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Microglia Receptors in Animal Models of Traumatic Brain Injury

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Abstract

Microglia have been implicated as a key mediator of chronic inflammation following traumatic brain injury (TBI). The animal models of TBI vary significantly based on the type of brain injury (focal versus diffuse). This has made it extremely difficult to assess the role of microglia and the window of microglia activation. Hence, the focus of this review is to summarize the time course of microglia activation in various animal models of TBI. The review explores the repertoire of secondary injury mechanisms such as aberrant neurotransmitter release, oxidative stress, blood-brain barrier disruption, and production of pro-inflammatory cytokines that follow microglia activation. Since receptors act as sensors for activation, we highlight certain microglia receptors that have been implicated in TBI pathology, including fractalkine receptor (CX3CR1), purinergic receptor (P2Y12R), Toll-like receptor (TLR4), scavenger receptors, tumor necrosis factor receptor (TNF-1R), interleukin receptor (IL-1R), complement receptors, and peroxisome proliferator-activated receptor (PPAR). In addition to describing their downstream signaling pathways in TBI, we describe the functional consequences of their activation and the implication in behavioral outcomes. Taken together, this review will provide a holistic view of the role of microglia and its receptors in TBI based on animal studies.

Keywords Microglia · Brain injury · Receptors

Introduction

Traumatic brain injury (TBI) is one of the leading causes of mortality and morbidity around the world. In 2013, in the USA alone, there were about 2.8 million emergency room visits, among which there were 282,000 hospitalizations, and 56,000 deaths related to TBI. The three leading causes of TBI related hospitalizations include falls (47%), impact by striking objects (15%), and automobile accidents (14%) [1]. TBI accounts for approximately 30.5% of all injury-related deaths in the US. Over the past decade, there has been a sharp increase in incidents of TBI resulting from combat-related injuries as well as insurgent activities on civilian population [2]. In 2010, the direct medical costs of TBI were 76.5 billion dollars [3]. Although there has been a lot of effort focusing on treatment modalities for TBI, there has not been much success in developing a therapeutic strategy to treat TBI-associated deficits. Accordingly, over 30 stage III clinical trials failed to show significant improvement in TBI patients [4]. This is probably due to lack of clear understanding of the secondary mechanisms in the evolution of injury pathology and due to highly heterogeneous nature of TBI phenotype [4]. This has led scientists and researchers to look for novel methods to delay and prevent TBI-induced pathology.

Microglia are the immune cells in the brain and have been implicated in pathogenesis following TBI. In this review, we highlight the response of microglia to injury, specifically, the involvement in secondary injury mechanisms such as neurotransmitter release, oxidative stress, and blood-brain barrier (BBB) breakdown after TBI. We then describe some of the receptors that are known to be critical in microglia activation and response following TBI.

Microglia Response to Brain Injury

Microglia constantly survey the central nervous system (CNS) microenvironment for any changes in homeostasis using their

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highly motile processes. In their resting state, microglia possess a rod-shaped soma with processes extending out symmetrically in all directions [5]. Processes are motile with an average extension and retraction rate of 1.47 μm per minute and ranging from 0.4 and 3.8 μm per minute, respectively. Upon microglia activation a series of characteristic morphological changes occur. Usually, the motility change of their processes from undirected to targeted movement towards the injury site [5]. The processes begin to retract and the soma enlarges and become spherical in shape [6]. Finally, microglia begin to migrate to the site of injury at a rate of 1–2 μm per hour [5].

The classification of microglia activation has long been debated. The classical method of macrophage classification was borrowed and applied to microglia and categorizes activated states as either M1 (proinflammatory) state or M2 (anti-inflammatory) state [7, 8]. The M1state is initiated by events such as TBI, wherein, the microglia synthesize and release excess superoxide, nitric oxide, proinflammatory cytokines, and chemokines. Although the secretion of these compounds by microglia is primarily for host defense, often an exaggerated response follows an insult resulting in by-stander injury of the surrounding tissue [9]. When in M2 state, microglia produce anti-inflammatory cytokines (IL-4, IL-10, IL-13, IL-18) which promotes matrix remodeling, angiogenesis, tissue repair, and regeneration among other functions [10].

The application of the nomenclature of macrophages to microglia from the study of peripheral macrophages is often considered to be irrelevant in classifying microglia [11]. First, the M1/M2 definition was derived from exposing isolated cells to purified stimuli in vitro. These conditions are rarely found in vivo. Second, the cardinal regulators of macrophages bias are never found in vivo in isolation. Third, M1 and M2 states fail to emerge as an isolated pure phenomena in vivo. Fourth and possibly most important, macrophage polarization was developed using monocyte or bone-marrow-derived macrophages, that invade infected, traumatized or neoplastic tissues. By contrast, microglia are resident tissue macrophages, originating from extra-embryonic yolk sac [12], distinct from the circulating hematopoietic system [13] and highly adapted to their environment [14].

A recent study showed that activated microglia could exist in both states simultaneously where individual cells produce danger-associated molecular patterns (DAMPS) or pathogen-associated molecular patterns (PAMPS) [15]. This implies that activated microglia phenotypes fall along a spectrum as opposed to two binary states [16]. Depending on the stimulus present in the local microenvironment, microglia will be polarized to either the M1 or M2-like states. Particularly in TBI, the repertoire of microglia/macrophage activation is very diverse depending upon the type of mechanical impact, severity, and location of impact (discussed in paragraph below). Hence, it is suggested that a new classification be created based on but not limited to transcriptomic and proteomic profiles, regional heterogeneity, sexual dimorphism, function in healthy nervous system, and pattern of response to changes caused by trauma, infection, systemic inflammation, tumor, ischemia, and neurodegeneration [11].

There are currently 4 major animal models used to simulate the heterogeneous pathology of human TBI. These include weight drop injury (WD), controlled cortical impact injury, (CCI), fluid percussion injury (FPI), and blast / diffuse brain injury [17]. The WD model mimics closed head injuries frequently associated with falls, dropping of heavy objects in construction sites which lead to cerebral contusions found in TBI. It is performed by dropping a weight from a predetermined height onto the skull or exposed dura. In a modified version of WD model, also known as the closed head injury model, a metal plate is placed above the skull to distribute weight over a larger area and prevent skull fracture. WD model in mice showed signs of diffuse neuronal loss, neuroinflammation, markers of apoptosis, and short- and long-term cognitive impairments [18]. Similar to the WD model, CCI injury uses a solid impactor to damage exposed dura. To increase the reproducibility of the injury a pneumatic or electrochemical device is used. This mechanism also reduces rebound injury produced by gravity-driven devices [19]. By adjusting location, shape of impactor, velocity, and the depth of brain deformation, different types of injuries can be produced. CCI injuries typically manifest as cortical tissue loss, axonal injury, BBB dysfunction, and/ or subdural hematoma [20–23].

In FPI injury model, a craniotomy is performed to expose a portion of the dura. The injury is inflicted by directing a fluid pulse, produced by a pendulum striking a piston of fluid reservoir, against the exposed dural surface [19]. The injury model is characterized by a locally diffuse injury producing vascular and axonal damage and produces an amalgamation of cortical contusion and diffuse subcortical neuronal injury [17]. Studies have varied the location of injury site, but most commonly, the injury is performed lateral to the sagittal suture (LFPI) or medially (CFPI) [19]. The blast/ diffuse injury attempts to replicate the shockwaves from explosive devices to cause a diffuse brain injury. To recreate the Friedlander waveform produced in explosion from live explosives, gas driven shock tubes are used. Blast/ diffuse injury is characterized by diffuse cerebral brain edema, extreme hyperemia, a delayed vasospasm, and diffuse axonal injury [2, 24].

Microglia activation follows a different temporal pattern depending upon the type and severity of brain injury (Fig. 1). CCI and FPI are the most studied among different injury mechanisms, and therefore, microglia activity state has been thoroughly investigated. Markers such arginase (Arg-1) [61], CD206 [25, 62], and YM-1 [26, 62] are used to identify M2 activated microglia versus CD16 [62], CD 86 [25, 62], which are markers for M1 activated microglia. In TBI models, such as blast and weight drop, only the time profile of microglia activation has been studied. For instance, following CCI

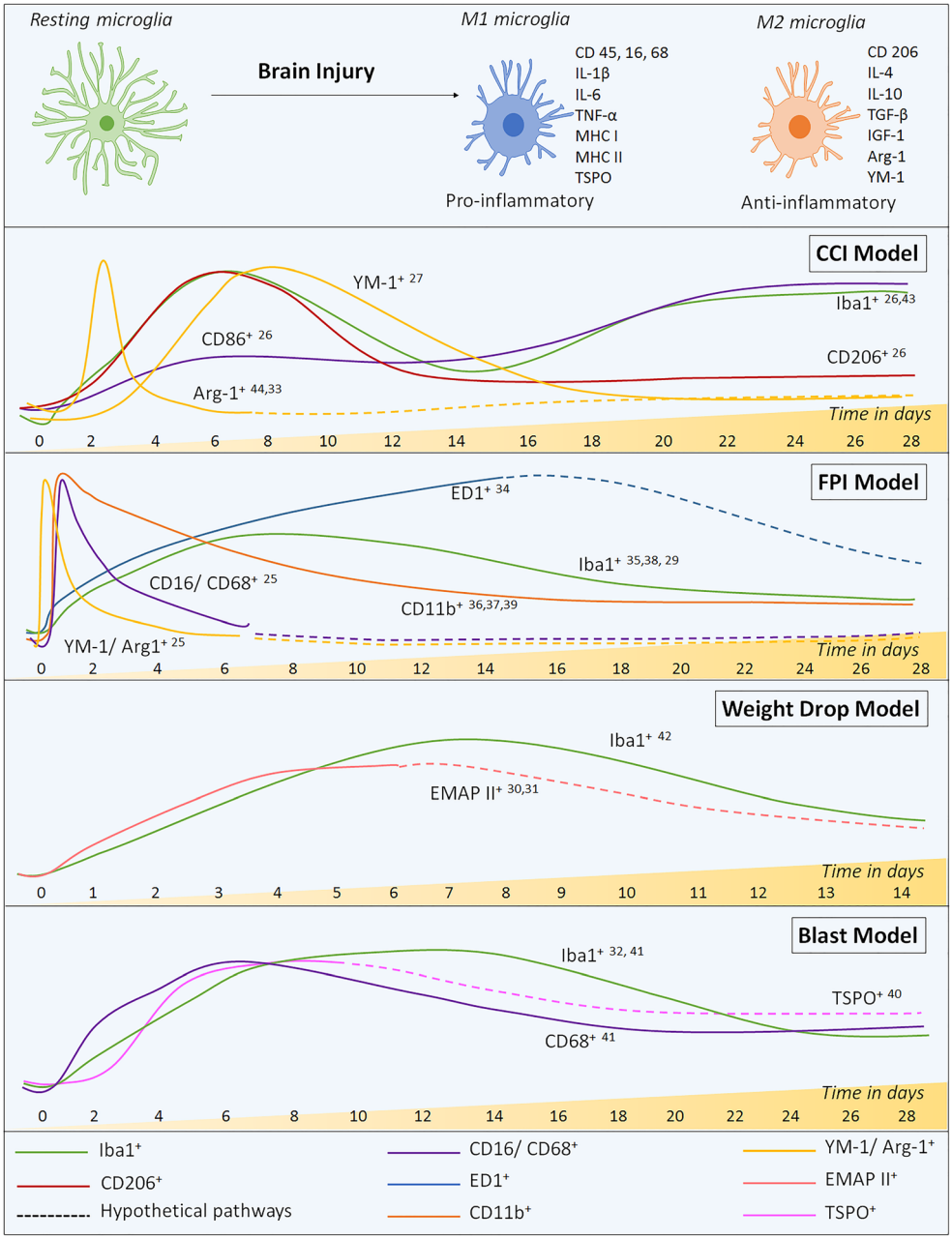

Fig. 1 Microglia activation markers and time-course in various animal models of traumatic brain injury. The top panel depicts the two forms of microglia activation states: M1 and M2 and the markers used to identify each state. The lower panels illustrate how the expression levels of the microglia activation markers (Iba1, ED1, CD11b, CD16, CD68, YM-1, Arg-1. EMAP II and TSPO) change with $t = 0$ representing time of injury in various animal injury models. Note that the y-axis denoting expression levels is arbitrary and is used to show the upregulated/peak expression of the particular protein. Solid lines indicate proven studies, while dotted lines represent hypothetical expression. The numbers in superscript refers to the cited literature. In addition to portraying the stages of microglia activation, this illustration reveals that there is no absolute standard for defining microglia activation. Further, the evidence for long-term chronic activation of microglia following brain injury is lacking [25–60]

injury, M2-like microglia increase in the first week following injury. The number of M2 microglia peak at 5 days post injury but decreases rapidly in number immediately afterwards [25, 63]. M1 microglia begin to increase in the cortex, striatum and corpus callosum at 1 week [63], peaking at 4 weeks following injury [25]. M2 type microglia predominate in the acute phase of injury while the M1 phase of microglia remain during the chronic phase after focal injury produced by CCI. Similar to focal injury, diffuse injury produced by FPI induced transient activation of M2 type of microglia that resolved within 7 days after injury, whereas, M1 type microglia remained in their activated amoeboid morphology for up to 30 days following injury [63].

It is interesting to note that microglia activation patterns differ not only temporally but also spatially following brain injury. The spatial variability in microglia response to injury may depend upon regional differences in mechanical loading and/ or the intrinsic property of the tissue. Despite the limited studies on mechanical signaling in microglia, a recent study showed cultured microglia cells were susceptible to mechanical changes [64]. In line with this, another study showed that mechanical loading was capable of modulating microglia proliferation, activation, and chemotaxis [65]. The response of microglia to injury may also depend on the intrinsic property of the tissue such as microglia/ blood vessel distribution and neuronal vulnerability within the region. There is a lower occurrence of

microglia in gray matter areas compared to the white matter. Regionally, the lowest of occurrence is the cerebellum (0.3%), frontal (4.7%), parietal (3.6%) and occipital (2.9%) lobes of the cerebrum with highest expression levels in the white matter track of the medulla oblongata (16.9%) [66]. A recent study showed that microglia activation paralleled the pattern of neuronal loss in a mouse model of CCI injury [67] which is in line with another study that observed prominent occurrence of activated microglia in regions of neuronal loss including the ipsilateral cortex, hippocampus, and thalamus after injury [68]. In a blast model of brain injury, microglia activation was found to be closely associated around the blood vessels suggesting that the difference in the distribution of microglia and blood vessels may underlie some of the regional vulnerabilities to injury [6].

Delineating the Functions of Microglia and Macrophages in Brain Injury

TBI causes a dramatic increase in microglia/macrophages in the area of injury. This increased number is contributed in part by local proliferation of resident microglia and infiltration of bloodborne-macrophages [69–71]. Blood-borne macrophages and microglia have distinct roles in TBI pathology and progression, however are difficult to distinguish since they share many common characteristics. Recent identification of microglia-specific markers, advent of transgenic animal models and techniques such as flow cytometry has made the distinction feasible [72, 73]. Using flow cytometry, Hsieh et al. distinguished macrophages ($CD45^{high}$, $CD11b^{+}$, $Ly6G^{-}$) from microglia ($CD45^{low}$, $CD11b^{+}$, $Ly6G^{-}$) and found that the populations contributed distinctly to inflammation after CCI injury [74]. Another study used $CX3CR1^{GFP/+}CCR2^{RFP/+}$, in which CX3CR1-positive resident microglia were labeled with GFP and CCR2-positive infiltrating monocytes are labeled with RFP. Specifically targeting CCR2 macrophages with CCX872, a novel Phase I CCR2 selective antagonist, significantly reduced TBI-induced macrophage accumulation and inflammation [75]. Similarly, mice lacking CCR2 ($CCR2^{-/-}$) with reduced macrophage infiltration after TBI, demonstrated improved functional recovery and neuronal survival [76]. These investigations on delineating the functional role of microglia and macrophages are limited and have only been performed in a few TBI models. Hence, further examination on dissecting the temporal and spatial contribution of resident microglia and infiltrating monocytes to the neuro-inflammatory profiles following TBI is much warranted.

Microglia-Mediated Secondary Mechanisms in Brain Injury

Depending on the type of TBI, the secondary injury may involve a wide array of mechanisms including oxidative stress, production of pro-inflammatory cytokines, BBB disruption, cell death, mitochondrial dysfunction and neurotransmitter release [77, 78]. Studies conducted thus far, have reported the involvement of microglia receptor activation in not only altering microglia morphology and motility, but also in neurotransmitter release, modulating neuron-glia synaptic transmission, secretion of cytokines, generation of reactive oxygen species and production of nitric oxide. Here, we summarize the microglia-mediated secondary mechanisms following brain injury.

Aberrant Neurotransmitter Release

Activated microglia contribute to neuronal excitotoxicity by releasing neurotransmitters in response to several external stimuli. The known neurotransmitters released by microglia include glutamate and ATP. Glutamate release by microglia can be triggered by activation through multiple receptor systems. For instance, microglia release of glutamate may be induced by secreted amyloid precursor protein (APP) [79] or amyloid β [80]. Similarly, TNF-α can induce the release of glutamate by upregulating glutaminase. Microglia are capable of releasing sufficient amount of glutamate to contribute to neural degeneration [81]. Such excess release of glutamate has been reported following ischemic brain injury [82]. However, there has been no study investigating the microglia release of glutamate in TBI models. The excess glutamate may activate pre and post-synaptic glutamate receptors in neurons leading to excitotoxicity. Alternatively, they can activate microglia glutamate receptors including AMPA receptor [83–85], metabotropic glutamate receptors [86–89] and NMDAR [90–92], resulting in a cascade of secondary events.

Adenosine triphosphate (ATP) is the other commonly released neurotransmitter by microglia. ATP release from microglia cells can be induced by bacterial endotoxin lipopolysaccharide (LPS) [93, 94]. Lysophosphatidic acid (LPA) induces the release of ATP via activation of the LPA_3 receptor [95]. High intracellular calcium levels have been shown to induce ATP release in microglia [96]. Extracellular ATP was shown to enhance radiation-induced brain injury through microglial activation and paracrine signaling via P2X7 receptor [97]. ATP release following brain injury triggers a microglia response via purinergic signaling [98]. The purinergic receptors in microglia are abundant and are implicated in important functions such as cytokine production (P2X receptors), motility (P2Y12 receptor) and in phagocytosis (P2Y6 receptors) [99–101]. The expression and function of these receptors in neuronal/glial cells in neuropathologies have been reviewed previously [102] and their role in TBI and is worthy of investigation.

Oxidative Stress

Under normal physiological conditions, there is a delicate balance between reactive oxygen/nitrogen species (ROS/RNS) and their removal via antioxidants. Following TBI, the balance can be disrupted leading to an excess buildup of ROS [103, 104]. Accumulation of ROS/RNS is known to mediate cellular damage via lipid peroxidation, protein modification, and/or DNA strand breaks [105]. Activated microglia produce superoxide by the enzymatic activity of NADPH oxidase (NOX), a multi-subunit enzyme that catalyzes the production of superoxide from oxygen [106]. Microglia, like all phagocytic cells, express NOX2 [107]. NOX 2 generates superoxide molecules which help in the neutralization of foreign pathogens [108]. It was shown that NOX2 mediated ROS production was strongly upregulated in M1 but not M2 polarized microglia in CCI injury. Inhibiting NOX2, by using selective peptide inhibitor gp91ds-tat or NOX2 knockout mice, reduced markers for M1 activated microglia, limited tissue loss, and improved motor recovery. Inhibition of NOX2 also promoted M2-like activation in microglia [109]. In FPI injury, inhibition of NOX with apocyanin had no effect on neuromotor function but reduced the release the proinflammatory cytokines IL-1β, and TNF-α at 3 and 24 h after injury [110]. Recently, it was shown that NOX2 expression was increased at 24 h after moderate blast injury (180 kPa) and this directly correlated with elevated ROS production [111]. Activation of cytokine receptors such as IL-2R [112, 113], IL-15R [114], TNFR1 [115], INF-γR and thrombin receptor [116] in microglia have also been implicated in ROS production. ROS production by microglia may also be mediated by Notch-1 receptor [117, 118], dopamine receptor D_1, D_2 [45, 119], and Angiotensin II receptor [120].

BBB Disruption

The CNS vasculature differs from the rest of the vasculature in that it has intricate connections and innervations with neural cells particularly astrocytes (astrocyte end feet), pericytes and microglia to form the functional BBB, a specialized structure that selectively separates the brain parenchyma from the peripheral blood. Studies on the interaction between microglia and BBB in both physiological and pathological conditions are limited and have recently gained more attention [121, 122]. The perivascular microglia communicate with the endothelial cells and survey the influx of blood-borne components into the CNS. Hence, any disruption of the BBB as reported following brain injury, can prime, and attract microglia [6].

Microglia activation dependent alterations to BBB after TBI is thought to be predominantly mediated by neuroinflammation and oxidative stress [123–125]. Therefore, most TBI studies that investigate both microglia activation and BBB disruption focus on shifting microglia from their proinflammatory M1state to their anti-inflammatory M2 state. For instance, following CCI injury binding of 2 arachidonylglycerol (2-AG) (agonist) to the cannabinoid receptor in microglia shifted microglia at 3 and 7 days from M1 to M2 activated phenotypes. This shift in activation was coupled with the reduction of BBB permeability at the same time point [126]. Reduction in the release of pro-inflammatory cytokines and reduction of inducible ROS production prevented further degradation of BBB [126]. Pretreatment with apocynin (NOX inhibitor) prevented BBB disruption following WD injury [127], as well as in blast injury model [128]. Microglia as the major source of NOX mediated ROS production are implicated as the cause for the increase in permeability of the BBB following injury [127]. In a mouse model of mild blast injury, microglia activation was restricted to regions close to the blood vessel microdomains, as evidenced by rapid microglial process retraction and increased amoeboid morphology [6]. Taken together, these TBI studies confirm that there is a close association between microglia activation and BBB disruption and vice-versa following injury.

Release of Cytokines

Neuroinflammation is one of the key mediators of secondary injuries following brain injury. The acute response includes secretion of pro-inflammatory cytokines within minutes following injury. The activation of resident microglial cells, alongside the infiltration of peripheral macrophages, is key mediator of neuroinflammatory responses after TBI. Several studies have attempted to discriminate the differential roles of resident microglia and infiltrated monocytes after brain/ spinal cord injury [69, 129, 130]. In this review, we highlight the contribution of microglia to the release of pro-inflammatory cytokines, however, the role of infiltrating monocytes/ macrophages in secreting cytokines and overall TBI pathology cannot be overlooked.

Upon the detection of foreign macromolecules such as DAMPS/PAMPS, microglia can release a wide range of cytokines and chemokines. These molecules guide the expression of adhesion molecules, signal peripheral immune cells to infiltrate the injury site, and further release pro-inflammatory mediators and growth factors that regulate neuronal death or regeneration [131]. Many studies have investigated cytokines and chemokines expression following TBI. These studies have focused on levels of cytokines found in homogenized tissue section or CSF. These studies attribute the increased expression of cytokine to the activity of activated microglia. This assertion may be correct, but microglia's contribution to the inflammatory environment is unlikely to be exclusive [132].

Following CCI injury, levels of IL-1β and IL-18 increased in brain homogenates surrounding the contusion site. Levels of IL-1β peaked at 6 h post injury and decreased to control level by 7 days. IL-18 levels gradually increased over the 7 d observation period. Microglia-specific release was confirmed by colocalization of NLRP-3 inflammasome and its associated components (ASC and caspase1) in microglia cells but not with astrocytes or neurons [133]. Chio et al. found that administration of Etanercept, a TNF-α receptor antagonist, attenuated the release of TNF-α following FPI leading to reduced motor and neurological deficits as compared to the control and saline-treated groups. At 72 h after injury, TNF-α secreted by microglia increased in ischemic cortex, white matter, hippocampus, and hypothalamus. Double immunostaining confirmed that neuronal and astrocytic TNF-α levels were not significantly different between control, saline- and etanercept-treated groups leading to the conclusion that microglia was the prominent source of TNF-α production following diffuse TBI [134].

Bachstetter et al. showed that p38α (MAPK14) protein kinase plays a role in the production of TNF-α and IL-1β by cultured microglia cells [44]. Using midline FPI model they investigated whether myeloid-specific deletion of p38α influenced microglia cytokine production following injury. Unexpectedly they found that during the acute phase (0–12 h), release of IL-1β, IL-6, and TNFα was greater in the p38α knockout (KO) compared to the wild-type injured animal. This increase could not be accounted for by the increase in infiltrating immune cells (macrophages and neutrophils) or by astrogliosis, as cell numbers were decreased in the KO animals relative to the WT. In the chronic phase (7 days), levels of IL-1 were significantly reduced in the p38α KO animals as compared to the WT injured animals. These findings suggest that microglia may not contribute significantly to inflammation in the acute phase but is responsible for the pro-inflammatory environment found in the chronic phase of injury [27].

Microglia release proinflammatory cytokines such as IL-1β upon ligand binding to the NMDAR [90], angiotensin II receptor [120], and IFN-γR [131]. Release of TNF-α has been reported upon activation of AMPA receptor [83, 84], NMDAR [90], kainate receptor [85, 91], metabotropic glutamate receptor [87, 89, 135, 136] α_{1a}, α_{2a}, β_1 adrenergic receptor [137], IFN-γR [131], TLR2 [138], TLR3 [139], TLR9 [140], CD-14 [141] and thrombin receptors [141]. Release of IL-6 upon GABAR [142] α_{1a}, α_{2a}, $\beta_1$adrenergic receptor [137], TNFR1 [143], IFN-γ [131], IL-1R1 [144], TLR2 [138], TLR3 [139], TLR5 [140], TLR9 [140], CD-14 [141], Thrombin receptor [116] activation. Release of IL-12 was noted upon activation of GABAR [142], IFNγR [145], TLR3 [139], TLR9 [140], CD-14 [141], and thrombin receptors [116].

Microglia are also capable of releasing chemokines such as release of CCL2 upon IFN-γR [145] TLR2 [138] activation. Release of CCL3 upon IL-13R [146, 147] CD-14 activation. Release of CCL5 upon IL-3R [146, 147] activation. Release of CXCL-10 upon TLR3 [139] and TLR4 [139] activation. Release of CXCL2 upon CD-14 [141] activation. Once released, these factors affect adjacent cells such as astrocytes and/or neurons in a paracrine manner since these cells possess receptors for these factors. Additionally, these factors could also affect microglia in an autocrine manner. In both scenarios, the net effect exerted by these factors includes lipid peroxidation, immune cell recruitment, BBB disruption, and the development of cerebral edema [148–150].

Microglial Receptors in Brain Injury

The microglia express a repertoire of receptors which act as sensors for specific ligands in the neuronal parenchyma. A comprehensive list of receptors expressed in microglia, the known receptor agonists/ antagonists, their physiological function and the functional relevance of receptor activation is provided in Supplementary Table 1. Although many receptors have been indicated to be part of microglia sensor system (Supplementary Table 1) only a fraction of them are activated during TBI (Table 1). In the following section, we summarize some of the microglia receptors most investigated in TBI, their downstream signaling pathway (Fig. 2), the functional consequences of their activation and the implication in behavioral outcomes.

Chemokine Receptor (CX3CR1)

Microglia in the CNS are characterized by the prominent expression of the chemokine receptor 1 (CX3CR1). The sole ligand for the receptor is fractalkine (CX3CL1) which is produced by neurons. CX3CL1 is known to induce microglia activation and release of proinflammatory factors [177]. Following brain injury, affected neurons release CX3CL1 allowing for microglia activation [178]. The schematic in Fig. 2 summarizes the known intracellular signaling pathways associated with CX3CR1 receptor activation in microglia. It has been shown that CX3CL1 induces chemotaxis of microglia cells via chemokine macrophage inflammatory protein-1α (MIP-1α) to the site of neuronal damage [179]. CX3CL1 is also known to induce microglia activation through intracellular phosphorylation of microglial p38 mitogen-activated protein kinase (MAPK) [180, 181]. Further, treatment of cultured microglia with CX3CL1 promoted cell survival and inhibited Fas ligand-induced cell death via the Akt signaling pathway [182].

In a mouse model of CCI, they found that CX3CR1 KO mice had reduced cellular damage in the cortex and fewer

Table 1 Microglia receptors in various TBI models

Injury Model	Receptor	Animal model	Microglia marker	Time points	Effect of Receptor antagonist/blocker in TBI conditions
CCI	Insulin-like growth factor 1 receptor (IGF1R)/ SOC2 [151]	Mouse C57Bl/6, SOCS2 transgenic (Tg) over-expression	CD11b (general), CD206(M2), and CD16/32 (M1)	3 days, 7 days, 33 days, 35 days	Injury induces higher number of M1 than M2 microglia • Erythropoitin treatment (IP injection) 7 days daily ○ EPO treatment had no effect on behavior • SOCS2Tg animals showed ○ Improved motor function by 7 days ○ Showed smaller lession at 7 days but not at 35 days post injury ○ No effect on cortical neurogenesis after TBI ○ Increased number of newly proliferated microglia (7 day) not at 35 day ○ Increase in M2-like and but no increase in M1 microglia in perilesional area at 7 day ○ Area covered by CD11b + cells not different between genotypes
	IL-1βR/ IL-1β [152]	Mouse C57BL / 6	Mac2	1 day, 3 days, 7 days, (immuno) 2 days, 5 days, 12–15 days	Microglia activation began at day 1 and peaked at day 7. Activated microglia appeared in the vicinity of the cortical contusion and ipsilateral hippocampus. • IgG2a/k IL-1β neutralizing antibody administered vio osmotic pump for 2 weeks. IL-1β neutrilization - ○ Reduced number of activated microglia at day 3 and 7 ○ Reduced number of cortical neutorphils and infiltrating activated T-cells ○ Reduced lession volume and hemispheric tissue loss ○ No effect on motor function loss but treatment reduced memory decline
	IL-4R/Il-4 [46]	Mouse C57Bl/6 (3 month and 24 month)	Iba-1 (general), M1 markers (IL-1β, TNFα) M2a marker (Arg-, Ym,CD68, iNOS, Mrc, Fizz-1, CCL2, and CCL3) M2c markers (IL-4Rα, TGFβ, SOC3)	24 h, 7 days	• Significant increase in IL-4Rα in both young and adult mice with a greater increase in young animals • IL-4Rα activation shown by STAT6 expression upregulated in both young and adult mice with greater levels in young mice. • Age produced imbalance of M1 and M2 patterns with significant increase in M1 and M2a genes and lower expression of M2c • Increase in activated microglia in the hippocampus of aged TBI mice compared to young mice
	Sigma-1 Receptor [153]	Mouse C57Bl/6 (10–-12 weeks)	Iba-1	days 1, 3, 7, 14, 21, and 28	• PRE-084 selective sigma 1 agonist treatment given 15 min after TBI ○ Decreased lesion volume and brain water content (day 3 and 28) ○ Improved neurological recovery (mNSS) on day 21 and 28 but no effect on days 1–14 ○ Decrease in neurodegeneration by 57% ○ Attenuated Iba intensity at 3 days ○ Decreased Nitrosative and oxidative stress at 3 h after TBI
	Cannabinoid-2 Receptor [154]	Mouse C57Bl/6 (8 weeks)	Iba-1	48 h	• CB2R agonist 0–1966 vip IP injection at 1 and 24 h after injury ○ Improved Llocomotor performance and exploratory behavior ○ Decreased Edema (water content) and substance P immunoreactivity ○ Decreased number of Iba positive cells ○ Fewer Iba positive cells showed activated morphology
			Iba-1		

Table 1 (continued)

Injury Model	Receptor	Animal model	Microglia marker	Time points	Effect of Receptor antagonist/blocker in TBI conditions
	CX3CR1 [132, 155, 156]	Mouse C57Bl/6 (3 month) Mouse C57Bl/6 Mouse C57Bl/6	Cd11b (general) M2 (Ym1, CD206, TGFβ) M1 (Marco, CD 68) Cd11b (general) M1: Cd68 M2: Ym1	2 days, 1 week, 2 weeks, 4 weeks, 8 weeks, 18 weeks, 1 year and 1.5 years 24 h, 7 days, 15 days, 30 days 1 day, 2 days, 4 days. 7 days, and 5 weeks	• At 7 days total number of microglia increased over control but returned to control levels at 4 months • Levels of activated microglia remained increased in both the ipsilateral and contralateral cortex • Levels of CX_3CR1 increased 2 days after injury and persisted for 1.5 years following injury • Heterozygous $CX_3CR1^{\pm}$ mice ○ Only females had less degeneration of brain tissue ○ No change in microglia number but fewer infiltration macrophages and lymphocytes • CX_3CR1 ($CX_3CR1^{-/-}$) knockout animals ○ Reduced motor deficit, cell death, and neuronal loss at acute phase (24 h-15 days). ○ Greater cognitive disfunction, and increasecd neuronal death at chronic phase (30 days). ○ CX3CR1 deficiency correlates with increased microglial proliferation ○ M2 marker increase at 7 days only in knockout animals but not detected at 15 and 30 day ○ Significant reduction in iNOS and IL-1. ○ M1 phenotype (Marco, and CD68) was dominant at the chronic phase
	Adenosine A1 Receptor [157]	Mouse C57Bl/6 A1AR KO mice	Iba	24 h, 7 days	• A1AR KO transgenic mice showed ○ Significant increased in Iba-1 staining compared to WT in six of the eight brain regions examined including ipsilateral CA3, cortex, and thalamus, and contra-lateral CA1, cortex and thalamus ○ No change in cortical volume between knockout and WT
	TLR4 [47, 158]	Mouse C3H/OuJ, C3H/HeJ non functional TLR4 Mouse C57BL/10ScNJ (TLR4 knockout) And control	Iba M1: iNOS, TNF-α M2: Arg-1 VEGF, IL-10	1 day, 3 days, 4 days, 5 days, 7 days	• TLR4 expression restricted to microglia within the peri-contusional cortex • VGX-1027 TLR4 antagonist administered via tail vein 15 min before or up to 8 h after TBI ○ Injury increase TLR4 gene and protein expression in ipsilateral cortex between 6 and 24 h ○ C3H/HeJ mice and VGX treated mice at 4 h had similar effect on edema volume ○ Reduced IL-6 expression • TLR4 knockout mice showed ○ Improved recovery of learning and memory ○ Decreased brain edema volume ○ Attenuated expression of M1 markers at 3 and 7 days and increase in M2 marker at same time point ○ Number of microglia increased peaking at 3d and increased levels compared to control at 7 days
	mGluR5 [159, 160]	Mouse C57Bl/6 (3 months) Mouse C57Bl/6 (3 months)	Iba CD11b M2: Arginase-1 Ym-1)	1 day, 3 days, 7 days, 14 days, 21 days, and 28 days	• At 3 h and 24 h post injury mice received an ip injection of VU0360172 a possive allosteric modulator of mGluR5 or MTEP (a slective mGluR5 antagonist) + VU0360172 ○ VU0360172 improved motor recovery at day 28

Table 1 (continued)

Injury Model	Receptor	Animal model	Microglia marker	Time points	Effect of Receptor antagonist/blocker in TBI conditions
			M1: iNOS, CD68 ED-1	1 day, 7 days, 14 days, 15 days, 16 days, 17 days, 21 days	○ VU0360172 had no effect on spatial lerning ○ VU0360172 reduced cortical tissue loss and reduced hippocampal regeneration ○ VU0360172 polarized microglia to the M2 phenotype ○ VU0360172 reduced the upregulation of NOX-2 induced by mGluR5 activation • 30 min post-injury, mice received a single intracerebroventricular (ICV) injection of CHPG or CHPG and MPEP ○ CHPG treated animals had improved sensorimotor proformance on dat 14 and 21 ○ CHPG + MPEP performed similar to vehicle-treated animals ○ CHPG animals improved spatial learning on day 15, 16, and 17 ○ CHPG reduced lession volume ○ Level of ED1 were decreased in CHPG groups indicating lower microglia activation ○ Inhibition of NADPH odidase does not enhance neuroprotective effect of CHPG
	TNFR [161]	Mouse C57Bl/6WT/ p55(−/−) and p75(−/−)	CD11b M2: Ym-1	48 h, 4 weeks	• p55(−/−) and p75(−/−) trangenic mice ○ P55 (−/−) mice showed the greatest deficit followed by p75 (−/−) and finally WT. Observed at both 48 h and 4w ○ P55 (−/−) mice showed significantly reduced injured area compared to WT and p75 (−/−) ○ At 24 h P55 (−/−) mice showed a reduced number of damaged cells ○ 3 zones characterized by different morphology of microglia, Border of contusion (ameboid), Transition zone (ramified and ameboid), and periferal zone (ramified) ○ Zone 1 and 2 had significant reduction in microlgia activation in P55 conpared to WT and P75 ○ Ym1 increased immunoreactivity in p55 (−/−) compared with p75 (− /−) mice
	Peripheral benzodiazepine receptor [48, 162]	Rat Sprague–Dawley Adult rat	ED-1 DC68	6 h, 1 day, 3 days, 14 days 7 days	• PTBR antagonist [3H]PK11195 to visualize recepter density • [3H]PK11195 specific binding was uniformly distributed in rat brain with the highest density in striatal cortex (83.4 fmol/mg tissue) and the lowest density in the caudate-putamen (49.4 fmol/mg tissue) ○ Increase in ED1 by 40–79% at day 3 and increase by 106–185% at 14 days post injury. ○ Binding positively correlated with the degree of microglial activation, and to a lesser degree with reactive astrocytosis ○ Binding is higher in regions with neuronal loss
	NLRP3 [133]	Mouse C57BL/6 (age 10–12 weeks)	Iba-1	6 h, 1 day, 3 days, 7 days	• Protein expression of NLRP-3, ASC, and Caspase-1 localized to microglia • Hyperbaric oxygen treatment ○ Attenuated motor deficits ○ Alleviated cerebral edema ○ Decreased levels of IL-1β and IL-18 ○ Inhibited mRNA and protein expression of NLRP-3, ASC, and Caspase-1
	PPAR [49, 163, 164]	Rat Sprague–Dawley Rat Sprague–Dawley Mouse C57BL/6	Iba-1 CD11b GSI B_4	Day 1–5 motor function Day 14–18 spatial learning Day 21 biochemistry	• Rosiglitazone PPAR-γ agonist treatment (6 mg/kg at 5 min, 6 h and 24 h post injury) ○ Improved motor function (d 1–5) ○ No effect on spatial learning

Table 1 (continued)

Injury Model	Receptor	Animal model	Microglia marker	Time points	Effect of Receptor antagonist/blocker in TBI conditions
				25 h, Day 10–14 spatial learning, day 16 biochemical analysis	○ No effect on contusion volume ○ Increased cell survival in CA3 region of hippocampus (d21) ○ Microglia activation decreased in CA1 and cortex and trend in CA3 and thalamus
				1 day, 2 days, 7 days	rosiglitazone treatment ○ Attenuates TNFα gene expression (24 h) ○ no mRNA reduction in the matrix metallopeptidase gene, MMP9 the cytokine-inducible enzyme, iNOS, or in COX2, a gene whose expression is increased after inflammation • Pioglitazone (PPAR-γ agonist), or Pioglitazone and the antagonist T0070907 treatment at 10 mg/kg beginning 15 min after the injury and subsequently every 24 h for 5 days ○ Significant increase in mitochondrial function was observed ○ Reduction in lession size by 55% ○ Few microglia cells and fewer activated microglia basses on morphology in treated group ○ Administering the antagonist removed the therapuetic effect of Pioglitazone treatment • Rosiglitazone treatment or Rosiglitazone + GW9662 (PPAR-γ antagonist) (of 6 mg/kg was given 5 min, 6 h and 24 h after TBI ○ Induced 2.1 fold increase in PPAR-γ mRNA expression with Rosiglitazone treatment increasing 4.4 fold from sham(1 day) ○ Decreased cortical contusion volume (day 7) ○ Decreased Tunnel positive cells mainly neurons(day 2) ○ Decreased GSI-B_4+ cells (activated microglia ○ mRNA levels of the pro-inflammatory genes IL6, MCP1 and ICAM1 were significantly lower in the rosiglitazone-treated group (1 day) ○ Increased expression of HSP and antioxidant genes (1 day) ○ Administering the antagonist removed the therapuetic effect of Rosiglitazone treatment
FPI	TSPO [28]	Rat Sprague-Dawley	Iba-1 Classical activation: TNFα, and CD45 Acquired deactivation: TGF-βI, TGF-βRII, Alternative activation: ARG1	7 days, 21 days	• Measured receptor density using [3H]PK-11195 • Rats given anti-inflammatory dug ibuprofen (20 mg/kg) ip daily for 7 days • Transient S1BF and sustained VPM microglial activation after diffuse brain injury shown by morphological changes and enhanced iba staining • Increased TSPO binding density especially in the S1BF and VPM at 7 days • Classical activation and acquired deactivation gene expression was increased transiently at 7 days postinjury with no change in alternative activation observed
	TLR4 [165]	Mouse C57Bl/6	Iba-1	1 day, 3 days, 7 days	• VEGI treatment mice were injected i.p. on three consecutive days of 2 h, day1 and day2 ○ Reduced contical contusion volume ○ Reduced blood-brain barrier permeability (day 7) ○ Decrease in Iba positive cells in the contusion margin

Table 1 (continued)

Injury Model	Receptor	Animal model	Microglia marker	Time points	Effect of Receptor antagonist/blocker in TBI conditions
					○ Expression of TLR4 reduced by 19.73% and 61.09% compared to saline treated injured animnals(day 1 and 3) ○ Decrease in NF-κB which requires TLR4 activation ○ Reduced the IL-1β, TNF-α and iNOS expression (day 1 and 3)
	CX3CR1 [69]	Mouse C57Bl/6 Cx3cr1 defecient	Iba	3 days	CX3CR1 deficiency had no effect ○ Cavity volume ○ Monocytic reaction ○ Microglia activation
	IL-1R [166]	Mouse	Mac-2	1 day, 2 days, 9 days, day 14–21	IL-1β-neutralizing antibody resulted in ○ Normalized behavior profile in the MCSF test (day 2 and 9) ○ Increased memory in MWM (day 14–21) but no effect on learning (MWM) ○ Treatment had no effect on microglia number or ventricle size
	PPAR [167]	Rat Winstar	Iba	24 h, 48 h	• i.p. administered by 1 mg/kg Pioglitazone or vehicle 10 min after the TBI induction ○ Reduced lipid peroxidation and protein oxidative products in the cortex ○ TBI-induced COX-2 overexpression was not significantly affected by treatment ○ No significant effect of the treatments on the cortical IL-lβ, IL-6. And TNFα ○ Reduced both percentage of iba possitive cells as well as decreased the number of activated microglia based on morphology ○ Reduced cortical edema formation
Weight drop	NMDAR [168, 169]	Mouse C57Bl/6	F4/80	1 day, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days	• Minocycline injected i.p. 45 mg/kg at 30 min post injury and every subsequent 12 h until sacrificed ○ Transient improvement in neurological recovery following injury ○ Improved motor performance at day 1 post injury ○ Reduces periconusional lesion volume on day 1 but no effect on day4 ○ NO significant effect on apoptotic cells ○ Decrease of 43% in the density of activated microglia in the treated group ○ Reduced cortical IL-1β level
	EPO receptor [170]	Rat Sprague-Dawley	CD68	1 h, 2 h, 1 day, 7 days, 14 days	• Marmarou model followed by 30 min of hypoxic (Hx, 12% O2) or normoxic ventilation, and were administered recombinant human EPO-α (5000 IU/kg) or saline at 1 and 24 h post-injury ○ Significantly improved sensorimotor and cognitive recovery when administered to TAI rats with Hypoxia ○ Reduced axonal damage in white matter ○ Maintained neuronal density ○ Reduced IL-1β to sham levels (2 h) ○ increase in receptor density, expresses on both neurons and microglia but only a subset of microglia cells expressed the receptor
	TLR2 [29]	Rat Sprague-Dawley	EMAPII	24 h, 48 h, 96 h	• Few TLR2+ cells expressed day 1 • accumulation of TLR2+ cells became significant on day 2 and increased at day 4 • Nearly all TLR2+ cells in the lesion area were double labeled with EMAPII (activated microglia)

Table 1 (continued)

Injury Model	Receptor	Animal model	Microglia marker	Time points	Effect of Receptor antagonist/blocker in TBI conditions
					• TLR2+ cells in the subcortical white matter expressed GFAP(astrocyte)
	TLR4 [29, 171]	Rat Sprague-Dawley Rat Sprague-Dawley	EMAPII	24 h, 48 h, 96 h 0 h, 6 h, 12 h, 18 h, 24 h, 48 h. 72 h, 7 days, 10 days, 14 days, 21 days	Study 1: • Significant accumulation of TLR4+ cells at day 1 • Increasing continuously until day 4 in both the lesion area and ipsilateral subcortical white matter. TLR4 protein expression in vehicle TBI group increased significatly at 12, 18, 24, 48, and 72 h peaking at 24 h. • TLR4+ cells in the lesion area colocalized with EMAPII, while TLR4+ cells in the subcortical white matter colocalized with GFAP positive astrocytes. • MYD88 levels found same pattern as TLR4 showing activation of the receptor Study 2: • TLR4 proteins were localized to microglia and neurons but not astrocytes. Only morphologically active microglia expresssed TLR4. • PACAP38 peptide Intracerebroventricular treatment was injected before TBI or 24 h after LPS injection • Pretreatment with PACAP38 caused a significant reduction in neurological and motor deficits day 1–21 ○ Decreased edema volume ○ Inhibited TLR4 expression in injured cortex and hipocampus ○ Decreased number of TLR4 expressing microglia but microglia still exhinited reactive morphology ○ Suppressed expression of proteins in the MyD88/NF-jB pathway in the injured cortex and hippocampus
	metabotropic glutamate receptor 5[172, 173]	Rat Sprague-Dawley (250-300 g) Rat Sprague-Dawley (250-300 g)	ED-1 ED-1	24 h 0.5 h, 1 h, 6 h, 12 h 24 h, 3 days	• mGluR5 protein levels rise was significant at 24 h and remained upregulated until 3 days • mGLuR5 mRNA levels upregulated at 0.5 h and peaked at 1 h then decreased below control levels at 24 h • mGluR5 colocalized with NeuN(neurons), GFAP(astrocyte) and ED-1(microglia) • CHPG (mGluR5 agonist) single intracerebroventricular injection ○ Treatment reduced cerebral edema (24 h) ○ Attenuated neuronal degeneration ○ Decreased number of activated microglia ○ Decreased protein levels and mRNA levels of IL-1b, IL-6 and TNF-a ○ Reduced number of degenerating neurons
	P2X4R [30]	Rat Lewis (8–9 weeks)	EMAP-II	24 h, 48 h, 96 h, or 144 h	• P2X4R expression in neurons and perivascular cells did not change with TBI • Morphology and distribution of P2X4R+ cells similar to EMAP-II+ cells • P2x4R+ cells significant increase at day 1 and increasing to maximal levels at day 4 and 6 • intraperitoneal (i.p.) injections of dexamethasone (1 mg/kg, in 1 ml saline, every 2 days ○ Increase in EMAP-II cells at 1 day and 2 days peaking at day 4 and 6 ○ Attenuated increase only on day 1 and 2 not on day 4 or 6 ○ Decreased P2X4R cells day 1 and 2 but no affect on day 4 and 6
		Mouse C57/BL6	CD11b	3 h, 6 h, 24 h, 48 h, 72 h	• TNF/FAS KO mice influenced cognitive deficits independent of cell death

Table 1 (continued)

Injury Model	Receptor	Animal model	Microglia marker	Time points	Effect of Receptor antagonist/blocker in TBI conditions
	TNFR1 and Fas receptor [174]	WT, TNFa knockout (TNFa KO), and TNFa/Fas double-KO			• IBA injured cortex, hippocampus, corpus callosum, periventricular white matter, and choroid plexus at 48 and 72 h after injury • Tumor necrosis factor-a mRNA, Fas mRNA, and TNFa protein were increased in the brain at 3 to 6 h after injury
Blast	CB2 [175, 176]	Mouse C57BL/6 Mouse C57BL/6	CD68 Iba-1, MHC-II	3 days, 2 months, 3 months 3 days, 1 week, 2 weeks, 8 weeks	• Were injected intraperitoneally daily with 6 mg/kg SMM-189 (CB2 agonist) or vehicle for 14 days beginning 2 h after blast exposure ○ SMM-189 biases the CB2 receptor conformation to an inactive state leading to Phosphorylation of CREB ○ Phosphorylation of CREB, promotes transcription Of M2 genes and represses transcription of M1genes ○ Blast alone less than 95% of microglia had no evidence of pCREB (3 days) ○ In treated most if not all microglia exhibited pCREB ○ cortical and striatal neuron loss is reduced by treatment by 50% ○ Reduced motor deficit • injected mice with 6 mg/kg SMM-189 i.p. or vehicle daily for 14 days beginning 2 h after 50-psi blast ○ In vitro SMM-189 decrease microglia expression of IFN-γ, IL-6, IL-10, TNF-α, IL-8, MCP-1, MIP-1β, TARC, MDC, and eotaxin-3 ○ Microglia activation using IBA found by third day in the right dorsal lateral geniculate nucleus and the upper layers of the right superior colliculus ○ Microglia activation evident by third day more prominent by at 1 week, and no longer prominent by 2–8 weeks ○ Microglia activation oberved in brain region with axonal pathology ○ nearly all activated microglia appear to have prominent nuclear labeling for pCREB after daily SMM-189 ○ prevented motor deficits observed in vehicle-treated blast animals ○ reduced deficits invisual acuity ○ treatment reduced depressive symptoms
	Complement type three receptors (CR3), [31]	Rat winstar	ED-1 MHC-II	1 day, 4 days, 7 days, 14 days, 21 days and 28 days	• Expression of CR3 (OX42) increased as early as day 1 in both white and gray matter • Cells appeared hypertrophied and bearing short stout processes. • Immunoreactivity of microglia began to decrease at 21 days and returned to control levels by 28 days

sensorimotor deficits at 4 days post injury. In contrast, at 5 weeks, the CX3CR1 KO mice showed greater sensory motor deficits than that of control mice [156]. These results suggest that microglia-mediated fractalkine receptor signaling is associated with early toxicity but subsequent protection against TBI-induced pathology [156]. Drawing from this study, microglia seem to exacerbate injury outcome at the acute phase, however, it plays a more neuroprotective role at the chronic phase after injury. This was supported by another report that demonstrated a time-dependent role for CX3CL1/CX3CR1 signaling after TBI [132]. They showed that microglia exhibited M2 phenotypic markers (Ym1, CD206, and TGFβ) in the acute phase and predominantly exhibited M1 phenotypic markers CD68 in the chronic phase, owing to the differential outcomes to CX3CR1 deletion after TBI [132]. Moreover, CX3CR1 signaling has been implicated in the infiltration of peripheral immune cells and the resultant neurodegeneration [155]. Taken together, CX3CL1/CX3CR1 signaling modulates microglia activation, and depending upon the type and time of injury, either protects or exacerbates the injury response following TBI.

Purinergic Receptor (P2Y12R)

Microglia respond to extracellular changes in ATP concentration via numerous purinergic receptors. Microglia express both P2Y receptors coupled to G-proteins, as well as, P2X receptors coupled to ligand gated cation channels [183]. In this review, we focus on purinergic receptor P2Y12R, a microglia-specific receptor [184] that mediates microglial chemotaxis towards site of injury [185]. Activation of P2Y12R results in the opening of K+ channel and increased cAMP levels that is implicated in microglia surveillance and chemotaxis towards injury site [186, 187] (Fig. 2). A recent study identified a two-pore domain channel, namely, THIK-1 as the potassium channel involved in microglia ramification and surveillance [186]. However, THIK-1 did not account for site-directed chemotaxis of microglia processes suggesting that another K+ channel may be coupled with P2Y12R and warrants further investigation [186, 187].

In addition to promoting microglia dynamic properties, ATP strongly activates microglia P2Y12R and stimulates the production of cytokines (IL-4, IL-6, IL13, and TNF-α) and chemokines (CCL3) by elevating the intracellular calcium levels [188, 189]. P2Y12R expression in activated microglia is controversial. A number of studies report increased expression of P2Y12R in activated microglia [190–192]. However, there are equally compelling studies that claim that P2Y12R is expressed exclusively in non-activated microglia [50] or alternatively activated microglia [188]. This discrepancy can be explained by the direct correlation between P2Y12R expression and ramified state of microglia [193]. Hence, although these studies claim microglia activation, the expression levels of P2Y12R is a good indication of level and direction of transformation that occurs to the microglia morphological and dynamic state (hyperramified with chemotactic processes versus hyporamified microglia with amoeboid soma).

Microglia P2Y12R is well known for its role as facilitator of process extension and migration following focal injury [193, 194]. In a pig model of diffuse central FPI, microglia processes converged on axonal swellings and exacerbated diffuse axonal injury [195]. Microglia process convergence towards swollen axons and dendrites are mediated by P2Y12R [196, 197]. Recently, P2Y12R-dependant microglial closure of injured blood-brain barrier was shown [98]. Given the cellular specificity of P2Y12R in microglia, it would be the ideal target for targeting microglia activation after TBI.

Toll-like Receptor 4 (TLR4)

Toll-like receptors (TLRs) are first-line molecules for initiating immune responses. Microglia being the only innate immune cells in the CNS, they highly express TLRs, particularly TLR4. Some of the known ligands of TLR4 include lipopolysaccharide (LPS) [198], fibrinogen, heat shock proteins (HSP), high mobility group box protein 1 (HMGB-1) and monosodium urate [199]. TLR signaling initiates acute inflammatory response by promoting the release of proinflammatory cytokines. Ligand binding to TLR4 activates either a MyD88-dependent NF-κB activation or MyD88-independent activation of interferon regulatory factor–3 (IRF-3) activation and the subsequent expression of IFNβ [200] (Fig. 2). In MyD88 deficient mice, Esen and Kielian found that the microglia was only partially inhibited, implying that both MyD88 dependent and independent pathways are functional in microglia [198].

The expression of TLR4 has been shown to be upregulated in various animal models of TBI [171]. Administration of pituitary adenylate cyclase-activating polypeptide (PACAP30), a known TLR4 antagonist, reduced the cognitive and motor decline, neural apoptosis and reduced brain edema in a WD model of TBI [171]. The effects of PACAP30 were strongly associated with microglia-mediated release of IL-1β, and TNF-α, implicating TLR4 in microglia activation and inflammation [171]. Release of excess ~~(~~HMGB1~~)~~, a ligand for TLR4 was reported in TBI patients, as well as in CCI animal model [158]. Genetic or pharmacological (VGX-1027) inhibition of TLR4 attenuated the microglial neuroinflammatory response (IL-6) and limited post-traumatic edema [158]. In line with this, another study demonstrated that deletion of TLR4 (TLR4 KO) resulted in lower M1 phenotypic genes and higher expression of M2 phenotypic markers in microglia [47]. Consequently, the TLR4 KO mice exhibited decreased infarct volumes and improved

outcomes in behavioral tests after TBI [47]. Taken together, TLR4 deficiency contributes to regulating microglia to switch to the M2 phenotype, which ameliorates neurological impairment after TBI.

Scavenger Receptors

Scavenger receptors are a group of evolutionally conserved proteins expressed on the surface of microglia/macrophages and are implicated in initiating phagocytosis, cell adhesion and uptake of ligands [201, 202]. The scavenger receptors known to be expressed in microglia include scavenger receptor-A (SR-A), SR-BI, CD36, and RAGE [201]. Although little is known about the role and function of microglia scavenger receptors in TBI, in this section, we discuss CD36 and RAGE which have been reasonably investigated in animal models of brain injury.

CD36 Receptor

The CD36 receptor, abundantly expressed on microglia/macrophages [203], is used as a marker for microglia activation (M2 state) in TBI [32, 75].

CD36 receptors are activated by the ligand thrombospondin-1 (TSP-1) [204]. Sometimes, the presence of a co-receptor such as TLRs is required for activation, in which case, ligands such as DAMP and oxLDL can also activate CD36 receptors [205, 206]. The activation of CD36 activates different intracellular signaling pathways depending on the ligand, co-receptor, and cell type (Fig. 2). In microglia, CD36 with CD47 activates specific Src family kinases (Lyn, Fyn or Syk) [207], and phosphorylates Vav [208] leading to NADPH oxidase-mediated generation of ROS and promoting phagocytosis [208, 209]. Whereas, co-assembly of CD36 with TLR4/6 is implicated in an inflammatory response through the activation of NLRP3 inflammasome [210].

Although much is known about microglia CD36 in phagocytosis and inflammation, much of this information comes from studies on ischemic injury or AD. The investigation of CD36 in TBI is important because M2-like microglia/macrophages, enriched with CD36, may present a stronger phagocytic ability to remove dead neurons than the M1-like phenotype [211]. Hence, promoting the expression of CD36 may be an ideal therapeutic intervention for attenuating tissue damage and improved recovery following TBI.

RAGE Receptor

The receptor for advanced glycation end products (RAGE) is a multiligand receptor that propagates inflammatory response in various CNS disorders. RAGE expression has been found in microglia, in addition to neurons, astrocytes and endothelial cells in the normal brain [212]. The expression of RAGE and one of its ligands high-mobility group box 1 (HMGB1) was found to be increased in rat and human brains after TBI [213]. They showed that RAGE expression increased mainly in the cytoplasm of phagocytic microglia in the regions surrounding the contused area following TBI [213]. In addition to RAGE, HMGB1 also activates TLR receptors [199]. The intracellular signaling pathway of RAGE involves the key adaptor proteins, MyD88 and TIRAP, which it shares in common with TLR4 signaling [214] (Fig. 2). Activation of these cascades is implicated in the production and release of proinflammatory cytokines, TNFα, IL-1, IL-6, and IL-8, and several chemokines [215, 216].

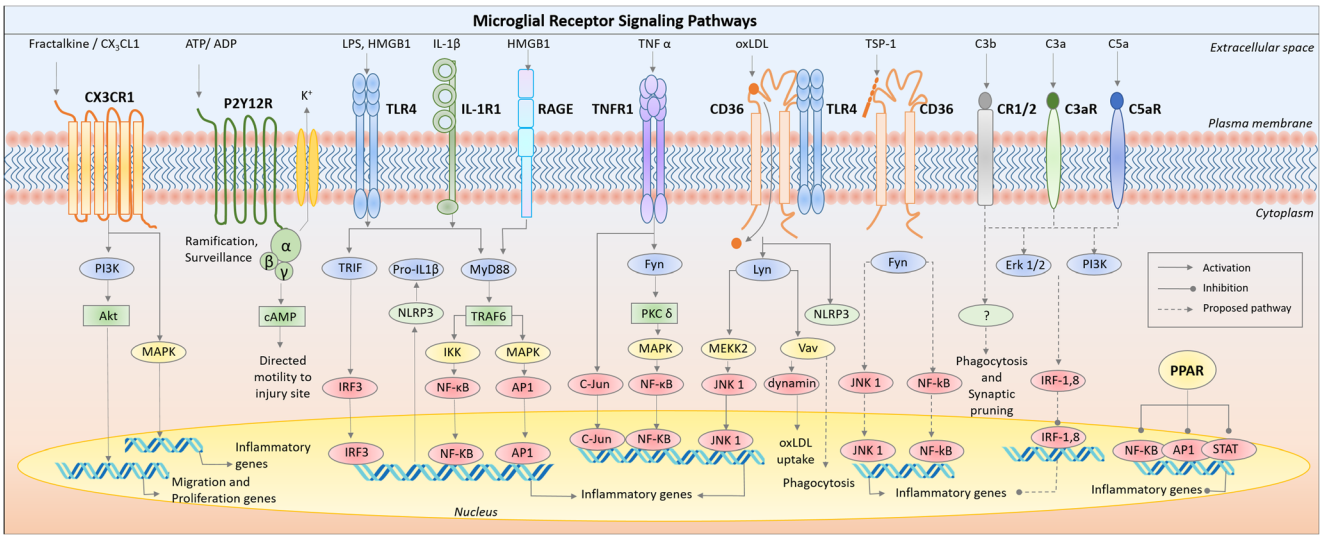

Fig. 2 A schematic depicting various molecular signaling pathway of microglial receptors including CX3CR1, P2Y12R, TLR4, IL1R1, RAGE, TNFR1, CD36, CR1/2, C3aR, C5aR and PPAR

To investigate the role of HMGB1 and RAGE in TBI, Weber et al. used mice deficient in RAGE (RAGE $^{-/-}$) in a CCI model of brain injury [217]. They showed that systemic hypoxia, acute lung injury and pulmonary neutrophilia were attenuated in RAGE −/− mice, suggesting that HMGB1-RAGE axis plays a role in TBI-induced lung dysfunction. In a hemorrhage-induced brain injury model, the expression of HMGB1 and all of its receptors (RAGE and TLR2/4) was upregulated. However, treatment with the RAGE antagonist (FPS-ZM1) significantly reduced the infiltration of inflammatory cells and the expression of IL-1β and MMP-9 after injury. Moreover, the mRNA level of RAGE was also decreased by treatment with anti-HMGB1 mAb after hemorrhagic injury [218]. These studies suggest that RAGE, expressed in microglia or other cells, may be the predominant receptor for HMGB1 in the pathogenesis of inflammation in brain injury.

It is important to note that scavenger receptors have been proposed as targets for therapy in a variety of CNS disorders, including Alzheimer's disease (AD). Hence, understanding the role of scavenger receptors in brain injury may have a major impact on the development of novel therapeutic interventions for the treatment of TBI.

Interleukin-1 Receptor1 (IL-1R1)

Microglia are the prominent source of cytokine interleukin-1 (IL-1) production, yet little is known about the expression of the receptor IL-1R1 in them. Highest expression of IL-1R1 is found on endothelial cells with low expression in microglia and astrocytes [219]. The ligands of the IL-1R1 include IL-1α and IL-1β. The activation of IL-1R1 is transduced through both the NF-kB and the mitogen-activated protein kinase (MAPK) pathways [220]. Upon ligand binding IL-1R accessory protein (IL-1RAP) is recruited. Similar to TLR4 signaling, the formation of the IL11R1 and IL-1RAP heterodimer initiated signal transduction by allowing for recruitment of MyD88 and IL-1R associated kinase 4 (IRAK4), TNFR-associated factor 6 (TRAF6) [220] (Fig. 2).

It has been shown that proliferating microglia express high amounts of IL-1R1 [221]. IL-1β exacerbated, whereas IL-1R agonist attenuated neuronal injury and microglial activation after excitotoxic damage in organotypic hippocampal slice cultures [222]. In a CCI model, neutralization of IL-1β prevented the activation of IL-1R and reduced the activation of microglia at 3 and 7 days post injury [152]. Subsequently, a reduction in lesion volume attenuated cognitive deficits and decreased hemispheric tissue loss [152]. In mice lacking IL-1R1, fewer amoeboid microglia/macrophages appeared adjacent to the injured brain tissue and those microglia present at early post-injury intervals retained their resting morphology in a penetrating brain injury model [223]. This was followed by a significant reduction in inflammatory response such as Cox-2, IL-1, and IL-6 release [223]. These results implicate IL-1R1 in microglial activation after TBI. Since microglia are not the sole expressers of IL-1R1, the recently developed IL1R1$^{loxP/loxP}$ transgenic mouseline [224] can be used to study the microglia-specific role of IL-1R1 in TBI pathology.

NLRP3 inflammasome is a major mediator of IL-1β production via activation of caspase-1. Studies have reported the activation of NLRP3 inflammasome in blunt models of TBI, whereas very few studies were performed in blast TBI [225, 226]. Our interest focus on the NLRP3 inflammasome is due to its known expression in microglia cells [227–229] and that microglial activation is well known in various forms of TBI. NLRP3 the most studied inflammasome is typically found in innate immune cells and is found to be activated by a wide range of stimuli such as viral, bacterial, and fungal components [230, 231], endogenous danger signals such as extracellular ATP [232–234], amyloid-β [227], uric acid crystals [227, 234, 235], and environmental micro particles such as silica crystals [236]. Originally thought to be expressed exclusively in microglia NLRP3 is now found to be expressed in neurons. The time course for expression following TBI differs among the two cell types. Whereas, early (acute) expression is found in neurons and later (subacute) expression to be found in microglia [237]. Weight drop model measured colocalization at 3 days post injury. Liu et found that the mRNA levels of NLRP3 increased at 6 h, 3 days, and 7 days post injury but were at control levels at 24 h after injury. In line with mRNA levels, protein levels increased at all time points except the 6 h time point. NLRP3 was coexpressed in neurons, astrocytes and microglia at the 3 day time point. IL-1β peaked at 6 h and decreased to sham levels by day 7 [238].

Quian et al. found that IL-1beta levels peaked at 6 h and decreased steadily to control levels by day 7 in a mouse model of CCI. IL-18 levels were at control concentration at 6 h but increased at all time points peaking at 7 days. mRNA levels for NLRP3, ASC, and caspase-1 levels increased at 6 h and maximal at 7 days. Although both astrocytes and microglia were activated following injury only microglia were accompanied by strong NLRP3 expression [133].

Tumor Necrosis Factor Receptor (TNFR1)

Microglia express both tumor necrosis factor-α (TNFα), as well as its receptors, TNFR1 (p55) and TNFR2 (p75) [239]. The two native receptors have differential intracellular signaling pathways. In this section, we focus on TNFR1, which contains a death domain. Activation of TNFR1 normally leads to cellular apoptosis; however, under specific conditions,

receptor activation can also lead to the activation of NFκB and contribute to cell survival. These divergent outcomes have been linked to receptor localization with receptor internalization leading to cell death and membrane localization supporting cell survival [240]. Upon ligand binding with TNFR1, the signal is transduced via transcription factors such as NF-κB and c-Jun which in turn are involved in immune, stress and inflammatory responses [241] (Fig. 2).

The expression levels of TNF- α and its associated receptors have been correlated with trauma severity in patients admitted with TBI [242]. Genetic deletion of TNFR1 (TNFR1 KO) showed attenuation of motor deficits at 4-weeks following CCI [161]. In contrast, absence of TNFR2 (TNFR2 KO) resulted in worsening of motor deficits as compared to the control [161]. The study showed that TNF-α-TNFR1 signaling was proinflammatory in nature whereas, TNF-α-TNFR2 signaling was anti-inflammatory in nature [161]. Surprisingly, an independent study observed no differences in motor or cognitive outcome in either TNFR1, TNFR2 KO, or TNFR1/TNFR2/Fas mice, versus wild-type mice following CCI [243]. These conflicting data may be attributable to differences in the severity of the CCI models used, as well as anesthetic agent, differences in background strain genetics in TNFR KO mice, and other model-specific factors in the studies [244].

As mentioned earlier, the downstream signaling of TNFR1 may be neuroprotective or neurotoxic depending upon the sub-cellular localization of the receptor. In the normal rat cortex, a portion of TNFR1 is located in lipid raft microdomains, where it is associated with the adaptor proteins TRADD (TNF receptor-associated death domain), TNF receptor-associated factor-2 (TRAF-2), the Ser/Thr kinase RIP (receptor-interacting protein), TRAF1, and cIAP-1 (cellular inhibitor of apoptosis protein-1), forming a survival signaling complex. Moderate TBI resulted in rapid recruitment of TNFR1, but not TNFR2 or Fas, to lipid rafts and induced alterations in the composition of signaling intermediates. Activation of TNFR1 after TBI induced the expression of caspase-8, thus initiating apoptosis and transient activation of NF-κB [245]. In CCI model, studies have identified co-expression of TNFR1 and TNFR2 in both microglia and endothelial cells, thereby implicating TNFR signaling in the pathogenesis of TBI [246, 247]. In brain injury models such as FPI and CCI, elevated TNF-α levels are found in the injured brain and inhibition of TNF- α and its receptors has been beneficial to postinjury cell death and functional outcome [163, 248]. However, in WD/concussive brain injury model, inhibition of TNF- α and Fas receptor resulted in cognitive decline independent of neuronal loss [174]. Hence, a better understanding of TNF-α -TNF1R signaling in the various injury models is needed to develop therapies targeting TNF1R for treatment of TBI.

Compliment Receptor

The complement receptors, part of the innate immune system, are expressed by astrocytes and microglia in the brain. The complement receptors expressed by microglia include CR1, CR2 C3aR, and C5aR [249–252]. The CR1 and CR2 are activated by C3b ligand, whereas, C3aR and C5sR are activated by C3a and C5a, respectively. The intracellular signaling following complement receptor activation involves ERK1/2 and PI3K that in turn suppresses transcription factors such as IRF-1 and IFR-8, reducing the expression of IL-12, IL23 and Il-27 [253, 254] (Fig. 2). A detailed review on complement systems and their role in various CNS disorders such as TBI have been described previously [255–257].

In the normal brain, the endogenous levels of complement ligands such as C3 and C5a are low. However, TBI is often accompanied by breakdown of the BBB which introduces a massive influx of complement components to the low endogenous levels, as well as, infiltration of adaptive immune cells capable of producing complement components [258]. In addition, TBI can also elevate the endogenous levels of C3, as noted in rat models of TBI and in head-injured patients [259–261].

The role of complement receptors in TBI was first shown by Kaczorowski et al., using soluble complement receptor 1 (sCR1) [262]. They showed that rats treated with sCR1 resulted in reduced brain neutrophil infiltration compared to vehicle-treated rats, suggesting that complement plays a pivotal role in the neuroinflammatory response induced by TBI [262]. This was further confirmed in mice lacking C3 ($C3^{-/-}$), in which there was reduced leukocyte infiltration, microglial activation, and edema following intracerebral hemorrhage-induced brain injury [263]. Similarly, in a CCI model of TBI, $C3^{-/-}$ mice showed reduced leukocyte infiltration compared to the wild-type mice; however, there was no difference in lesion size or behavioral deficits [264]. In a closed head injury model, mice lacking CR1/CR2 receptors demonstrated decreased astrocytosis, reduced microglial activation, and attenuated immunoglobulin M deposition in injured brains compared to wild-type mice [265].

Studies have also investigated the role of C5aR and its ligand C5a in TBI-induced secondary injury. To this end, mice lacking C5 ($C5^{-/-}$) or administration of C5aR antagonist resulted in reduced secondary damage in a cryoinjury model of TBI [266]. In an intracerebral hemorrhage-induced brain injury model, application of hexapeptide-derived macrocycle AcF (OPdChaWR), a C5aR antagonist, improved the spatial memory as well as general neurological outcomes [267]. This improvement correlated with a reduction in infiltrated leukocytes and edema formation [267]. In addition, a combination of C5aR and a C3aR antagonist compounded the observed neuroprotective effect [267]. Taken together, these studies suggest that targeting the complement system (receptors and/or their

ligands) may represent a promising future approach for therapeutic immunomodulation after TBI.

Peroxisome Proliferator-Activated Receptor (PPAR)

The peroxisome proliferator-activated receptors (PPAR) are a member of nuclear membrane receptor family and have been shown to be important for inflammatory signaling in microglia [149]. There are three isoforms of the receptor PPARα, PPAR δ/β, and PPARγ [268]. Of the three isoforms, only PPARα and PPARγ are implicated in inflammation. The numerous agonists and antagonists of PPARs are listed in Supplementary Table 1. Upon activation, the PPARs regulate inflammation via trans-reexpression of multiple inflammatory signaling systems such as nuclear factor-kappa B (NFκB), activator protein-1 (AP-1), signal transducer and activator of transcription (STAT) [269]. Although the endogenous ligand may not achieve critical concentration to activate the receptor a lot of research has gone into its role in TBI treatment.

Following CCI, mRNA levels of PPARγ have been reported to be elevated surrounding the injury site [49]. Agonists for both PPARα and PPARγ have been studied due to their ability to affect multiple signaling pathways and reduce TBI-induced neuropathology. Fenofibrate, a PPARα agonist, has been shown to reduce oxidative stress and inflammation after TBI [270, 271]. Similarly, Pioglitazone and Rosiglitazone, both PPARγ agonists, have been shown to reduce oxidative stress [49], inflammation [272–274], mitochondrial dysfunction [164, 275] and cell death [163, 272, 276] following CNS injury. Using rosiglitazone, a known PPAR-γ agonist, Liu et al. observed a decrease in expression of TNF-α, decreased microglia activation, increased neuronal survival and improved performance in motor function tasks at 24 h after CCI [163]. Pioglitazone also reduced lesion volume by 55% and prevented microglial activation in the tissue surrounding lesion after TBI [164]. In FPI injury model, a single dose of Pioglitazone administration reduced oxidative damage, decreased microglia activation, decreased neural degeneration, and reduced edema formation [167]. However, Pioglitazone administration was not found to have an influence on reactive astrogliosis [167]. It is important to note that PPAR expression in the brain in not exclusive to microglia [277]. Hence, whether the effect of the PPAR agonist/antagonists is due to the direct/ indirect action on microglia PPAR remains unclear. However, the pharmacological studies consistently show the involvement of PPAR signaling in microglial activation after TBI, making it a worthy therapeutic target.

Conclusion

In the various models of TBI, microglia activation varies based on the type and severity of injury. Microglia receptors act as sensors for identifying these subtle changes in the neuronal parenchyma and lead to various modes of microglia activation. Hence, the expression pattern of microglia receptors can be used as a signature to identify the injury severity/ mechanism following TBI. In the light of the above, it is evident that microglia receptor activation plays an important role in post-injury pathology and may be a sensitive diagnostic tool. Moreover, pharmacologically targeting microglia-specific receptors will prevent alterations in neuronal physiology, and thereby reduce unwanted side-effects. Hence, microglia receptors may be a potent therapeutic target for the treatment of brain injury. An ideal therapeutic strategy would be to potentiate the protective properties of microglia and attenuate its neurotoxic behavior by activating and inhibiting the appropriate anti-inflammatory and pro-inflammatory receptors, respectively.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no competing interests.

Abbreviations Akt, protein kinase B; AP-1, activator protein-1; APP, amyloid precursor protein; Arg-1, arginase-1; ATP, adenosine triphosphate; BBB, blood-brain barrier; CCI, controlled cortical impact/injury; cFPI, central FPI; cIAP-1, cellular inhibitor of apoptosis protein-1; CNS, central nervous system; CR, complement receptor; CX3CR1, chemokine receptor 1; CXCL1, fractalkine; DAMPS, danger associated molecular patterns; EC, endothelial cells; FPI, fluid percussion injury; GOAD, Gila open access database; HAPI, highly aggressively proliferating immortalized; HMGB1, high mobility group box protein 1; HSP, heat shock protein; IL-1R1, interleukin 1 receptor; IL-1β, interleukin 1β; IRAK4, IL-1R associated kinase 4; IRF-3, interferon regulatory factor–3; KO, knockout; LFPI, lateral FPI; LPA, lysophosphatidic acid; LPS, lipopolysaccharide; MAPK, mitogen-activated protein kinase; MIP-1α, macrophage inflammatory protein-1α; mRNA, messenger RNA; NADPH, nicotinamide adenine dinucleotide phosphate; NFκB, nuclear factor-kappa B; NOX, NADPH oxidase; PACAP30, adenylate cyclase-activating polypeptide; PAMPS, pathogens associated molecular patterns; PCR, polymerase chain reaction; PPAR, peroxisome proliferator-activated receptors; RAGE, receptor for advanced glycation end products; RIP, receptor-interacting protein; RNA, ribonucleic acid; RNA-seq, RNA sequencing; RNS, reactive nitrogen species; ROS, reactive oxygen species; STAT, signal transducer and activator of transcription; TBI, traumatic brain injury; TLR4, Toll-like receptor 4; TNF α, tumor necrosis factor α; TNF-R1, TNFα receptor 1; TRADD, TNF receptor-associated death domain; TRAF-2, TNF receptor-associated factor-2; TSPO, translocator protein; WD, weight drop

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