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REVIEW ARTICLE

Macrophage migration inhibitory factor as a therapeutic target after traumatic spinal cord injury: a systematic review

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Abstract

Purpose Macrophages play an important role in mediating damage after Spinal cord injury (SCI) by secreting macrophage migration inhibitory factor (MMIF) as a secondary injury mediator. We aimed to systematically review the role of MMIF as a therapeutic target after traumatic SCI.

Methods Our systematic review has been performed according to the PRISMA 2009 Checklist. A systematic search in the scientific databases was carried out for studies published before 20 February 2019 from major databases. Two researchers independently screened titles. The risk of bias of eligible articles was assessed, and data were extracted. Finally, we systematically analyzed and interpreted related data.

Results 785 papers were selected for the title and abstract screening. 12 papers were included for data extraction. Eight animal studies were of high quality and the remaining two were of medium quality. One of the two human studies was of poor quality and the other was of fair quality. MMIF as a pro-inflammatory mediator can cause increased susceptibility to glutamate-related neurotoxicity, increased nitrite production, increased ERK activation, and increased COX2/PGE2 signaling pathway activation and subsequent stimulation of CCL5-related chemotaxis. Two human studies and six animal studies demonstrated that MMIF level increases after SCI. MMIF inhibition might be a potential therapeutic target in SCI by multiple different mechanisms (6/12 studies).

Conclusion Most animal studies demonstrate significant neurologic improvement after administration of MMIF inhibitors, but these inhibitors have not been studied in humans yet. Further clinical trials are need to further understand MMIF inhibitor utility in acute or chronic SCI.

Level of Evidence I Diagnostic: individual cross-sectional studies with the consistently applied reference standard and blinding.

Keywords Systematic review · Spinal cord injury · Macrophage migration inhibitory factors · macrophage

Background

Spinal cord injury (SCI) is a devastating type of neurological trauma with limited therapeutic opportunities [1]. The pathophysiology of SCI involves primary injury, including immediate cell death and tissue damage, and secondary injury [2], including hemorrhage; breakdown of the blood-spinal cord barrier (BSB); electrolyte imbalances; neurotransmitter accumulation and excitotoxicity, such as glutamate excitotoxicity; and various other sequelae such as lipid peroxidation, free radical production, and edema [3–5]. Among all secondary injury mechanisms, the heightened inflammatory response is the major contributor to lesion expansion [2], further loss of neurologic function, and decease in functional recovery from SCI [6, 7]. On the molecular level, SCI is followed acutely by an inflammatory response facilitated by various pro-inflammatory cytokines and chemokines [8]. This response is characterized by an influx of blood-borne inflammatory cells and activation of endogenous cells, and may last for years after initial SCI [9].

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Macrophage migration inhibitory factor (MMIF, or in some studies, MIF) first discovered in T-cells [10], is a potent pro-inflammatory cytokine that is secreted by many cell types [11, 12]. MMIF is identified as a phenyl pyruvate tautomerase (EC 5.3.2.1) [13], and has been found to increase in pre-clinical mouse models of acute and chronic SCI [14–17]. Following SCI, MMIF is primarily secreted from neurons [18, 19], Neural Stem/Progenitor Cells (NSPCs) [20] and activated macrophage/microglia [21]. MMIF has been shown to play a significant role in modulating the production of various pro-inflammatory cytokines after spinal cord injury [12, 22]. It also has chemokine-like characteristics [20, 23] and can act as a survival factor for NSPCs. The interaction of the MMIF-CD74 [24] axis with other chemokines causes activation of astrocytes and excessive inflammation, resulting in secondary damage [25]. Both M1 (neurotoxic) and M2 (neuroprotective) phenotypes of human macrophages migrate toward higher levels of MMIF at the site of damage via interaction with chemokine receptors [26]. Additionally, MMIF has been shown to induce cell proliferation in macrophages [27]. While initial stimulation of M1 macrophages by MMIF is important for the removal of myelin and cellular debris [28], continued stimulation and recruitment of M1 macrophages leads to an imbalance between M1 and M2 macrophages. The resulting increase in inflammation leads to features of secondary injury including continued cell death, demyelination, and tissue damage [3].

Although various studies have been conducted on the effects of the MMIF on secondary damage [15], its role in spinal cord injury is poorly understood. Previous literature suggests that MMIF may be a potential therapeutic target for SCI [10, 16, 20, 21, 29]; however, there is no consensus on modulating cellular factors as a means of preventing neuronal damage after SCI. The purpose of this study is to systematically review the effectiveness of interventions targeting MMIF on preventing neuronal damage after traumatic SCI.

Methods

The present study was conducted with the aim of systematically reviewing the effect of MMIF on preventing neuronal damage after traumatic spinal cord injury. This review and the associated analyses were performed according to preferred reporting items for systematic reviews and meta-analysis. This systematic review has been done according to the PRISMA 2009 Checklist [30], and the search strategy was designed by a medical informatics specialist.

Research question and Search strategy

Selection of research questions was based on the PICO (population, intervention, comparison and outcome). Database searches were done using the MeSH terms and keywords of related articles and expert opinions. Gray literature search was performed manually via Google Scholar. Then, a systematic search was carried out without limitation for studies published until 20 February 2019 from selected electronic databases including the Cochrane Library, PubMed, EMBASE, Web of Science and Scopus. A table outlining our full search strategy can be found in Supplementary Table 1. Our main search terms included "MIF/MMIF" and "spinal cord injury." Selected electronic databases were queried using the search terms detailed in Supplementary Table 1.

Inclusion and exclusion criteria

This study includes cohort, prospective, and retrospective analysis, as well as interventional studies. We selected studies that met our criteria: original articles that mentioned spinal cord injury* "in animal (in vitro/in vivo) OR human (in vitro/in vivo)" in the title/abstract AND Macrophage Migration-Inhibitory Factors OR Macrophage Inhibitory Factors OR MIF OR MMIF. We have included studies that mention anti-MMIF effect of interventions.

All models of traumatic spinal cord injury, including transection, hemi-section, contusion, and compression, were investigated at all levels of the spinal cord sensory or motor injury. Review articles, case reports, and case series involving fewer than 10 patients and studies where only an abstract was available were excluded. We also searched review articles for references on related topics. It should be noted that due to our specific search, we did not search 'macrophage' alone and did not consider "activated automated macrophage" treatment for SCI. Therefore, we did not include the RCT of Lammertse et al. [31, 32] in phase 2, which showed the negative effects of activated macrophages in a human study.

Assessment of quality and risk of bias in included studies

Two independent reviewers assessed risk of bias on the basis of the following criteria advised by Hassannejad et al. [33] for pathophysiological events after experiments on traumatic spinal cord injury: 1. species; 2. using appropriate tests; 3. the Severity of injury; 4. level of injury; 5. age/weight; 6. number of animals per group; 7. designation of strain; 8. definition of control; 9. description of statistical analysis; 10. Regulation and ethics; 11. Blindness of assessor; 12.

Table 1 Risk of Bias form of included articles

Authors, year	Species	Age/weight of animal mentioned	Designation of strain	Number of samples/per groups	Level of injury	Measures severity of injury	Consideration of genetic background	Method of allocation to intervention	Have a control group	Description of the reasons to exclude animals from the experiment during the study	Regulation and ethics	Definition of control group	Using appropriate tests for evaluation of outcome	Blindness of assessor	Description of statistical analysis	Quality
Bank et al, 2015 [14]	*	*	*	*	*	*			*	*	*		*		*	-
Stein et al.,2013 [1]	*			*					*	*	*					-
Benedict et al., 2012 [35]	*	*	*		*	*	*	*	*	*	*	*	*	*	*	high
Emmetsberger et al, 2012 [28]	*	*	*		*	*	*	*	*	*	*	*	*	*	*	high
Hu et al. 2013 [37]	*	*	*	*	*			*	*	*	*	*	*		*	high
Huo et al., 2017 [36]	*		*	*	*				*			*	*		*	medium
Koda et al, 2004 [16]	*	*	*	*	*	*					*		*			medium
Nishio et al., 2009 [10]	*				*		*	*	*	*	*	*	*			high
Saxena et al., 2015 [2]	*	*	*	*	*	*	*		*	*	*	*	*	*	*	high
Su et al., 2017 [38]	*	*			*		*				*	*	*		*	high
Zhou et al., 2018 [25]	*	*	*		*	*	*	*			*	*	*		*	high
Zhang et al., 2019 [39]	*	*	*	*	*	*	*		*		*	*	*		*	high

No risk of bias: white (*); risk of bias is unclear due to insufficient descriptions in the article, gray; high risk of bias: black.

Genetic background; 13. Method of allocation to treatments; 14. Have a control group 15. Description of the reasons to exclude animals from the experiment during the study.

If each column had no risk of bias, it scored as positive (white color); if each column showed a high risk of bias, it scored as negative (black color). If the risk of bias was unclear due to insufficient descriptions in the article, it showed as gray. Differences in the assessment were discussed during a consensus meeting. A total score was computed by adding the number of positive scores, and high quality (low risk of bias) was defined as fulfilling 8 or more (more than 50%) of the 15 internal validity criteria. Finally, the risk of bias was assessed for each included animal studies in the data extraction form (Table 1).

The study quality assessment tools of the National Heart, Lung, and Blood Institute of the National Institutes of Health (NIH) for observational cohort and cross-sectional studies were used to assess the quality of included human studies (Table 2) [34]. Since we do not have a similar qualitative assessment for animal studies, we used criteria advised by Hassannejad et al. [33] to assess the quality of animal studies.

Data extraction

The same two review authors who performed the risk of bias assessment conducted the data extraction independently from one another. Data were extracted into a standardized paper form. If there was a difference of opinion between review authors, two expert team members in traumatic spinal cord injuries were consulted to make a final decision.

Results

Description of studies

We identified 1,152 articles in initial search in databases, from which 367 similar titles removed. A total of 785 articles were initially screened through the evaluation of titles and abstracts, among which 751 articles were excluded. Thirty-four studies were deemed relevant and of acceptable format for full-text retrieval. Of these 34 papers, eight were excluded as they were review papers, and 14 papers did not present the least requisite data. Finally, after the elimination of duplicate reports and quality assessment of the articles, 12 studies were included in our review (Fig. 1).

The characteristics of included studies are presented in Table 3. Two studies (observational on both sexes) were performed on the human subject [1, 14], four studies [2, 16, 35, 36] as in vivo, and six experiments on both in vivo and in vitro animal models [10, 25, 28, 37–39].

In total, data from 472 animals (health control = 94, SCI = 178, and treatment = 200) and 79 patients (uninjured = 42 and SCI = 37) were extracted. Three [10, 35,

Table 2 Results of quality assessment of the observational included studies using NIH(35) criteria

Author	Bank et al. [14]	Stein et al. [1]
1. Was the research question or objective in this paper clearly stated?	YES	YES
2. Was the study population clearly specified and defined?	YES	YES
3. Was the participation rate of eligible persons at least 50%?	NO	NO
4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study pre specified and applied uniformly to all participants?	YES	YES
5. Sample size justification, power description, or variance and effect estimates provided?	NO	NO
6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?	YES	YES
7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?	YES	NA
8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?	YES	NA
9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	YES	YES
10. Was the exposure(s) assessed more than once over time?	NA	NA
11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	YES	YES
12. Were the outcome assessors blinded to the exposure status of participants?	NR	NR
13. Was loss to follow-up after baseline 20% or less?	NO	NA
14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?	NO	NO
Quality rating	Fair	Poor

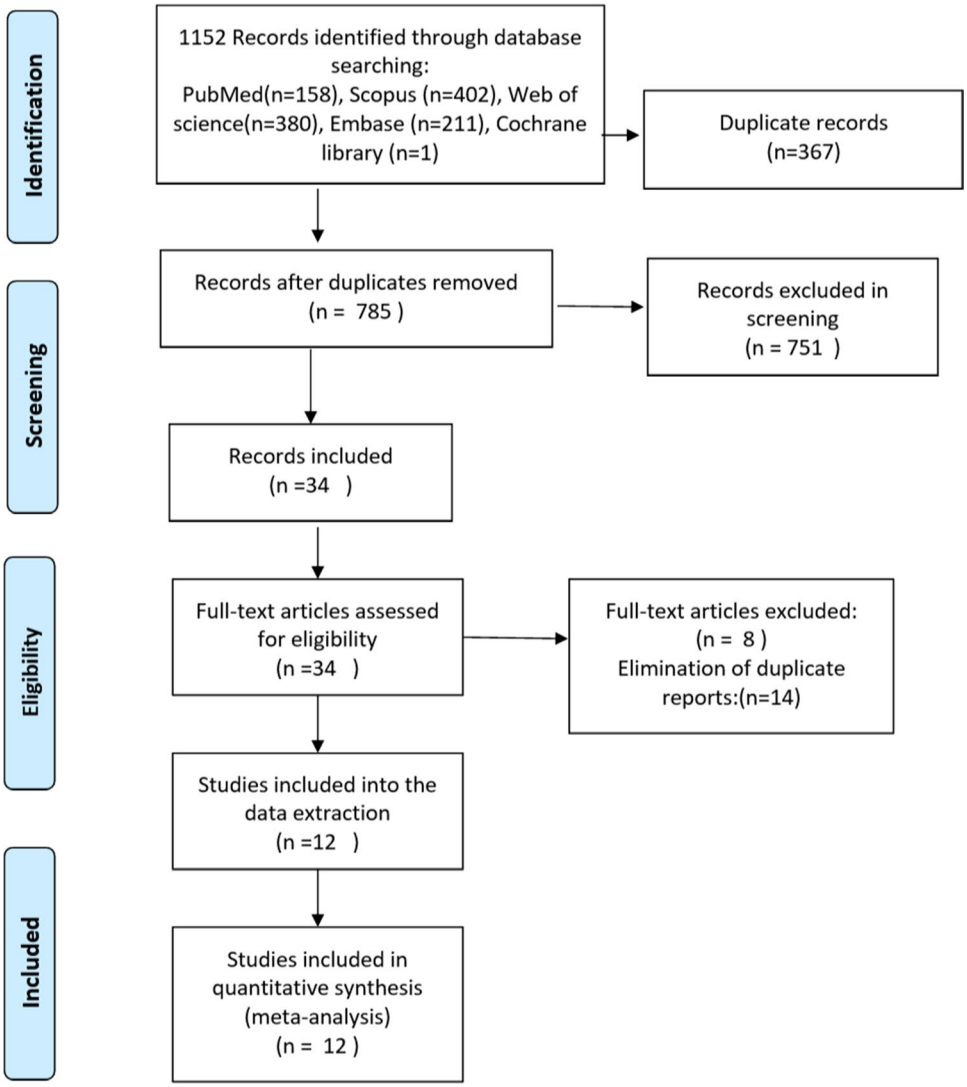

Fig. 1 PRISMA flow chart of summarized search procedure

36] and seven [2, 16, 25, 28, 37–39] experiments were performed on female and male rats, respectively.

The most common injury models in the included studies were contusion with eight experiments [2, 16, 25, 35–39], followed by compression with one [10], and hemi-section with one [28]. The most common mechanism of SCI in human subjects was motor vehicle crashes (16 patients), followed by fall (15), sport (4), violence (1), and other (4) [1, 14].

Risk of bias and quality assessment

The quality of all ($n = 12$) included studies was assessed. According to the NIH Checklist, of the two included human observational studies, one was considered as a study with poor [1] quality and the other as fair [14] (Table 2). Based on a checklist designed by our group in another study for assessing animal study ROB, of the remaining 10 animal studies, 2 were medium quality and the rest were high quality (Table 1).

Changing MMIF concentration after SCI

MMIF level was elevated during spinal cord injury as a reactive pro-inflammatory factor. Some studies [1, 14, 16, 38, 39], both human and animal, showed that MMIF level was increased after SCI compared with control subjects ($p < 0.001$). Both observational studies on acute and chronic spinal cord injury involving human patients [1, 14] stated that MMIF levels were higher in the injured patients than uninjured patients. While neither of these studies (fair [14] and poor [1] quality) have good power due to limited sample number and potential confounding variables (mostly in a

Table 3 Characteristics of included studies that survey the role of MMIF inhibitors in the prevention and/or promote damage after SCI

Authors, year	Study design	Type of sample	Sample size,	Gender, species, age, weight	Intervention/ observation	Type of injury	Levels of injury	Severity of injury	Follow-up	Key finding(s)
Bank et al. [14]	Observational	Human	Acute SCI: male($n=16$), Female ($n=2$) Uninjured control: Male = 15, Female = 3	Both sexes, ≥ 18 years	Measured MMIF plasma level for two weeks	Fall = 10 Motor vehicle = 4 Sport = 2 Other = 2	C1-3 = 3 C4-5 = 8 C6-8 = 4 T1 = 1 T6 = 1 T12 = 1	Mild = 1 Moderate = 4 Severe = 12 NA = 1	15 days for MMIF level trend, 95 days for survival	Elevated MMIF (sixfold) in SCI vs. uninjured control at 0 to 3, 4 to 7, and 8 to 11 DPI Survived patients = 14 Maximum MMIF level tended to be higher in non-survivors
Stein et al. [1]	Observational	Human	Chronic SCI: Male($n=16$) Female ($n=6$) Uninjured control: Male = 13 Female = 6	Both sexes, ≥ 18 years	MMIF plasma activity	Fall = 5 Motor vehicle = 12 Sport = 2 Violence = 1 Other = 2	Cervical = 15 Thoracic = 7	NA		Elevated MMIF (about twofold) in SCI vs. Uninjured - Maximum MMIF level tended to be higher in cervical level
Benedict et al. [35]	Experimental	Animal	Control (SCI without treatment) = 7 low-dose of Sulforaphane (SF) = 8 -High-dose SF = 7	Female, Sprague Dawley rats, 250-280 g	In vivo: Administration of two doses of SF, low-dose (10 mg/kg, IP) or high-dose (50 mg/kg, IP) on corn oil as vehicle in the control group, at 10 min and 72 h after injury	Contusion	T9	Moderate	Hindlimb locomotor score (BBB) = days 1, 4, and 7 after injury, and then weekly Horizontal ladder testing = 5w Catwalk-assisted quantitative gait analysis = 5w Urinary MIF activity assay = 96 h	MIF activity in SCI was higher than the control group. But SF treatment attenuates the MIF activity High-dose SF: Improves hindlimb function; increases serotonergic axons caudal to the SCI lesion

Table 3 (continued)

Authors, year	Study design	Type of sample	Sample size,	Gender, species, age, weight	Intervention/ observation	Type of injury	Levels of injury	Severity of injury	Follow-up	Key finding(s)
Emmetsberger et al. [28]	Experimental	Animal	In vivo: Control (SCI without treatment) = 7, MIF/TKP for 7 days = 7, MIF/TKP for 14 days = 7 In vitro: Control = 6, MIF/TKP = 6, LPS = 6, MIF/TKP + LPS = 6	Male, C57/BL6 mice	In vivo: administration of MIF/TKP for 7 and 14 days following SCI In vitro: Administration of MIF/TKP (5 mM), LPS (20 ng/ml), and MIF/TKP + LPS for 4 days	Hemi-section	T8	Severe	30 days	MIF/TKP inhibits microglia Astrogliosis was attenuated with MIF/TKP Lesion volume was found to be smaller when microglial/macrophage activation was inhibited with MIF/TKP MIF/TKP treatment blunted the T-cell response MIF/TKP treatment increases the number of myelinated axons Treatment with MIF/TKP reduces axonal dieback
Huo et al. [36]	Experimental	Animal	Control = 35, SCI = 35, Electrical Field Stimulation (EFS) + SCI = 35	Female, Sprague Dawley rats	In vivo: rats received EFS (0 ± 0.5 mV) immediately after SCI	Contusion	T10	Moderate	48 h	EFS treatment decreased secondary inflammatory response of SCI; and decreased the MIF tautomerase activity in the injured group in comparison with control group after 12 h, 24 h, and 48 h

Table 3 (continued)

Authors, year	Study design	Type of sample	Sample size,	Gender, species, age, weight	Intervention/ observation	Type of injury	Levels of injury	Severity of injury	Follow-up	Key finding(s)
Koda et al. [16]	Experimental	Animal	Control = 24 SCI = 24	Male, Wistar, 8-week-old, 200 g	In vivo: MMIF protein (North blotting), Immunohistochemistry, lectin histochemistry were measured 6 h, 24 h, 3 days, 1 week, or 2 weeks after SCI	Contusion	T8	Moderate	2w	MMIF mRNA expression after compression SCI peaked in 3d and went back to normal in 1w Control group MMIF expression: mainly in glial cells of white matter and poorly in neurons of gray matter After injury MMIF expression increased mainly in some round and small cells in the dorsal and lateral funiculus

Table 3 (continued)

Authors, year	Study design	Type of sample	Sample size,	Gender, species, age, weight	Intervention/ observation	Type of injury	Levels of injury	Severity of injury	Follow-up	Key finding(s)
Nishio et al. [10]	Experimental	Animal	knockout (KO) = 23 Wild-Type mice (WT) as control = 24	Female, MMIF KO mice	In vivo: assessment of hand-limb motor function 1–6 weeks (once a week) after SCI -In vitro: Assessment number of dead cells	Compression	T7-8	Moderate	6w	There was no significant difference in motor- function score between the WT and KO mice until three weeks after injury The average recovery score in KO mice six weeks after transplantation was 4.45, and the corresponding score in WT mice was 2.91 MMIF deletion attenuated glutamate insult of CGN in vitro MMIF deletion facilitated recovery of hindlimb motor function after 3w Histochemical assessment shows more neurons survived in KO than WT mice 42 days after SCI

Table 3 (continued)

Authors, year	Study design	Type of sample	Sample size,	Gender, species, age, weight	Intervention/ observation	Type of injury	Levels of injury	Severity of injury	Follow-up	Key finding(s)
Hu et al. [37]	Experimental	Animal	40 SCI subjects in control group and 40 SCI subjects in the Tetramethylpyrazine group	adult male Sprague–Dawley (SD) rats, weighing 250 to 300 g	In vivo:	Contusion	T10	Moderate	21 days	The expression of MMIF was increased after SCI, which could be inhibited by Tetramethylpyrazine treatment. Tetramethylpyrazine had potent anti-inflammatory properties and could improve function recovery after contusion SCI
Saxena et al. [2]	Experimental	Animal	Control = 6 SCI = 6 SCI + Chicago sky blue (CSB) = 6	Male, Sprague Dawley rats, (2–4 months old, 300–350 g	In vivo: at 48 h, 96 h, 1 week, or 2 weeks post-injury, animals were intravenously administered a 200 µL CSB with three different sized (40, 200, and 1000 nm) nanoparticles	Contusion	T9	Moderate	96 h	CSB addition attenuated MMIF and other inflammatory cytokines in primary microglia and macrophages Inflammation-associated transcripts (e.g., arginase) were upregulated in the spinal cords of animals with SCI in comparison with sham-operated animals Animals treated with nano-CSB showed better preservation of vascular integrity

Table 3 (continued)

Authors, year	Study design	Type of sample	Sample size,	Gender, species, age, weight	Intervention/ observation	Type of injury	Levels of injury	Severity of injury	Follow-up	Key finding(s)
Su et al., [38]	Experimental	Animal	In vivo: SCI rats = 6 In vitro: Control = 6 MMIF-treated = 18	Male, Sprague Dawley, 1–2 days, 180–220 g	In vivo: Assessment mRNA expression of MMIF In vitro: Measured inflammatory cytokines in astrocytes that treatment with 0–2.5 µg/ml recombinant MMIF for 24 h	Contusion	T9	Moderate	7 days	MMIF expression after 4d and 7d post-SCI increased in astrocytes and microglia MMIF treatment in astrocytes increased expression of TNFa, IL1b and NFkb MIF signaling in astrocytes is through CD74

Table 3 (continued)

Authors, year	Study design	Type of sample	Sample size,	Gender, species, age, weight	Intervention/ observation	Type of injury	Levels of injury	Severity of injury	Follow-up	Key finding(s)
Zhou et al. [25]	Experimental	Animal	In vivo: MMIF treated = 6 CCL5 treated = 6 In vitro: Control = 6 MMIF-treated = 18	Male, Sprague Dawley, 1–2 days, 180–220 g	In vivo: 1. Assessment hindlimb locomotor function after MMIF or CCL5 treatment on 0, 7, 14, and 21 days after SCI 2. Determination of MMIF and CCL5 expression following spinal cord injury In vitro: Measured CCL5 production in astrocytes that treatment with 0–2.5 μg/ml recombinant MMIF for 24 h	Contusion	T9	Moderate	7 days	MMIF facilitated the expression of chemokine CCL5 in the astrocytes of injured rat spinal cord Expression of CCL5 was regulated by the MMIF/CD74 axis in astrocytes MMIF inhibitor attenuated CCL5 expression of astrocytes in vitro MMIF promoted CCL5 production of astrocytes through JNK signaling CCL5 primarily potentiated migration of IL-13-treated macrophages

Table 3 (continued)

Authors, year	Study design	Type of sample	Sample size,	Gender, species, age, weight	Intervention/ observation	Type of injury	Levels of injury	Severity of injury	Follow-up	Key finding(s)
Zhang et al. [39]	Experimental	Animal	In vivo: SCI COX2 inhibitor (NS398) = 6 In vitro: SCI = 6 MMIF-treated = 18 NS398 treated = 6	Male, Sprague Dawley, 1–2 days, 180–220 g	-In vivo: Determine protein levels of MMIF, COX1, and COX2, as well as the isoforms of PGE2 synthase In vitro: Determine COX2 production in astrocytes that treatment with 0–2.5 µg/ml recombinant MMIF for 24 h	Contusion	T9	Moderate	7 days	Protein levels of MMIF and COX2, but not of COX1, synchronously increased following spinal cord injury Adding MMIF inhibitor (4-IPP) attenuates COX2 and mPGES-1 protein levels and PGE2 production MMIF treatment could elevate PGE2 level in primary cultured astrocytes in a dose-dependent manner Administrated NS398 leads to decrease of PGE2 in cultured astrocytes Activation of COX2 was essential for MMIF-induced production of PGE2

NA: Not available

study on chronic SCI patients [1]), the studies were important in understanding whether MMIF was involved in both primary and secondary injury (acute and chronic) after SCI [1, 14]. In Stein et al. [1] subjects with chronic SCI with a mean time of 12 ± 1.5 years after injury were enrolled, and the distribution of AIS grades were as follows: A (64%), C (14%), and D (23%). Bank et el. [14]. evaluated the MMIF level in acute SCI patients; most patients were AIS grade A.MMIF level tended to be higher in non-survivors compared with survivors and cervical SCI patients compared with other sites of injury, but it enough to be considered a biomarker for outcome and severity of injury ($p \leq 0.1$). Six studies showed that MMIF activity or MMIF gene expression could be affected by MMIF inhibitors in animal models of SCI (Table 4) [2, 10, 35–37, 39]. Table 5 shows the changing MMIF level after SCI in included articles.

Role of MMIF in the achievement of post-SCI damages

We did not find any interventional studies focusing on the effect of MMIF or its inhibitors on human SCI in our systematic review. After gathering information from animal studies, it was generally accepted that after spinal cord injury, MMIF acts as an upstream mediator of the pro-inflammatory molecular cascade and activates inflammatory signaling pathways [38, 39]. MMIF does this by interacting with MMIF receptors (CD74) on astrocytes and macrophages [25, 35, 39], which consequently lead to adverse events such as increased susceptibility to glutamate-related neurotoxicity [10], increased nitrite production [2], activation of ERK [38] and COX2/PGE2 [39] signaling pathways, and stimulation of CCL5-related chemotaxis [25]. Note that one study with high quality indicated that microglial inhibitory factor (MIF/TKP), by acting on microglia and macrophages could attenuate axonal damage after SCI by inhibiting cell migration. MIF/TKP also induces proliferation and differentiation of oligodendrocyte precursor cells and reduces axonal dieback [28].

Possible beneficial effects of MMIF inhibitors

Molecular and histopathological outcomes

Four studies with high quality suggested that MMIF inhibitory molecules, such as sulforaphane, Chicago sky blue (CSB), tetramethylpyrazine and 4-IPP could ameliorate inflammation via different pathways [2, 35, 37, 39]. In addition to MMIF inhibitors, electrical field stimulation, such as that reported by Huo et al. [36], could inactivate MMIF tautomerase activity directly and may directly and indirectly lead to offset of Ca^{2+} influx at the spinal cord injury site. Nishio et al. [10] have also demonstrated that after the deletion of the MMIF gene, neuronal apoptosis post-SCI markedly decreased in comparison with control group ($p < 0.01$). All models of injury in this animal study were contusion injury except the study by Nishio et al. [10], which involved compression. With the exception of Stein et al.[1], which addressed chronic SCI patients, the rest of the human and animal studies addressed acute SCI.

Inflammatory cytokines (e.g., IL-1, TNF-α, IL-4, IL-10, and IL-13) released by glial cells, especially astrocytes, are recognized as some of the most important factors in the development of post-SCI damage. The role of MMIF in increasing these cytokines was demonstrated by three studies [2, 25, 38], and inhibitors of MMIF may be considered as potential new therapies for SCI. Stimulation of the COX2 production pathway is another mechanism of MMIF-induced post-SCI damage. Zhang et al. [39] demonstrated that MMIF can increase COX2/PGE2 products and, consequently, elevate inflammatory cytokines such as TNF-α. Subjects treated with 4-IPP as an MMIF inhibitor had a decreased level of COX2 in astrocytes and at the lesion site ($p < 0.05$). Benedict et al. [35] has investigated the role of sulforaphane on MMIF and postulated that treatment at low-dose ($n = 8$) or High-dose ($n = 7$) of sulforaphane increased the number of serotonergic axons caudal to the lesion site ($p = 0.03$). In another study [2] examining the effect of nano Chicago sky blue (nano-CSB) on MMIF, CSB was shown to inhibit MMIF tautomerase activity. Animals receiving nano-CSB also had higher amounts of white matter sparing at the lesion site and showed better preservation of vascular integrity at the center of injury site compared to control ($p < 0.05$). In a study by Hu et al. [37] comparing the effect of tetramethylpyrazine (TMP) in control and treatment groups, expression of MMIF was significantly reduced in the treatment group and was associated with better recovery of hindlimb function of rats based on Basso, Beattie, and Bresnahan (BBB) score. All studies mentioned in this section had a low risk of bias.

Behavioral outcomes

Three out of the 12 studies examined pre-clinical outcomes [2, 10, 37]. A study conducted by Saxena et al.[2] used Basso, Beattie, and Bresnahan (BBB) score to measure behavioral outcomes and showed that treatment with sulforaphane (10 or 50 mg/kg) improves the (BBB) score and subscore and horizontal ladder performance as a functional recovery ($p < 0.01$). Number of severe missteps in horizontal ladder performance decreased between weeks 3 and 5 compared to the control group ($p < 0.05$). Nishio et al.[10] used a 15-point hindlimb motor function score to assess functional recovery and showed that the MMIF gene knockout group had a significant difference in motor function score versus wild type at 21 days after injury ($p < 0.01$). MMIF gene knockout facilitated the recovery of hindlimb motor

Table 4 MMIF inhibitors effects on SCI

MMIF inhibitors effects on SCI			
Intervention	Mechanism of action on MMIF	Measurement tool	Conclusions
Sulforaphane (10 or 50 mg/kg) (Benedict) [35]	inactivation of MMIF tautomerase activity, by interacting with MMIF-CD74	Hindlimb behavioral tests: Basso, Beattie, and Bresnahan (BBB) score Horizontal ladder performance Quantitative immune-reactivity image analysis: Sparing or sprouting of serotonergic axons caudal	Behavioral: Improve the (BBB) score and subscore and horizontal ladder performance ($p<0.01$) Decrease in severe missteps between weeks 3 and 5 compared to the control group ($p<0.05$) Histopathological: Increased number of serotonergic axons caudal to the lesion site ($p=0.03$)
MMIF gene knockout (Nishio) [10]	Glutamate neurotoxicity resistance induction	Hindlimb behavioral tests: 15-point scale hindlimb motor function score(69) Immunohistochemistry: Counting NeuN/caspase-3-active or APC/caspase-3- active double-positive cells	Behavioral: Significant difference in motor-function score between the WT and KO 21 days after injury ($p<0.01$); MMIF gene knockout facilitated recovery of hindlimb motor function after 3w Histopathological: Number of apoptotic neurons in the KO mice was significantly smaller than that of the WT mice 24 and 72 h after SCI ($p<0.01$)
Tetramethylpyrazine (treated intraperitoneally 200 mg/kg) (Hu) [37]	The expression of MMIF was significantly reduced by Tetramethylpyrazine treatment	Locomotor activity: Basso, Beattie, and Bresnahan (BBB) score Immunohistochemical analysis: Cord sections were incubated with anti-MMIF antibody and cell counting was performed	Tetramethylpyrazine treatment is beneficial in restoring the hindlimb function Tetramethylpyrazine decreasing expression of MMIF in cellular level
Electrical field stimulation (0 ± 0.5 mV) (Huo) [36]	Inactivation of MIF tautomerase activity Offset the Ca2+ influx at the spinal cord injury site	Rosengren et al. procedure (13)	Molecular: Lowered MIF tautomerase activity 12 h ($p<0.01$), 24 h ($p<0.01$) and 48 h ($p<0.01$) after the surgery. $n=5$ per group
Nano Chicago sky blue (CSB) (Saxena) [2]	-Inhibition of MMIF tautomerase activity Nitrite production attenuation Alleviate MIF-mediated inflammation	Luxol fast blue staining Colorimetric assay [Griess assay (70)]	Histopathological: Animals receiving nano-CSB had a higher amount of white matter sparing at the lesion site in comparison with the controls ($p<0.05$) Animals treated with nano CSB showed better preservation of vascular integrity at the epicenter and at sites away from the injury ($p<0.05$)

Table 4 (continued)

MMIF inhibitors effects on SCI			
Intervention	Mechanism of action on MMIF	Measurement tool	Conclusions
4-iodo-6-phenylpyrimidine(4-IPP) 100 µM (Zhang)[39] Knocked down of CD74 receptor of astrocyte by siRNA2 (Zhang) [39]	Inhibit activation of COX2/ PGE2 signaling in spinal astrocyte/ microglia by MMIF Decrease in CCL5 protein levels through CD74 membrane receptor interaction Prevention of CCL5-related chemotaxis produced by astrocytes is primarily involved in promoting migration of M2 macrophages Triggers COX2/PGE2 signaling through CD74 membrane receptor	ELISA Immunostaining Quantitative-PCR	Molecular: MMIF inhibitor 4-IPP at the lesion sites resulted in remarkable a decrease of COX2 and mPGES-1 protein levels ($p < 0.05$) Treatment of 4-IPP attenuated the expression of COX2 in the astrocytes ($p < 0.05$) Significant decrease in CCL5 protein levels ($p < 0.05$) Histopathological: Significant reduction of microglia migration ($p < 0.05$) Molecular: Protein levels of COX2 and mPGES-1 remarkably decreased following CD74 knocked down interference ($p < 0.05$) Production of PGE2 was Significantly inhibited by CD74 siRNA following MMIF stimulation. ($p < 0.05$)
MMIF effects in SCI			
Recombinant MMIF administration (Su) [38]	MMIF-CD74 interaction leads to ERK pathway cascade activation	RT-PCR analysis	Molecular: Expression of TNF-α, NFκB, Ch25h and Pla2g2a and IL-1β significantly increased after treatment with recombinant MMIF ($P < 0.05$)
MIF/TKP effects on SCI			
Microglial inhibitory factor (MIF/TKP) (Emmetsberger) [28]	MIF/TKP Inhibit cell migration MIF/TKP induce proliferation and differentiation of oligodendrocyte precursor cells MIF/TKP reduces axonal dieback	Immunohistochemistry Immunofluorescent staining	Histopathological: MIF/TKP reduces levels of inhibitory chondroitin sulfate proteoglycans (CSPG) and lesion volume ($p < 0.05$) MIF treatment resulted in significantly higher numbers of proliferating NG2 + oligodendrocyte precursor cells early after injury in comparison to control group ($p < 0.05$)

Table 5 MMIF level after SCI and different human and animal studies including MMIF inhibitors

Author Year Reference number	The level of MMIF increased after SCI	Observational/interventional
Bank [14]	+	Acute Human
Stein 2013 [1]	+	Chronic Human
Benedict [35]	NA	Sulforaphane
Emmetsberger [28]	NA	MIF/TKP Reverse: knife hemisection—minimal inflammation vs contusion
Huo [36]	NA	EFS
Koda [16]	+	mRNA peak 3d; normal in 1 w
Nishio [10]	NA	KO mice
Saxena [2]	NA	CSB
Su [38]	+	MMIF increased in astrocytes/microglia
Zhang [39]	+	4IPP
Zhuo [25]	NA	CCL5
Hu [37]	+	tetramethylpyrazine (TMP)

NA=Not available

Six studies have shown that following SCI, MIF increases [1, 14, 16, 37–39]. These studies confirm elevation of MIF in acute [14] and chronic [1] SCI in human, and in animal SCI [16, 38, 39]. There is no study to show normal or decreased level of MIF following human or animal SCI. Regarding the effects of MIF, studies have shown the negative histopathologic and behavioral effect and secondary damage following high MIF [2, 10, 35, 36, 39]. Only one study has shown histopathologic (and not functional) improvement following MIF [28]. This study used micro-knife for hemisection. There is evidence that knife injury produces minimal inflammatory response compared with contusion injury [58]. Therefore, using knife for evaluation of inflammation may not be a suitable method

The mRNA of MIF increases following SCI, peaking in three days and becoming normal in a week [16]. The knockout mice confirmed that inhibition of MIF results in both functional recovery and decreased cellular death [10]. The different MIF inhibitors that have been used to improve functional recovery [10, 35, 37] and histopathology [2, 10, 35, 37, 38] include Sulforaphane [35], EFS [36], CSB [2], and 4IPP [39]

function after 3 weeks. In the study conducted by Hu et al. [37] comparing physical activity during 21 days of injury in the control and treatment groups, hindlimb locomotor activity and BBB score improved gradually in both groups. Compared to the control group, the TMP group showed a significantly improved hindlimb activity score on day 7 after injury (day 7, $p < 0.05$; days 14 and 21, $p < 0.01$). All 3 studies had a low risk of bias.

Discussion

We systematically evaluated the effect of MMIF and its inhibitors in SCI and sought to find whether MMIF inhibitors are a valid treatment option. Reviewed studies showed higher MMIF levels in both acute and chronic SCI than in the control group [1, 14]. Furthermore, several studies demonstrated that inhibition of MMIF leads to improved hindlimb functional recovery, improved neuronal survival, and reduced neuronal apoptosis and recovery time [10]. Although human studies [1, 14] have reported increased levels of MMIF after spinal cord injury, MMIF concentrations were similar to those in other acute inflammatory conditions such as sepsis, burns, and trauma [40–43]. According to the reviewed articles, evidence was obtained regarding the effects of various substances on MMIF. It is already known that MMIF has mitogenic, pro-inflammatory and immune-regulated activity due to binding to CD74 on the surface of astrocytes. Su et al. [38] also confirmed this fact by applying recombinant MMIF, and noted that CD74 is an important molecule in the MMIF mediatory process. This interaction activates extracellular signal-regulated kinases (ERK), which mediates prostaglandin E2 (PGE2) generation via increased cyclooxygenase-2 (COX-2) production. The authors also suggested that MMIF proinflammatory activity not only activates the ERK pathway, but also increases proinflammatory molecules such as *TNF-α, NFκB*.

In this regard, Zhang et al. [39] used the genomic effects of *siRNA2* and the knockdown of astrocyte CD74 receptors to decrease levels of COX2 and prostaglandin E2 (PGE2). This result was in line with the study of Su et al. [38]

Activation of ERK1 by MMIF can also stimulate immune cell recruitment to the site of spinal cord injury through the increase in chemokine ligand 5 (CCL5) [25]. Zhang et al. [39] found that 4-iodo-6-phenylpyrimidine (4-IPP) decreases CCL5 protein levels through CD74 membrane receptor interaction and prevents CCL5-related chemotaxis triggered by astrocytes involved in promoting migration of

M2 macrophages. The major limitation of these studies is that they were limited to animal models. Additionally, the examined outcomes are only at the molecular level and did not involve functional outcomes. Glucocorticoids also have an inhibitory effect on MMIF, but studies have suggested that they have the paradoxical effect of stimulating MMIF secretion rather than inhibiting its secretion [44–46].

Three important studies [10, 35, 37] have investigated functional outcomes, the results of which are consistent with other studies. Nishio et al. showed that MMIF deletion did not change macrophage accumulation on the third day after the injury, but that deletion of MMIF inhibited toxic glutamate-dependent death. Injected of recombinant human MMIF also reversed this deadly cellular inhibition [10]. Nishio et al. showed that MMIF gene knockout facilitated recovery of hindlimb motor function after 3 weeks. Benedict et al. showed improvement in BBB score in injured mice, compared to the control group, by injecting sulforaphane into mice with spinal cord injury [35]. Hu et al. reduced the expression of MMIF by injecting mice intraperitoneally with Tetramethylpyrazine. As a result, the study found that Tetramethylpyrazine treatment is beneficial in restoring hindlimb function [37].

Emmetsberger et al. have shown that MIF/TKP inhibited microglia and macrophages, dramatically reducing *TNF-α* production both in vitro and in vivo [28]. They illustrated how macrophage inhibition reduces secondary damage and reduces astrocyte hypertrophy. Additionally, MIF/TKP inhibition can be therapeutic by reducing *TNF-α,* as *TNF-α* itself is neurotoxic [28]. According to a group of studies, activated microglia and macrophages that were transplanted into in vitro SCI cells caused tissue preservation and neuronal regeneration, as well as maintained functional recovery, through the release of trophic and anti-inflammatory factors [47–51]. Therefore, depending on its state of activation, macrophages can produce neurotoxic or neurotrophic factors. Heterogeneous subsets of macrophages called M1 (neurotoxic) and M2 (neuroprotective) are both present after injury, but M1 prevails immediately after injury and causes a pro-inflammatory effect that may overcome neuroprotective activity [52, 53]. The predominance of M1 macrophages and lower number of M2 macrophages after SCI may contribute to secondary damage [54].

One of the limitations of our study is the small sample size of the animal studies, which can lead to an increased risk of selection bias. Additionally, based on our database search, there is a lack of previous systematic reviews or meta-analyses. In some articles, the effects of interventions are not due to anti-MMIF activity only, as MMIF has other effects on various molecules that must be considered. Human studies are also scarce, and most of them focused on the potential impact on CNS macrophage biology [29]. Due to our specific analysis, we did not search for SCI intervention using the term 'macrophage.' We therefore did not include Lammertse [31] et al.'s randomized controlled trial (phase 2). Also another analysis by Kigrel et al. [55] focused on developing 'Pro Cord', a novel therapy for SCI (Phase I/II clinical trials in humans).

Other studies focus on non-macrophage-mediated treatment modalities. Yoon et al. [56] carried out a phase I/II, open-label, and nonrandomized study with 35 complete spinal cord injury patients receiving autologous human bone marrow cell (BMC) and granulocyte macrophage-colony stimulating factor (GM-CSF). Further human studies are needed with larger sample sizes, as well as clinical trials for an MMIF-inhibitor drug in acute or chronic SCI. Similar studies will be needed: 1-for dose- and time-dependent measurement of MMIF in both animal and human studies, 2-to gain more accurate knowledge of the origin of MMIF secretion; 3-to differentiate M1/M2 macrophages and understand their interaction with subsequent SCI MMIFs, and 4-to use sensitive techniques [57] to quantify activated macrophages.

In summary, our evaluation of the therapeutic effect of MMIF inhibition as a means of reducing the complications of SCI has included a systematic review of studies performed before February 2019, and suggests that in most studies, MMIF inhibition can improve outcomes in animal models.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest except Alex R Vaccaro.

Availability of data and material The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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References

1. Stein A, Panjwani A, Sison C, Rosen L, Chugh R, Metz C, Bank M, Bloom O (2013) Pilot Study: elevated circulating levels of the proinflammatory cytokine macrophage migration inhibitory factor in patients with chronic spinal cord injury. Arch Phys Med Rehabil 94:1498–1507. https://doi.org/10.1016/j.apmr.2013.04.004
2. Saxena T, Loomis KH, Pai SB, Karumbaiah L, Gaupp E, Patil K, Patkar R, Bellamkonda RV (2015) Nanocarrier-mediated inhibition of macrophage migration inhibitory factor attenuates secondary injury after spinal cord injury. ACS Nano 9:1492–1505. https://doi.org/10.1021/nn505980z
3. Hagg T, Oudega M (2006) Degenerative and spontaneous regenerative processes after spinal cord injury. J Neurotrauma 23:264–280
4. Hall ED (2011) Antioxidant therapies for acute spinal cord injury. Neurotherapeutics 8:152–167
5. Tator CH, Fehlings MG (1991) Review of the secondary injury theory of acute spinal cord trauma with emphasis on vascular mechanisms. J Neurosurg 75:15–26
6. Bartholdi D, Schwab ME (1997) Expression of pro-inflammatory cytokine and chemokine mRNA upon experimental spinal cord injury in mouse: an in situ hybridization study. Eur J Neurosci 9:1422–1438. https://doi.org/10.1111/j.1460-9568.1997.tb01497.x
7. Hawthorne AL, Popovich PG (2011) Emerging concepts in myeloid cell biology after spinal cord injury. Neurotherapeutics 8:252–261
8. Nas K, Yazmalar L, Şah V, Aydın A, Öneş K (2015) Rehabilitation of spinal cord injuries. World J Orthop 6:8–16. https://doi.org/10.5312/wjo.v6.i1.8
9. Fleming JC, Norenberg MD, Ramsay DA, Dekaban GA, Marcillo AE, Saenz AD, Pasquale-Styles M, Dietrich WD, Weaver LC (2006) The cellular inflammatory response in human spinal cords after injury. Brain 129:3249–3269. https://doi.org/10.1093/brain/awl296
10. Nishio Y, Koda M, Hashimoto M, Kamada T, Koshizuka S, Yoshinaga K, Onodera S, Nishihira J, Okawa A, Yamazaki M (2009) Deletion of macrophage migration inhibitory factor attenuates neuronal death and promotes functional recovery after compression-induced spinal cord injury in mice. Acta Neuropathol 117:321–328. https://doi.org/10.1007/s00401-008-0476-x
11. Bloom BR, Bennett B (1966) Mechanism of a reaction in vitro associated with delayed-type hypersensitivity. Science 153:80–82. https://doi.org/10.1126/science.153.3731.80
12. Calandra T, Roger T (2003) Macrophage migration inhibitory factor: a regulator of innate immunity. Nat Rev Immunol 3(10):791–800. https://doi.org/10.1038/nri1200
13. Rosengren E, Åman P, Thelin S, Hansson C, Ahlfors S, Björk P, Jacobsson L, Rorsman H (1997) The macrophage migration inhibitory factor MIF is a phenylpyruvate tautomerase. FEBS Lett 417:85–88. https://doi.org/10.1016/S0014-5793(97)01261-1
14. Bank M, Stein A, Sison C, Glazer A, Jassal N, McCarthy D, Shatzer M, Hahn B, Chugh R, Davies P, Bloom O (2015) Elevated circulating levels of the pro-inflammatory cytokine macrophage migration inhibitory factor in individuals with acute spinal cord injury. Arch Phys Med Rehabil 96:633–644. https://doi.org/10.1016/j.apmr.2014.10.021
15. Chalimoniuk M, King-Pospisil K, Metz CN, Toborek M (2006) Macrophage migration inhibitory factor induces cell death and decreases neuronal nitric oxide expression in spinal cord neurons. Neuroscience 139:1117–1128. https://doi.org/10.1016/j.neuroscience.2005.12.056
16. Koda M, Nishio Y, Hashimoto M, Kamada T, Koshizuka S, Yoshinaga K, Onodera S, Nishihira J, Moriya H, Yamazaki M (2004) Up-regulation of macrophage migration-inhibitory factor expression after compression-induced spinal cord injury in rats. Acta Neuropathol 108:31–36. https://doi.org/10.1007/s00401-004-0853-z
17. Yang Y, Xie Y, Chai H, Fan M, Liu S, Liu H, Bruce I, Wu W (2006) Microarray analysis of gene expression patterns in adult spinal motoneurons after different types of axonal injuries. Brain Res 1075:1–12. https://doi.org/10.1016/j.brainres.2005.12.060
18. Alexander JK, Cox GM, Tian JB, Zha AM, Wei P, Kigerl KA, Reddy MK, Dagia NM, Sielecki T, Zhu MX, Satoskar AR, McTigue DM, Whitacre CC, Popovich PG (2012) Macrophage migration inhibitory factor (MIF) is essential for inflammatory and neuropathic pain and enhances pain in response to stress. Exp Neurol 236:351–362. https://doi.org/10.1016/j.expneurol.2012.04.018
19. Bacher M, Meinhardt A, Lan HY, Dhabhar FS, Mu W, Metz CN, Chesney JA, Gemsa D, Donnelly T, Atkins RC, Bucala R (1998) MIF expression in the rat brain: implications for neuronal function. Mol Med 4:217–230
20. Ohta S, Misawa A, Fukaya R, Inoue S, Kanemura Y, Okano H, Kawakami Y, Toda M (2012) Macrophage migration inhibitory factor (MIF) promotes cell survival and proliferation of neural stem/progenitor cells. Development. https://doi.org/10.1242/jcs.102210
21. Leyton-Jaimes MF, Kahn J, Israelson A (2018) Macrophage migration inhibitory factor: a multifaceted cytokine implicated in multiple neurological diseases. Exp Neurol 301:83–91
22. Hausmann ON (2003) Post-traumatic inflammation following spinal cord injury. Spinal Cord 41:369–378
23. Abe R, Shimizu T, Ohkawara A, Nishihira J (2000) Enhancement of macrophage migration inhibitory factor (MIF) expression in injured epidermis and cultured fibroblasts. Biochimica et Biophysica Acta Mol Basis of Dis 1500:1–9. https://doi.org/10.1016/S0925-4439(99)00080-0
24. Bai F, Asojo OA, Cirillo P, Ciustea M, Ledizet M, Aristoff PA, Leng L, Koski RA, Powell TJ, Bucala R, Anthony KG (2012) A novel allosteric inhibitor of macrophage migration inhibitory factor (MIF). J Biol Chem 287:30653–30663. https://doi.org/10.1074/jbc.M112.385583
25. Zhou Y, Guo W, Zhu Z, Hu Y, Wang Y, Zhang X, Wang W, Du N, Song T, Yang K, Guan Z, Wang Y, Guo A (2018) Macrophage migration inhibitory factor facilitates production of CCL5 in astrocytes following rat spinal cord injury. J Neuroinflammation 15:253–253. https://doi.org/10.1186/s12974-018-1297-z
26. Bernhagen J, Krohn R, Lue H, Gregory JL, Zernecke A, Koenen RR, Dewor M, Georgiev I, Schober A, Leng L, Kooistra T, Fingerle-Rowson G, Ghezzi P, Kleemann R, McColl SR, Bucala R, Hickey MJ, Weber C (2007) MIF is a noncognate ligand of CXC chemokine receptors in inflammatory and atherogenic cell recruitment. Nat Med 13:587–596. https://doi.org/10.1038/nm1567
27. Shi X, Leng L, Wang T, Wang W, Du X, Li J, McDonald C, Chen Z, Murphy JW, Lolis E, Noble P, Knudson W, Bucala R (2006) CD44 Is the signaling component of the macrophage migration inhibitory factor-CD74 receptor complex. Immunity 25:595–606. https://doi.org/10.1016/j.immuni.2006.08.020
28. Emmetsberger J, Tsirka SE (2012) Microglial inhibitory factor (MIF/TKP) mitigates secondary damage following spinal cord injury. Neurobiol Dis 47:295–309. https://doi.org/10.1016/j.nbd.2012.05.001
29. Gensel JC, Donnelly DJ, Popovich PG (2011) Spinal cord injury therapies in humans: an overview of current clinical trials and their potential effects on intrinsic CNS macrophages. Expert Opin Ther Targets 15:505–518
30. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JPA, Clarke M, Devereaux PJ, Kleijnen J, Moher D (2009)

The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. J Clin Epidemiol 62(10):1-e34
31. Lammertse DP, Jones LAT, Charlifue SB, Kirshblum SC, Apple DF, Ragnarsson KT, Falci SP, Heary RF, Choudhri TF, Jenkins AL, Betz RR, Poonian D, Cuthbert JP, Jha A, Snyder DA, Knoller N (2012) Autologous incubated macrophage therapy in acute, complete spinal cord injury: Results of the phase 2 randomized controlled multicenter trial. Spinal Cord 50:661–671. https://doi.org/10.1038/sc.2012.39
32. Wyndaele JJ (2012) Autologous incubated macrophage treatment failed to show a difference in the neurological outcome in patients with acute, complete spinal cord injury. Spinal Cord 50:645
33. Hassannejad Z, Sharif-Alhoseini M, Shakouri-Motlagh A, Vahedi F, Zadegan SA, Mokhatab M, Rezvan M, Saadat S, Shokraneh F, Rahimi-Movaghar V (2016) Potential variables affecting the quality of animal studies regarding pathophysiology of traumatic spinal cord injuries. Spinal Cord 54:579–583. https://doi.org/10.1038/sc.2015.215
34. https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools
35. Benedict AL, Mountney A, Hurtado A, Bryan KE, Schnaar RL, Dinkova-Kostova AT, Talalay P (2012) Neuroprotective effects of sulforaphane after contusive spinal cord injury. J Neurotrauma 29:2576–2586. https://doi.org/10.1089/neu.2012.2474
36. Huo X, Zhang G, Wu C, Zhang C (2017) Electric field stimulation protects injured spinal cord from secondary inflammatory response in rats. Annu Int Conf IEEE Eng Med Biol Soc 2017:1958–1961. https://doi.org/10.1109/EMBC.2017.8037233
37. Hu JZ, Huang JH, Xiao ZM, Li JH, Li XM, Lu HB (2013) Tetramethylpyrazine accelerates the function recovery of traumatic spinal cord in rat model by attenuating inflammation. J Neurol Sci 324:94–99. https://doi.org/10.1016/j.jns.2012.10.009
38. Su Y, Wang Y, Zhou Y, Zhu Z, Zhang Q, Zhang X, Wang W, Gu X, Guo A, Wang Y (2017) Macrophage migration inhibitory factor activates inflammatory responses of astrocytes through interaction with CD74 receptor. Oncotarget 8:2719–2730. https://doi.org/10.18632/oncotarget.13739
39. Zhang Y, Zhou Y, Chen S, Hu Y, Zhu Z, Wang Y, Du N, Song T, Yang Y, Guo A, Wang Y (2019) Macrophage migration inhibitory factor facilitates prostaglandin E2 production of astrocytes to tune inflammatory milieu following spinal cord injury. J Neuroinflammation 16:85–85. https://doi.org/10.1186/s12974-019-1468-6
40. Padovani-Claudio DA, Liu L, Ransohoff RM, Miller RH (2006) Alterations in the oligodendrocyte lineage, myelin, and white matter in adult mice lacking the chemokine receptor CXCR2. Glia 54:471–483. https://doi.org/10.1002/glia.20383
41. Merrill JE, Scolding NJ (1999) Mechanisms of damage to myelin and oligodendrocytes and their relevance to disease. Neuropathol Appl Neurobiol 25:435–458
42. Rosenberg LJ, Teng YD, Wrathall JR (1999) 2,3-Dihydroxy-6-Nitro-7-Sulfamoyl-Benzo(*f*)Quinoxaline reduces glial loss and acute white matter pathology after experimental spinal cord contusion. J Neurosci 19:464–475. https://doi.org/10.1523/JNEUROSCI.19-01-00464.1999
43. Streit W, Semple-Rowland S, Hurley S, Miller R, Popovich P, Stokes B (1998) Cytokine mRNA Profiles in contused spinal cord and axotomized facial nucleus suggest a beneficial role for inflammation and gliosis. Exp Neurol 152:74–87. https://doi.org/10.1006/exnr.1998.6835
44. Nikolic I, Vujicic M, Saksida T, Berki T, Stosic-Grujicic S, Stojanovic I (2013) The role of endogenous glucocorticoids in glucose metabolism and immune status of MIF-deficient mice. Eur J Pharmacol 714:498–506. https://doi.org/10.1016/j.ejphar.2013.06.037
45. Calandra T, Bernhagen J, Metz CN, Spiegel LA, Bacher M, Donnelly T, Cerami A, Bucala R (1995) MIF as a glucocorticoid-induced modulator of cytokine production. Nature 377:68–71. https://doi.org/10.1038/377068a0
46. Xu L, Li Y, Sun H, Zhen X, Qiao C, Tian S, Hou T (2013) Current developments of macrophage migration inhibitory factor (MIF) inhibitors. Drug Discov Today 18:592–600. https://doi.org/10.1016/j.drudis.2012.12.013
47. Lazarov-Spiegler O, Solomon AS, Zeev-Brann AB, Hirschberg DL, Lavie V, Schwartz M (1996) Transplantation of activated macrophages overcomes central nervous system regrowth failure. FASEB J Off Publ Fed Am Soc Exp Biol 10:1296–1302. https://doi.org/10.1096/fasebj.10.11.8836043
48. Prewitt CM, Niesman IR, Kane CJ, Houle JD (1997) Activated macrophage/microglial cells can promote the regeneration of sensory axons into the injured spinal cord. Exp Neurol 148:433–443. https://doi.org/10.1006/exnr.1997.6694
49. Rabchevsky AG, Sullivan PG, Scheff SW (2007) Temporal-spatial dynamics in oligodendrocyte and glial progenitor cell numbers throughout ventrolateral white matter following contusion spinal cord injury. Glia 55:831–843. https://doi.org/10.1002/glia.20508
50. Rapalino O, Lazarov-Spiegler O, Agranov E, Velan GJ, Yoles E, Fraidakis M, Solomon A, Gepstein R, Katz A, Belkin M, Hadani M, Schwartz M (1998) Implantation of stimulated homologous macrophages results in partial recovery of paraplegic rats. Nat Med 4:814–821. https://doi.org/10.1038/nm0798-814
51. Schwartz M, Moalem G, Leibowitz-Amit R, Cohen IR (1999) Innate and adaptive immune responses can be beneficial for CNS repair. Trends Neurosci 22:295–299. https://doi.org/10.1016/s0166-2236(99)01405-8
52. Guerrero AR, Uchida K, Nakajima H, Watanabe S, Nakamura M, Johnson WE, Baba H (2012) Blockade of interleukin-6 signaling inhibits the classic pathway and promotes an alternative pathway of macrophage activation after spinal cord injury in mice. J Neuroinflammation 9:40–40. https://doi.org/10.1186/1742-2094-9-40
53. Kigerl KA, Gensel JC, Ankeny DP, Alexander JK, Donnelly DJ, Popovich PG (2009) Identification of two distinct macrophage subsets with divergent effects causing either neurotoxicity or regeneration in the injured mouse spinal cord. J Neurosci Off J Soc Neurosci 29:13435–13444. https://doi.org/10.1523/JNEUROSCI.3257-09.2009
54. Kong X, Gao J (2017) Macrophage polarization: a key event in the secondary phase of acute spinal cord injury. J Cell Mol Med 21:941–954. https://doi.org/10.1111/jcmm.13034
55. Kigerl K, Popovich P (2006) Drug evaluation: ProCord - a potential cell-based therapy for spinal cord injury. IDrugs : the investigational drugs journal 9:354–360
56. Yoon SH, Shim YS, Park YH, Chung JK, Nam JH, Kim MO, Park HC, Park SR, Min B-H, Kim EY, Choi BH, Park H, Ha Y (2007) Complete spinal cord injury treatment using autologous bone marrow cell transplantation and bone marrow stimulation with granulocyte macrophage-colony stimulating factor: phase I/II clinical trial. Stem Cells 25:2066–2073. https://doi.org/10.1634/stemcells.2006-0807
57. Donnelly DJ, Gensel JC, Ankeny DP, van Rooijen N, Popovich PG (2009) An efficient and reproducible method for quantifying macrophages in different experimental models of central nervous system pathology. J Neurosci Methods 181:36–44. https://doi.org/10.1016/j.jneumeth.2009.04.010
58. Sledge J, Andrew Graham W, Westmoreland S, Sejdic E, Miller A, Hoggatt A, Nesathurai S (2013) Spinal cord injury models in non human primates: Are lesions created by sharp instruments relevant to human injuries? Med Hypotheses 81:747–748. https://doi.org/10.1016/j.mehy.2013.07.040

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