurological disability after TBI
- Acute release of DAMPs activates myeloid cells after TBI
- DAMP-induced myeloid cell activation initiates adaptive immunity after TBI
- We provide a mechanistic framework for immune targeting to improve TBI outcomes

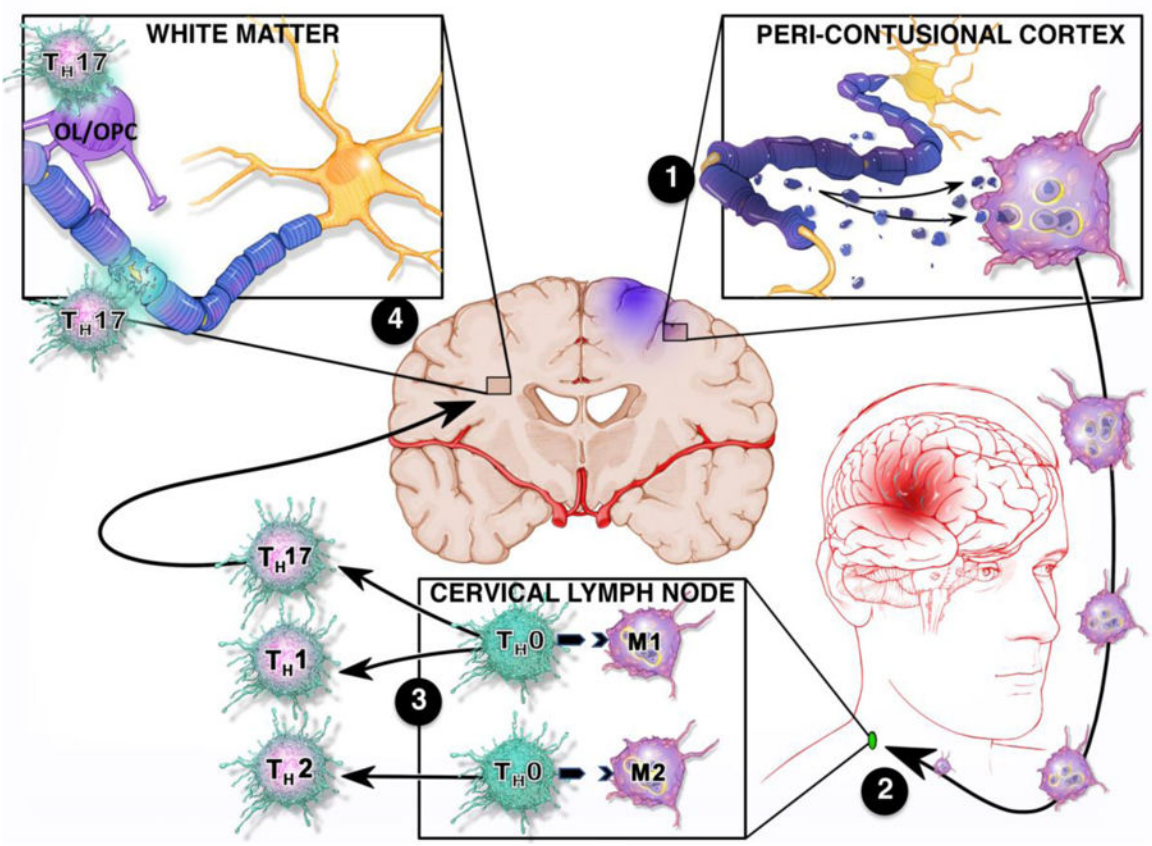

FIGURE 1. Proposed mechanism of white matter injury after TBI

(1) Following TBI, the release of DAMPs from necrotic neurons activate and polarize microglia and infiltrating macrophages toward a pro-inflammatory M1 phenotype. Activated macrophages phagocytose dead/dying cells and myelin debris to initiate the process of neurological recovery. (2) Antigen loaded, M1 macrophages migrate to deep cervical lymph nodes to present antigen (e.g. myelin) to naïve T cells (T_H0) cells. (3) M1 macrophages, which predominate after TBI, drive pro-inflammatory T_H1/T_H17 polarization to provide long-lasting, antigen-specific immunity by direct MHC Class II dependent antigen presentation and/or via the release of phenotype specific cytokines. (4) The subsequent migration of T_H1/T_H17 cells into the CNS leads to maladaptive immune responses against white matter (e.g. neurons, oligodendrocytes (OL), oligodendrocyte progenitor cells (OPC)). White matter loss results in further tissue destruction, secondary DAMP release, and chronic perpetuation of a pro-inflammatory feedback loop that culminates in neurological dysfunction.