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Stem Cell Therapy Modulates Microglial Polarization and Secretion in traumatic brain injury

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Abbreviations: ASC-ST: Secretome Of Adipose-Derived Mscs; CCL2: (C-C Motif) Ligand 2; CNS: Central Nervous System; Damps: Damage-Associated Molecular Patterns; PID: Post-Injury Day ; Evs: Extracellular Vesicles; Hadsc-Ex: Human Adipose Mesenchymal Stem Cell-Derived Exosomes; Hmgscs: Human Meningioma Stem-Like Cells; Iba1: Ionized Calcium-Binding Adaptor Molecule 1; IL-4, 10: Interleukin-4, 10; INF-γ: Interferon-Gamma; Inos: Inducible Nitric Oxide Synthase; MHCII: Major Histocompatibility Complex Class II; Mscs: Mesenchymal Stem Cells; Nfκb: Nuclear Factor Kb; Nscs: Neural Stem Cells; SCI: Spinal Cord Injury; SHED-Ex: Stem Cells From Human Exfoliated Deciduous Teeth-Originated Exosomes; TBI: Traumatic Brain Injury; TGF-B: Transforming Growth Factor-Beta; TNF-A: Tumor Necrosis Factor-A.

Abstract

Physical trauma to the Central Nervous System (CNS) activates different responses at the cellular level. Microglia as one of the first mediators of the inherent immune response in CNS plays a vital role in neuronal tissue damage and consequent neuroinflammation. Various characteristic features of microglia, such as gene expression, morphology, and functional activity can be affected by different pathological conditions. Once microglia chronically activated following a Traumatic Brain Injury (TBI), the release of pro-inflammatory mediators and reactive oxygen species is increased, which may lead to further neural tissue damage. To date, most studies in the field of microglia in brain injuries have focused on the inhibition of microglia activation. During the last decades, stem cell therapy has made remarkable progress in the field of neuroinflammation via the modulation of microglia responses and polarization. Stem cell therapy following brain injuries improves alteration in microglial phenotypes and enhances secretion of neuroprotective factors from microglia. Therefore, we reviewed the current information about the effects of stem cells on microglia-related neuroinflammation after TBI. We also discussed microglial secretion after brain injuries in response to stem cell therapy in preclinical TBI models. Further investigations on this topic may lead to deep insights into the application of stem cells in acute brain injuries.

keywords: Microglia; Neuroinflammation; Stem cell; Traumatic brain injury.

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Introduction

Brain injury is characterized by physical damage to the brain tissue that might be a temporary or permanent injury, which affects the function of the brain and causes morbidity or mortality [1,2]. Pathophysiological features of Traumatic Brain Injury (TBI) can be divided into primary and secondary injury stages. During the primary injury, mechanical forces cause cell damage, diffuse axonal injury, and crushing of blood vessels [3]. On the other hand, secondary brain injury is caused by physiological changes to the initial damage [3]. Secondary brain injury is accompanied by several events, such as edema, hematomas, and free radicals that ultimately lead to the loss of the blood-brain barrier [4]. The inflammatory response is one of the main processes that link primary injury to secondary injury. Furthermore, neuronal damage is also mediated by the release of pro-inflammatory mediators. Inflammatory responses are started by microglial activation [5,6]. Consequently, other resident cells within the Central Nervous System (CNS), such as astrocytes and the cerebrovascular endothelial cells, are enrolled [7].

The initial inflammatory signaling pathway activates microglia and astrocytes to migrate to the damaged area [8]. In the lesion area, microglia begins to release cytokines and chemokines in response to injury after detecting Damage-Associated Molecular Patterns (DAMPs) [9]. Once activated, microglia recruits peripheral immune cells to infiltrate the brain tissue [10]. Polarization states and activation of microglia are altered by the inflammatory environment [11]. Chronic microglial activation can increase proinflammatory cytokines production, neuronal death, and microenvironments alterations [12]. Despite the evidence for the substantial role of microglia in the pathogenesis of TBI, few studies to date have investigated the modulation of microglial polari zation states in preclinical TBI models.

During the last decades, stem cell therapy has been introduced as a promising therapeutic option for neurological disorders, especially TBI [13]. Stem cells through several mechanisms can alleviate the pathological changes in injured host tissue [14]. It can be classified into three categories including cell replacement therapy, bystander effect, and bio-bridge [14]. In cell replacement action, stem cells can largely replace with dead or dying cells in host tissue. In the bystander/paracrine mechanism, transplanted stem cells secret several substances, such as anti- inflammatory mediators, anti-oxidative stress molecules, and neuroprotective agents to repair the damaged tissue. In the last mechanism, transplanted stem cells activate and recruit host stem cells in the regenerative process. Multiple lines of evidence indicate that the anti-inflammatory bystander effect of stem cells can target microglia polarization states and responses [15]. Therefore, we reviewed conclusively the data on microglial polarization and responses after stem cell therapy in TBI.

Microglia in TBI at a glance

Microglia is one of the most important components of the innate immune system that forms approximately 5% to 10% of the total adult brain cells [16]. Microglia has different states from ramified morphology (resting state) to an amoeboid form (activated state). These behavioral and phenotypic changes appear in response to DAMPs and other extracellular signals, which are produced by the neurons and damaged cells after TBI (Figure 1A) [17-19]. Two distinctive microglial polarization states have been defined, the M1 type (pro-inflammatory phenotype) and the M2 type (anti-inflammatory phenotype). M1 releases pro-inflammatory cytokines, chemokines, and free radicals, enhances oxidative stress production, and plays a role in the pathophysiology of various neurological disorders [20]. Furthermore, the M1 type plays a pre- apoptotic function through the secretion of high values of tumor necrosis factor-α (TNF-α) and low levels of interleukin-10 (IL-10). On the other hand, The M2 type exerts anti-inflammatory properties and secrets neurotrophic factors. M2 type also supports phagocytic activity and re- pairing in CNS through regenerative processes, such as neurogenesis, angiogenesis, oligodendrogenesis, and myelination [17-19]. Besides, that M2 type microglia secretes low levels of TNF- α and high levels of IL-10 that help the survival and progrowth signaling pathways. Activation of microglia M1 type inhibits neurogenesis and increases neuronal death during the acute phase of TBI but the M2 state improves neurogenesis and tissue repair [21].

Another significant aspect of microglia activation/response is to act in a Spatio-temporal manner after TBI. As an example, it has been reported that M2 type labeled with $CD163^{+}$ expressed around the lesion site and maximum expression of M2 type marker was observed on day 5 after injury and then decreased to the control level following focal injuries in the rat [12,22,23]. In contrast, it was evident that the M1 type is continuously expressed for months to years by single moderate or repeated mild TBI [24]. Additionally, microglia-specific gene temporal expression identified during the chronic period after a TBI injury indicates that the microglial phenotype tends to be a chronic pro-inflammatory state [25]. Therefore, the microglial pro-inflammatory phenotype in TBI pathogenesis may delay repair and contribute to long-lasting consequences of neurological deficits.

Despite the evidence for the important roles of microglia in the pathogenesis of TBI, few studies to date have investigated the intervention on the microglia polarization states, proliferation, and secretion after brain injury. In the following section, we review the current knowledge about stem cell therapy on microglial behavior after TBI and discuss the challenges and hopes in this field.

Effects of stem cell therapy on activated microglia after TBI

As mentioned above, stem cell therapy makes a promising tool for the treatment of TBI. One of the possible mechanisms of stem cell involvement in TBI is to alleviate microglial behaviors, such as polarization states, proliferation, and secretion (Table 1). It was evident that stem cells inhibit neuroinflammatory pathways by switching microglia polarization and inhibiting the production of pro-inflammatory cytokines (Figure 1B). Transplantation of Mesenchymal Stem Cells (MSCs) enhanced the number of M2 type and M2/M1 ratio by secreting interleukin-4 (IL-4) for 1 week after the treatment [26]. Additionally, bone marrow MSCs drive M2 polarized microglia in the lesion site after 7 days post-injury (dpi) in a TBI model [27]. Bone marrow-derived MSCs not only reduced the level of pro-inflammatory cytokines, such as IL-1β, IL- 6, IL-17, TNF-α, and Interferon-gamma (IFN-γ), but also increased the production of anti- inflammatory cytokines, such as IL-10 and transforming growth factor-beta (TGF-β) [28]. It has been also indicated that bone marrow-derived MSCs improve the functional outcomes of TBI through the production of chemokine (C-C motif) ligand 2 (CCL2) chemokine and IL-10 cytokine on 7 dpi [27]. Moreover, intracerebrally grafted human Neural Stem Cells (NSCs) inhibited microglial activation as indicated by an increase in the brain M2/M1 ratio and enhance the expression of M2 anti-inflammatory phenotype after

TBI in C57BL/6 mice [29]. These microglial alterations were accompanied by the boosted expression of anti-inflammatory IL-4 receptor α and reduced pro-inflammatory IFN-γ [29].

On the other hand, stem cells can modulate neuroinflammation through the paracrine soluble factors known as stem cell secretome that consists of Extracellular Vesicles (EVs), including exosomes, microvesicles, membrane particles, peptides, and small proteins [30]. Secretomes derived from stem cells reduce the lesion volume and debris by inhibiting the microglia proliferation in the injury site. In the same way, exosomes derived from MSCs reduced the expression of CD68-positive cells and inhibited nitric oxide release in microglia in rats subjected to spinal cord injury [31]. Li and colleagues investigated the effect of stem cells from human exfoliated deciduous teeth-originated exosomes (SHED-Ex) on the production of pro-inflammatory cytokines and microglial polarization in vitro LPS-induced inflammation model [32]. They showed that M1 polarization-associated markers (i.e. CD11b, CD86, CD16, MHCII, and inducible isoform of nitric oxide synthases (iNOS) A parenthesis were considerably decreased at the mRNA levels in the BV-2 microglial cell line [32]. M2 polarization-associated markers (i.e. CD206, IL-10, and Arginase 1) were meaningfully increased at the mRNA levels in the BV-2 microglial cell line compared with the LPS group [32]. They also found that SHED-Ex could inhibit the concentrations of TNF-α and IL-6 in the microglia supernatants in a dose-dependent manner [32]. Furthermore, intravenous infusions of EVs derived from MSCs in aged rhesus monkeys (Macaca Mulatta) with cortical injury showed a phenotypic switch of inflammatory hypertrophic microglia towards anti-inflammatory, which was associated with a rapid motor function recovery [33]. Accordingly, the injection of the secretome of adipose-derived MSCs (ASC-ST) improved TBI-induced neuroinflammatory conditions by intensifying the number of M2 phenotypes while decreasing the number of M1 phenotype microglia [34]. Furthermore, ASC-ST ameliorated neurological function by reducing IL-6 and TNF-α levels, whereas increasing TGF-β and tumor necrosis factor-stimulated gene 6 protein (TSG-6) [34].

Recently, a novel mechanism has been suggested by which stem cells-derived exosomes enter microglia/macrophages and repress their activation during brain injury [35]. For instance, human adipose mesenchymal stem cell-derived exosomes inhibited microglia/macrophages activation by inhibiting nuclear factor κB (NFκB) and P38 mitogen-activated protein kinase signaling in LPS-induced inflammatory model [35]. Overall, these studies suggest that stem cells and their secretion ameliorate neuroinflammation and shift microglia towards restorative functions. The next chapter describes additional and adjuvant procedures that improved stem cell effects on microglial behaviors after TBI.

Adjuvant procedures improve stem cells effects on microglia responses

Studies indicate that the therapeutic impact of stem cells may be more effective when transplanted with a supportive artificial microenvironments (Table 2) [36,37]. To this point, different types of scaffolds have been introduced and investigated as a substrate to improve the effect of stem cells on TBI functional outcomes. Scaffolds by increasing survival and differentiation of transplanted stem cells play critical roles in functional improvement. In the course of microglia modulation following TBI, several experimental studies have examined the concurrent transplantation of stem cells and scaffolds. As an example, our team focuses on the use of self- assembling nano peptides, a member of the hydrogel scaffolds, with human stem cells in TBI models. In our recent works, the human meningioma stem-like cells (hMgSCs) and MSCs implanted in a three-dimensional scaffold (RADA4GGSIKVAV; R-GSIK) significantly decreased the apoptosis, reactive gliosis, and lesion volume at the injury site compared to stem cells groups alone [38,39]. Besides, we observed the expression of ionized calcium-binding adaptor molecule 1 (Iba1) protein significantly decreased when the TBI group was treated with stem cells and scaffolds that were associated with the inhibition of toll-like receptor 4, IL-1β, and TNF [38,39]. Prior to these works, we evaluated human neural stem/progenitor cells and human adipose-derived stromal/stem cells seeded in PuraMatrix hydrogel (PM) in rats subjected to acute TBI. Our results indicated that simultaneous scaffold and human stem cell transplantation can significantly decrease the Iba-1-positive cells by reducing the level of TNF-α, IL-1α, and IL-6 [40].

In the line of supportive microenvironments, the use of small molecules is recommended [41]. For example, treatment of bone marrow MSCs with MDL28170, a calpain inhibitor, before transplantation can significantly increase cell viability, improve motor function, and decrease lesion area via the inhibition of microglial activation and NFκB-Ikb signaling pathway, as well as through the reduction of proinflammatory cytokines, such as IL-1β, IL-6, and TNF- α in a TBI model [42].

Another strategy for improving the effects of stem cells on neuroinflammation is a genetic modification of stem cells that can increase the expression of desirable proteins [26]. For instance, MSCs have been engineered to overexpress anti-inflammatory cytokines IL-13 and IL- 10 in rodent models of brain injury [43-47]. Transplantation of interleukin IL-13-producing mesenchymal stem cells (IL-13 MSCs) significantly decreased the number of resident microglia and improved functional recovery in a mouse model of spinal cord injury (SCI) [44]. Moreover, transplantation of IL-13 MSCs can promote a phenotypic switch by increasing Arginase 1 expression as an M2a macrophages/microglia marker and decreasing major histocompatibility complex class II (MHCII) as an M1 macrophages/microglia marker on day 14 after ischemic stroke [43]. Likewise, the IL-13 MSCs grafted in the hippocampus with an epileptogenic insult significantly activated M2 type phenotype as indicated by the arginase1 expression at the trans- planted site both at the 2-week and 9-week post-injection time [45]. The therapeutic potential of MSCs engineered to overexpress IL-10 was investigated in rats following the medial frontal cortex injury. IL-10 overexpression from MSCs improved pathological changes by a shift from a pro-inflammatory state (CD86-positive cells) to an anti-inflammatory state (CD163-positive cells) [47]. Another important cytokine that promotes an M2 macrophage phenotype is IL-4 [48]. Recently, the delivery of IL-4 after TBI was investigated by genetically MSCs-modified to overexpress IL-4 expression (IL-4 MSCs) [26]. IL-4 MSCs induce a strong M2-like macro- phage response and stimulate anti-inflammatory gene expression after TBI [26].

So far this paper has focused on current knowledge about microglial responses following stem cell therapy during the TBI. The following section will discuss pitfalls and future perspectives in this field.

Table 1: Stem cell therapy on microglia activation/responses.

Effective factor	Effect on microglia	Study	Species, strain, sex	Injury model	Type of stem cells	Number of in- jected cells/concen- tration	Rout of injection	Injec- tion time post-injury	Main finding	References
Stem cell effects	proliferation	Su- pinder S. Bedi, et al., 2013	Male rat	CCI	Multipotent adult progeni- tor cells	2×10^6 cells/kg & 10×10^6 cells/kg	IV	2 h & 24 h	Number of activated Micro- glia in the dentate gyrus (Iba1) ↓	[53]
	Proliferation & Secretion	Zhang et al., 2013	Male Spra- gue-Dawley rat	weight- drop	Bone marrow MSCs	4×10^6 cells	IV	2 h	Microglia activation ↓ IL-1β, IL-6, IL-17, TNF-α, IFN γ ↓ IL-10, TGFβ ↑	[28]
	Proliferation	Su- pinder S. Bedi, et al., 2013	Male Spra- gue Dawley rat	CCI	Autologous bone marrow-derived mono- nuclear cells	2×10^6 cells/kg	IV	72 h	Apoptosis of pro-inflamma- tory activated microglia in the ipsilateral hippocampus ↑	[54]
	proliferation	Skard elly et al., 2014	Male Spra- gue-Dawley rat	CCI	Human neural progenitor cells	1×10^5 cells & 5×10^5 cells	IC & IV	24 h	Microglia (CD11b) activation ↑	[55]
	proliferation	Zanier et al., 2014	Male C57Bl/6J mice	CCI	Human bone marrow MSCs	15×10^4 cells	IC	1 day	M2 polarization ↑ CCL2, IL-10, IGF1, IL-1β ↑	[27]
	Proliferation & Polarization	Gao et al., 2016	Male C57BL/6 mice	CCI	Human neural stem cells	0.5×10^5 cells	IC	24 h	M1 polarization ↓ M2 polarization ↑ M2/M1 ratio ↑	[29]
By-stander effects	Polarization	Li Y, et al., 2017	Male Wistar rats	free- falling method	Stem cells from human exfoli- ated deciduous teeth-origi- nated exosomes (SHED-Ex) co- culture activated BV-2 microglia	1000 µg/ml SHED-Ex	IC	At injury time	M2/M1 ratio ↑	[32]
	Polarization	Kathe- rine A. Rup- pert, et al., 2018	Male Spra- gue-Dawley rat	Acute Spinal Cord Injury	Human MSCs- Derived Extra- cellular Vesicles	1×10^9 Ev/ml	IV	3 h	Reactive Microglia (Iba1) ↓ M1 microglia (CD32 and CD86) ↓ M2 Microglia (CD200R, CD163 and RT1B) ↓	[52]
Proliferation & Secretion		Gierin Thomi, et al., 2019	Wistar rat pups	left common carotid artery cauteri- zation 2 h later and ex- posure to hy- poxia for 65 min	Exosomes de- rived hWJ-MSC	50 mg/kg	In- tranasal	At injury time	Proliferation of microglia ↓	[56]
Proliferation & Secretion		Wei Liu, et al., 2019	Female rat	SCI	Bone marrow MSCs-exosome	200 µg of total protein of BMSCs-Exos	IV	At in- jury time	CD68+ Microglia cells ↓ TNF-α, IL-1β, and IL-6 ↓	[31]
Proliferation & Polarization		Ve- ronica Go, et al., 2019	Female rhe- sus monkey	cortical injury	MSCs-derived extracellular vesicles	4×10^{11} particles/kg	IV	24 h & 14 d	M1 polarization ↓ M2 polarization ↑	[33]
Polarization & Secretion		Xu C, et al., 2020	Male Spra- gue-Dawley rats	CCI	Secretome of adipose-de- rived MSCs	250g/0.1mL	IV	7 days	M2 polarization M1 polarization ↓ IL-6, TNFα ↓	[34]
Polarization & Secretion		Chen Y, et al., 2020	Male Spra- gue-Dawley rats	Weight- drop	Human adipose MSCs + hADSCs-de- rived exosomes (hADSC-ex)	5×10^5 cells (hADSC) 20 µg total pro- tein (hADSC- ex)	ICV	24 h	IL-1β, IL-6, TNF-α ↓ M1 polarization ↓ M2 polarization ↑	[35]

Abbreviations: CCI: Controlled Cortical Impact; HwJ: human Wharton Jelly; MSCs: Mesenchymal Stem Cells; IV: Intravenous; SCI: Spinal Cord Injury; ICV: Intracerebroventricular; IC: Intracerebral.

Table 2: Adjuvant procedures on microglia responses in stem cell therapy.

Study	Animal	Injury model	Supporting fac- tor	Stem cell type	Number of in- jected cells/ concentration of supportive materials	Injection method	Injection time post- injury	Main finding	References
Sajad Sahab Negah, et al., 2020	Male Wistar rats	CCI	Nano-scaffold	MSCs	5×10^5 cells	IC	At injury time	Reactive microglial cells (Iba1) ↓ TLR4, TNF, and IL6 ↓	[39]
Sajad Sahab Negah, et al., 2019	Male Wistar rat	CCI	Nano-scaffold	Human meningi- oma stem-like cells	5×10^5 cells	IC	At injury time	Iba-1 positive cells ↓ TLR4, TNF, IL1b ↓	[38]
Jahanbazi J.A, et al., 2018	Male Wistar rat	CCI	Nano- scaffold	Human NS/PCs + ADSCs	5×10^5 cells	IC	30 min	Number of Microglia (Iba1) ↓ TNF-α, IL-1α, IL-6 ↓	[40]
Jiangnan Hu, et al., 2019	Male Sprague Dawley rat	Weight- drop	Calpain inhibitor MDL28170	Bone marrow- MSCs	1×10^5 cells & 1.0 µl of 50 mM MDL28170	IC	MDL28170 : 30 min BMSC: 24 h	Microglia activation (Iba1) ↓	[42]
Daniel J. Kota, et al., 2016	Rat	CCI	Propranolol	Human bone mar- row MSCs	1×10^6 cells/kg Propranolol (10 mg/kg)	IV Propranolol: IP	MSCs: 72 h Proprano- lol:1 h	Inhibit microglia/mac- rophage (Iba1) ↓	[41]
Enam S.F, et al., 2020	Male C57BL/6N mice	CHI	Genetic manipu- lation (increase IL4)	MSCs	3×10^5 cells	Intrahippo- campal	2 days	M2-like phenotype ↑ M2:M1 ratio ↑ IL-4, IL-6 ↑	[26]
Peruzzaro S. T, et al., 2019	Male Sprague Dawley rats	CCI	Genetic manipu- lation (overexpress IL- 10)	Bone marrow MSCs	8×10^5 cells	IC	36 h	The percent ratio of CD163/CD86 ↑ IL10 ↑ TNF-α ↓	[47]
Dooley D, et al., 2016	$CX3CR1^{EGFP/+}$ $CCR2^{RFP/+}$ mouse	SCI	Genetic manipu- lation (overexpress IL- 13)	Bone marrow- MSCs	1.5×10^5 cells	Intraspinal	At injury time	Resident microglia ↓ Alternatively activated macrophages ↑	[44]

Abbreviations: CCI: Controlled Cortical Impact; SCI: Spinal Cord Injury; hNS/PCs: Human neural stem/progenitor cells; hADSCs: human Adipose-Derived Stromal/Stem cells; CHI: Closed head injury; MSCs: Mesenchymal Stem Cells; IC: Interacerebral; IP: itraperitonealy

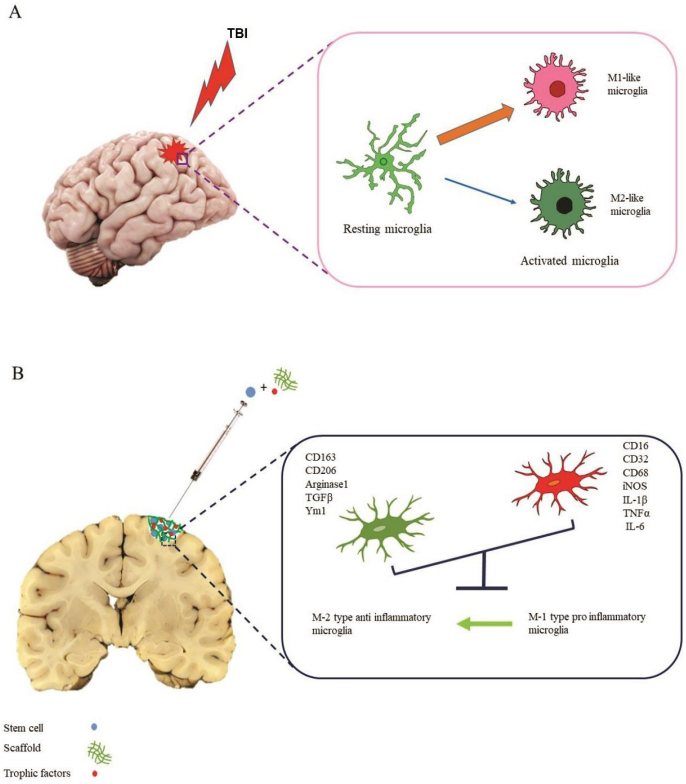

Figure 1: A schematic overview of microglia changes after traumatic brain injury (TBI). A) TBI activates microglia from resting-state into activated-state. B) Stem cell therapy modulates TBI pathological changes by switching microglia polarization. Abbreviation: Cluster of Differentiation (CD16, 32, 68, 163, 206); Inducible nitric oxide synthase (iNOS); Interleukin 6 (IL-6, 1β); Tumor Necrosis Factor alpha (TNFα); Transforming growth factor-beta (TGF-β); (Arginase I) is a cytosolic manganese-dependent enzyme; (Ym1) is an eosinophilic chemotactic factor.

Pitfalls and conclusion remarks

Microglia activity is a highly dynamic process that can vary in different pathological conditions, as well as during pathological processes. Investigation of different therapeutic strategies after TBI has shown the increase of M2-like markers is associated with improvements in histopathologic and cognitive symptoms.

Researches have evaluated the M1 polarization is detrimental in CNS diseases that due to secreting pro-inflammatory cytokines at first, and M2 polarization is helpful because of the release of the particular neurotrophic factors. In recent years, some studies have shown inhibition of inflammation due to the reduction of neuronal regeneration may not be the best way to treat TBI patients with severe secondary injury [49].

After TBI for proper tissue regeneration, we need suitable function and cooperation between M1-like and M2-like phenotypes for decreasing inflammation, increase proliferation, and regeneration [50]. It is increasingly evident microglia function is not consistent with the M1/M2 polarization pattern during neurodegenerative diseases, which means that M1 activity isn't always harmful and M2 activity is not necessarily useful. Microglia M1 may be neurotoxic in some conditions, but on the other hand, it is effective in regenerating damaged axons [51].

Stem cells can target microglial polarization states in the course of TBI but sometimes the functional outcomes are not as we expected. As an example, stem cells engineered to overexpress IL-4 increased the only M2-like macrophages after diffuse TBI. However, this effect did not considerably impact functional outcomes [26]. On the other hand, it has been reported that human MSC-Ev can diminish both M1 and M2 microglia types after SCI [52]. While functional outcomes, such as locomotor recovery scores significantly improved among animals treated with MSC-Ev [52]. The major limitations of insufficient functional outcomes/controversial reports in some preclinical studies regarding microglial activation and responses can be due to inadequate levels of cytokines or M2 type microglia, a lack of adjusted measure in behavioral assessments, diversity of TBI models, or uselessness of a cell phenotype in a complicated environment. To overcome these confounding variables, the mixture of phenotypic criteria and molecular underpinning can be suggested to explain carefully the action of microglia in response to stem cell therapy after TBI. As a result, attention to controversial evidence is necessary to translate these findings into clinical practice.

To summarize, studies have been shown that microglia not only can be the main target for cell therapy in TBI but also may be an important tool to improve the chronic phases of acute brain injuries. Stem cell therapy could alleviate microglial activation/responses by shifting microglia polarization, inhibiting pro-inflammatory cytokines secretion, and decreasing microglia proliferation. Although this study focuses on pre-clinical fundings, shifting microglia polarization toward the M2 type requires a clinically relevant strategy for TBI. It is suggested to investigating the effects of stem cells on different phenotypic markers of microglia subtypes polarization and their cytokines. Further investigations on this topic may lead to deep insights into the application of stem cells in acute brain injuries.

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