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Microglial polarization pathways and therapeutic drugs targeting activated microglia in traumatic brain injury

Liping Shi[1, 2], Shuyi Liu[1, 2], Jialing Chen[1, 2], Hong Wang[1, 2, *], Zhengbo Wang[1, 2, *]

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From the Contents

Abstract

Traumatic brain injury can be categorized into primary and secondary injuries. Secondary injuries are the main cause of disability following traumatic brain injury, which involves a complex multicellular cascade. Microglia play an important role in secondary injury and can be activated in response to traumatic brain injury. In this article, we review the origin and classification of microglia as well as the dynamic changes of microglia in traumatic brain injury. We also clarify the microglial polarization pathways and the therapeutic drugs targeting activated microglia. We found that regulating the signaling pathways involved in pro-inflammatory and anti-inflammatory microglia, such as the Toll-like receptor 4 /nuclear factor-kappa B, mitogen-activated protein kinase, Janus kinase/signal transducer and activator of transcription, phosphoinositide 3-kinase/protein kinase B, Notch, and high mobility group box 1 pathways, can alleviate the inflammatory response triggered by microglia in traumatic brain injury, thereby exerting neuroprotective effects. We also reviewed the strategies developed on the basis of these pathways, such as drug and cell replacement therapies. Drugs that modulate inflammatory factors, such as rosuvastatin, have been shown to promote the polarization of anti-inflammatory microglia and reduce the inflammatory response caused by traumatic brain injury. Mesenchymal stem cells possess anti-inflammatory properties, and clinical studies have confirmed their significant efficacy and safety in patients with traumatic brain injury. Additionally, advancements in mesenchymal stem cell-delivery methods—such as combinations of novel biomaterials, genetic engineering, and mesenchymal stem cell exosome therapy—have greatly enhanced the efficiency and therapeutic effects of mesenchymal stem cells in animal models. However, numerous challenges in the application of drug and mesenchymal stem cell treatment strategies remain to be addressed. In the future, new technologies, such as single-cell RNA sequencing and transcriptome analysis, can facilitate further experimental studies. Moreover, research involving non-human primates can help translate these treatment strategies to clinical practice.

Key Words: animal model; anti-inflammatory drug; cell replacement strategy; central nervous system; mesenchymal stem cell; microglia; neuroinflammation; non-human primate; signaling pathway; traumatic brain injury

Introduction

Traumatic brain injury (TBI) is generally the result of a mechanical insult, such as a fall or impact, which triggers a head event leading to focal craniocerebral hemorrhage, epidural/subdural hematoma, and direct axonal injury (Celorrio et al., 2024; Zhu et al., 2024). This primary injury can potentially induce a secondary injury, which is characterized by disruption of blood–brain barrier (BBB) permeability, neuronal dysfunction, synaptic structure breakdown, astrocyte hyperplasia, leukocyte proliferation, axonal degeneration, cell death, and persistent neuroinflammation. Collectively, these factors contribute to the neurological impairments observed post-TBI (Kim et al., 2023; Oddo et al., 2023; Svedung Wettervik et al., 2023). Furthermore, these injuries can lead to functional impairment, long-term neurological and psychiatric sequelae, such as anxiety, depression, post-traumatic stress disorder, Alzheimer's disease, chronic traumatic encephalopathy, Parkinson's disease, and amyotrophic lateral sclerosis, and, in severe cases, death (Jiang et al., 2019). Therefore, TBI has become a major public health issue and socioeconomic burden. Although this type of injury cannot be completely prevented, mitigation of the progression of secondary injury pathology is an important treatment strategy (Gyoneva and Ransohoff, 2015).

As a key participant in the pathogenesis of TBI, inflammation can serve as an important focus for early intervention in the treatment of brain injury (Lou et al., 2024). Reducing inflammation may help alleviate further damage caused by TBI to some extent (Corps et al., 2015). Microglia, the resident immune cells of the central nervous system (CNS) (Jassam et al., 2017; Feng et al., 2024; Huo et al., 2024), are preferentially activated in response to TBI and play crucial roles in neuroinflammation. In this review, we summarize the functions of microglia and their changes following TBI, including the polarization mechanisms of M1-like and M2-like subtypes. We also discuss the current therapeutic drugs that target microglia, which are essential for managing neuroinflammation after TBI. We explore the therapeutic benefits of pharmacological interventions and mesenchymal stem cell (MSC) treatments in the context of TBI, highlighting the advantages and challenges associated with each approach. Additionally, we outline a series of ideas for future research aimed at advancing TBI treatment and enhancing our understanding of the potential of these modalities to facilitate neurorecovery and improve patient outcomes.

Literature Retrieval Strategy

The articles used in this review were retrieved mainly using keywords such as "traumatic brain injury," "microglia," "animal models," "neuroinflammation," "signaling pathways," "anti-inflammatory drugs," and "mesenchymal stem cells." The US Centers for Disease Control and Prevention database was used to search for clinical data related to TBI. The search terms were as follows: traumatic brain injury, number of illnesses

[1]State Key Laboratory of Primate Biomedical Research, Institute of Primate Translational Medicine, Kunming University of Science and Technology, Kunming, Yunnan Province, China; [2]Yunnan Key Laboratory of Primate Biomedical Research, Kunming, Yunnan Province, China
*Correspondence to: Zhengbo Wang, PhD, wangzb@lpbr.cn; Hong Wang, PhD, wangh@lpbr.cn.
https://orcid.org/0000-0002-4717-5137 (Zhengbo Wang)

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and deaths, major population groups, causes of illness and death, region or country. We conducted a comprehensive search of the latest PubMed articles on TBI epidemiology, clinical diagnosis, and conventional treatment (e.g., Carney et al., 2017). The literature regarding animal models of TBI from 1988 to 2024 was searched in the PubMed database using the following terms: "traumatic brain injury" and "animal models," "animal experiments," "animal physiology," or "animal behavior." After screening titles and abstracts, we included studies that focused on rodents (such as rats and mice), rabbits, dogs, pigs, and non-human primates (NHPs). Non-scientific experiments and review articles were excluded from our analysis.

Additionally, we explored the role of microglia in TBI by searching the PubMed database with the following terms: "central nervous system" and "microglia," as well as "traumatic brain injury" and "microglia." Subsequently, we conducted further searches for content related to the occurrence and development of microglia, their classification, nomenclature, function, single-cell RNA sequencing (scRNA-seq), and neuroinflammation. Furthermore, we performed an electronic search for "signaling pathways associated with microglial cells in traumatic brain injury" in the PubMed database, focusing on articles published from 2012 to 2023. The search terms included "traumatic brain injury," "microglia," and "signaling pathways." We then refined our search to include the following terms: "cell phenotypic transformation," "neuroinflammation," "pro-inflammatory factors," "cytokines," and "epigenetic modification."

Drugs for the treatment of microglia in TBI were searched through the PubMed database using the following search terms: "traumatic brain injury," "microglia," and "drugs." After the results are obtained, further searches are made for content related to treatment strategies and therapeutic effects by using the following terms: "inhibition of inflammation," "inhibition of signaling pathways," "neuroprotection," and "cell phenotypic transformation." Finally, the relevant literature for "mesenchymal stem cells in preclinical and clinical treatment of traumatic brain injury" in the PubMed database was electronically searched. The search terms are as follows: "traumatic brain injury," "mesenchymal stem cells or stem cell transplantation," "microglia," "models or preclinical applications," and "human or clinical applications." A further search for content related to treatment strategies and therapeutic effects was performed using the following terms: behavioral improvement, functional recovery, immune regulation, suppression of inflammation, neuroprotection, nerve repair, and cell phenotypic transformation.

Epidemiology of Traumatic Brain Injury

TBI is a major public health issue and socioeconomic burden, ranking as one of the leading causes of death and disability (Raees et al., 2022; Gao et al., 2024). According to a systematic analysis from the Global Burden of Disease Study 2021, approximately 52.7 million people worldwide sustain TBI each year (Collaborators, 2024). The incidence and causes of TBI vary widely across countries, and are influenced by differences in healthcare systems and socioeconomic conditions. The survival rates of patients with TBI are significantly correlated with factors such as age, clinical scores, injury severity, computed tomography (CT) findings, and Gross Domestic Product per capita. Global data indicate that low- and middle-income countries report three times as many TBI cases as high-income countries.

In low- and middle-income countries, including China, traffic accidents are the primary cause of TBI, which particularly affect vulnerable road users such as pedestrians and non-motor vehicle drivers. In some low-income countries, especially in the Middle East, shootings have also emerged as a leading cause of TBI. Overall, the main causes of TBI remain concentrated among traffic accidents, falls, sports-related injuries, and violence. Interestingly, the incidence of TBI decreased during the coronavirus disease 2019 (COVID-19) pandemic, likely due to reduced outdoor activity and participation in physical and recreational activities (Yuan et al., 2023). Recommendations to mitigate the incidence of TBI include enhancement of road traffic safety education and implementation of stronger protective measures in sports activities. Although many epidemiological studies on TBI have focused on quantifying its prevalence, the true prevalence remains unknown due to the complex causative factors and individual differences among patients.

The current diagnosis of TBI typically requires a medical evaluation and imaging tests, along with a review of the patient's medical history (Carney et al., 2017). Initial assessment of the patient's injuries is often performed using several scales, such as the Glasgow Coma Scale (GCS), which is a common clinical tool for evaluating the level of consciousness. The GCS measures the degree of consciousness disturbance based on the patient's eye responses, verbal abilities, and motor functions. A head CT scan can detect intracranial hemorrhage and skull fractures, while a head magnetic resonance imaging (MRI) scan can provide detailed images of brain tissue. Additionally, an electroencephalogram (EEG) can reveal epileptic activity and abnormal brain function (Smith et al., 2019). On the basis of their scores and medical diagnoses, patients can be classified as showing mild, moderate, or severe TBI. Typically, 80% of patients experience mild TBI, commonly known as a concussion. Mild TBI can lead to symptoms such as headaches, nausea, and temporary loss of consciousness; however, these symptoms can often be alleviated with conservative treatments, including analgesics, anti-epileptic medications, and antidepressants.

Moderate-to-severe TBI can result in prolonged coma, memory problems, cognitive difficulties, and even death. Thus, surgical interventions may be necessary, including craniotomy, hematoma removal, and decompression. Additionally, combining physical, speech, occupational, and psychological rehabilitation therapies is essential to help patients return to normal life as much as possible. Moderate and severe TBI are often associated with high rates of disability and mortality, and they can increase the risk of degenerative diseases in affected individuals. Current treatments primarily focus on interventions aimed at correcting the pathophysiology of the condition, but effective treatment strategies remain limited. Researchers are continually exploring new therapeutic approaches, including pharmacological interventions, cell therapy, and neuroprotective strategies, to improve the outcomes for patients with TBI.

Animal Models Help Reveal the Pathology of Traumatic Brain Injury

TBI arises from a multitude of distinct external forces, which vary in their mechanisms of action, magnitude, and spatial impact. The clinical presentations and pathological characteristics of patients with TBI exhibit a wide spectrum of variability due to the complexity and heterogeneity of the brain (Rosenbaum and Lipton, 2012). Consequently, TBI manifests as a multifaceted and dynamic process. On the basis of the mechanisms and pathological changes associated with the injury, TBI can be divided into primary and secondary injuries (Razavi et al., 2025). Primary injury refers to brain damage that occurs as a direct result of a traumatic event, encompassing conditions such as cerebral concussion, brain contusion, brain laceration, diffuse axonal injury, and cerebral vascular rupture. This primary injury can potentially instigate secondary injuries, which are initially characterized by disruption of BBB permeability (Logsdon et al., 2015). The BBB is a protective structure composed of astrocytes and vascular endothelial cells that acts as a defense mechanism at the periphery of the CNS to shield the brain from peripheral immune responses (George et al., 2022). When traumatic events occur, BBB permeability is compromised, leading to the breakdown of tightly connected endothelial cells and passage of macromolecules, eventually resulting in brain edema (Hernandez et al., 2023). Additionally, inflammatory factors derived from the blood can enter the brain and stimulate glial cells, inducing a chronic neuroinflammatory response. Chronically activated microglia further promote the expression of pro-inflammatory cytokines, exacerbating neuroinflammation. Over time, excessive and uncontrolled inflammation can impair neuronal function and the integrity of the BBB, leading to neuronal dysfunction, synaptic breakdown, astrocyte hyperplasia, leukocyte proliferation, axonal degeneration, cell death, and persistent neuroinflammation. These processes ultimately contribute to the neurological impairments following TBI (Svedung Wettervik et al., 2023). Understanding the pathology of TBI is essential for developing effective treatment strategies. Various preclinical animal models have been established to study the pathophysiology of TBI and explore therapeutic interventions. Early TBI models primarily utilized zebrafish, fruit flies, rabbits, and other small animals. However, with the increasing application of rodent models, rats and mice have become the mainstream subjects of research.

TBI animal models can be divided into four

types on the basis of the nature of the damage: mechanical force damage models, pressure-damage models, explosion damage models, and repeated mild damage models, as detailed in **Table 1**. Commonly used models for mechanical force injury include the weight-drop injury (WDI) model and the controlled cortical impact (CCI) model. In the WDI model, brain damage is induced by dropping a weight onto the dura mater or skull from a controlled height, with the weight and the height of the drop determining the severity of the injury (Marmarou et al., 1994). This model results in cortical contusions, hemorrhagic lesions, BBB disruption, immune cell infiltration, and glial cell activation, mirroring the pathology observed in TBI patients. In the CCI model, brain damage is caused by the impact force generated when a high-speed moving air-driven metal probe strikes the exposed dura mater (Lighthall, 1988). In comparison with the WDI model, the CCI model offers better repeatability, stability, and a more accurate pathological replication of TBI. It effectively simulates cortical tissue loss, BBB dysfunction, and neuronal impairment following injury. Commonly used pressure-damage models include the fluid percussion injury (FPI) model and the penetrating ballistic-like brain injury (PBBI) model (Davis et al., 2010). In the FPI model, brain injury is induced by rapidly injecting a specific volume of normal saline into the cranial cavity, deforming and displacing brain tissue. This results in intracranial hemorrhage, brain swelling, and asymptomatic gray matter injury, mirroring the pathological features of TBI without causing skull fractures. On the other hand, the PBBI model simulates damage from a high-energy projectile and shock wave, with the extent of injury being dependent on the trajectory of the projectile and the energy transferred, which leads to extensive intracranial hemorrhage akin to moderate and severe TBI. Blast traumatic brain injury (bTBI) refers to the TBI caused by blast waves and projectiles, a significant concern in modern warfare. bTBI models include the free-field explosion model, explosion tube model, small explosion source model, and advanced blast simulator (ABS) model (Campos-Pires et al., 2018). Notably, the ABS model does not utilize explosives; instead, it is powered by compressed gas. Repeated mild TBI is often observed in contact sports (such as boxing, basketball, and football) and in cases of domestic violence. Although mild brain injuries are frequently overlooked, repeated mild TBIs can lead to catastrophic or fatal consequences (Fehily and Fitzgerald, 2017).

While numerous rodent models of TBI have been extensively cited in this review, facilitating the investigation of TBI pathophysiology and the development of innovative therapeutic strategies, the translation of these preclinical findings to clinical practice presents considerable challenges. The interspecies differences between rodents and humans are the primary factor complicating the direct extrapolation of outcomes from rodent TBI models to humans. Additionally, the distinct physiological and metabolic profiles of rodents in comparison with humans may hinder accurate modeling of disease progression and fail to adequately replicate the complex etiology and cascade of secondary injury mechanisms characteristic of TBI in patients. Furthermore, the significant divergence in motor behaviors and cognitive functions between rodents and humans limits the comprehensive assessment of neural functional recovery associated with TBI. Moreover, variability in preparation protocols and operational consistency across TBI animal models can lead to discrepancies in model characteristics, compromising the uniformity and reliability of research outcomes. These considerations highlight the need for large-animal models such as NHPs and pigs, which exhibit greater anatomical and physiological similarities to humans, in future research endeavors. Pig brains, in particular, show a significant degree of anatomical and histological resemblance to human brains, especially in terms of dimensions, structures, and developmental patterns. These similarities enable the porcine model to more accurately simulate the type, location, and severity of injuries observed in human TBI. Currently, the established models in pigs include porcine models for diffuse axonal injury, CCI, and FPI (Kinder et al., 2019). Several treatment strategies have also been validated in porcine TBI models. For example, polynitroxylated PEGylated hemoglobin has been found to have neuroprotective effects in a CCI pig model with hemorrhagic shock; it was shown to preserve neocortical gray matter, including dendritic microstructures, as well as white matter axons and myelin (Wang et al., 2023). NHPs also share a significant degree of genetic homology with humans and possess sophisticated brain functional architectures and neural activities that are unmatched among other experimental animals. As a result, they can serve as optimal models for investigating human neurological disorders. For instance, in a rhesus monkey model of superficial TBI, the transplantation of neural stem cells combined with the injection of growth factors resulted in the survival of neural stem cells for at least 1 year and their differentiation into neurons (Liu et al., 2024). This study represents the first exploration of the reparative efficacy of neural stem cells following their transplantation into the superficial cerebral cortex of rhesus monkeys post-TBI, highlighting the unique advantages conferred by NHP models in transformative neurobiological research. Nonetheless, the use of large-animal models in research is associated with increased financial and resource demands as well as heightened ethical considerations. Therefore, researchers should aim to carefully balance scientific rigor with ethical constraints while advancing TBI research toward clinical relevance. Preclinical models of TBI can reproduce the pathophysiological process by simulating the damage caused by external mechanical forces; this approach can confirm the pathological changes in TBI patients and provide a platform for researchers to observe the post-TBI changes in neurons, neurotransmitters and related signaling pathways. In addition, the model can help researchers evaluate the effects of different treatments and provide an experimental basis for the development of therapies. On the basis of the pathological phenotypes of TBI patients and TBI animal models described above, the neuroinflammatory response can be considered to be a conserved signature of long-term pathophysiology. Therefore, we chose the microglia, the resident immune cells in the CNS, as the target to review the inflammatory process of TBI.

Table 1 | **Common animal models of TBI and their characteristics**

Category		Clinically relevant patient type	Type of injury	Advantage	Disadvantage	Reference
Mechanical injury	Feeney WDI	Simulate focal or diffuse injury in a patient caused by fall or impact	Contusion of the cerebral cortex	The method is simple and the condition is easy to control.	High fatality rate	Estrada-Rojo et al., 2018
	Marmarou WDI		Diffuse injury	The method is simple and the condition is easy to control.	High fatality rate	Foda and Marmarou, 1994
	CCI		Cortical deletion	Good repeatability, accurate injury.	Expensive equipment	Lighthall, 1988
Stress injury	FPI	Simulate injury mainly caused by falls and sports accidents, and reproduce the contusion and bleeding caused by brain tissue deformation and displacement	Intracranial hemorrhage and brain swelling	Good repeatability and high stability.	The pathogenic mechanism and clinical difference are great.	Dixon et al., 1987
	PBBI		Intracranial hemorrhage and increased intracranial pressure	The treatment is similar to the clinical conditions.	Standardization and special equipment are required.	Davis et al., 2010
Blast injury	bTBI	Simulates pure diffuse damage caused by bomb shock wave propagation to soldiers and people in the field	Blast wave damage	The injuries are similar to war wounds.	Special equipment and jet effects are required.	Kovacs et al., 2014
	ABS		Blast wave damage	Indoor operability and high safety.	Diaphragm fragments are susceptible.	Campos-Pires et al., 2018
Repeated mild injury		Simulates mild injuries from prolonged activities such as simulated contact sports and domestic violence	Diffuse brain injury	The injury is clinically similar.	Need to standardize	Fehily and Fitzgerald, 2017

ABS: Advanced blast simulator; bTBI: blast-induced traumatic brain injury; CCI: controlled cortical impact; FPI: fluid percussion injury; PBBI: penetrating ballistic-like brain injury; WDI: weight-drop injury.

Functions of Microglia in Traumatic Brain Injury

Functions of microglia in the central nervous system

The CNS includes the brain and spinal cord and consists of neuroectodermal cell tissue, macrophages, and resident immune cells. These resident immune cells play crucial roles in modulating immune responses during the development, health, and disease of the organism. The primary types of resident immune cells in the CNS are microglia and CNS-associated macrophages (Checa-Ros et al., 2021). Microglia reside within the parenchyma of the CNS, while CNS-associated macrophages and other immune cells are located at the boundaries of the CNS and the choroid plexus (Carney et al., 2017). Microglia originate from early myeloid progenitor cells in the yolk sac of the embryo rather than from the bone marrow. These progenitor cells migrate to the developing neural tube and undergo proliferation (Ginhoux et al., 2010; Barry-Carroll and Gomez-Nicola, 2024). Once mature, microglia colonize the entire parenchyma and possess the ability to divide continuously (Schulz et al., 2012), distinguishing them from neurons and forming the basis for their complex functions.

Previous studies have shown that microglia account for 5%–20% of the total glial population in the CNS, 5% of the glial populations in the cerebral cortex and corpus callosum, and 12% of those in the hippocampus, basal ganglia, and substantia nigra. These variations may contribute to the differing vulnerabilities of various neurons (Tan et al., 2020; Prinz et al., 2021). Microglia perform essential physiological functions by expressing a variety of receptor families, including scavenger receptors, low-density lipoprotein receptor families, receptor tyrosine kinases, and pattern recognition receptors (Merighi et al., 2022). The chemokine receptor family and integrins promote microglial migration and localization within the CNS, facilitating their ability to bind, phagocytose, and remove target cells (Mecca et al., 2018). Additionally, microglia express receptors for neurotransmitters and neuropeptides, enabling communication between neurons and microglia, as well as the secretion of neurotrophins and support for neural regeneration (Carniglia et al., 2017).

Under normal physiological conditions, microglia monitor the brain's microenvironment in a resting state and facilitate the maintenance of brain homeostasis by removing cell debris and toxic substances. They are also involved in various physiological activities, such as reducing synaptic strength and number during sleep (Choudhury et al., 2020) and mediating the forgetting of long-term memories through complement-dependent synaptic elimination (Wang et al., 2020a). Moreover, microglia with a unique amoeboid morphology invade the corpus callosum and engulf oligodendrocyte progenitor cells during early postnatal development, prior to myelination, in a fractalkine receptor (C–X3–C motif chemokine receptor 1)-dependent manner to modulate the ensheathment of axons (Irfan et al., 2022). The characteristics of microglia vary with developmental stages and the brain microenvironment. For instance, microglia exhibit different activation states during development and adulthood, with environmental factors influencing their highly dynamic morphology (Colombo et al., 2022). Currently, the functional status of microglia is primarily analyzed through their morphological and molecular characteristics; however, the precise contributions of microglia to the CNS under both physiological and pathological conditions require verification through specific cell and gene ablation studies *in vivo*.

Classification of microglia

With advancements in technologies and research methods, more microglial phenotypes are being discovered. These newly identified phenotypes are often specific to particular diseases, brain regions, and functions, providing a crucial foundation for studying the pathological processes underlying the development of specific diseases and for developing targeted interventions. In this review, we briefly summarize the studies on microglial phenotypes and their nomenclature.

Microglia exhibit distinct activated features depending on their microenvironment. Traditionally, researchers have classified microglia into two "opposite" states: the "classical activation" state (M1 phenotype) and the "alternative activation" state (M2 phenotype) (Colton and Wilcock, 2010; Wu et al., 2021). In this classification scheme, M1 microglia are considered pro-inflammatory cells that participate in the inflammatory response by releasing pro-inflammatory factors such as interferon-gamma (IFN-γ), tumor necrosis factor (TNF)-α, and interleukin (IL)-1 beta. This activity can lead to a dysregulated inflammatory response, exacerbating tissue damage and neuronal death (Colton and Wilcock, 2010; Wu et al., 2021). Conversely, M2 microglia are seen as anti-inflammatory cells that secrete anti-inflammatory factors and upregulate neuroprotective factors, including IL-10 and transforming growth factor-beta (Fu et al., 2022). Despite the longstanding use of this simple classification, a group of multidisciplinary experts has recently proposed a new conceptual framework and recommendations for microglial nomenclature (Izzy et al., 2019). They argue that the current dichotomy of "resting *versus* activated" or "M1 *versus* M2" microglia is insufficient to capture the diverse states and functions of microglia. For example, studies based on *in vitro* activators have shown that M2 microglia can be further divided into three subtypes characterized by different stimulating factors and markers: M2a, M2b, and M2c (Kreider et al., 2007; Kisucká et al., 2021). Among these, the M2a subtype is marked by IL-4 and IL-13 and is the cell subtype that emerges during the initial stage of microglial activation. M2a microglia can compete with the M1 phenotype for arginine, acting as an anti-inflammatory subtype. The M2b subtype represents a mixed activation state of microglia, capable of producing both pro-inflammatory and anti-inflammatory cytokines. The M2c subtype can be triggered by IL-10, which helps to shut down the immune response of microglia (Walker and Lue, 2015). Furthermore, scRNA-seq, transcriptomics, and proteomics analyses can be used to define microglial states in terms of morphology and function across various stages, including development, aging, and disease. For instance, Zheng et al. (2021a) utilized scRNA-seq to compare microglial differences between the mouse cortex and spinal cord. They first identified three clusters of microglia in the cortex and two clusters in the spinal cord using genetic markers such as C–X3–C motif chemokine receptor 1 (CX3CR1), transmembrane protein 119 (Tmem119), and the recombinant purinergic receptor P2Y, G protein coupled 12. They discovered that two major clusters of cortical microglia express classical homeostasis genes (including CX3CR1, Tmem119, colony-stimulating factor 1 receptor, and purinergic receptor P2Y, G protein coupled 12) and designated them as homeostatic microglia (HOM-M). Cortical HOM-M can polarize into HOM-M1 and HOM-M2, expressing anti-inflammatory and neuroprotective mediators such as regulator of G-protein signaling-10. These findings suggest that cortical HOM-M may play a significant role in maintaining inflammation and homeostasis in the CNS. The spinal cord HUM-M subtype cannot further polarize into distinct clusters. Another microglial subtype, termed inflammatory microglia (IFLAM-M), is characterized by the expression of inflammatory genes that regulate the immune response, including IL-1α, IL-1β, chemokine (C–C motif) ligand 3, and chemokine (C–C motif) ligand 4. IFLAM-M can be divided into two clusters, IFLAM-M1 and IFLAM-M2, in the spinal cord of 4-month-old mice. IFLAM-M1 expresses genes associated with acute response and inflammation, such as activating transcription factor 3, zinc finger protein 36, Jun, chemokine (C–C motif) ligand 3, chemokine (C–C motif) ligand 4, TNF, and IL-1α. In contrast, IFLAM-M2 expresses genes that modulate microglial activation, including cluster of differentiation 14, G protein coupled receptor 84, complement component 5a receptor 1, and complement component 3a receptor 1. However, IFLAM-M does not differentiate further in the cortex. These results suggest that region-specific mechanisms control the expression of microglia phenotypes and the differentiation of microglia in different CNS regions (Zheng et al., 2021a). Shih et al. (2023) have demonstrated regional differences in gene characteristics in the microglia in the cerebellum, frontal cortex, and hippocampus of pigs. Their analysis identified 150 genes with significant variation across these regions, with 85 genes being most highly expressed in cerebellar microglia, 53 in frontal cortex microglia, and 12 in hippocampal microglia. Microglia in the frontal cortex and hippocampus were significantly enriched in genes that regulate the complex assembly of proteins, including ras homolog gene family member A, capping actin protein of muscle Z-line subunit α 1, H3 histone family 3A, ras-related protein 1B, RIO kinase 3, thymosin β4 Y-linked, actin-related protein 2/3 complex subunit 5, purinergic receptor P2Y, G protein coupled 12, actin-related protein 2/3 complex subunit 5-like, and WASH complex subunit 2C. Additionally, these microglia were associated with pathways related to the assembly of regulatory proteins, such as heterogeneous nuclear ribonucleoprotein K, mago nashi homolog, microfibril-associated protein 1, heterogeneous nuclear ribonucleoprotein M, corepressor interacting with RBPJ, splicing factor 3a subunit 3, nudix (nucleoside diphosphate linked moiety

X)-type motif 21, SYF2 protein, cell division cycle 40 homolog, and cleavage and polyadenylation specific factor 3. In contrast, the genes of microglia in the cerebellum of pigs were particularly distinct from those in the frontal cortex and hippocampus. For instance, the genes in cluster 17 were highly expressed in the cerebellum and included those encoding colony-stimulating factor 1, heat shock protein B1, and legumain, which are related to chemotactic regulation. Additionally, cerebellar microglia express higher levels of genes related to the complement and major histocompatibility complex class II pathways. While the microglia in rodents, pigs, and humans have been confirmed to share common transcriptional profiles and characteristics, species-specific expression subsets also exist (Shih et al., 2023). Böttcher et al. (2019) found that human microglia exhibit regional heterogeneity, and they identified eight phenotypic markers that distinguish human microglial clusters. These markers include cluster of differentiation 11c (CD11c), cluster of differentiation 206 (CD206), cluster of differentiation 45 (CD45), cluster of differentiation 64 (CD64), cluster of differentiation 68 (CD68), CX3CR1, human leukocyte antigen DR (HLA-DR), and interferon regulatory factor 8 (IRF8). However, the specific types and functions of human microglia require further investigation. Currently, there is no consensus on the classification and nomenclature of microglia. Researchers generally refer to microglia that promote inflammation as being in a pro-inflammatory state, while those that inhibit inflammation are considered to be in an anti-inflammatory state. In the following section, we will review the transformation and functions of microglia in TBI.

Microglia in traumatic brain injury

As mentioned above, microglia play a crucial role in regulating the inflammatory response by altering their morphology and numbers in response to changes in the brain microenvironment. They are the key first responders in TBI (Bolte and Lukens, 2021), rapidly mobilizing to the injured area within minutes after the injury occurs. Peripheral immune cells and astrocytes also participate in this response. When traumatic events occur, microglia undergo morphological changes mediated by purinergic receptors, including purinergic receptor P2Y, G protein-coupled receptor 6, P2X4 receptors, and P2Y purinergic receptor 12. Additionally, receptors such as Tyro3, Axl, myeloid epithelial-reproductive receptor, and tyrosine kinase facilitate their transition into an activated state (Fourgeaud et al., 2016; Wu et al., 2021). Within a few hours, neutrophils are gradually recruited to the injured area, where they release reactive oxygen species (ROS) and pro-inflammatory cytokines. This process disrupts the BBB, allowing these cells to enter the CNS and potentially induce neuronal cell death and enhance the immune response (Roth et al., 2014; Corps et al., 2015). Furthermore, microglia begin to proliferate within 24 hours after the injury and can remain active for weeks. Activated microglia release cytokines, chemokines, ROS, and neuroprotective factors in the injured area (Orihuela et al., 2016; Navabi et al., 2024).

In the early stage of injury, the rapid response of microglia is beneficial for brain repair; however, their continued activation can be detrimental. scRNA-seq has been employed to map microglial responses at various stages of TBI. One scRNA-seq study revealed that microglia exhibit significant aggregation at the transcriptomic level 7 days post-injury, with increased expression of interferon-1 and neurodegenerative or injury-related genes. This period marks the transition from acute to chronic TBI. The gene expression of IL-4, IL-10, and IFN-γ in microglia displays a biphasic pattern between 14 and 60 days after injury. This mixed inflammatory pattern reflects the complex changes occurring in microglia during TBI (Witcher et al., 2021). The results indicate that the expression of several key markers, including cluster of differentiation 52, interferon-induced transmembrane protein 3, interferon regulatory factor, recombinant mouse interferon α-inducible protein 27-like protein 2A, and signal transducer and activator of transcription 1, is enriched in microglial clusters associated with TBI. This enrichment is a characteristic feature of the inflammatory response and is accompanied by a corresponding reduction in the expression of homeostatic genes, including those encoding transforming growth factor β1, CX3CR1, and Tmem119. The analysis of cortical neurons also revealed suppression of genes associated with dopamine signaling, long-term potentiation, calcium signaling, and synaptogenesis. These findings indicate functional deficits in neuronal plasticity at 7 days post-TBI and neuronal connectivity at 30 days post-TBI. Several days after the injury, neutrophils continue to be recruited and release cytokines such as IL-1, IL-6, and TNF. When overactive immune responses occur, the formation of astrocytic scars inhibits the regeneration of damaged neuronal axons, leading to chronic inflammation and increased non-infectious cell death, which exacerbates the condition (Shi et al., 2019). Many studies have demonstrated that microglia exert different functions in TBI-related neuroinflammation (Hosomi et al., 2020; Hegdekar et al., 2023). In the study by Wu et al. (2021), cluster of differentiation 86/cluster of differentiation 11B-positive microglia were classified as pro-inflammatory M1-like microglia, while cluster of differentiation 206/cluster of differentiation 11B-positive microglia were classified as anti-inflammatory M2-like microglia (Wu et al., 2021). The levels of M2-like microglia were found to typically peak in the first week after injury and then decrease to normal levels within 4 weeks, whereas the levels of M1-like microglia continuously increased during the same period (Jin et al., 2012). Tam and Ma (2014) similarly categorized microglia in TBI into M1 and M2 microglia. M1 microglia activated pathways involving nuclear factor-kappa B (NF-κB) and inducible nitric oxide synthase, leading to the production of pro-inflammatory factors, including TNF-α, IL-1β, IL-6, superoxide, ROS, and nitric oxide. In contrast, M2 microglia promoted tissue repair and secretion of neurotrophins and anti-inflammatory cytokines, such as transforming growth factor-beta (TGF-β) (Tam and Ma, 2014). Microglia can initiate inflammatory cascades throughout the brain. Johnson et al. (2013) found that activated microglia in TBI can span extensive areas of the corpus callosum, with neuroinflammation in this region persisting for decades. Hosomi et al. (2020) utilized positron emission tomography to track upregulated translocation proteins, revealing that activated microglia in focal TBI contribute to neuroinflammation. They also demonstrated that the distal neuroinflammation induced by regional microglia can persist for decades, even if inflammation at the site of injury is reduced. This projection of inflammation associated with distal chronic brain injury may lead to the development of neurodegenerative diseases following TBI (Hosomi et al., 2020). The dynamic changes and persistence of inflammation suggest that modulation of inflammatory pathways could provide an extended window for treatment, potentially preventing the development of secondary pathology and promoting subsequent neurological recovery.

In addition, many researchers have also identified an aggregation of rod-shaped microglia in TBI (Harrison et al., 2015; Ziebell et al., 2017). Microglial rod cells (Stäbchenzellen) were first described by Franz Nissl in 1899, and their presence in the brain is closely associated with the pathology of infectious diseases and sleep disorders, typically found in human autopsy cases of paralysis of the insane, a disease of the pre-penicillin era, and best known today from human immunodeficiency virus (HIV)-1-infected brains (Nissl, 1899). Microglial rod cells have been implicated in cortical "synaptic stripping," but their exact role has remained unclear. Ziebell et al. (2012) recently found many rod-shaped IBA1-positive microglia in the brain of a mouse model of diffuse TBI, especially in the primary sensory barrel fields. In the absence of contusion, IBA1-positive microglia appear to elongate with their processes extending from the apical and basal ends. These cells abut one another and lie adjacent to the cytoarchitecture of dendrites and axons, showing no alignment with astrocytes and oligodendrocytes. Rod microglia develop over the first week, peaking at 7 days post-TBI and persisting for at least 4 weeks. IBA1-positive rod microglial cells differentially express other known markers for reactive microglia, including OX-6 and cluster of differentiation 68. These findings are the first to demonstrate a predominance of rod microglia following experimental diffuse TBI and their role in neuronal circuit reorganization (Ziebell et al., 2012). Subsequently, Witcher et al. (2018) found that in a mouse model of diffuse brain injury, resident microglia undergo structural transformation to form rod microglia in response to neuronal damage. Their study also observed that the tips of rod microglia align with the apical dendrites of pyramidal neurons in the sensory cortex, suggesting that this response may have a selective neuroprotective effect. The role of rod microglia during TBI and their impact on recovery remains a significant question, particularly in relation to their involvement in neuroinflammation. The development of relevant molecular tools may provide a valuable approach to studying the formation and functional mechanisms of rod microglia (Giordano et al., 2021). These microglial responses are illustrated in **Figure 1**. Taken together, these studies highlight the need for more comprehensive approaches to investigate the complex functions of microglia. Next, we will review the pathways involved in the microglial responses to TBI and summarize the relevant therapeutic strategies.

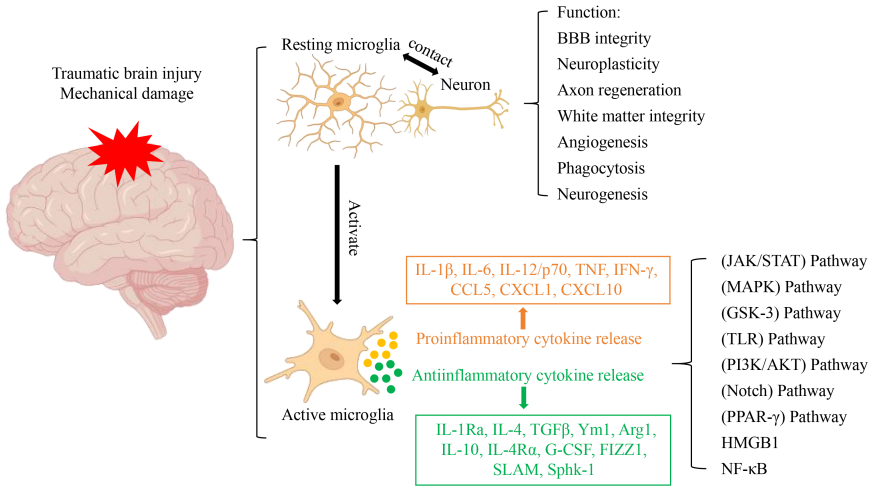

Figure 1 | **Overview of the different states and functions of microglia in TBI.**
Microglia play important neuroprotective roles in the normal physiological environment, but they are activated in response to traumatic brain injury (TBI). Activated microglia can be divided into two subtypes: M1 and M2. M1 microglia are associated with pro-inflammatory functions, while M2 microglia are involved in anti-inflammatory responses, with each subtype engaging different signaling pathways. In the figure, the bidirectional black arrows indicate interactions between resting microglia and neurons. Orange arrows signify that the substance within the box is a pro-inflammatory cytokine, while green arrows indicate that the substance in the box is an anti-inflammatory cytokine. Created with BioRender.com. Arg1: Arginase 1; BBB: blood–brain barrier; CCL5: chemokine ligand 5; CXCL1: chemokine (C-X-C motif) ligand 10; CXCL10: chemokine (C-X-C motif) ligand 10; FIZZ1: found in inflammatory zone 1; G-CSF: granulocyte colony-stimulating factor; GSK-3: glycogen synthase kinase 3; H MGB1: high mobility group box-1 protein; IFN-γ: interferon-gamma; IL: interleukin; JAK/STAT: Janus kinase/signal transducer and activator of transcription; MAPK: mitogen-activated protein kinase; NF-κB: nuclear factor-kappa B; PI3K/AKT: phosphatidylinositol 3-kinase and protein kinase B; PPAR-γ: peroxisome proliferator-activated receptor gamma; SLAM: signaling lymphocyte activation molecule; Sphk-1: sphingosine kinase 1; TGF-β: transforming growth factor-β; TLR: Toll-like receptor; TNF: tumor necrosis factor.

Signaling Pathways Involved in Microglial Changes in Traumatic Brain Injury

The transformation of microglial phenotypes is dependent on regulatory factors and signaling pathways. A better understanding of these mechanisms may be beneficial for the development of therapeutic strategies and drugs targeting microglial inflammation. In this section, we will provide a brief overview of the classical signaling pathways and related regulators of microglia in TBI.

Toll-like receptor/nuclear factor-kappa B signaling pathway

Toll-like receptors (TLRs), such as TLR2 and TLR4, are a family of transmembrane pattern recognition receptors (Cui et al., 2020). TLR2 is associated with autophagy and is expressed in microglia, monocytes, macrophages, and dendritic cells (Ma et al., 2020). TLR4 is expressed in microglia, astrocytes, and macrophages in the brain. TLR4 can be activated by the lipopolysaccharide in microglia (Ciesielska et al., 2021), and it binds to the adaptor protein myeloid differentiation factor 88 (MyD88) to activate NF-κB. NF-κB is a major transcription factor that regulates immune development, immune response, and inflammation (Masson et al., 2015). Its activation can regulate the expression of pro-inflammatory genes and cell survival genes. Activation of TLRs can promote pro-inflammatory microglial polarization, leading to damage in the corpus callosum and white matter tract *in vivo* (Yang et al., 2018). Studies using a TLR4-deficient mouse model of Parkinson's disease have demonstrated lower levels of neuroinflammation (Campolo et al., 2019; Heidari et al., 2022). The diagnosis and treatment of TBI have mainly focused on inhibiting the TLR-4/NF-κB pathway to attenuate pro-inflammatory microglial activation. Stepharine can inhibit the TLR4/NF-κB pathway to decrease microglial activation, thereby improving neuronal death in mice with middle cerebral artery ischemia (Hao et al., 2020). Vascular endothelial growth inhibitors reduce excessive neuroinflammation by suppressing the TLR4/NF-κB pathway after TBI, thereby decreasing pro-inflammatory microglial polarization (Gao et al., 2015). Quercetin exerts neuroprotective effects by inhibiting NF-κB to diminish the microglial activation in TBI (Wu et al., 2019). These studies have demonstrated the associations among pro-inflammatory microglial activation, TLR-mediated innate immunity, and pro-inflammatory gene expression. Further research with precise experimentation is needed to gain deeper insights into the contribution of the TLR/NF-κB signaling pathway in TBI.

Mitogen-activated protein kinase signaling pathway

Mitogen-activated protein kinases (MAPKs) are important transmitters of signals from the cell surface to the interior of the nucleus. They are a group of serine-threonine protein kinases that can be activated by different extracellular stimuli, such as cytokines, neurotransmitters, hormones, cellular stress, and cell adhesion. MAPKs include four subfamilies: extracellular signal-regulated kinases (ERKs) (Illes et al., 2021), ERK5, p38 mitogen-activated protein kinases (p38 MAPKs), and c-jun N-terminal kinases (JNKs). These MAPK subfamilies are involved in different signal transduction pathways and have different functions. For example, ERKs can regulate cell growth and differentiation, and ERK5 also can regulate processes such as cell proliferation and differentiation, while JNK and p38 MAPK signaling pathways play important roles in modulating the expression of pro-inflammatory factors (Liu et al., 2020). MAPKs are also involved in the MAPK/NF-κB pathway, which plays important roles in microglial activation and the expression of inflammatory genes in many different disease (Park et al., 2020; Wang et al., 2020c; Zhang et al., 2024). Bazedoxifene can attenuate the impairment of cognitive function and increase BBB permeability in rats subjected to TBI by activating inflammatory cascades. This action occurs through the inhibition of the MAPK/NF-κB pathway, thereby reducing BBB damage (Lan et al., 2019). Additionally, methionine sulfoxide reductase A has been shown to inhibit the MAPK/NF-κB signaling pathway, decreasing microglial activation and pro-inflammatory effects (Fan et al., 2020a). Consequently, NF-κB can enhance the expression of pro-inflammatory factors and promote the polarization of pro-inflammatory microglia.

Janus kinase/signal transducer and activator of transcription signaling pathway

Janus kinase/signal transducer and activator of transcription (JAK/STAT) signaling pathways are essential for neuroinflammation in the CNS (Ruganzu et al., 2021). JAK is a tyrosine kinase with a typical kinase domain. The JAK family consists of four members: Janus kinase (JAK)1, JAK2, JAK3, and tyrosine kinase 2. The combinations of these members correspond to different cytokine signaling pathways. When a cytokine binds to its receptor on the cell membrane, the receptor is activated, leading to the transmission of signals to JAK. Activated JAK undergoes phosphorylation and binds to ligands, which facilitates the phosphorylation of STAT, a substrate and downstream signaling molecule of JAK. The phosphorylated STAT proteins then form dimers and translocate to the nucleus to regulate the expression of inflammatory genes (Xin et al., 2020). Inhibition of JAK/STAT signaling pathway phosphorylation can promote the polarization of anti-inflammatory microglia and reduce the expression of inflammatory cytokines (Qu et al., 2019). The various proteins within the JAK/STAT signaling pathway play diverse roles in microglial inflammation. For instance, activation of JAK2/STAT1 induces the expression of genes encoding inflammatory factors such as IL-1β, TNF, and chemokine (C–X–C motif) ligand 10 (Porro et al., 2019). In contrast, activation of JAK2/STAT3 stimulates M1-like microglial polarization, leading to pro-inflammatory cytokine and chemokine production, which can cause damage in the hippocampus (Fan et al., 2022). Conversely, activation of STAT6 promotes the polarization of anti-inflammatory microglia (Yang et al., 2017; Li et al., 2023b). Raible et al. (2015) found that the extent of JAK/STAT pathway activation and the decrease in gamma-aminobutyric acid type A receptor α1 subunit levels are dependent on injury severity in a CCI model. Furthermore, reducing JAK/STAT pathway activation after severe experimental TBI reverses the decline in gamma-aminobutyric acid type A receptor α1 protein levels and improves vestibular motor recovery. Although the effects of the JAK/STAT pathway in microglia are not yet fully understood, modulating

this signaling pathway may help mitigate microglial activation and inflammation following TBI, indicating that STAT molecules could serve as targets for the development of JAK/STAT pathway inhibitors (Hu et al., 2021). Further studies are needed to clarify the potential roles of the JAK/STAT signaling pathway in TBI and its involvement in microglial inflammation.

Phosphoinositide 3-kinase/threonine kinases signaling pathway

Stimulation of G protein-coupled receptors and receptor tyrosine kinases can initiate the activation of serine and threonine kinases, including AKT, leading to the phosphorylation of AKT residues T308 and S473 and the activation of phosphoinositide 3-kinase (PI3K) (Manning and Toker, 2017). The activated PI3K/AKT signaling pathway plays important roles in the immune response within both healthy and diseased CNS (Chu et al., 2021; Choi et al., 2022). Deficiencies in PI3K/AKT signaling in rodent models result in functional defects within specific subsets of leukocytes. Moreover, NF-κB is one of the downstream transcription factors of the PI3K/AKT signaling pathway. In rodent models, lipopolysaccharide can activate the PI3K/AKT signaling pathway, leading to microglial activation in the cortex, hippocampus, and thalamus, as well as an increase in the expression of inflammatory factors (Willis et al., 2020). Bhat et al. (2021) found that an mGluR5-positive allosteric modulator (PAM) shows neuroprotective effects following experimental TBI. Their study demonstrated that VuPAM promotes an anti-inflammatory response in microglia by inhibiting the Akt/glycogen synthase kinase-3 β/cAMP response element-binding signaling pathway. A recent study indicated that SH2 domain-containing inositol 5′ phosphatase-1 can reduce microglial immune responses and lessen tissue damage after moderate-to-severe pediatric TBI in mice by regulating PI3K/AKT signaling (Chu et al., 2023). These findings suggest that hyperactivation of the PI3K/AKT signaling pathway promotes the transformation of microglia into an inflammatory phenotype. Conversely, low levels of activated PI3K/AKT signaling can induce an anti-inflammatory phenotype in microglia (Linton et al., 2019). Collectively, these studies imply that modulating the intensity of PI3K/AKT signaling may be a viable target for mitigating long-term neuroinflammation triggered by microglia following TBI.

Notch signaling pathway

The Notch signaling pathway is a cell contact-dependent intracellular signaling pathway that is highly conserved among different species and involved in the development of almost all of systems (Back, 2017; Zhang et al., 2023). It mainly includes four Notch receptors and five ligands of the Delta-Serrate-LaBag family (jagged 1, jagged 2, delta-like protein 1, delta-like protein 3, and delta-like protein 4) (Nowell and Radtke, 2017). Notch transmembrane receptors are generated in the endoplasmic reticulum and then transported to the plasma membrane. Activation of these receptors can increase the proteolytic enzyme cleavage on the surface of microglia, releasing the Notch intracellular domain from the cytoplasm into the nucleus (Majumder et al., 2021). The Notch intracellular domain regulates cell proliferation, stem cell differentiation, cell death, and microglial polarization (Majumder et al., 2021). Previous studies have shown that the Notch signaling pathway mediates the release of TNF-α, IL-1β, IL-6, and other pro-inflammatory factors of activated microglia in TBI (Shang et al., 2016; Yao et al., 2022). Transient activation of Notch signaling has been observed to regulate the proliferation and differentiation of neural stem/progenitor cells in the injured brain following TBI (Anderson et al., 2020). Additionally, the Notch signaling pathway interacts with other signaling pathways in microglia. For instance, Notch signaling can regulate the expression of the CYLD lysine 63 deubiquitinase, promoting the activation of NF-κB, p38 MAPK, and JNK pathways in microglia (Yao et al., 2013, 2020).

High mobility group box 1

High mobility group box 1 (HMGB1) is a non-histone nuclear protein that performs DNA-binding, chaperone, and bending activities within the nucleus. It plays a critical role in mediating infection, tissue injury, and inflammation, shuttling from the nucleus to the cytoplasm under various stress conditions. In the extracellular environment, HMGB1 acts as an immune adjuvant, effectively activating T cells, macrophages, and dendritic cells (Kang et al., 2014). Studies have shown that HMGB1 can activate Toll-like receptor 4 (TLR4) through both MyD88-dependent and non-MyD88-dependent pathways (Meijer and van der Vaart, 2014; Lei et al., 2022). This activation triggers a signaling cascade that can occur directly via the NF-κB pathway or indirectly through the PI3K or MAPK pathways, stimulating microglia to release inflammatory factors (Liu et al., 2016; Chen et al., 2018). Furthermore, previous studies have revealed the regulatory effects of HMGB1 on microglial polarization, which can significantly improve the prognosis of TBI (Nishibori et al., 2019; Sun et al., 2020). Consequently, the use of anti-HMGB1 monoclonal antibodies has been suggested as an effective therapeutic strategy for TBI (Okuma et al., 2012).

Subsequent research indicated that HMGB1 can induce the polarization of M1 microglia. Inhibition of the HMGB1 receptor for advanced glycation end products (RAGE) axis has been shown to reduce microglial polarization in rats with spinal cord injury, providing neuroprotective effects (Fan et al., 2016, 2020b; Manivannan et al., 2020). Additionally, the HMGB1 inhibitor baicalin can inhibit lipopolysaccharide-induced neuroinflammation in mice and help mitigate neurocognitive dysfunction (Li et al., 2020). Moreover, HMGB1 serves as a common biomarker for TBI, neuroinflammation, epileptogenesis, and cognitive dysfunction, indicating its potential utility in diagnosing these conditions (Paudel et al., 2018).

In summary, microglial activation plays important roles in both primary injury and neuroinflammation-triggered secondary injury in TBI. Various signaling pathways can activate the expression of downstream transcription factors and pro-inflammatory factors, leading to pro-inflammatory microglial polarization. Regulating these signaling pathways may help reduce the inflammatory response triggered by microglia in TBI and provide neuroprotective effects. A diagram illustrating these pathways is shown in **Figure 2**. Furthermore, many therapeutic strategies and drugs for the microglial inflammatory response in TBI have been developed.

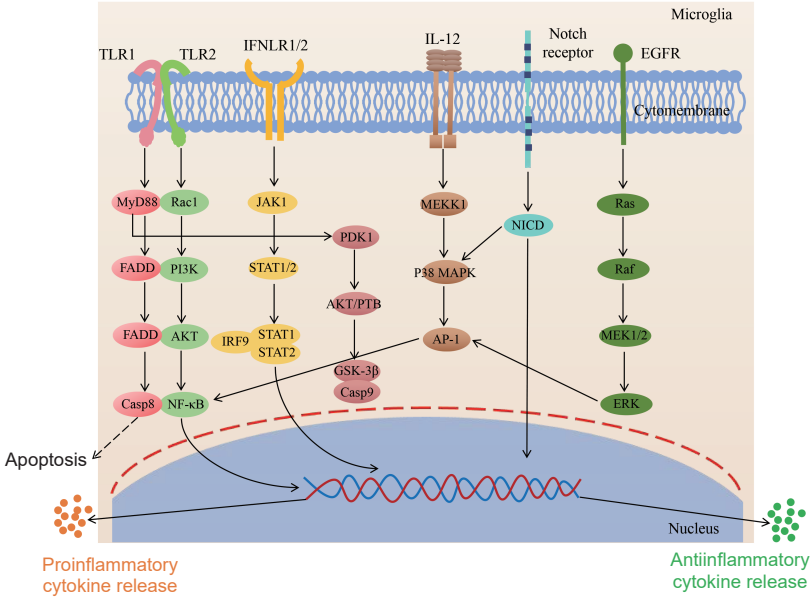

Figure 2 | **Overview of the signaling pathways in activated microglia.**
The receptor proteins on the cell membrane of activated microglia, such as TLR1/2, IFNLR1/2, IL-12, Notch receptor, and EGFR, also become activated. These receptors bind to downstream ligands and related cytokines, which then enter the nucleus. This process promotes the release of both pro- and anti-inflammatory factors in microglia. Additionally, these pathways show interactions. AKT: protein kinase B; AP-1: activator protein 1; Casp9: caspase 9; EGFR: epidermal growth factor receptor; ERK: extracellular signal-regulated kinase; FADD: Fas-associated protein with a novel death domain; GSK-3β: glycogen synthase kinase 3β; IFNLR: interferon lambda receptor; IL: interleukin; IRF9: interferon regulatory factor 9; JAK: Janus kinase; MAPK: mitogen-activated protein kinase; MEK1/2: mitogen-activated protein kinase kinase1/2; MEKK1: MAPK/ERK kinase kinase 1; MyD88: myeloid differentiation primary response gene 88; NF-κB: nuclear factor-kappa B; NICD: Notch intracellular domain; PDK1: pyruvate dehydrogenase kinase 1; PI3K: phosphatidylinositol 3-kinase; PTB: polypyrimidine tract binding protein; Rac1: RAS-related C3 botulinum toxin substrate 1; STAT: signal transducer and activator of transcription; TLR: Toll-like receptor.

Signaling pathways involved in M2-like microglial polarization

In addition to the pathways mentioned earlier, several other pathways promote M2-like microglial polarization. Previous studies have shown that IL-4 can inhibit the expression of pro-inflammatory factors, increase the production of anti-inflammatory factors, and induce M2-like microglial polarization (He et al., 2020; Jiang et al., 2020a). These effects are mediated by the peroxisome proliferator-activated receptor gamma (PPAR-γ) signaling pathway. PPAR-γ, a member of the nuclear receptor superfamily of ligand-inducible transcription factors, is highly expressed in microglia. It can inhibit the nuclear translocation of P65 and antagonize the activators of NF-κB, thereby blocking the NF-κB signaling pathway (Jiang et al., 2019). Consequently, activation of the PPAR-γ signaling pathway can reduce microglial inflammation and provide neuroprotective effects (Jiang et al., 2020b). In addition to the PPAR-γ pathway, multiple receptors can also promote M2-like microglial polarization, such as the triggering receptor expressed on myeloid cells 2 (TREM2). Studies have shown that knocking out TREM2 in microglia can increase M1-like polarization and enhance the inflammatory response (Wang et al., 2020b; Jiang et al., 2023). Conversely, overexpressing TREM2 can induce M2-like microglia and alleviate neuroinflammation. Acetylcholine promotes M2-like polarization through the alpha-7 nicotinic acetylcholine receptor via the JAK2/STAT3 pathway (Sekiyama et al., 2012). The angiotensin type III receptor also activates M2-like microglia (Labandeira-Garcia et al., 2017). Additionally, numerous anti-inflammatory cytokines—such as IL-4, IL-13, IL-10, IL-33, TGF-β, glial cell line-derived neurotrophic factor, insulin-like growth factor 1, and milk fat globule epidermal growth factor 8—can facilitate the transformation of M1-like to M2-like microglia (Tang and Le, 2016; Colonna and Butovsky, 2017; Shi et al., 2017).

The role of epigenetic modification in traumatic brain injury

Microglial activation and functionality are intricately regulated by a spectrum of epigenetic modifications in TBI, which control the expression of key genes (Zima et al., 2022). These modifications play crucial roles in modulating neuroinflammatory responses, cellular demise, neuronal regeneration, and reparative processes within the CNS (Zheng et al., 2022; Zima et al., 2022). The epigenetic landscape encompasses several mechanisms, among which DNA methylation is the most prevalent. This modification primarily targets cytosine residues within CpG islands and is heritable through DNA methyltransferases during cellular division, thereby maintaining stable gene expression patterns. After TBI, DNA methylation is involved in regulating genes associated with neuroinflammation, influencing both the activation status and inflammatory phenotype of microglia (Smolen et al., 2023). This includes the methylation-mediated silencing of anti-inflammatory genes and the increased methylation of pro-inflammatory gene promoters, which can exacerbate inflammatory cascades. Compounds that target protein methyltransferases and histone demethylases are being investigated as potential therapeutic agents to counteract the epigenetic alterations in gene expression and cellular function caused by DNA methylation. This approach represents a promising avenue for intervention in TBI pathology (Mateen et al., 2017).

Furthermore, the post-translational modification of histones, including acetylation and methylation, represents a pivotal epigenetic mechanism that modulates gene expression. These modifications are intricately linked to the regulation of cellular stress responses, cell cycle progression, and apoptotic pathways in TBI, influencing cellular survival and death (Gupta et al., 2019). Non-coding RNAs, such as long non-coding RNAs and microRNAs, exert regulatory effects on gene expression through interactions with DNA, RNA, or proteins. Specifically, certain microRNAs have been shown to amplify the inflammatory response of microglia by suppressing the expression of genes relevant to inflammation (Gupta et al., 2019). Additionally, enhancer activity, chromatin remodeling, and other epigenetic processes are likely modulated by epigenetic signaling cascades activated in the aftermath of TBI, further contributing to the intricate regulatory network that governs cellular fate and function following such injuries. The application of epigenetic modifications extends beyond the development of targeted therapeutic strategies for TBI (Sahafnejad et al., 2023). It also includes the capability to detect early pathological changes in TBI through the identification of specific epigenetic markers, which can serve as sensitive indicators of initial injury (Grady et al., 2021). Moreover, these markers can be instrumental in assessing the efficacy of therapeutic interventions. In addition to their clinical applications, epigenetic markers also serve as valuable research tools, aiding scientists in unraveling the complex molecular mechanisms underlying TBI. This enhanced understanding is crucial for devising innovative treatment approaches and advancing the frontiers of neurorehabilitation.

Drugs Targeting Microglia in Traumatic Brain Injury

Many drugs can promote the transformation of microglia from an M1-like to an M2-like state. Astaxanthin, for example, can modulate neuroinflammation by inhibiting the NF-κB pathway, reducing the production of pro-inflammatory cytokines, and limiting neuroinflammation associated with chronic microglial activation (Medoro et al., 2023). Naringenin has been shown to alleviate neuropathic pain by inhibiting the activation of glial cells and downregulating the expression of inflammatory mediators (Hu and Zhao, 2014). Additionally, naringin can induce the activation of adenosine monophosphate-activated protein kinase α/protein kinase Cδ and upregulate suppressors of cytokine signaling 3 *in vivo* and *in vitro*, thereby showing anti-inflammatory and neuroprotective effects (Wu et al., 2016). Moreover, several phytochemicals, including rosemarinic acid, curcumin, and platanoside, have been shown to target microglia and exert neuroprotective effects in the context of neuroinflammation. Detailed information on these compounds and their respective targeted pathways is provided in **Table 2**. Phytochemicals offer several notable advantages, including their natural origins, a wide variety of options, low toxicity, and high safety profiles (Kumar et al., 2023). However, the screening process for phytochemicals presents numerous challenges, including the lack of efficient methods to identify suitable natural ingredients for specific disorders (Atanasov et al., 2021). Additionally, the varying extraction methods for active ingredients represents an additional level of technical complexity, and the stability of these phytochemicals can be affected by various external factors, which may compromise the precision and consistency of the final preparations (Najmi et al., 2022). Similarly, several chemical drugs can also provide neuroprotective effects by targeting the aforementioned signaling pathways, and some of these potential drugs have entered clinical trials, as detailed in **Table 3**.

Fingolimod (FTY720, 2-amino-2-[2-(4-octylphenyl) ethyl]-1,3-propylene glycol) is a sphingosine-1-phosphate receptor agonist (Huwiler and Zangemeister-Wittke, 2018) that is believed to have neuroprotective effects on central lesions. It protects the BBB and inhibits inflammation and apoptosis. Previous studies have shown that consecutive administration of FTY720 for 3 days can increase M2-like microglia and reduce axonal damage and immune responses in a mouse model of TBI (Wang et al., 2020d; Han et al., 2024). However, conflicting therapeutic effects have been observed in different damage models (Qin et al., 2017). This contradiction may be related to the differences in the modeling methods used and the pathways of action in different brain microenvironments. For instance, varying modeling methods may cause different degrees of damage to the BBB, resulting in inherent differences in the subsequent pathological and inflammatory phenotypes, which in turn can lead to varying drug therapeutic effects. Consequently, more reliable evidence regarding the efficacy of FTY720 in the treatment of TBI is needed. Further exploration of the drug's targets and mechanisms is warranted, and studies using different animal models can help identify the most suitable patient populations for FTY720 based on the specific types of TBI represented by these models.

Minocycline (MINO) is a broad-spectrum antibiotic that can serve as both an antimicrobial and anti-inflammatory agent in the CNS following TBI. Studies have shown that MINO reduces microglial polarization by inhibiting the MAPK pathway and NF-κB (Kobayashi et al., 2013) and significantly improves spatial learning and memory in TBI mouse models (Hanlon et al., 2016; Sangobowale et al., 2018). Additionally, MINO promotes M2 microglial polarization through the neuronal receptor tyrosine kinase-2/brain-derived neurotrophic factor pathway in cases involving cerebral hemorrhage (Miao et al., 2018). MINO targets microglia to enhance the prognosis of abnormal neurobehavior in an explosion-induced TBI model. These findings indicate the potential for further exploration of the pharmacology and pharmacodynamics of MINO in subsequent studies. However, a study involving neonatal TBI confirmed that MINO is ineffective in reducing microglial activation and injury-induced defects

Table 2 | **Preclinical studies of neuroinflammation for TBI**

Drug	Animal model (animal; model type; sex)	Dose (mode; time; dose)	Key point	Reference
rhEPO	C57BL/6J mice; CCI; male.	Intraperitoneal injection; mode: 1. 6 doses of rhEPO weekly for 1 mon; 2. 9 doses of rhEPO weekly for 6 mon; 5000 U/kg rhEPO.	rhEPO induced neuroprotection after TBI, which also activated the MAPK/CREB signaling pathway and increased excitatory synaptic density in amygdala.	Celorrio et al., 2022
Progesterone	SD rat; CCI; male.	Intramuscular injection; 1 and 6 h after injury; 10 mg/kg.	Progesterone significantly reduced cerebral edema, which also improved the recovery of motor, sensory, and spatial learning disabilities.	Wali et al., 2016; Fritzemeier et al., 2023
Atorvastatin	C57BL/6 mice; CCI; male.	Intragastric gavage; once a day for 3 d before TBI; 10 mg/kg per day.	Atorvastatin achieved neuroprotection by activating the nuclear factor E2-related factor 2 /heme oxygenase-1 signaling pathway, ameliorated TBI-induced neurological deficits, and attenuated brain edema and apoptosis.	Feng et al., 2023b
Minocycline	SD rat; blast injury; male.	Intravenous injection; 4 h after blast injury; 3 mg/kg.	Minocycline reduced cognitive impairment and exhibited long-term neuroprotective effects.	Perumal et al., 2023
Enoxaparin	CD1 mice; ICR; CCI, male.	Subcutaneous injection; 2, 8, 14, 23 and 32 h after injury; 1 mg/kg.	Enoxaparin suppressed leukocyte mobilization, partially diminished brain edema, and promoted neurological recovery.	Suto et al., 2019
Resveratrol	SD rat; CCI; male.	Intraperitoneal injection; daily for 3 d after injury; 100 mg/kg.	Resveratrol significantly reduced brain edema, motor deficits, and neuron loss, which also improved spatial cognitive function.	Feng et al., 2016
Pioglitazone (PEG400)	C57BL/6J mice; CCI; male.	Intraperitoneal injection; 0.25, 3, 12 or 24 h after injury; 100 μL (1:1 DMSO and PEG400).	Pioglitazone rescued synaptic mitochondrial deficits after mild focal brain contusion.	Hubbard et al., 2023
Astaxanthin	SD rat; MCAO; male.	Intraperitoneal injection; daily for 7 d after MCAO; 10 mg/kg or 5 mg/kg.	Astaxanthin promoted M2 microglial polarization by inhibiting NF-κB and JNK signaling pathways.	Pan et al., 2017; Wen et al., 2017
Naringenin	Wistar rat; CCI; male.	Intragastric injection; daily for 7 d before and after injury; 100 mg/kg.	Naringenin inhibited the activation of NF-κB and MAPK signaling pathway, reduced the production of TNF-α, prostaglandin E2, and NO, and promoted the release of anti-inflammatory IL-10 and TGF-β.	Cui et al., 2014; Zhang et al., 2018
Rosmarinic acid	SD rat; TBI; male.	Oral gavage; daily for 7 d after injury; 50 mg/kg.	Rosmarinic acid downregulated microglia Iba-1 and inhibited microglial activation.	Özevren et al., 2020
Curcumin (vitamin B2)	C57BL/6 mice; TBI; male.	Intraperitoneal injection; 1, 3, 5, 7 and 14 days after injury; three different doses groups: 50, 100, and 200 mg/kg.	Curcumin downregulated the p38/mitogen-activated protein kinase signaling pathway and inhibited the inflammatory factors (IL-1β, IL-6 and TNF-α) to reduce inflammation after TBI.	Li et al., 2022
Fingolimod (FTY720)	C57BL/6 mice; CCI; male.	Intraperitoneal injection; daily for 30 d after injury, 1 mg/kg.	Fingolimod reduced the inflammatory response and attenuated TBI-induced cardiorespiratory injury.	Qian et al., 2020
Reatorvid (TAK-242)	SD rat; TBI; male.	Intravenous injection; 10 min before injury; 0.5 mg/kg.	Reatorvid significantly attenuated hippocampal neuron damage, reduced hippocampal autophagy marker protein LC3-II, and downregulated NF-κB p65, TNF-α, and IL-1β in the hippocampus.	Feng et al., 2023a

Key findings of each study included in table are highlighted. Comprehensive references provide additional information on the studies. CCI: Controlled cortical impact; ICR: Swiss mice form Institute of Cancer Research; IL: interleukin; MAPK: mitogen-activated protein kinase; MCAO: middle cerebral artery occlusion; MINO: minocycline; NF-κB: nuclear factor-kappa B; rhEPO: recombinant human erythropoietin; SD: Sprague–Dawley; TBI: traumatic brain injury; TGF-β: transforming growth factor beta; TNF-α: tumor necrosis factor-α.

Table 3 | **Clinical drugs for TBI treatment**

Drug and clinical No./ references	Dose (mode; time; dose)	Volunteer characteristics (sex; time of injury; GCS/DRS)	Mechanism
TXA, NCT01402882	Intravenous injection; 1 g over 10 min and 1 g over 8 h; total 2 g.	Male and female, older than 16 yr; patients within 3 h of injury; GCS ≤ 12.	TXA reduces the proteolytic action of plasmin on fibrin clots, inhibiting fibrinolysis and stabilizing established blood clots.
Amantadine NCT00970944 (Ma and Zafonte, 2020)	Oral; daily for 4 wk; 100 mg for 2 wk, if change on DRS less than 2 points after wk 2, dose was increased to 150 mg; if change on DRS less than 2 points after wk 3, dose was increased to 200 mg.	Male and female between 16 and 65 yr; patients within 4–16 wk of injury; DRS ≥ 12.	Amantadine is an antagonist at the phencyclidine binding site, which is located within the channel of the N-methyl-D-aspartate receptor complex.
Cyclosporine (NeuroSTAT®), NCT01825044 (Hansson and Elmér, 2023)	Intravenous injection; 5 mg/kg per day; totally 5 d.	Male and female between 18 and 75 yr; NA; GCS of 4–8.	Cyclosporine is an immunosuppressant agent that prevents the opening of the mitochondrial permeability transition pore by inhibiting mitochondrial matrix cyclophilin.
Rosuvastatin, NCT00990028	Oral; 2 mg per day; totally 10 d.	Male and female, between 16 and 60 yr; NA; GCS < 13.	Rosuvastatin alters the immune response after brain injury by modulating TNF-α, IL-6, IL-1.
NCT01058395 (Meythaler et al., 2019)	Intravenous injection; 800 mg per 12 h; totally 7 d.	Males between 18 and 75 yr; Patients within 6 hours of injury; GCS ≤ 12.	MINO inhibits the microglial activation, caspase-mediated apoptosis, and the excitotoxic NMDA pathway.
EPO, NCT00987454 (Skrifvars et al., 2021)	Subcutaneous injection; on study d 1, 8 and 15; 40,000 IU.	Males between 15 and 65 yr; patients within 24 h of injury; NA.	EPO inhibits the level of inflammatory factors (IL-1β, TNF-α, cell adhesion molecule-1), which also reduces the recruitment of neutrophil and microglia.

DRS: Disability Rating Scale; EPO: erythropoietin; GCS: Glasgow Coma Scale; IL: interleukin; NA: not applicable; NMDA: N-methyl-D-aspartic acid; TBI: traumatic brain injury; TNF-α: tumor necrosis factor-α; TXA: tranexamic acid.

(Kovesdi et al., 2012). This discrepancy may be related to the significant differences between rodents and humans, highlighting the need for successful treatment strategies validated in NHP models before clinical translation.

Resatorvid (TAK-242, ethyl (6R)-6-[N-(2-chloro-4-fluorophenyl)]) belongs to a class of low molecular weight, fat-soluble compounds that can cross the BBB and act as antagonists of the TLR4 signaling pathway, playing a significant role in neuroinflammation. TAK-242 binds to the intracellular domain of TLR4 (Cys747) to inhibit its activity (Hua et al., 2015). Previous animal studies have shown that TAK-242 targets the TLR4-MyD88/TIR-domain-containing adapter protein pathway,

inducing the interferon β-NF-κB signaling pathway to inhibit autophagy and neuroinflammation, and thereby improving cognitive function in TBI mouse models (Hua et al., 2015; Feng et al., 2017; Zhu et al., 2021). Similar studies have demonstrated that administering TAK-242 via the caudal vein before TBI can downregulate NF-κB, p65, TNF-α, and IL-1β expression through the NF-κB signaling pathway, reducing autophagy and neuroinflammatory activity and significantly mitigating neuronal damage (Feng et al., 2023a; Gong et al., 2023). However, the optimal dosage, time window, and mechanism of action of TAK-242 require further confirmation through clinical trials.

Erythropoietin (EPO) is an important cytokine in the human body. EPO is primarily produced in the kidneys and liver, and it promotes the growth and differentiation of bone marrow erythroid progenitor cells. EPO has been used clinically since 1980, primarily for the treatment of renal anemia. As research on EPO has progressed, its functions have become increasingly understood, including its role in neuroprotection (Hemani et al., 2021). The EPO receptor is highly expressed on the surface of microglia following TBI, suggesting that EPO may play a significant role in the injury response. EPO activates the Akt/mechanistic target of rapamycin/NF-κB pathway (Xu et al., 2013), promoting the transformation of M1-like microglia to M2-like microglia, which helps rescue brain damage and improve related behaviors in a middle cerebral artery occlusion animal model (Wang et al., 2017a). However, the mechanisms by which EPO exerts its therapeutic effects and the optimal timing for EPO administration remain unclear.

Colony-stimulating factor 1 (CSF-1) is a growth factor involved in the differentiation of macrophages and monocytes (Hemani et al., 2021). It typically interacts with receptors on the cell membrane of microglia, promoting their proliferation and differentiation. Inhibition of the CSF-1 receptor can reduce the polarization of M1 microglia and provide neuroprotective effects in mouse models of ischemic stroke (Liu et al., 2020). Previous studies have demonstrated that CSF-1 can enhance cognitive ability following both primary injury (24 hours post-injury) and secondary injury (3 months post-injury) in TBI mouse models (Li et al., 2020; Wang et al., 2022). Additionally, CSF-1 has been shown to reduce activated microglia, leading to improved neurological function (Henry et al., 2020). Research in animal models suggests that the treatment window for CSF-1 may be significantly extended by controlling the inflammatory response related to microglia after TBI (Todd et al., 2021; Wangler and Godbout, 2023). Therefore, further animal experiments and clinical studies on CSF-1 are necessary to support its broader application.

In the realm of preclinical research, pharmacotherapeutic interventions have shown promising results in rodent models. However, translating these findings into clinical applications for humans presents significant challenges, primarily due to the inherent physiological, metabolic, and immunological differences between rodents and humans (Blais et al., 2017). These distinctions can profoundly impact the assessment of drug pharmacokinetics and pharmacodynamics, complicating the direct extrapolation of safety evaluations from rodent models to human patients (Beck and Meyerholz, 2020). As a result, there is a crucial need for further evaluation using NHP models, which are more closely related to humans in terms of phylogeny. This approach is essential for improving the predictive accuracy of drug responses and ensuring the safety and efficacy of therapeutic strategies in clinical settings.

The translation of drug dosages from preclinical animal models to clinical applications in patients is a complex endeavor (Walford, 2019). This process requires careful consideration of interspecies variability in drug metabolism and sensitivity. In this context, a variety of statistical methodologies have proven to be instrumental in predicting the appropriate therapeutic dosage for human subjects (Kirchmair et al., 2015). Notably, predictive algorithms that leverage the correlation between animal and human body weights and body surface area are commonly used to estimate human drug dosages. Additionally, analyzing pharmacokinetic profiles can help predict the minimum effective dose needed to achieve the desired pharmacological response (Yamaguchi et al., 2022). The emergence of machine learning and artificial intelligence has introduced a new paradigm in dosage optimization. These advanced technologies, with their ability to analyze vast datasets of drug-related information, can predict drug kinetic parameters with unprecedented precision (Kim et al., 2021; Du et al., 2024). Consequently, they can help identify the most effective and safe dosage ranges, thereby enhancing the drug development process and refining therapeutic strategies for patient care.

In addition to the challenges previously mentioned, the transition of drug research from animal models to humans requires a critical evaluation of the long-term toxicological effects and potential tumorigenicity associated with pharmaceutical agents (Valic et al., 2020). This assessment is essential and necessitates a comprehensive analysis that integrates drug toxicokinetics with species-specific sensitivities. Such an approach is vital for ensuring thorough safety profiling of drugs before their administration in clinical settings (Sombogaard, 2020). Furthermore, translating preclinical findings to clinical trials involves strategic selection of the target patient population and determination of appropriate dosing regimens. This includes establishing drug dosage, the route of administration, and the treatment duration tailored to the diverse needs of patient cohorts. These decisions are crucial, since they directly impact the integrity and outcomes of clinical trials. Careful selection of these parameters is essential to mitigate risks, optimize therapeutic efficacy, and adhere to the ethical standards of clinical research.

Mesenchymal Stem Cells Treat Traumatic Brain Injury by Targeting the Inflammation of Microglia

In addition to the newly developed drugs targeting neuroinflammation, surgical intervention often represents a better option for patients with moderate-to-severe TBI. For instance, craniotomy is frequently performed to remove the bone flap for decompression. While advances in acute clinical care have improved the survival rates following TBI, the disabilities caused by secondary injuries continue to burden patients. The loss of neurons after TBI is permanent, and the accompanying neuroinflammatory response exacerbates neuronal damage. Currently, no single treatment strategy can prevent neuronal death or restore neuronal function. As a result, cell transplantation has emerged as a promising therapeutic approach. Stem cell transplantation therapy can replace lost brain cells, secrete neurotrophic factors, and recruit other cells to damaged areas. This strategy aims to repair damaged brain cells by reducing inflammation and regulating the immune response, ultimately improving patients' cognitive and motor abilities.

MSCs are stem cells with multidirectional differentiation potential, low immunogenicity, and low tumorigenicity (Mundra et al., 2013). These cells are widely distributed in various tissues, including the umbilical cord, bone marrow, and adipose tissue, making them easy to obtain and isolate without ethical concerns. Studies have demonstrated that MSCs can secrete a variety of chemokines, interleukins, and growth factors in pathological conditions. They play a crucial role in regulating the inflammatory microenvironment at the injury site and promoting tissue repair (López-García and Castro-Manrreza, 2021). For instance, in response to inflammatory factors such as IFN-γ, MSCs can secrete anti-inflammatory cytokines, including chemokine ligand 5, transforming growth factor (TGF), and IL-6, which inhibit the migration and proliferation of M1 macrophages while promoting the generation of M2 macrophages (López-García and Castro-Manrreza, 2021). Additionally, MSCs can enhance the proliferation, differentiation, and inflammatory responses of T cells and B cells by producing immunosuppressive molecules such as nitric oxide and prostaglandin E2 (Ren et al., 2008; Zhang et al., 2019). Due to these characteristics, MSCs have emerged as an ideal cell type for cell therapy and have been widely utilized in both experimental and clinical studies.

A study published in 2022 found that human MSCs injected into the cerebral ventricles of mice 4 hours after CCI injury significantly reduced neural function deficits within 48 hours. This treatment reduced the expression of inflammatory cytokines and inhibited the expression of the NOD-like receptor protein 3/Caspase-1 p20/Gasdermin D pathway in the cerebral cortex, in addition to reducing microglial pyroptosis (Feng et al., 2022). Related research in the field of stem cell genetic engineering has indicated that the therapeutic effects of engineered MSCs are superior to those of direct MSC transplantation. Typically, MSC transplantation can release repair-promoting cytokines, such as IL-10, which reduce astrocyte formation after TBI by directly inhibiting the pro-inflammatory cytokine TNF-α. In a related study, Peruzzaro et al. (2019) enhanced MSCs to overexpress IL-10 through transfection with an IL-10 viral vector. After transplantation of these modified MSCs into CCI rats, they observed significant improvements in the behavior of the CCI rats and a reduction in the number of cluster of differentiation 86 (CD86)-positive cells (Peruzzaro

et al., 2019). Similarly, MSCs cannot endogenously synthesize key signals that induce the M2 phenotype, such as IL-4. To address this, Enam et al. (2020) enhanced MSCs by synthesizing IL-4 mRNA, allowing them to express IL-4 immediately. The transplantation of these modified MSCs promoted the polarization of microglia to the M2 phenotype, thereby increasing the expression of anti-inflammatory genes after TBI.

On the basis of the findings from these animal studies, clinical research into stem cell therapy strategies has garnered significant attention. Bone marrow-derived mononuclear cells (BMMNCs) and MSCs are frequently utilized in clinical studies on TBI due to their safety and effective therapeutic outcomes. The current study illustrates the treatment of TBI through MSC transplantation, as shown in **Figure 3**.

Instead of using pure MSCs, the earliest clinical studies reported in the literature utilized BMMNCs, which are a heterogeneous mixture of immune cells and stem cells, including MSCs (Liao et al., 2015; Cox et al., 2017). For instance, Cox et al. (2011) conducted an investigational study involving the treatment of 10 children aged 5–14 years with intravenous injections of autologous BMMNCs within 48 hours after TBI. These patients did not exhibit transfusion-related toxicity, and their hemodynamics and visceral function assessments revealed no abnormalities. Additionally, MRI scans showed no loss of brain tissue after TBI. All patients showed no individual abnormalities and survived the treatment. The study concluded that bone marrow collection and intravenous monocyte infusion for severe TBI in children are both feasible and safe, with potential therapeutic effects on CNS structural protection (Cox et al., 2011).

Liao et al. (2015) evaluated the efficacy of treatment for TBI in 10 children aged 5–14 years who received intravenous autologous BMMNCs within 48 hours of injury. The primary measure of this study was the intensity of treatment required to counteract the increase in intracranial pressure caused by the neuroinflammatory response following TBI. Other measures included the Pediatric Logistic Organ Dysfunction score to assess the extent of multiple organ dysfunction in children as well as the number of days of intracranial pressure monitoring, which served as a proxy for the duration of neurointensive care required. Data monitoring indicated that in children receiving cell therapy, infusion of intravenous BMMNCs was associated with lower treatment intensity early after severe TBI. Furthermore, both intracranial hypertension resulting from TBI and organ dysfunction following neurological intensive care were reduced. The cells may directly decrease the levels of factors that contribute to brain edema. These results support preclinical data indicating that autologous BMMNC treatment alleviates the effects of early post-traumatic inflammation. However, due to the small sample size of the study and the heterogeneity of individual brain injuries, accurately classifying early injury grades and collecting early data proved challenging. As a result, relevant data for long-term comparison could not be obtained (Liao et al., 2015).

In addition, a study by Cox et al. (2017) demonstrated that intravenous infusion of autologous BMMNCs was safe and feasible for treating severe TBI in 25 adults, with no adverse effects reported. The treatment also resulted in a reduction in the expression of several key inflammatory cytokines in the brain, including IL-1β, IFN-γ, TNF-α, and IL-10, thereby alleviating the inflammatory response in the affected brain regions (Cox et al., 2017). With advancements in cell isolation and culture technology, most clinical trials of stem cell therapy now focus on directly extracting MSCs from various sources for TBI treatment. MSCs are found in many tissues, including bone marrow, cord blood, cord tissue, placental tissue, and adipose tissue. Among these, MSCs derived from umbilical cord tissue are noted for their high quality, purity, and abundance. Most MSCs used in autologous transplantation are derived from the bone marrow.

Wang et al. (2013) transplanted umbilical cord MSCs via lumbar puncture in 20 patients with TBI sequelae over 1 year. After treatment, the patients experienced significant improvements in various neurological functions, including self-care ability, motor skills, and communication. However, due to the small sample size and the limited sensitivity of the scales used to assess sphincter control—which affects patients' excretory function and social cognitive abilities—no significant improvements were observed in these areas (Wang et al., 2013). In the same year, Tian et al. (2013) transplanted autologous bone marrow MSCs through lumbar puncture in 97 patients with TBI and various complications. The treatment was found to be safe for patients with TBI complications, including persistent vegetative states and motor disorders. However, only 38 patients showed improvements in consciousness and motor function. This limited efficacy may be attributable to external factors that affect the status of MSCs during *in vitro* culture. Additionally, the results indicated that the treatment was more effective in younger patients than in older patients, likely because younger individuals have a more favorable underlying environment for stem cells to exert their therapeutic effects (Tian et al., 2013).

Wang et al. (2017b) induced patients' autologous BM-MSCs to form neural stem cell–like cells, which were then transplanted into patients with severe TBI through intravenous injection (seven patients) or lumbar puncture (three patients). The results indicated that cell therapy did not cause serious adverse events or fatalities. Most patients showed improvements in nerve function during follow-up, and the serum levels of neurotrophic factors, such as nerve growth factor and brain-derived neurotrophic factor, were higher post-treatment than at the baseline. The MSC-derived neural stem cell–like cells can be directly targeted for neuronal repair in TBI treatment. However, the optimal timing and dosage of cell transplantation need to be determined through further research. Additionally, the study had a small sample size and lacked a blinded control group; thus, the possibility of a placebo effect in the treatment outcomes could not be ruled out. The studies outlined above describe the current application of MSCs in TBI therapy. The occurrence and development of MSCs, as well as their clinical applications in other neurological diseases, are illustrated in the timeline (**Figure 4**).

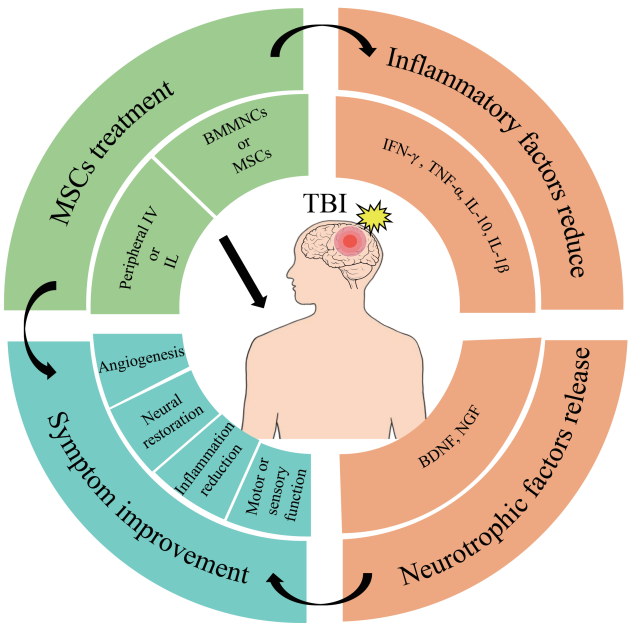

Figure 3 | **Effects of cell therapy on TBI in humans.**
After TBI caused by mechanical impact to the human brain, cell transplantation can be performed via peripheral intravenous or lumbar injection using cells such as bone marrow monocytes and bone marrow-derived mesenchymal stem cells. These cells then migrate to the site of the brain injury to exert their therapeutic effects. Cell therapy is followed by a reduction in the release of pro-inflammatory factors in the brain, including IFN-γ, TNF-α, IL-10, and IL-1β, along with an increased release of neurotrophic factors such as BDNF and NGF. The specific outcomes of this therapy include reduced inflammation, neuronal repair, angiogenesis, and improvements in motor and sensory functions. BDNF: Brain-derived neurotrophic factor; BMMNCs: bone marrow-derived mononuclear cells; IFN-γ: interferon-γ; IL: interleukin; IV: intravenous injection; MSCs: mesenchymal stem cells; NGF: nerve growth factor; TBI: traumatic brain injury; TNF-α: tumor necrosis factor-α.

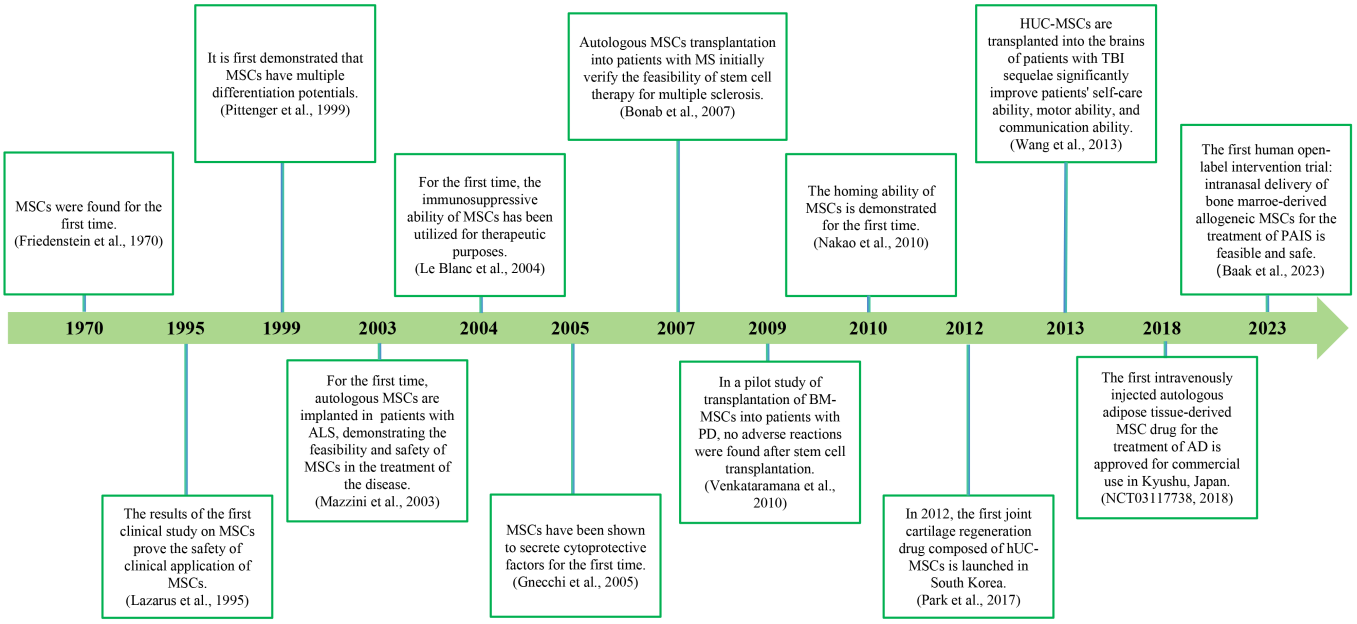

Figure 4 | **Timeline of the development of mesenchymal stem cells and their clinical application in neurological diseases.**
This timeline highlights the significant breakthroughs in the clinical research and application of MSCs. In 1970, Friedenstein et al. confirmed the existence of MSCs through animal experiments. In 1995, Lazarus et al. conducted the first clinical research on MSCs by extracting and culturing these adherent stromal cells from the bone marrow of patients with malignant hematological diseases. They subsequently re-infused the cultured cells to observe clinical effects, thereby demonstrating the safety of these stromal cells. In 1999, Pittenger et al. demonstrated that human MSCs could differentiate into chondrocytes, adipocytes, cardiomyocytes, bone marrow stromal cells, and thymic stromal cells *in vivo*, providing direct evidence of the multilineage differentiation potential of MSCs. In 2003, Mazzini et al. showed that *ex vivo* expansion and transplantation of autologous MSCs into the spinal cords of patients with amyotrophic lateral sclerosis were safe and well-tolerated. In 2004, Le Blanc et al. utilized allogeneic semi-compatible MSCs to treat graft-*versus*-host disease, marking the first clinical study to harness the immunosuppressive capabilities of MSCs for therapeutic purposes. In 2005, Gnecchi et al. were the first to experimentally demonstrate that MSCs could secrete cytoprotective factors. In 2007, Bonab et al. highlighted the feasibility of using autologous bone marrow MSC therapy for multiple sclerosis in a preliminary clinical report. Venkataramana et al. (2010) transplanted autologous BM-MSCs into the subventricular region of PD patients in 2009 through stereotactic surgery without serious adverse events after transplantation. However, this study was limited by the small number of participants and could not conclusively prove the effectiveness of the treatment. The results were published in January 2010. Nakao et al. (2010) were the first to experimentally demonstrate the homing properties of MSCs. In January 2012, the first MSC drug for the treatment of arthritis, "Cartistem," was approved for marketing in South Korea (Park et al., 2017). In 2013, Wang et al. validated the transplantation of hUC-MSCs into the brains of patients with post-TBI sequelae, which improved patients' self-care, mobility, and communication abilities. In 2018, the first autologous adipose tissue-derived MSC drug for the treatment of Alzheimer's disease, "AstroStem," was approved for marketing in Kyushu, Japan. Baak et al. (2022) conducted the first human study of the use of intranasal allogeneic BM-MSCs to treat perinatal arterial ischemic stroke. This study demonstrated the feasibility of the treatment and showed no serious adverse events in patients followed up to 3 months of age. AD: Alzheimer's disease; ALS: amyotrophic lateral sclerosis; BM-MSCs: bone marrow-derived mesenchymal stem cells; hUC-MSCs: human umbilical cord mesenchymal stem cells; MS: multiple sclerosis; MSCs: mesenchymal stem cells; PAIS: perinatal arterial ischemic stroke; PD: Parkinson's disease; TBI: traumatic brain injury.

Although MSCs hold great potential for treating TBI, many existing cell therapy strategies face challenges, including low efficiency in cell migration to injured sites, poor integration, and low survival rates *in vivo*. Consequently, researchers are actively seeking ways to optimize the delivery of MSCs in clinical treatments. This includes the combination of innovative biomaterials, the application of cellular exosomes, and genetic engineering techniques to enhance the overall effectiveness of cell therapy.

Guan et al. (2013) developed a porous and biodegradable collagen scaffold to create a stable environment for the retention and proliferation of BM-MSCs. These cells were then transplanted into brain injury sites in CCI rats via stereotactic localization. This approach significantly improved the therapeutic effects of cell transplantation, leading to enhanced sensory and motor functions, improved spatial learning, and increased brain metabolic activity in the rats, while minimizing the spread of cells to non-specific sites. Additionally, the authors employed non-invasive *in vivo* imaging techniques to obtain quantitative information about the biological distribution and proliferation of the transplanted stem cells, further enhancing the accuracy of the transplantation results.

Zhang et al. (2015) intravenously injected exosomes produced by BM-MSCs into a rat model of CCI, and their results were the first to demonstrate that these exosomes can effectively promote functional recovery in CCI rats. Specifically, they found that the rats showed significantly enhanced spatial learning ability, as well as sensory and motor functions. They also discovered that treatment with BM-MSC-derived exosomes induced endogenous angiogenesis in the brain, promoting neurogenesis and reducing inflammation in rats following brain injury to a certain extent.

After exosome treatment, the number of microglia and astrocytes at the injured site were lower than those in the PBS treatment group (Zhang et al., 2015). In addition to application strategies involving biomaterials and the use of BM-MSC exosomes alone, some researchers have explored combinations of these methods to create innovative cell-delivery systems. For example, Liu et al. (2023) utilized 3D-printing technology to construct a collagen/chitosan/BMExos (3D-CC-BMExos) scaffold, which integrates exosomes derived from hUC-MSCs stimulated by brain-derived neurotrophic factor (BMExos) into the collagen/chitosan matrix. These scaffolds are then transplanted into the brain injury sites of CCI rats via stereotaxic injection for treatment. The collagen/chitosan scaffolds can bridge the injured areas and exhibit good biocompatibility, while the BMExos play a crucial role in the recovery of neural networks. The application of this biological scaffold significantly enhanced the recovery of cognitive and sensorimotor functions in TBI rats (Liu et al., 2023).

Moreover, MSCs themselves can be processed to develop new delivery therapies, such as secreting cytokines or extracting organelles. MSCs can express the pro-repair cytokine IL-10, which reduces pro-inflammatory markers and activates other inflammatory markers, like cluster of differentiation 163. Peruzzaro et al. (2019) exploited this property by genetically engineering BM-MSCs to overexpress IL-10. The modified cells were then injected into the brains of CCI rats through stereotaxic surgery, allowing for stable introduction of IL-10 into the injured brain. This treatment significantly improved fine motor function and reduced brain inflammation in TBI rats, including decreased activation of microglia and reduced levels of TNF-α in the cortex.

In another approach, Bamshad et al. (2013) injected hUC-MSC-derived mitochondria stereotaxically into the brains of TBI rats to provide healthy and functional mitochondria to the injured areas. This treatment supplies the energy required for the damage repair process and mitigates complications, particularly the progression of secondary brain damage. Additionally, it promotes

the recovery of sensorimotor skills, reduces neuronal apoptosis, encourages neurogenesis, and prevents astrocyte proliferation and microglial activation. As research in these areas continues to evolve and optimize, it will provide valuable support and reference data for the improved application of MSCs in the treatment of TBI.

In conclusion, MSCs demonstrate significant therapeutic potential for treating TBI. However, some challenges remain to be addressed and certain aspects require refinement. One of the key advantages of MSCs is their pluripotent capacity to differentiate into various cellular lineages, including neurons and glial cells, which is crucial for facilitating reparative processes and functional rehabilitation of tissues compromised by TBI (Zhang et al., 2022). Moreover, the intrinsic immunomodulatory capabilities of MSCs are beneficial for modulating immune responses and mitigating neuroinflammation (Li et al., 2023a). Additionally, the paracrine effects of MSCs, which are mediated through the secretion of a variety of growth factors and cytokines, promote angiogenesis and inhibit apoptosis, thereby enhancing neuroprotective and reparative mechanisms (Gnecchi et al., 2016; Asgari Taei et al., 2022). Furthermore, the favorable safety profile and tolerability of MSCs further broaden their potential for clinical applications.

Nevertheless, several limitations associated with MSCs warrant attention. While MSCs have demonstrated short-term efficacy in clinical settings, their long-term therapeutic effects and mechanisms of action require more in-depth investigation. Additionally, the post-transplantation survival rate of MSCs and their ability to integrate within host tissues require improvement. At present, standardized protocols for the optimal delivery route and cell dosage for MSCs are lacking, and definitive guidelines are pending the results of future clinical trials. Furthermore, the heterogeneity of MSCs derived from various sources, along with their distinct biological characteristics, may affect the uniformity of treatment efficacy. Despite the considerable body of research on stem cell therapy for human TBI, most of the existing studies have focused on outcomes such as intracranial pressure, secretion of neurotrophic factors, and recovery of nerve function, with less emphasis on tracking inflammation in the brain. Future studies should prioritize monitoring changes in inflammatory factors, inflammation-related pathways, and immune regulation following stem cell therapy (Kodali et al., 2023; Tang et al., 2023).

In light of the clinical research challenges mentioned above, numerous preclinical studies are now utilizing single-cell sequencing, transcriptome analysis, and other advanced technologies to investigate the pathological changes associated with TBI in animal models, analyze the underlying mechanisms, and evaluate the therapeutic effects of stem cells from various sources. These studies can provide a foundational basis for future clinical research (Enam et al., 2020; Zheng et al., 2021b; Xing et al., 2022). Looking ahead, with the transition from NHP trials to human clinical trials, optimizing *in vitro* culture and induced differentiation methods for stem cells will be crucial in addressing limitations related to the availability of autologous or allogeneic cells. Additionally, exploring the optimal timing, dosage, and injection methods for cell therapy in TBI will be important to develop a viable cell therapy protocol for clinical treatment.

Limitations

In this review, we focused on the dynamic states of microglia under both physiological conditions and TBI, along with targeted therapeutic strategies. However, we did not extensively address the dynamic changes of microglia in other neurological diseases. Additionally, the complex molecular mechanisms underlying the interactions between microglia and neurons were not presented in detail.

Summary and Prospects

Given the global impact of TBI, an extensive body of research has been conducted to elucidate its underlying mechanisms and develop effective treatment strategies, with particular emphasis on the pivotal role of microglia. This review attempts to provide an overview of the dynamic states of microglia during both physiological conditions and following TBI, encompassing their involvement in anti-inflammatory and pro-inflammatory signaling pathways as well as the therapeutic approaches based on these pathways. For instance, (1) NF-κB serves as a crucial inflammatory transcription factor that acts downstream in multiple signaling pathways. Targeting its regulation can potentially suppress microglial inflammation and mitigate neuronal cell death. The development of drugs that can specifically target NF-κB signaling, either by blocking its activation or by promoting its inhibitory pathways, could provide a novel therapeutic strategy for TBI. Furthermore, NF-κB targeting could be combined with other therapeutic approaches, such as the use of MSCs, to enhance the overall neuroregenerative effects post-TBI. Additional research is needed to elucidate the precise mechanisms by which NF-κB signaling influences TBI pathology and to identify optimal strategies for its pharmacological manipulation. (2) The associations among the TLR family, the MyD88 ligand, and autoimmunity have been demonstrated. Efforts to further modulate this pathway may help mitigate the detrimental effects of autoimmunity in TBI. For instance, modulating TLR-mediated immune responses through the application of TLR agonists or antagonists may be instrumental in mitigating neuroinflammation associated with TBI. Such modulation could pave the way for the development of innovative pharmacotherapies and therapeutic interventions, thereby potentially enhancing the clinical outcomes for patients with TBI. Furthermore, investigations of the interplay between TLR signaling and neural regeneration, including neuronal differentiation and synaptic plasticity, may offer novel insights into neuroprotective strategies. (3) ERK plays a pivotal role in signal transduction pathways, and additional investigations on the interactions between upstream activators and downstream substrates of ERK will facilitate a comprehensive analysis of the signaling mechanism between glial cells and neurons in TBI. Small-molecule compounds, including potent ERK activators and inhibitors, offer a targeted approach to manipulate ERK signaling, thereby exerting precise control over cellular processes. Furthermore, the integration of ERK pathway modulation with MSC transplantation holds significant potential for augmenting treatment efficacy. Such combinatorial strategies may provide synergistic effects, optimizing cellular responses and enhancing the therapeutic outcomes in regenerative medicine and beyond. (4) Given the substantial interspecies disparities between rodents and humans, enhancing the clinical translational efficacy of TBI treatment modalities will require the use of animal models that exhibit greater phylogenetic proximity to humans, such as NHPs. Additionally, the establishment of large-animal TBI models that encompass a spectrum of injury types, including both focal and diffuse lesions, is imperative to more comprehensively represent the clinical spectrum of TBI. These strategies are instrumental in facilitating the translation of innovative TBI therapies from the preclinical domain to clinical practice.

MSCs can be used to treat TBI by modulating the inflammatory response; however, this area of research has limitations. For instance, in clinical studies, MSCs are typically administered intravenously (Bagno et al., 2022; Sun et al., 2022), and their therapeutic effects predominantly depend on the anti-inflammatory factors produced by MSCs *in vivo*. Unfortunately, these effects on the CNS are limited by the presence of the BBB. Additionally, tracking dynamic changes in the anti-inflammatory effects of MSCs *in vivo* among clinical TBI patients presents a significant challenge, but it is crucial for refining this therapeutic strategy. In future preclinical and clinical investigations, researchers should focus on optimizing MSC culture, expansion, and cryopreservation protocols. These efforts should aim to enhance the therapeutic efficacy of MSCs while minimizing potential adverse effects.

This may involve either removing the nucleus from transplanted MSCs or enhancing their ability to secrete anti-inflammatory factors by adding specific cell culture factors *in vitro*. Furthermore, integrating advanced imaging modalities with other tracking techniques is essential for monitoring the *in vivo* distribution, engraftment, and functionality of MSCs. Therefore, exploring this approach further in future studies is worthwhile.

Positron emission tomography (PET) is a crucial technique to monitor the dynamic changes of the microglia following MSC transplantation in patients with TBI. PET offers significant advantages in evaluating cell survival and migration. Notably, PET has superior sensitivity, allowing for detection of tracers at minute concentrations, which is instrumental for tracking cell distribution and migratory patterns. Moreover, the functional imaging capabilities of PET allow assessment of cellular metabolic activity, providing insights into the physiological status of the transplanted cells. For instance, using tracers such as ^{18}F-flurodeoxyglucose can facilitate the evaluation of glucose metabolism, offering a comprehensive understanding of cellular dynamics within the host organism. Additionally, the whole-body imaging and quantitative analytical capabilities of PET,

when combined with data from other imaging modalities such as MRI and CT, can provide precise localization and functional information about MSCs. This multimodal approach is crucial for more accurate assessment of the post-transplant cellular environment. Moreover, exploring synergistic combination therapy strategies that integrate pharmacological interventions with MSC-based treatments may yield enhanced therapeutic outcomes and open new avenues for clinical application. A recent study has also highlighted the potential of new materials derived from MSC exosomes, which can directly cross the BBB through intranasal administration and demonstrate a stronger homing ability to the CNS than pure cells (Peng et al., 2022). Furthermore, MSCs can be combined with biomaterial scaffolds to improve the targeted delivery of cellular therapeutics and other bioactive factors to the brain. This combination can facilitate the reconstruction of compromised neural circuits, thereby promoting neural regeneration and functional recovery. In addition, the use of biomaterial scaffolds may provide a supportive microenvironment that enhances MSC engraftment, survival, and differentiation, which is essential for restoring neural tissue integrity following injury. Thus, exploring this approach further in future studies is worthwhile.

We hope that this review serves as a reference for future researchers in the field, while also offering insights into the potential transcription factors or targets involved in microglial interactions. This may facilitate the development of more targeted therapeutic interventions against these factors or targets.

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