Chinese Journal of Traumatology 21 (2018) 125–136

Contents lists available at ScienceDirect

Chinese Journal of Traumatology

journal homepage: http://www.elsevier.com/locate/CJTEE

Review Article

Potential immunotherapies for traumatic brain and spinal cord injury

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ARTICLE INFO

Article history:
Received 4 February 2018
Accepted 8 February 2018
Available online 18 April 2018

Keywords:
Brain injury
Spinal cord injury
Innate and adaptive immunity
Inflammatory response
Immunotherapy
Secondary injury

ABSTRACT

Traumatic injury of the central nervous system (CNS) including brain and spinal cord remains a leading cause of morbidity and disability in the world. Delineating the mechanisms underlying the secondary and persistent injury versus the primary and transient injury has been drawing extensive attention for study during the past few decades. The sterile neuroinflammation during the secondary phase of injury has been frequently identified substrate underlying CNS injury, but as of now, no conclusive studies have determined whether this is a beneficial or detrimental role in the context of repair. Recent pioneering studies have demonstrated the key roles for the innate and adaptive immune responses in regulating sterile neuroinflammation and CNS repair. Some promising immunotherapeutic strategies have been recently developed for the treatment of CNS injury. This review updates the recent progress on elucidating the roles of the innate and adaptive immune responses in the context of CNS injury, the development and characterization of potential immunotherapeutics, as well as outstanding questions in this field.

Introduction

Traumatic brain injury (TBI) remains a major cause for death and disability worldwide. In the United States alone, TBI contributes to the deaths of nearly 50,000 people each year, with more than 282,000 hospitalizations and 2.5 million emergency department visits in 2013.[1,2] In Europe, TBI caused about 82,000 deaths with 2.1 million hospitalizations in 2012.[3] In China, TBI caused 194,850 deaths (12.99/100,000 population).[4] These figures may underestimate the scope of the TBI epidemic because mild TBI often goes unreported. Those who survive a TBI can face temporary or permanent disabilities such as impaired cognitive function, movement, sensation (e.g., vision or hearing), or emotional functioning (e.g., personality changes, depression). These issues not only affect patients, but can have lasting effects on families and communities. In addition, TBI has linked to post-traumatic stress disorders, chronic traumatic encephalopathy, and chronic neuroinflammation.

Additionally, traumatic spinal cord injury (SCI) has emerged as a significant economic burden for society, with direct costs ranging from 500,000 to 2 million US dollars accrued over the life-time for one patient. Around the world, approximately 250,000–500,000 people suffer from SCI each year.[5] In the United States, around 17,000 new cases of SCI occur each year and 240,000–337,000 people live with SCI.[6] About 52% of SCI survivors are paraplegic, while 47% are considered quadriplegic. The average age at injury has increased from 29 years in the 1970's to 42 years in 2016.[7]

Both TBI and SCI affect individuals of all ages and genders. Both of these disorders cause significant morbidity and mortality, with initial mechanical primary injuries and persistent secondary injuries. The secondary injury contributes largely to the neurological impairment seen in patients. Several mechanisms underlying the secondary injury have been identified: excitotoxicity caused by impaired glutamate homeostasis,[8,9] free radicals/oxidative

Abbreviations: APC, antigen-presenting cells; ASC, apoptosis-associated speck-like protein containing a carboxy-terminal CARD; BBB, blood-brain barrier; CNS, central nervous system; CSF, cerebral spinal fluid; DAMP, danger-associated molecular patterns; ECM, extracellular matrix; HDAC, histone deacetylase; HMGB1, high-motility group box 1; Hsp, heat shock proteins; IL, interleukin; IVIG, intravenous immunoglobulin G; MHC, major histocompatibility complex; NFκB, nuclear factor κB; NLR, nucleotide-binding domain leucine-rich repeats; PAMP, pathogen-associated molecular patterns; RAGE, receptor for advanced glycation end products; SCI, spinal cord injury; TBI, traumatic brain injury; Th, T helper cells; TLR, Toll-like receptors.

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Peer review under responsibility of Daping Hospital and the Research Institute of Surgery of the Third Military Medical University.

https://doi.org/10.1016/j.cjtee.2018.02.002

stress/lipid peroxidation,[10,11] calcium overload,[12,13] autophagy,[14] and sterile neuroinflammation.[15] Recently, the sequential activation of resident and recruited immune cells has been extensively investigated for their participation in the secondary inflammatory/immune responses after CNS injury. Many treatments for TBI and SCI have been developed, including early neuroprotective therapies such as surgical decompression, methylprednisolone, and blood pressure augmentation, as well as recently developed neuroprotective interventions such as Riluzole, Minocycline, magnesium, therapeutic hypothermia, and cerebral spinal fluid (CSF) drainage.[16] Some promising clinical trials are also under way for several drug targets such as Minocycline, Cethrin™, anti-NOGO antibody, cell-based approaches, and bioengineered biomaterials.[17] In the past years, immunomodulatory strategies have been showing great potential for success. In this review, we will emphasize the importance of the immune response in the secondary injury and explore the future potential of immunotherapies for the treatment of both TBI and SCI.

The paradigm shifts of CNS immunity

The CNS has been long viewed as an immune-privileged organ due to its tolerance to antigen-induced immune responses. This mutated or slow innate immune response may result mainly from the presence of the blood–brain barrier (BBB), which relative impermeability is maintained by the tight junctions and basal lamina of brain endothelial cells, and the end feet processes of perivascular astrocytes. In addition, the lack of classical lymphatic drainage and antigen-presenting cells (APC) like dendritic cells within the brain parenchyma, as well as the low levels of major histocompatibility complex (MHC) class I and II molecules may contribute to the limited immune responses within the CNS. Therefore, the presence of any immune cells with the CNS parenchyma was traditionally perceived as a hallmark of pathology and the immune response plays a detrimental role after CNS injury. However, this paradigm has been changed over the last two decades.[18,19] Increasing sets of evidence demonstrate that the immune system keeps up a constant state of immunosurveillance, scouting for signals not only from external pathogens, but also from damaged tissue, particularly in the case of sterile injuries such as TBI, SCI, stroke, etc.[20] The immune system plays key role in tissue homeostasis under healthy (physiological) conditions in addition to the pathogenic aggravation of sterile inflammatory responses after CNS injury.[18]

It is known that the resident microglia and astrocytes within the CNS participate the innate immune responses. Under physiological conditions, there are millions of immune cells circulating in the CSF, and populating the meninges and the epithelium of the choroid plexus. These immune cells include T cells, B cells, monocyte/macrophages, dendritic cells, and neutrophils. The meningeal lymphatic vessels within the CNS have been discovered recently, and function by draining meningeal immune cells and macromolecules from the CSF into the deep cervical lymph nodes.[21–24] This is supported by the observation that CNS-derived antigens induce an immune response in the deep cervical lymph nodes.[25–27] Interestingly, this response is skewed towards B-cells for a humoral response, possibly to avoid a more detrimental inflammatory T-cell response. Dendritic cells from CSF have been found to migrate to B-cell follicles of the cervical lymph nodes.[28,29]

The paradigm changes for CNS immune-privilege provide a new understanding of CNS immunity (immunosurveillance and tolerance) under healthy/physiological conditions. Additionally, the preexisting immune system within the CNS may account for the predominant role of the readily-available immune response in initiating or mediating the secondary injury after CNS primary injury. Both resident immune cells (microglia, astrocytes) and infiltrating immune cells (T cells, B cells, monocytes, and macrophages) play beneficial and detrimental roles in CNS injury. Such duality in the roles of the innate/adaptive immune responses relies on the timing, types and interventions of the injury.[30] For neurodegenerative diseases such as Multiple Sclerosis or Alzheimer's disease, immunotherapies blocking immune/inflammatory responses has shown considerable efficacy.[31,32] However, the innate and adaptive immunity after TBI or SCI may help clear detrimental extracellular debris such as aggregated or misfolded proteins at certain time points after injury.[33–35]

Innate immune response after CNS injury

Activation of innate immune cells

The initial inflammatory response to CNS injury can be a mechanism for the innate immune response, and is characterized by the initial generation of danger-associated molecular patterns (DAMPs), the production of inflammatory cytokines/chemokines by the resident innate immune cells (microglia and astrocytes), and the subsequent recruitment of infiltrating innate immune cells (Fig. 1). These infiltrating innate immune cells include monocytes (which subsequently differentiate into macrophages), mast cells, granulocytes (basophils, eosinophils and neutrophils), dendritic cells and natural killer cells. Within minutes after CNS injury, alarmins such as interleukin (IL)-33, ATP, heat shock proteins (Hsps), and high-motility group box 1 (HMGB1) are promptly released from the damaged meninges, glial limitans, and parenchymal white matter.[36,37] IL-33 is highly expressed in CNS, particularly in oligodendrocytes and astrocytes,[38,39] and plays a crucial role in CNS injury by recruiting microglia/macrophages.[39,40] These immediate alarmins bind to the pathogen-associated molecular patterns (PAMPs) and DAMP sensors such as Toll-like receptors (TLRs) and purinergic receptors in the innate immune cells, inducing the subsequent activation of nuclear factor κB (NFκB) signaling and stimulation of inflammatory gene expression or cytokine release.[41–43] These inflammatory alarmins also induce complement activation and the recruitment of neutrophils, monocytes and T cells to the injury site.[15,39]

HMGB1 is a nuclear-localized DNA-binding transcription factor ubiquitously expressed. HMGB1 expression is increased after TBI and SCI.[36,44] It is released by damaged cells after CNS injury and also actively secreted by inflammatory macrophages.[45] It is a potent inflammatory stimulus via its receptors such as TLR4 and the receptor for advanced glycation end products (RAGE).[36] Both TLR4 and RAGE participate in the innate immune/inflammatory responses via NFκB activation.[46] HMGB1 promotes the development of macrophages with a neurotoxic phenotype both *in vitro* and *in vivo*.[36]

Monocytes are the major types of the initial infiltrating innate immune cells after CNS injury and contribute to the propagation of the sterile inflammation.[47,48] Monocytes are categorized as $CD115^{+}Ly6C^{hi}CD62^{+}CCR2^{hi}$ classical, $CD115^{+}Ly6C^{lo}CD62^{-}CCR2^{lo}$ non-classical and an intermediate subset that expresses a varying spectrum of these markers.[49,50] Classical monocytes infiltrate into the injured sites to generate tissue macrophages.[51] Non-classical monocytes, known as patrolling monocytes, survey vascular endothelium such as the BBB and only extravasate under pathological conditions.[52] The non-classical/patrolling monocytes express high levels of the CX3CR1 fractalkine receptor that allow their migration to CX3CRL1-expressing cells after TBI.[53] The roles of monocytes appear to be significant, as global monocyte depletion in CCR2 knockout mice is associated with significant improvements in brain edema, motor coordination, and working memory.[54,55]

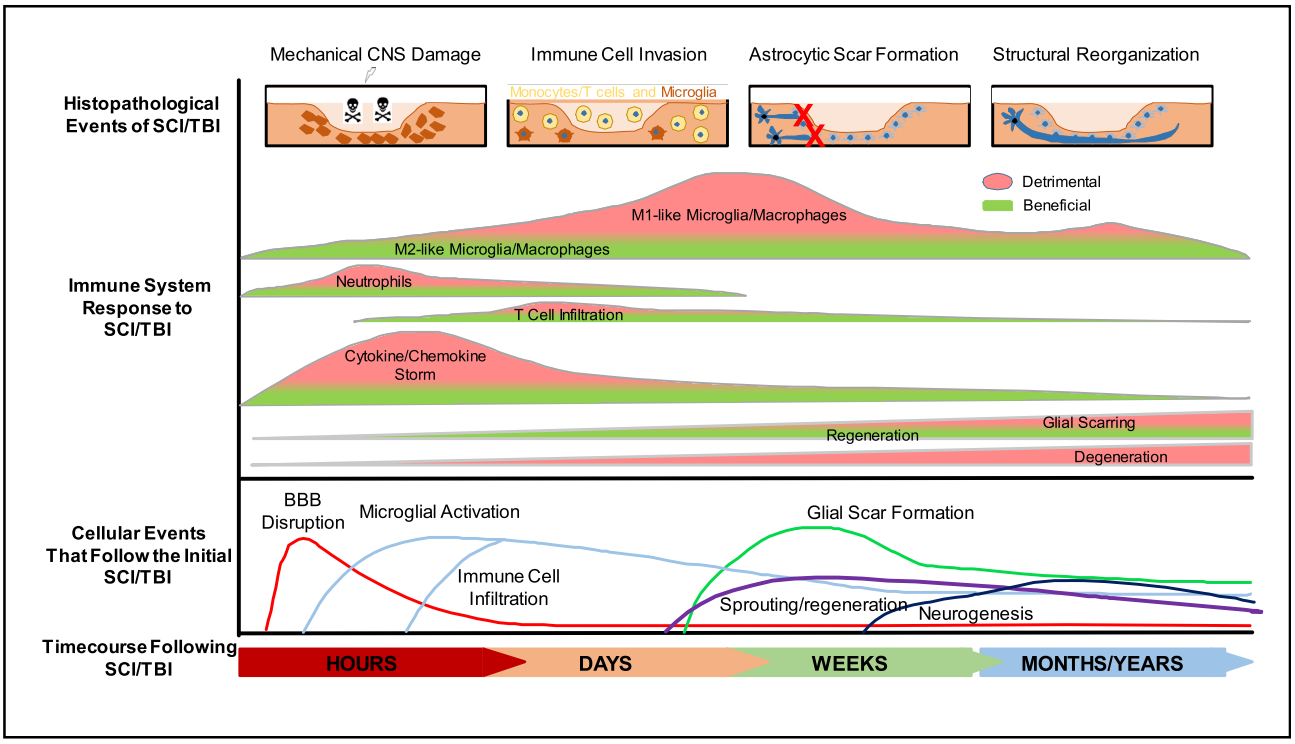

Fig. 1. Time course and dual roles of innate and adaptive immune responses after CNS injury. Within hours, primary mechanical damage of CNS may cause disruption of cell membrane, vasculature and BBB, leading to prompt release of alarmins and activation of resident immune cells, followed by secondary inflammatory/immune responses. Over the next days/weeks, continuous infiltration and subtype conversion of immune cells cause beneficial/detrimental effects on neural regeneration, and astrocytic activation induces glial scarring and regenerative failure. Limited neurogenesis and neural regeneration occur over months/years after CNS injury. Adapted from.[2,243]

Additionally, targeting $CCR2^{+}$ macrophages with CCX872, a novel Phase I CCR2 selective antagonist, significantly reduced TBI-induced inflammatory response and improved hippocampal-dependent neurocognitive function.[56] However, selective depletion of classical monocytes alone had no effect on neutrophil recruitment to the site of injury.[47] Selective deletion of patrolling monocytes in CX3CR1 knockout mice significantly reduces neutrophil infiltration after TBI[47] and SCI,[57] implying the important role of patrolling monocytes in mediating CNS injury. Therefore, targeting of CX3CR1 signaling may represent a selective immunotherapy for CNS injury. However, patrolling monocytes are redundent in the progression and recovery of stroke,[58] or exhibit neuroprotective function in sterile excitotoxicity model.[59]

The infiltrating neutrophils are highly migratory and possess high phagocytic ability to clean the damaged elements within the brain parenchyma after CNS injury.[60,61] Neutrophils also participate in BBB breakdown and subsequent brain edema formation.[62,63] The infiltrating dendritic cells can be activated by the damaged cells and present antigens to T cells, leading to adaptive immune response.[64,65]

Mast cells are myeloid cells, mainly participating in the pathogenesis of allergic reactions. In addition to the extensive presence within tissues exposed to the external environment, such as the skin, gut, and respiratory tract, mast cells have been observed in the CNS, particularly the leptomeninges[66] and perivascular space.[67,68] Mast cells respond to CNS injury by releasing inflammatory mediators including proteases and vasoactive amines such as GnRH, tryptase, and histamine. These inflammatory mediators induce microglia activation and neuroinflammation. The meningeal mast cells also damage the BBB and recruit neutrophils and activated T cells to the injury site. Therefore, inhibition of mast cells may prove to be a neuroprotective therapy for CNS injury.[69,70]

Key role of inflammasomes in the secondary injury of CNS

The inflammasome is a multiprotein intracellular complex serving as an innate immune responder to pathogenic microorganisms and sterile damaging/stress signals. It regulates the activation of caspases, particularly caspase-1, leading to the generation of highly pro-inflammatory cytokines IL-1β and IL-18. Inflammasome also induces an inflammasome-specific form of cell death named pyroptosis.[41,43] PAMPs or DAMPs are recognized by the pattern recognition receptors including TLRs, nucleotide-binding domain leucine-rich repeats (NLRs), C-type lectins and membrane-bound, retinoic acid-inducible gene-I-like receptors. These pattern recognition receptors are mainly expressed in innate immune cells such as microglia, and astrocytes. Activation of TLRs induces the priming of inflammasomes through NFκB signaling while NLRs stimulate the assembly of inflammasome in most cell types.[41–43] Different type of TLRs detects various DAMPs and PAMPs.[71] Thirteen TLRs have been identified, although TLR11, TLR12 and TLR13 have yet to be discovered in humans.[71] TLR3, TLR7 and TLR9 recognize cellular and microbial nucleic acids. TLR2 and TLR4 detect cellular Hsp60 and Hsp70. TLR5 detects bacterial flagella. NLRs can be activated by endogenous cellular products such as uric acid crystals and aggregated peptides. NLRs also detect cytosolic ion fluxes induced by ATP-stimulated activation of purinergic receptors.

Several inflammasome complexes are identified in CNS, among which, NLRP1 and NLRP3 are the most studied.[72–74] The inflammasome complexes exist in a pre-assembled state prior to their activation, allowing a rapid activation of the innate immune system after CNS injury.[75] Each inflammasome complex contains a cytosolic sensor (i.e. NLR), an adaptor protein (i.e. apoptosis-associated speck-like protein containing a carboxy-terminal CARD, ASC) and

an effector caspase.[76] The exact compositions of each inflammasome relies on environmental niche factors and injury types.[77] Activation of these inflammasomes produces the mature/active form of caspase-1 leading to the generation of proinflammatory cytokines IL-1β and IL-18, which contribute to the secondary inflammatory response after CNS injury.[78]

Dual roles of activated microglia/macrophages and astrocytes after CNS injury

Microglia play a key role in the innate immune response within CNS. Microglia are phenotypically dynamic in both morphology and function, ranging from resting ramified steady state (M0), to the activated non-phagocytic (M1) or a phagocytic (M2) polarized state.[79] M1 microglia act like APCs and are stimulated by IFN-γ, IL-6 and TNFα. The M2 microglia state has recently been further categorized into M2a, M2b and M2c states based on different stimulation, antigenic marker and function. The M2a state is stimulated by IL-4 and IL-13, and works to suppress inflammation.[80,81] The M2b state is stimulated by TLRs, while M2c state is stimulated by TGF-β, IL-10, and apoptotic cells.[82,83]

Microglia not only survey the CNS, but also exhibit fundamental roles in regulating neurogenesis,[84] neuronal polarization and synaptic remodeling/plasticity.[85] Microglia within the non-pathological CNS monitor their environmental niche by extending and retracting their motile processes. Microglia determine neuronal differentiation and maturation by releasing various growth factors. Microglia support the formation and maturation of synapses. Under pathological conditions, microglia are very reactive, undergoing rapid activation, proliferation, and structural changes. They are the first line of immune defense against invading pathogens and/or local damaging signals. They can sense various types of inflammatory mediators such as cytokines/chemokines, glycolipids, lipoproteins, peptides, nucleotides, misfolded protein aggregates, and other abnormally processed proteins. They also produce various types of pro- and anti-inflammatory cytokines/chemokines, growth factors, matrix molecules and others. These inflammatory mediators induce phenotypic changes in these microglia and mediate their possible detrimental or beneficial functions after CNS injury.[86–88]

Astrocytes not only provide trophic support for neurons, but also play integral roles in many processes such as synaptic pruning, neurotoxin removal, neurogenic stimulation, blood flow regulation, and potassium/sodium buffering. In response to TLR and NLR signals, astrocytes produce the majority of innate immune/inflammatory mediators, including cytokines such as IL-1β, IL-6, chemokines such as CCL2, CXCL1, CXCL10, and CXCL12 and several complement components.[89,90] Astrocytes can be activated by various pathological factors including pro-inflammatory cytokines such as IL-1β. Reactive microglia also activate astrocytes.[91,92] Astrocyte-specific inflammatory signaling plays a key role in the secondary injury after SCI and TBI.[93–95] NFκB signaling has been well known to participate the inflammatory response during the secondary CNS injury. It plays a dual role in the pathogenesis and functional recovery after CNS injury.[96] Astroglial NFκB inhibition in a transgenic mouse model significantly improved functional recovery, increased white matter preservation and axonal sparing after SCI[97,98] and ischemic brain injury.[99] This protective effect may result from the reduction of various inflammatory cytokines/chemokines such as CXCL10, CCL2, and TGF-β[97] and the promotion of oligodendrogenesis.[100] These reactive astrocytes also form a glial scar that produces axonal growth inhibitors and prevents axonal regeneration.[101] Chondroitin sulfate proteoglycans are the key component of astroglial scarring and are significantly down-regulated by the astroglial NFκB inhibition.[97] Therapeutic modulation of the chondroitin sulfate proteoglycans is an attractive approach to improve neuroregeneration and functional recovery after CNS injury.[102]

Adaptive immune response after CNS injury

The adaptive immune response occurs after CNS injury, most prominently within the deep cervical lymph nodes, the meningeal spaces (including the CSF), and the local injury site (Fig. 1). The T cell responses may be specific to CNS-restricted antigens. Recent studies showed that immune T cells enter CSF and meningeal spaces via meningeal blood vessels.[23] The mechanisms underlying the entry of the meningeal T cells into the parenchyma remain largely unknown. It is possible that meningeal T cells infiltrate the parenchyma through some chemokines.[103] Several evidences showed that T cells enter the meninges and the CSF through leptomeningeal and dura blood vessels or through the choroid plexus.[104,105]

Upon CNS injury, T cells undergo extravasation through a chemokine gradient and adhesion molecule upregulation on the luminal surface of the vascular endothelium.[103] The binding of very late antigen 4 (VLA4, also named Integrin α4β1) to vascular cell adhesion molecule 1 (VCAM1) is important for T cell extravasation and homing into the CNS.[106,107] Inhibition of this interaction by a neutralizing antibody against VLA4 attenuates T cell extravasation.[107–109]

T cells recognize antigens through their surface-bound T cell receptor, and are generally classified into $CD8^+$ cytotoxic T cells and $CD4^+$ helper T cells (Th). $CD8^+$ T cells detect antigens presented by MHC class I (MHC I) molecules while $CD4^+$ T cells recognize MHC II antigens primarily presented by APCs like dendritic cells, macrophages and B cells.[110] Upon activation by their specific peptides, $CD4^+$ T cells proliferate and, when exposed to certain secondary stimuli, differentiate to combat the specific threat.[111] Upon various stimulation, Th cells differentiate into several subtypes including Th1, Th2, Th9, Th17, T regulatory and T follicular helper cells. The subtypes are characterized largely by the lineage-specific cytokines.[112] For example, Th1 cells generate IL-2, and INFγ, Th2 cells produce IL-4, IL-5 and IL13, Th9 cells generate IL-9, IL-10 and IL-21, while Th17 cells produce IL-17 and IL-23. T follicular helper cells express CD40L and secrete IL-21 and IL-4.[113] Under physiological conditions, the lymphocytes (mainly T cells) patrol the border surrounding the CNS, such as meninges, CSF and choroid plexus, and regulate neurobehavioral function.[114] For example, genetic depletion of meningeal T cells or pharmacological trapping of T cells in the deep cervical lymph nodes impairs neurocognitive function in animal models.[115,116] However, the molecular mechanism underlying the patrolling role of immune cells remains largely unknown.

The adaptive immunity response also involves B cells, which express unique antigen-specific receptors via genome rearrangement and produce antibodies. Both TBI and SCI stimulated B cells to generate pathogenic antibodies, which subsequently contribute to the secondary tissue damage and neurological dysfunction after SCI.[117,118]

Immunotherapy at the innate immune response after CNS injury

The innate immune response plays a major role in the sterile inflammation and neuroregenerative failure after CNS injury. The general immunosuppression regimens using broad steroids such as methylprednisolone have been extensively employed to treat patients with SCI or TBI for decades. Unfortunately, these immunosuppression regimens remain unsuccessful because they suppress

both the pro- and anti-inflammatory activities of the innate immune response.[119,120] Recently, selective immunomodulatory approaches have been developed to ameliorate the pro-inflammatory M1-like response and promote the anti-inflammatory M2-like positive tissue remodeling. Macrophages/microglia play a key role in the innate immune response. Thus, immunomodulatory therapy targeting macrophages/microglia is becoming promising in treatment of CNS injury.

Minocycline targeting microglia after TBI and SCI

Minocycline is a clinically available tetracycline-class antibiotic that exhibits extensive neuroprotective effects at multiple stages after CNS injury.[121] Most mechanisms involve the capability of suppressing innate immune responses after CNS injury, including inhibiting microglia activation,[122–124] attenuating HMGB1 translocation,[122] suppressing caspase-1[125] and downregulating the release of pro-inflammatory mediators such as IL-1β, TNFα, and Cox2 after CNS injury.[121] Several preclinical animal studies presented highly promising therapeutic benefits of minocycline in promoting neuroregeneration and improving neurobehavioral outcomes after SCI[121,126,127] and TBI.[123,128] Additionally, Phase II Clinical trials showed positive results in improving motor score after SCI.[129] As a result, a Phase III clinical trial entitled 'Minocycline in Acute Spinal Cord Injury' has been started.[130]

Extracellular matrix (ECM) and exosomes at innate immune cells after CNS injury

The xenogeneic ECM bioscaffolds have been extensively employed to decrease scar formation and promote tissue repair.[131] The autologous microglia/macrophages can be pre-polarized with ECM or other immunomodulatory factors *ex vivo* to acquire an M2-like phenotype before transplantation back into the patients.[132–134] Additionally, cell therapies using autologous macrophages have been shown to improve TBI and SCI.[135] Due to potential cell-related side effects or injection difficulties for macrophage or stem cell injection, exosomes have been developed to replace the cell therapy because of their multifaceted benefits: low immunogenicity, high efficacy, efficient BBB permeability, active cellular communications, and microglial phagocytosis stimulation.[136–138] The exosomes deliver various types of RNA, proteins, cytokines, lipids and other signaling molecules. After TBI or SCI, the CSF harbors increased number of exosomes that contain cytoskeletal proteins, neurite-outgrowth related proteins, and synaptic proteins, ECM proteins, and complement protein C1q subcomponent subunit B.[139–141] By altering the encapsulated components via ECM-polarization or genetic engineering, exosomes can be selectively produced to modulate the beneficial immune response after CNS injury.[137,142,143] For example, exosomes loaded with ASC siRNA can cross the injured BBB *in vivo* and reduce the ASC protein levels in the spinal cord after injury, leading to a significant decrease in caspase-1 activation and IL-1β production.[144] NLRP1 inflammasome proteins exist in exosomes derived from CSF of SCI patients[144] and TBI patients.[145] These inflammasome-containing exosomes may fuse with peripheral immune cells to activate inflammatory and immune response.[72,73] Therefore, immunotherapy targeting inflammasome-containing exosomes might be a promising strategy for the treatment of CNS injury.[146]

Lipid-lowering drugs for immunomodulation

The lipid-lowering drugs such as statins have extensive immunomodulatory and anti-inflammatory properties. Among statins, atorvastatin exhibits neuroprotective effect in many preclinical studies on both TBI[147–154] and SCI.[155–158] Although many mechanisms may contribute to atorvastatin's neuroprotective effects, the microglia/macrophage polarization may play a more predominant role.[159] Acute atorvastatin administration in mice with TBI effectively reduced inflammatory responses by suppressing microglia/macrophage activation and immune cell invasion.[159] Several clinical trials with atorvastatin showed very promising therapeutic effects for TBI[147] and SCI,[160] but some clinical studies did not identify any improvement in functional recovery.[148,160] The discrepancies may result from different modeling, treatment patterns and sample sizes. Further clinical trials with larger cohort sizes and longer multi-center evaluation periods are needed.

Inflammasomes as therapeutic targets for CNS injury

The priming and activation of inflammasomes are the major components of the innate immune response and sterile inflammation after CNS injury.[41,77,144] Thus, immunotherapies targeting the inflammasome response might be a promising anti-inflammatory approach for CNS injury (TBI and SCI). Although the complexities and mechanisms underlying the inflammasome response after CNS injury remain under extensive investigation,[77,144] several proof-of-concept studies hold promising in contacting the inflammasome assembly and activation.[161]

Early studies showed that treatment with anti-ASC neutralizing antibody immediately after fluid-percussion brain injury in rats significantly improves the histopathology and functional recovery.[162] Such treatment reduced caspase-1 activation, IL-1β production and XIAP cleavage.[162] The CSF from TBI patients can activate neuronal AIM2 inflammasome and ASC oligomerization.[163,164] Blocking pyroptosis using caspase-1 inhibitors (Ac-YVAD-cmk, VX-765) or pannexin-1 inhibitors (Probenecid and Brilliant Blue FCF) prevents inflammasome-mediated inflammation and improves CNS injury.[161,163] Omega-3 fatty acids attenuate neuroinflammation and improve neurological outcome via inhibiting the NLRP3 inflammasome activation.[165] Propofol, a lipid-soluble intravenous anesthetic, has been shown to protect against TBI via inhibiting ROS-dependent activation of the NLRP3 inflammasome.[166] The angiotensin II receptor antagonist Telmisartan reduces traumatic cerebral edema by inhibiting the NLRP3 inflammasome-mediated accumulation of IL-1β and IL-18.[167] Melatonin treatment attenuates the early brain injury after subarachnoid hemorrhage by inhibiting NLRP3 inflammasome-associated pyroptosis.[168] Treatment with estrogen or stromal cell-derived factor-1 alpha (SDF-1α) after SCI exhibits neuroprotective function via inhibiting local inflammasome activation.[169,170] Resveratrol attenuates the inflammatory response and ameliorates TBI by reducing ROS production and inhibiting NLRP3 activation via SIRT1.[171] The treatment with hyperbaric oxygen (HBO) alleviates the inflammatory response in experimental TBI via modulating microglial NLRP3 inflammasome signaling and reducing IL-1β/IL-18 accumulation.[172,173] NLRP3 inhibitors such as BAY 11-7082 (via NFκB) or A438079 (via P2X7) have been shown to inhibit the inflammatory response and improve functional recovery after TBI.[75,174] Mangiferin has been extensively used as an anti-inflammatory drug and its neuroprotective effect after CNS injury is also attributed to NLRP3 inhibition.[175] Several other treatments for neuroprotective effects against SCI have been shown to target inflammasomes, such as heme oxygenase-1[146], Rho kinase inhibitor fasudil[176], the citus flavonoid glycoside rutin[177] and quercetin[178], the natural triterpenoid compound asiatic acid[179] and the dopamine receptor agonist A-68930.[180]

However, some studies using Nlrp1 (−/−) and Asc(−/−) mice demonstrated a non-essential role of the NLRP1 inflammasome after TBI.[181] This may result from the developmental compensation

of this specific inflammasome knockout. Since IL-1β is the major end-point product of the inflammasome activation, the neuroprotective effect of the therapeutic treatment targeting IL-1β with blockers such as IL-1ra and IL-1β neutralizing antibodies after TBI[182,183] and SCI[184] also support the conclusion that inflammasome therapy holds highly promising for the treatment of CNS injury. Given the majority of preclinical studies targeting inflammasomes showed positive therapeutic benefits against TBI and SCI, clinical trials may be immediately needed for CNS injury.[185]

HDAC inhibitor for SCI and TBI

The histone deacetylases (HDAC) remove acetyl groups on a histone, allowing for tighter DNA wrapping around the histones, thus suppressing gene transcription. HDAC inhibitors have been widely developed and utilized to activate gene transcription. After TBI, treatments with various HDAC inhibitors such as Valproate, sodium butyrate, ITF2357, trichostatin-A, Scriptaid, and 4-dimethylamino-*N*-[5-(2-mercaptoacetylamino) pentyl]benzamide (DMA-PB) significantly mitigate neuroinflammation, improve motor functional recovery and promote learning/memory in several animal models.[186–190] These HDAC inhibitors preferentially upregulate the transcriptional expression of many neuroprotective genes involved in cell survival, proliferation, and differentiation.[191] Both grey matter and white matter tracts are significantly preserved by HDAC inhibition after TBI.[186,192] Similarly, several HDAC inhibitors such as Valproate and RGFP966 have been shown to have neuroprotective effect against SCI by suppressing inflammatory response, promoting neurogenesis and stimulating axonal regeneration.[193–196] The expression of HDAC3 is upregulated in the innate immune cells (microglia/macrophages) at the injury site after SCI.[196] For both TBI and SCI, the inhibition of microglia/macrophage activation is the major mechanism underlying the neuroprotective benefits from HDAC inhibition therapy.[186,194,196] These exciting preclinical findings provide a promising future therapy using HDAC inhibitors targeting microglia for the treatment of CNS injury.[193]

Nanoparticles or drugs targeting monocytes

Monocyte-derived macrophages contribute primarily to the initial inflammatory damage after CNS injury.[197] Selective blockage of monocyte infiltration during early stage of CNS injury may prevent detrimental effects of the early innate immune response while preserving the beneficial effects of the residential microglia/macrophages.[198] The highly negatively charged, synthetic, 500 nm-diameter immune-modifying nanoparticles have been used to sequester monocytes in the spleen where they undergo caspase-3-mediated apoptosis.[199] Thus, intravenous administration of the biodegradable nanoparticles after SCI safely and selectively limits monocyte infiltration into the injury site and significantly improves functional recovery after both moderate and severe SCI.[198] These immune-modifying nanoparticles may offer a promising treatment for CNS injury because of the multifaceted advantages and continuous improvement of the nanomedicine.[200]

Laquinimod is an immunomodulatory oral drug in the clinical practice for the treatment of multiple sclerosis[201,202] and other autoimmune diseases.[203] Its immunomodulation results mainly from the inhibition of the monocytes infiltration into CNS in neurodegenerative diseases.[204] A recent study shows that laquinimod treatment reduces lesion volume and axonal damage and restored neurogenesis after TBI.[205] Laquinimod might be a potential immunotherapy for CNS injury.

A new bioengineered protein comprised of the human leukocyte antigen (HLA)-DRα1 domain linked covalently to mouse MOG-35-55 peptide (DRα1-MOG-35-55) has been shown to modulate monocyte response[206,207] and improve histological and clinical outcomes after TBI.[208]

Immunotherapy at the adaptive immune response after CNS injury

Emerging neuroprotective therapeutics targeting B cells

Intravenous immunoglobulin G (IVIG)

IVIG contains polyclonal IgG and has been extensively used as a first-line therapy with a good pharmacological safety profile in the clinical patients with immunodeficiency and autoimmune diseases such as Guillain-Barre syndrome, chronic inflammatory demyelinating polyneuropathy and Kawasaki disease.[209,210] IVIG has been also examined for neuroprotective effects in ischemia-type insults.[210–212] In animal studies, IVIG administration acutely after SCI[213] or TBI[214] significantly improves neural functional recovery. IVIG not only suppresses the excessive immune responses via inhibiting inflammatory cytokine production, immune cell invasion/activation and complement activation in the CNS, but also reverses the concomitant immunosuppression against invading pathogens after CNS injury.[17,213,215–217] Given the long-term clinical use of IVIG for the treatment of autoimmune and immunodeficiency conditions and the promising efficacy for CNS injury in animal studies,[211,213,214] IVIG remains a potential candidate for clinical trials in SCI and TBI.[218,219]

Monoclonal antibodies after CNS injury

Robust B-cell response occurs after SCI by generating pathogenic antibodies.[117,118] B cell deficiency in RAG knockout mice improves functional recovery after SCI.[220] Antibody-mediated depletion of B cells through the glycoengineered anti-muCD20 antibody (18B12) in a mouse model significantly inhibits the NFκB-dependent production of pro-inflammatory mediators and improves functional recovery after SCI.[221] The therapeutic CD20 antibodies such as rituximab or obinutuzumab may provide a new immunotherapy for the treatment of CNS injury.

Targeting T cells (Peripheral and CNS)

Targeting T cell trafficking and infiltration is neuroprotective in CNS injury.[222] The chemokine CXCL10 is a potent recruiter for T cells and has been implicated in the pathogenesis of CNS injury.[223–225] CXCL10 antagonist[226] or neutralizing antibodies[227,228] have been shown to attenuate T cell infiltration, suppresses neuronal death, increase axonal regeneration and improve functional recovery after SCI.

Fingolimod is an orally-effective immunosuppressant targeting sphingosine 1-phosphate receptor S1P1, and clinically used for the treatment of relapsing-remitting multiple sclerosis.[229,230] It induces S1P1 internalization and sequesters lymphocytes in the lymph nodes, reducing the circulating population of lymphocytes and their trafficking into tissues.[231,232] In addition to multiple sclerosis and other autoimmune diseases, fingolimod therapeutic benefits have been reported in many other neurodegenerative diseases and CNS injury. For SCI, systemic treatment with fingolimod blocks neuroinflammation and improves motor function and bladder function.[233,234] Local administration of fingolimod reduces reactive gliosis, prevents neuronal death and improves motor functional recovery after SCI.[235] A 3-day consecutive fingolimod treatment starting at 1 h after TBI significantly reduces as many as 20 kinds of cytokines/chemokines and the infiltrated T and NK cells, but increases the percentage of regulatory T cells, and the concentration of anti-inflammatory IL-10.[236] Fingolimod attenuates the general microglia activation, BBB damage and axonal injury,

and improves neurological functions after TBI. Given the extensive clinical application and widely reported therapeutic efficacy, fingolimod or other immunosuppressor targeting T cell trafficking or extravasation may be a promising therapy for the treatment of CNS injury.[237]

However, the adaptive immune responses may also serve as a protective autoimmunity to help neurorepair after CNS injury.[238,239] In the protective autoimmunity, the adaptive immune cells (particularly T cells) recognize self-constituents and potentiate an autoreactive response.[240,241] Immunization with a synthetic peptide A91 derived from the myelin basic protein shows strong neuroprotective efficacy after SCI in preclinical studies.[240,242] However, the safety, dosage and schedule of this peptide need to be addressed before translating into clinical therapy.

Challenging questions and future directions

Both the innate and adaptive immune responses play key roles in the secondary injury progression of both TBI and SCI. Several immunomodulatory strategies are likely to see translation to patients within the next few decades. However, several challenging questions could be addressed or investigated for future studies. The patrolling immune cells, particularly T cells and monocytes at the border between CNS and immune system play important roles in both physiological and pathological conditions (Fig. 1). As of now, many unknown functions remain to be determined. For example, what factors or molecular mechanisms determine the specificity and diversity of meningeal immune cells? Additionally, how do these meningeal immune cells invade the CNS parenchyma during pathological states? How does the crosstalk between the resident and invading immune cells contribute to the initial inflammatory damages and late neurorepair process? Various subtypes of innate and adaptive immune cells in the CNS are identified. Their characteristics and functions and the mechanisms underlying the subtype mutual conversion remain to be better delineated. Most importantly, what is the timing/window and transit process for the beneficial or detrimental role of innate and adaptive immune responses after CNS injury? Novel immunotherapeutics are needed to guide the maladaptive immune responses to the favorable wound-healing responses after CNS injury. The peripheral immune system exhibits immunosuppression after CNS injury, but whether T cell exhaustion occurs within CNS and affects neurodegeneration or neurorepair during the chronic injury remains largely unknown.

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