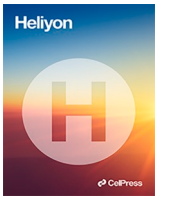
Heliyon 9 (2023) e22914

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon



Review article

Macrophage polarization in spinal cord injury repair and the possible role of microRNAs: A review

Jiawei Wang [a,b,2], Feng Tian [a,b,2], Lili Cao [a,b], Ruochen Du [c], Jiahui Tong [a,b], Xueting Ding [c], Yitong Yuan [c,**,1], Chunfang Wang [a,b,*,1]

[a] School and Hospital of Stomatology, Shanxi Medical University, Shanxi Taiyuan, China
[b] Shanxi Province Key Laboratory of Oral Diseases Prevention and New Materials, Shanxi Taiyuan, China
[c] Experimental Animal Center, Shanxi Medical University, Shanxi Taiyuan, China

ARTICLE INFO

Keywords:
Spinal cord injury
MicroRNA
Macrophage

ABSTRACT

The prevention, treatment, and rehabilitation of spinal cord injury (SCI) have always posed significant medical challenges. After mechanical injury, disturbances in microcirculation, edema formation, and the generation of free radicals lead to additional damage, impeding effective repair processes and potentially exacerbating further dysfunction. In this context, inflammatory responses, especially the activation of macrophages, play a pivotal role. Different phenotypes of macrophages have distinct effects on inflammation. Activation of classical macrophage cells (M1) promotes inflammation, while activation of alternative macrophage cells (M2) inhibits inflammation. The polarization of macrophages is crucial for disease healing. A non-coding RNA, known as microRNA (miRNA), governs the polarization of macrophages, thereby reducing inflammation following SCI and facilitating functional recovery. This study elucidates the inflammatory response to SCI, focusing on the infiltration of immune cells, specifically macrophages. It examines their phenotype and provides an explanation of their polarization mechanisms. Finally, this paper introduces several well-known miRNAs that contribute to macrophage polarization following SCI, including miR-155, miR-130a, and miR-27 for M1 polarization, as well as miR-22, miR-146a, miR-21, miR-124, miR-223, miR-93, miR-132, and miR-34a for M2 polarization. The emphasis is placed on their potential therapeutic role in SCI by modulating macrophage polarization, as well as the present developments and obstacles of miRNA clinical therapy.

1. Introduction

Spinal cord injury (SCI) is a devastating disorder of the central nervous system (CNS) that leads to motor dysfunction and often results in severe and persistent disability. An epidemiological survey reveals that the current global incidence rate of SCI ranges from

* Corresponding author. 56 Xinjian South Road, Yingze District, Taiyuan City, Shanxi Province, China.
** Corresponding author. 56 Xinjian South Road, Yingze District, Taiyuan City, Shanxi Province, China.
E-mail addresses: wjw66662022@163.com (J. Wang), tianfeng1077@163.com (F. Tian), 1372252500@qq.com (L. Cao), Doc_rochandu@sxmu.edu.cn (R. Du), jh.tong@outlook.com (J. Tong), dxtl0105@163.com (X. Ding), ytyuan@sxmu.edu.cn (Y. Yuan), wangchunfang@sxmu.edu.cn (C. Wang).
[1] These authors contributed equally to this work and share the corresponding authors.
[2] These authors contributed equally to this work and share the first authorship.

https://doi.org/10.1016/j.heliyon.2023.e22914
Received 22 March 2023; Received in revised form 17 November 2023; Accepted 22 November 2023
Available online 27 November 2023

approximately 10.4 to 83 cases per million per year, with falls and automobile accidents being the predominant etiological factors. The prevalence of acute SCI is increasing among the elderly population, primarily due to a rise in fall-related incidents [1,2]. SCI inflicts significant physical and psychological harm on patients. Currently, the most prevalent therapeutic approaches for SCI include surgery, medication therapy, and cell therapy. However, despite promising preclinical research findings, the translation of these therapies into clinical practice remains limited, and a definitive treatment for SCI is still lacking. Moreover, the high cost of therapy and the poor prognosis associated with SCI impose significant burdens on both affected families and society as a whole [3].

The local inflammatory response following SCI is a healing process initiated by the immune system in response to the injury. These lesions initially activate microglia and astrocytes, along with the cytokines they produce, and subsequently attract immune cells, such as macrophages, exacerbating the inflammatory response. Macrophages, as crucial components of the immune system, exhibit M1 classical activation and M2 alternative activation, thereby modulating the inflammatory response by adjusting these two distinct phenotypes and exerting diverse effects on tissue repair [4]. M1 macrophages contribute to exacerbated infiltration of inflammatory cells and hinder neuronal regeneration in SCI, whereas M2 macrophages mitigate inflammatory cell infiltration and foster axonal growth and functional recovery. Consequently, promoting the polarization of macrophages toward the M2 phenotype may hold promise as an effective therapeutic approach for SCI.

MiRNAs, a class of small non-coding RNAs consisting of 22 nucleotides, function as crucial regulators by destabilizing target mRNAs and preventing their translation [5]. Their discovery by Lee et al. marked a significant milestone, and subsequent studies have extensively demonstrated their role as key regulators of gene expression in both plants and animals [6,7]. Over the past few decades, the importance of miRNAs in pathophysiology and immunity has been strongly supported by a wealth of available data [8,9].

MiRNAs play a crucial role in modulating the inflammatory response by regulating macrophage polarization [10]. In view of this, we aim to investigate the influence of macrophages on the inflammatory microenvironment following SCI. Additionally, we will explore the expression profile of miRNAs in SCI and their impact on macrophage polarization during inflammation. This review aims to provide insights into the therapeutic potential of miRNA-mediated macrophage polarization in the context of SCI.

2. Data collection methods

The 'PubMed', 'Web of Science', and 'Google Scholar' databases were searched for original research publications and reviews on miRNA-mediated macrophage polarization to repair SCI up to June 1, 2022. The terms for the search included the following: SCI, macrophage polarization, regulatory mechanism of macrophage polarization, M1 macrophage, M2 macrophage, miRNA, RNAi, mesenchymal stem cells, The detailed search strategies are presented in Table 1.

3. Inflammatory response after SCI

SCI is categorized into primary injury and secondary injury. The primary injury encompasses hemorrhage and cell death resulting from direct mechanical damage. Subsequently, a cascade of events occurs, leading to secondary injuries, such as apoptotic cell death, disruption of blood flow, generation of free radicals, and inflammatory reactions. These secondary injuries significantly hinder the healing process and can even exacerbate functional deficits [11]. Among all secondary injuries, inflammatory responses persist the longest and directly or indirectly regulate the healing process after SCI, which has recently garnered considerable attention.

Inflammation following SCI is a complex process involving the release of damage-associated molecular patterns (DAMPs) by damaged cells, which trigger an inflammatory response. These DAMPs include adenosine triphosphate (ATP), high mobility group box 1 (HMGB1), interleukin-33 (IL-33), and other substances released as a result of cellular damage and death. These substances activate pattern recognition receptors (PRRs) and induce an autoimmune response [12]. Cellular and molecular signaling primarily mediate the inflammatory responses. Resident microglia, astrocytes, and the cytokines they produce, such as tumor necrosis factor-α (TNF-α),

Table 1
Summary of the search strategy used in the present article.

Items	Specification
Date of search	June 1, 2022
Databases and other sources searched	'Pubmed' 'Web of Science' 'Google Scholar'
Search terms used	'SCI' (title/abstract) 'macrophage polarization' (title/abstract) 'macrophage polarization' and 'signaling pathway' (title/abstract) 'SCI' and 'macrophage' (title/abstract) 'miRNA' (title/abstract) 'miRNA' and 'CNS' (title/abstract) 'SCI' and 'miRNA' and 'macrophage' (title/abstract) 'RNAi' (title/abstract) 'siRNA' (title/abstract) 'SCI' and 'MSC' (title/abstract)
Timeframe	2003–2023
Inclusion and exclusion criteria	Focus was placed on the original articles and reviews in the English language about the macrophage polarization in SCI repair and the possible role of miRNAs; articles that had no information about macrophage, SCI, and miRNA were excluded

interleukin-1 (IL-1), and interleukin-6 (IL-6), play a key role in orchestrating the inflammatory response and subsequent tissue damage. This inflammatory response triggers the production of inflammatory chemokines in cells, leading to the infiltration of various immune cells, including macrophages, neutrophils, and others, thereby amplifying the inflammatory response [13,14].

Among the various inflammatory factors, TNF-α, IL-1, and IL-6 have received significant attention. A study conducted by Isabelle and Steve demonstrated that the expression of interleukin-1β (IL-1β), TNF-α, and IL-6 was significantly increased within 24 h following SCI. The co-localization of mRNA in mice after SCI indicated that several cytokines were synthesized by microglia, macrophages, astrocytes, and neurons within the initial few hours [15]. The expression of IL-1 and IL-6 reached its peak at 12 h after injury, followed by a gradual decrease in the number of positive cells for all three cytokines from 24 h to day 7 post-injury [16]. Additionally, a second surge in TNF-α and IL-1 expression was observed 14 days after SCI, but only in mice and not in rats [17].

3.1. Neutrophils

Neutrophils represent the initial wave of infiltrating immune cells in response to SCI. They start appearing 4–6 h after injury and reach their peak at 24 h [18]. The early recruitment of neutrophils is crucial for setting up subsequent leukocyte-mediated tissue repair processes, such as revascularization and epithelialization [19]. However, depleting neutrophils that arrive early at the injury site after SCI has been shown to reduce the number of white blood cells adhering to endothelial cells, delay wound healing, result in less preservation of white matter and axons, and lead to poorer functional recovery [20]. While early neutrophil recruitment is necessary for wound healing, an excessive number of neutrophils can be detrimental to the tissue [21,22]. Inhibiting neutrophil elastase (NE), a hydrolase produced by neutrophils, can reduce the expression of inflammatory factors after SCI, alleviate secondary injury, and prevent glial scar formation [23]. Myeloperoxidase (MPO), another lysosomal protein present in neutrophils, is released into the extracellular space during degranulation. Following SCI, MPO elevates levels of reactive oxygen species (ROS) and accelerates neutrophil recruitment to the site of injury, impeding functional recovery [24].

3.2. Microglia

Microglia, a critical component of the long-term multiphase response following SCI, were immediately activated after injury, peaked 7 days later, and showed a secondary peak on day 60, persisting at the injured site for up to 180 days, as revealed by flow cytometry analysis of immune cell changes at the injured spinal cord site [25]. Microglia serve as the primary source of inflammation after SCI, producing various toxic and pro-inflammatory mediators that trigger signaling cascades and neurotoxic responses, leading to neuronal death and neurite damage [26]. Activated microglia can also release cytokines such as IL-1α and TNF-α, which can activate neurotoxic reactive astrocytes and contribute to neuronal death [27]. Activated microglia can also release cytokines such as IL-1α and TNF-α, which can activate neurotoxic reactive astrocytes and contribute to neuronal death [28]. Studies examining the impact of microglial cell depletion at the SCI site have shown that it interferes with glial scar formation, reduces nerve survival, and hinders motor recovery [28,29]. Therefore, promoting tissue repair following SCI requires careful consideration of the timing and techniques for dynamically modulating microglia.

3.3. Macrophage

Macrophages are recruited following neutrophil infiltration at the site of injury, and their numbers reach a peak on the seventh day after damage. They can be observed for several months thereafter, contributing to the release of cytokines such as IL-1, IL-33, and TNF-α following injury [30]. Although microglia and hematogenous macrophages share similar morphologies and are often challenging to distinguish, their distribution after infiltration differs. According to several studies, microglia are primarily distributed in the center and at the edges of the lesion area, while macrophages are predominantly distributed at the lesion's edges [31]. The post-SCI microenvironment tends to favor M1 polarization, which is associated with tissue damage and axonal retraction. These findings highlight the potential role of in situ M2 polarization of macrophages in facilitating SCI repair [32].

3.4. Astrocyte

Following injury, astrocytes undergo hypertrophy and extend their processes, transforming into reactive astrocytes. These reactive astrocytes initially contribute to tissue repair in the lesioned area but eventually form a glial scar that inhibits axonal regeneration. Additionally, astrocytes can engage in crosstalk with microglia through signaling pathways to regulate inflammation [33]. For instance, astrocytes can produce transforming growth factor-β (TGF-β) in response to interleukin-10 (IL-10) stimulation, leading to the suppression of microglial activation [34]. However, the hyperactivation of these cells can result in tissue destruction due to the excessive release of reactive oxygen species (ROS), reactive nitrogen species (RNS), and other toxins.

4. Macrophage polarization on SCI

Macrophages are widely distributed immune cells that play a crucial role in the body's defense against pathogens [35]. Polarization is a phenomenon in which macrophages develop distinct phenotypes in response to various stimuli. Mills introduced the terms "M1" and "M2" to describe the opposing immune responses of macrophages in Th1 and Th2 mice, representing the "classically activated" (pro-inflammatory) M1 macrophages and the "alternatively activated" (anti-inflammatory) M2 macrophages [36]. It should be noted

that M1 and M2 macrophages are induced by different factors, express different molecular markers, and produce characteristic cytokines (Table 2).

M1 macrophages are the most classical macrophages, usually induced by lipopolysaccharide (LPS), interferon-γ(IFN-γ), and Granulocyte-macrophage colony stimulating factor (GM-CSF), secreting pro-inflammatory cytokines such as IL-1β, TNF-α, interleukin-12(IL-12) and interleukin-18(IL-18), and expressing high levels of major histocompatibility complex Class II (MHC-II), cluster of differentiation (CD80), CD86, CD68, etc [37]. Activation of M1 macrophages is usually due to an innate immune response involving Toll-like receptor (TLR) induction [38]. M1 is known for its high antigen presentation capacity, production of IL-12 and interleukin-23 (IL-23), formation of toxic intermediates, including NO, and production of ROS [39].

M2 macrophages, also known as alternately activated macrophages, are mainly activated by IL-4, IL-13, and other factors, inhibit M1 macrophages by secreting anti-inflammatory cytokines such as IL-10 and TGF-β, as well as expressing CD206, CD163, Arginase-1 (Arg1), found in inflammatory zone 1(Fizz1) and YM1 [40]. Loke et al. used three methods to establish M2 gene expression profiles, including expressed sequence tag analysis, expression array analysis, and subtractive hybridization [41]. Mantovani classified M2 macrophages further into M2a, b, and c [42]. M2 macrophages negatively regulate inflammatory factors, reduce the inflammatory response, and participate in multiple biological processes such as wound healing, tissue repair, and metabolism [43,44].

Furthermore, macrophages play a dual role in a variety of diseases, including malignant and inflammatory diseases. They can, for example, act as antitumor agents while also promoting tumor progression. The following sections describe the dual effects of M1 and M2 macrophages on tissue repair following SCI, respectively.

4.1. Effect of M1 macrophages on SCI

M1 remains dominant after SCI for a long time, although it is neurotoxic and exacerbates secondary injury [45–47]. Neutrophils infiltrate and microglia activate within three days of SCI [48]. Microglia become hyperactive and release neurotoxic substances like ROS and RNS, resulting in neuronal apoptosis and tissue damage [49]. In addition, ROS cause oxidative damage to neurons, resulting in lipid peroxidation and intracellular accumulation of oxidized phospholipids, both of which contribute to ongoing secondary damage following SCI [50]. Furthermore, Sun et al. improved the recovery of motor function after injury by silencing IFN-γ signaling in macrophages by eliminating γδ T cells resulting in a significant reduction in the expression of pro-inflammatory factors in the cerebrospinal fluid of SCI mice [51]. However, it has also been demonstrated that M1 plays an essential role in pathogens' defense as well, most notably in Takayuki's work using a mouse model in which IFN-γ reduced the accumulation of axonal growth inhibitor chondroitin sulfate proteoglycans (CSPGs) and enhanced functional recovery after SCI [52], Masae et al. discovered increased macrophage activation and facilitated functional recovery after applying IL-12 at the site of injury [53].

4.2. Effect of M2 macrophages on SCI

M2 macrophages, as opposed to M1 macrophages, play an essential role in the recovery process after SCI, releasing anti-inflammatory cytokines and neurotrophic factors such as IL-10, TGF-β, and insulin-like growth factor (IGF) that stimulate axonal and neural regeneration after SCI. Some researchers have proposed that M2 macrophages could be effective candidates for cell transplantation therapy following SCI. shuhei Kobashi et al. used GM-CSF and IL-4 induced as M1 and M2 macrophages and transplanted into the spinal cord of injured mice, the results showed that the M2 group recovered more motor function and retrograde axonal transport from the neuromuscular junction to upstream of the injured spinal cord than the M1 group [54]. However, the scarcity of primary M2 macrophages severely limits the development of such therapies. On this basis, Han et al. proposed that tauroursodeoxycholic acid (TUDCA)-induced M2 macrophage transplantation could be used to inhibit astrocytes, increase anti-inflammatory effects, and facilitate axonal regeneration [55]. Although in the late stages of the lesion, M2 macrophages again secrete large amounts of pro-fibrotic factors, which form scarring and are detrimental to the healing process. Glial scars, on the other hand, serve to prevent the spread of the lesion to the peri-spinal region and to provide a favorable microenvironment that promotes wound healing in the early stages of SCI [56]. Overall, macrophage polarization toward the M2 phenotype is beneficial to SCI repair.

4.3. Pathways involving polarization

The coordinated control of a number of signaling pathways, primarily nuclear factor-κB (NF-κB), Janus kinase (JAK), signal transducer and activator of transcription (STAT), phosphatidylinositol 3-kinase (PI3K)-Akt, and Notch pathways, is required for macrophage polarization. (Fig. 1).

Table 2
Characteristics of macrophage subtypes.

Classification	M1 macrophages	M2 macrophages
Inducing factor	TH1 cytokine (IFN-γ,LPS,TNF-α , GM-CSF)	TH2 cytokines (IL-4,IL-10,IL-13)
Defining markers	iNOS, CD16/32, CD80, CD68 CD86, MHC II	CD206 , CD163 , Arg1,Fizz1,YM1
Chemokines	CCL19,CCL20, CXCL9,CXCL10, CXCL11,CXCL13	CCL13,CCL14, CCL1,CCL20, CXCL1

4.3.1. NF-κB/TLR signaling pathway

The NF-κB family consists of five proteins that play significant functions in the immune system: RELA (p65), NF-κB1 (p50; p105), NF-κB2 (p52; p100), c-Rel, and Rel-B [57]. NF-κB has been found to have anti-inflammatory effects in macrophages [58]. The following parts will go over its anti-inflammatory regulatory mechanism.

The TLR is a crucial component of the innate immune response and is capable of identifying various pathogen-related molecular patterns. TLR activation on macrophage surfaces induces the collection of the downstream protein myeloid differentiation factor 88 (MyD88) and activates its downstream NF-κB pathway, promoting M1 macrophage polarization [59].

It has been established that the inhibitor of κB kinaseβ(IKKβ), which controls NF-κB activation, suppresses Stat1 activity, which is essential for the pro-inflammatory regulation of IL-12 expression. As a result, IKKβ is involved in a negative feedback regulatory mechanism that inhibits M1 macrophage proinflammatory effects [60]. NF-κB1 is composed of two subunits, p50, and p105, and p50 is degraded from its precursor protein, p105. Tumor progression locus 2 (TPL-2) is a kinase component of the extracellular signal-regulated kinases 1/2 (ERK-1/2) pathway that is stabilized by the binding of the p105 and A20-binding inhibitor of NF-κB2 (ABIN-2) [61]. TPL-2, in turn, suppresses interferon β (IFN-β) production in macrophages [62]. Additionally, it has been demonstrated that p50, a homologous dimer, inhibits IFN-α/β and M1 polarization and is a crucial element of M2 polarization [63]. As a result, p50/p105 participates in a negative feedback regulatory mechanism that inhibits M1 macrophage activation.

Another subunit of the IKK complex is an inhibitor of κB kinase α(IKKα) kinase, which reduces inflammation by accelerating the turnover of NF-κB subunits RelA and c-Rel and removing them from proinflammatory gene promoters to inhibit NF-κB activity [64]. Further evidence indicates that the protein inhibitor of activated STAT1 (PIAS1) selectively blocks the binding of NF-κB and STAT1 to gene promoters, and inflammation induces IKKα-mediated PIAS1 phosphorylation, thereby limiting the inflammatory response [65]. As a result, IKKα acts as a negative feedback regulator of the proinflammatory pathway to suppress inflammation.

4.3.2. JAK/STAT signaling pathway

The JAK/STAT family of non-receptor tyrosine kinases, which consists of the four members Jak1, Jak2, Jak3, and tyrosine kinase 2 (Tyk2), is a crucial mechanism for the transmission of both growth factors and cellular signaling. STAT is a JAK substrate, signal

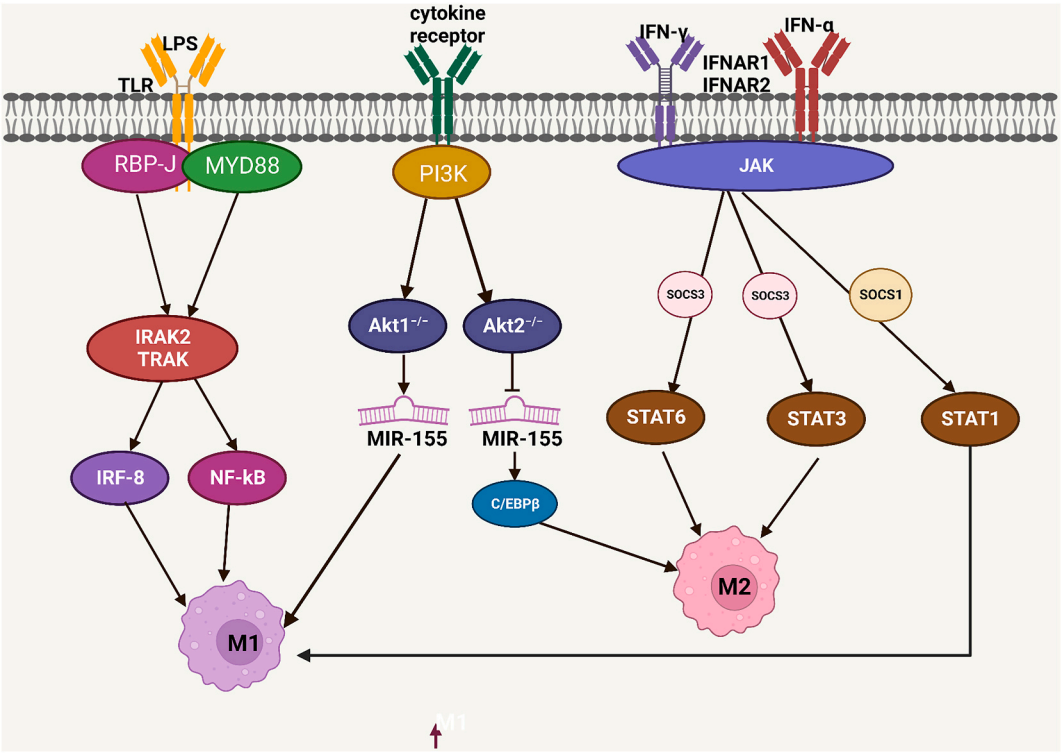


Fig. 1. Pathways involving macrophage polarization. The activation of TLR on the surface of macrophages induces the aggregation of MyD88, activates its downstream NF-κB pathway, and promotes the polarization of M1 macrophages. The up-regulation of C/EBP-β and Arg1 in Akt2$^{-/-}$ macrophages is at least partly due to the inhibition of miR-155, and RBP-J promotes the synthesis of IRF8 protein through TLR4, thereby promoting the polarization of M1 macrophages. STAT3 and STAT6 are correlated with the M2 phenotype, and STAT1 is correlated with the M1 phenotype. C/EBPβ: CCATT enhancer-binding protein β; TLR: Toll-like Receptor; IRF-8:Interferon regulatory factor 8; IRF-8:Interferon regulatory factor 8; RBP-J: recombining binding protein for immunoglobulin Jκ region; MyD88:Myeloid Differentiation Primary Response Gene88; JAK: Janus kinase; STAT: signal transducer and activator of transcription; SOCS: Suppressors of cytokine signaling; LPS:lipopolysaccharide; IRAK2:interleukin-1 receptor-associated kinase2; This figure is created using BioRender.

transducer, and transcription activator. STATs are classified into six categories (STAT1-6), with STAT3 and STAT6 being associated with the M2 phenotype and STAT1 being associated with the M1 phenotype. As will be discussed below, the JAK/STAT pathway participates in macrophage polarization through a variety of regulatory mechanisms.

IFN-α and IFN-γ action on the cell surface activates four Jak family kinases, which phosphorylate into STAT substrate proteins before being transported to the nucleus to initiate transcription [66]. It has been demonstrated that interference with the Jak-STAT signaling pathway in macrophages blocks the production of proinflammatory factors such as IL-6 and TNF-α [67]. In addition, interferon regulatory factor 4 (IRF4) has been shown to regulate macrophage polarization to reduce inflammation [68].

IL-4 and IL-13 signaling are important in M2 macrophages, and Stat6 is essential for IL-4-mediated biological responses [69]. Furthermore, some studies have distinguished between the activation pathways of IL-4 and IL-13 macrophages, concluding that IL-4 stimulates the activation of Jak1, which in turn regulates the activation of Stat3 and Stat6. IL-13 activates Jak2, which is upstream of Stat3 activation, as well as Tyk2, which controls Stat1 and Stat6 activation [70]Suppressors of cytokine signaling proteins (SOCS) bind to JAK and regulate STAT activation, with SOCS1 and SOCS3 being important in macrophage polarization [71,72]. SOCS3 phosphorylates STAT3 and thus inhibits IL-6 signaling in macrophages, several in vitro and in vivo studies have shown that STAT3/SOCS3 regulates inflammation [73,74] SOCS3 also inhibits the M1 proinflammatory phenotype via STAT1/3 [75]. Furthermore, SOCS1 regulates macrophage activation by inhibiting STAT6 gene expression [76]. As a result, the interaction between SOCS and STAT is critical in regulating macrophage polarization.

4.3.3. PI3K-Akt signaling pathway

PI3K is an upstream regulator of AKT that phosphorylates a series of downstream substrates such as apoptotic protein caspase9 activity and is involved in some of the pathophysiological processes of inflammatory diseases [77,78]. Akt consists of three serine-threonine kinases, Akt1-3. Phosphorylation of AKT promotes M1-polarization and inhibits M2-polarization in macrophages, thereby promoting inflammatory responses. PI3K-Akt is a downstream target of the mechanistic target of rapamycin (mTOR), which controls macrophage activation in a variety of ways.

TLR signaling activates PI3K, which is a negative regulator of M1 [79,80]. Several Akt kinases influence macrophage activation, with Akt1 favoring M1 activation and Akt2 favoring M2 activation [81]. The transcription factors CCAAT enhancer binding proteinβ (C/EBPβ) and STAT6 primarily regulate Arg1. Akt2 knockdown increases C/EBPβ expression and binding to the Arg1 promoter. However, C/EBPβ and Arg1 upregulation in $Akt2^{-/-}$ macrophages is at least partly due to miR-155 suppression [82]. Furthermore, Akt regulates macrophage activation via its downstream, and the PI3K-Akt-regulated transcription factor forkhead box O1 (FOXO1) regulates TLR4 inflammatory pathway signaling in macrophages [83].

There are two mTOR complexes, mTOR complex 1 (mTORC1) and mTORC2, which are inhibited by the tuberous sclerosis complex, which is made up of TSC1 and TSC2. MTORC1 is important in polarization; TSC1 deletion activates mTORC1, decreases AKT signaling activation, increases proinflammatory factor expression, and decreases anti-inflammatory factor expression, whereas deletion of TSC2 increases STAT3 activity and reduces M1 polarization [84,85]. Rapamycin, another mTORC1 inhibitor, stimulates the production of proinflammatory cytokines via NF-kB but inhibits the release of IL-10 via the transcription factor STAT3 [84]. The tumor suppressor protein phosphatase and tensin homolog (PTEN) is a negative regulator of AKT that reduces its activation by dephosphorylating AKT. PTEN inhibits PI2K by converting PI (3,3,4) P5 to PI (3,4) P5, and its deletion increases Akt activity and inhibits the inflammatory response of macrophages [86].

4.3.4. NOTCH signaling pathway

The Notch pathway is made up of ligands (Delta-like ligands Dll1, Dll3, Dll4, Jagged1, and Jagged2) and cell surface receptors (Notch1-4) that are primarily responsible for the pro-inflammatory polarization of macrophages in vitro and in vivo.

Dll4 triggers Notch signaling to mediate proinflammatory responses in M1 macrophages, and at the same time, it hindered the differentiation of M2 macrophages and promoted their apoptosis [85,87]. Dll4 also activates the NF-κB pathway, which is involved in macrophage inflammatory response. Notch plays an important role in regulating NF-κB mediated cell death and inflammation signaling pathways [87–89]. TLR responses activate Notch signaling in macrophages, which is then regulated by the activation of NF-κB, which is involved in the M1 proinflammatory response [90]. The main sensor of Notch signaling is the recombining binding protein for immunoglobulin Jκ region (RBP-J), and RBP-J promotes the synthesis of the transcription factor interferon regulatory factor 8 (IRF8) protein via TLR4, thereby promoting M1 macrophage polarization [91].

5. MiRNA repairs SCI by inducing macrophage polarization

5.1. Biological properties of miRNA

MiRNAs are short endogenous single-stranded RNA molecules of approximately 22 nucleotides in length that target mRNAs and reduce their expression to regulate gene expression in plants and animals, and they can control more than half of all human genes [92,93]. The majority of miRNAs are produced by Dicer enzymes that process the hairpin structure of single-stranded RNA precursors, and pre-miRNAs are then processed by two endonucleases to become mature miRNAs: First, Drosha enzymes collaborate with the RNA binding protein DiGeorge syndrome critical region gene 8 (DGCR8) to cleave pri-miRNA to generate the 70 nucleotides of pre-miRNA, which is then transported into the cytoplasm by Exportin 5 (XPO5); In the cytoplasm, Dicer enzymes then collaborate with trans-activation response RNA binding protein (TRBP) cleave the loop region of the mature miRNA precursor, which then binds to Argonaute protein (AGO) and forms the RNA-induced silencing complex (RISC) [93,94]. MiRNA biological functions are currently being

Table 3
Several classical mirnas involved in macrophage polarization.

miRNA	Phenotype promoted	Targets	Mechanism of Action	Ref.
miR-9	M1	PPARδ	MiR-9 targets the regulation of PPARδ in M1 macrophages, thereby blocking its anti-inflammatory effect.	[104]
miR-155	M1	SHIP1,PI3K/AKT, C/EBPβ	MiR-155 promotes inflammation by inhibiting the expression of SHIP1, an inhibitor of the PI3-AKT signaling pathway.	[105]
Let-7c	M2	C/EBP-δ,PAK1	Let-7c is expressed at a higher level in M2 macrophages, and inhibiting C/EBP-δ enhances anti-inflammatory polarization of M2; Let-7c inhibits the expression of PAK1, thus inhibiting the activation of the NF-κB pathway and thereby reducing the manifestation of inflammatory factors associated with M1.	[106, 107]
miR-127	M1	Bcl6, JNK pathway	MiR-127 targets B-cell lymphoma 6 (Bcl6) and promotes activation of the JNK signaling pathway, thereby enhancing the development of pro-inflammatory macrophages.	[108]
miR-34a	M2	Notch3	MiR-34a inhibits LPS-induced inflammatory responses via targeting Notch34.	[109]
miR-124	M2	STAT3,TACE	MiR-124 targets STAT3 reduced IL-6 production, targets TACE to reduce mature TNF-α production, thereby acting anti-inflammatory.	[110]
miR-146a	M2	TRAF1,IRAK146	MiR-146 targets IRAK1 and TRAF6, inhibiting the activity of the NF-κB pathway and hence reducing inflammatory reactions.	[111]
miR-21	M2	/	MiR-21 is positively regulated downstream of CSF-1R pTyr-721, promoting the expression of the M2 macrophage gene.	[112]
miR-21	M1	STAT3	MiR-21 targeting STAT3 enhances M1 macrophage polarization while inhibiting M2 macrophage polarization.	[113]
miR-223	M2	STAT3	MiR-223 inhibits the production of the pro-inflammatory cytokines IL-6 and IL-1β, but not TNF-α, through regulating the activation of STAT3 in macrophages.	[114]

identified primarily through the development of miRNA knockout models and transgenic overexpression experiments. Despite this, knocking out just one miRNA does not normally influence animal behavior, and even knocking out a large number of conserved miRNAs does not harm animal development. This is most likely due to the fact that animal regulation is dependent on numerous miRNA gene regulatory networks combining to guarantee ecological robustness rather than a single miRNA [92,95,96].

5.2. miRNA mediated macrophage polarization

MiRNAs have been shown to regulate macrophage polarization and play a crucial role in immune diseases, cancer, and inflammatory diseases [10,97]. Microarray analysis has been used in some studies to obtain the miRNA expression profiles of macrophage polarization in humans [98,99]and mice [100,101]; however, these studies only concentrate on a single time point hours or days after the addition of induction factors, necessitating further investigation of the dynamic time pattern of miRNA expression in macrophage polarization. Lu and colleagues used RNA-Seq and miRNA-Seq technology to measure the bone marrow-derived macrophages in 1, 2, 4, and 8 h of mRNA and miRNA expression. Among them, M1-specific miRNAs such as miR-222-5p and miR-29b-1-5p are classified as early reaction groups, while miR-155-3p, miR-9-5p/3p, let-7e-3p, and others are classified as late reaction groups. According to a differential expression (DE) analysis of M1 and M2 macrophages, M1 was associated with an immune response, while M2 was active in fundamental physiological functions like cell division and metabolism. About 67 % of the transcription factors that DE miRNAs target are members of the C2H2 zinc-finger family [102]. Melton and colleagues focused on the early time changes in miRNA expression following stimulation of macrophages, respectively in the early (0.5, 1, and 3 h) and late (24 h) detection of miRNA expression, and found that 0.5–3 h after stimulation is the best time window to study macrophage polarization. Based on statistical significance, 12 miRNAs with specific expressions were screened, among which the expression of miR-125a-5p increased in M1 macrophages at 12–24 h, while the expression decreased in M2 macrophages. Moreover, inhibiting the expression of miR-125a-5p could reduce VEGF and partially promote the polarization of M2 macrophages [103]. Several classical mirnas involved in macrophage polarization were also summarized (Table 3).

5.3. MiRNA-based therapy for diseases of the CNS

CNS disorders include a wide range of cerebrovascular diseases, peripheral neuropathies, and spinal cord lesions, all of which cause significant pain and may even be fatal. Recent research has demonstrated that miRNAs have the potential to treat neurological illnesses and play a significant role in neurodevelopment. First, miRNAs are dynamically regulated during CNS development, influencing neural stem cell (NSC) proliferation and differentiation, neuronal migration and integration, axonal and synaptic growth, and other key processes in neural development [115]. Second, early detection and treatment of various neurological diseases, as well as a better prognosis, are critical to their treatment. Great strides have been made in the use of miRNAs as biomarkers for disease diagnosis and prognosis with the development of technologies such as large-scale sequencing. Body fluids, such as blood or cerebrospinal fluid, are the most common source of miRNA biomarkers, and miRNAs can be isolated from exosomes, microvesicles, or lipoprotein complexes. On the other hand, a fundamental drawback is the inadequate state of the art in miRNA detection technologies [8,116]. Third, studies are being done on miRNAs as potential pharmacological targets for neurological disorders and as efficient drug delivery systems. MiRNA mimics and miRNA inhibitors are currently separated into two groups. Although miRNAs meet several criteria for drug development, their multi-targeting and off-target effect [117], gender and age bias in their expression [118], and other issues all pose challenges to miRNAs' real-world clinical application.

5.4. SCI advances in the study of miRNA profiles

Liu et al. used microarray analysis on adult rats to complete the first study of miRNA expression profiles after traumatic SCI. Over 30 % of miRNAs were significantly altered in the spinal cord in the first seven days after SCI, and bioinformatic analysis revealed that

Table 4
Research progress of miRNA expression profile after SCI.

Object	Testing time	Results	Potential targets	Source
Adult rats	Within seven days after SCI	30 up-regulated; 16 downgrades; Fourteen were upregulated 4 h after SCI, followed by downregulation 1 and 7 days after SCI	Inflammation; Oxidation, apoptosis	[120]
Adult rats	Within 14 days after SCI	MiR-124, miR-129 and miR-1, miR-146a act synergistically on neuroplasticity and repair	Neuronal loss is associated with apoptosis and abnormal cell cycle	[121]
Adult rats	1,3 and 7 days after SCI	SCI leads to an increase in micro-RNA downregulation over time, parallel to an increase in mRNA expression	Cell movement, protein movement, neurotransmission, and so on	[119]
Pig	1,3and5 days after SCI	Micro-RNA increased in a severity-dependent manner		[123]
Cerebrospinal fluid and serum from human patients	1and5 days after SCI	miR-9,miR-219 miR-10b,miR-21, miR-133,miR208 miR-499 and so on can be used as potential biomarkers		[124]

some inflammatory mediators such as TNF-α and IL-1 were potential targets of downregulated mRNAs following SCI. Some antioxidant genes, such as superoxide dismutase 1(SOD1) and catalase genes, have been identified as potential targets of several upregulated miRNAs following SCI, including miR-1, miR-206, miR-152, and miR-21, as well as some anti-apoptotic and pro-apoptotic mRNAs [119]. Similar experiments were carried out in another study to examine miRNA expression at three different time points (1, 3, and 7 days) after injury, revealing a significant increase in the number of miRNAs downregulated, particularly on day 7, in parallel with mRNA upregulation [120]. Another study concentrated on miRNA expression 14 days after SCI. Both miR-214 and miR-1 expression were significantly reduced after SCI and synergistically favored neural fate reprogramming. MiR-21 expression was transiently elevated and then decreased after SCI, whereas miR-146a expression was elevated for a prolonged period of 14 days, and both reduced inflammation to support tissue regeneration. Furthermore, miR-129 expression was reduced significantly, resulting in an abnormal cell cycle. The coordinated action of miR-21/miR-146a/miR-129 is critical for neuronal survival after SCI. These miRNAs work together to regulate neuron-associated apoptosis and abnormal cell cycle progression [121] (Table 4). However, the results of these studies, which were also microarray-based miRNA expression analyses, were somewhat different, which could be attributed to the severity of the damage as well as differences in microarray technology platforms, sampling, analysis time, and other techniques. However, the damage model is most likely the most significant cause of the disparity. De Biase et al. discovered that moderate injuries resulted in the most genetic changes at the site of impact, while both mild and severe injuries resulted in relatively few genetic changes. However, genetic changes increased with increasing injury at the rostral and caudal sites [122].

However, all of the preceding experiments were limited to murine models of SCI, implying that mammalian models of SCI, such as those in pigs, must be established before clinical trials can begin. Pigs are an important clinical trial model not only because of their anatomical similarities with humans but also because their miRNA profile is more conserved in humans than rodents, with 45 % of known pig miRNAs having direct human homologs that can be used to study miRNA changes in patients after SCI. Seth et al. sequenced miRNAs in post-SCI serum samples from pigs and discovered that miRNA amounts were proportional to injury severity and that miRNAs best-predicted outcome in the early post-injury period (one to three days after injury) [123]. Two years later, the authors built

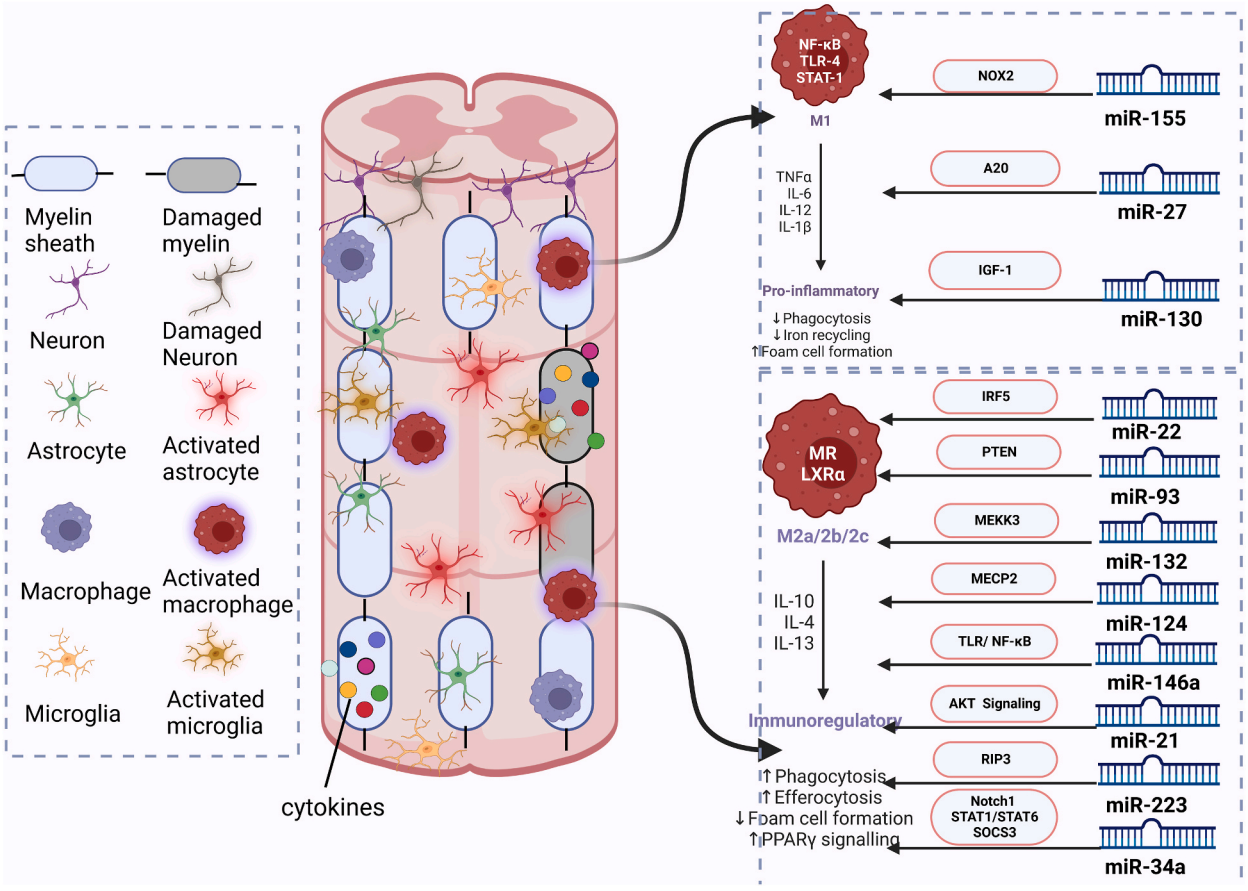


Fig. 2. MiRNAs associated with macrophage polarization in SCI. SCI post-inflammatory cell immersion, in which classical macrophage cell (M1) activation promotes inflammation and alternative macrophage cell (M2) activation inhibits inflammation. In addition, there are some miRNAs that, through corresponding targets or signal channels, activate M1 or M2 macrophage cells, including miR-155, miR-130a, and miR-27 for M1 polarization, as well as miR-22, miR-146a, miR-21, miR-124, miR-223, miR-93, miR-132, and miR-34a for M2 polarization. BioRender was used to make this figure.

on this foundation by sequencing relevant miRNAs in patients with acute SCI's cerebrospinal fluid and serum. MiR-9, miR-219, miR-10b, and miR-21, which are significantly differentially expressed in animal models, were found to be differentially expressed in human serum. MiR-133, miR-208, miR-499, and other miRNAs were also found to be increased in serum, and all of these miRNAs could potentially serve as biological markers. The authors discovered that 50 % of the miRNAs that were differentially expressed in porcine serum were also found to be differentially expressed in human patients after SCI, but the most significant difference between the two was that human serum miRNAs were not correlated with injury severity [124].

5.5. Therapeutic potential of miRNA-induced macrophage polarization in SCI

M1 macrophages are in a prominent position following SCI injury, causing inflammation and aggravating secondary injury and function loss [45]. In contrast to M1, M2 macrophages stimulate tissue repair and neural and axonal regeneration while inhibiting the spread of inflammation. However, their expression is uncommon and transitory. As a result, the polarization of macrophages into M2 macrophages is critical for effective SCI repair. A large number of studies have been conducted over the last decade on the effects of miRNA on macrophage polarization. First, the miRNA expression profiles of macrophage polarization were determined using the microarray and RT-qPCR array techniques. MiR-9, miR-127, miR-155, and miR-125b promote M1 polarization, whereas miR-124, miR-223, miR-34a, let-7c, miR-132, miR-146a, and miR-125a-5p promote M2 polarization [98,102]. These miRNAs that are involved in the polarization of M1 and M2 macrophages have some therapeutic promise, which may aid in the treatment of various inflammatory diseases, cancers, and other diseases. Several classic miRNAs related to M1 and M2 macrophage polarization following SCI are mentioned here (Fig. 2).

5.5.1. M1 polarization-related miRNAs in SCI

5.5.1.1. MiR-155. MiR-155 is the most extensively researched pro-inflammatory miRNA.Eis et al. discovered that miR-55 expression was enhanced in B lymphoma inflammation, leading to the discovery of its role in inflammation [125]. MiR-155KO suppresses the expression of associated genes in M1 macrophages but not in M2 macrophages, showing that miR-155 is important in driving the M1 phenotype [126]. Blocking miR-155 reduces the inflammatory response of type M1 macrophages; no other miRNA has the same potent pro-inflammatory effect as miR-155 [105]. MiR-155 inhibition has been demonstrated to offer therapeutic potential in a number of neurological disorders [127,128]. In vivo and in vitro silencing of miR-155 has revealed that deletion of miR-155 not only lowers inflammatory transmission in macrophages but also improves axonal development and functional recovery in mice [129]. Furthermore, NADPH oxidase 2(NOX2) is a major source of ROS, which has long been thought to be harmful, exacerbating damage by accelerating inflammation, oxidative stress, and severely impeding tissue repair, so therapeutic approaches to modulate ROS production by inhibiting NOX enzymes have been widely used in a variety of diseases [130]. It has been demonstrated that inhibiting NOX2 after SCI improves motor recovery by polarizing microglia/macrophages toward M2 [131]. Boris et al. investigated the fundamental mechanisms several years later. They discovered that the miR-155 pathway is involved in NOX2, resulting in post-traumatic macrophage activation and the production of pro-inflammatory factors [132].

MiR-155 upregulation is a significant signal in a variety of inflammatory disorders, and it has been employed as an inflammatory marker in several trials. However, inhibition of miR-155 has not been used in post-SCI inflammatory intervention trials. As a result, more research is needed to determine its clinical feasibility, cost-effectiveness, and whether other effector functions regulated by miR-155 after SCI are detrimental.

5.5.1.2. MiR-27. Research suggests that miR-27 may be involved in viral-related CNS dysfunction processes [133]. MiR-27-3p promotes inflammatory factor expression and M1 polarization of pulmonary macrophages (AMs) via targeted regulation of peroxisome proliferator-activated receptor γ(PPARγ) activation and TLR signal transmission [134]. Furthermore, the miR-27-3p/PPARγ axis is a key mechanism for exacerbating post-traumatic inflammation and the extent of injury in patients with acute brain death [135]. Based on these findings, Li and colleagues investigated the role of miR-27 in microglia activation and neural inflammation, hypothesizing that miR-27 increased the expression of inflammatory factors such as TNF-α and IL-6 by targeting regulation of TNF-α-induced protein 3 (A20), exacerbating neuropathy after injury and providing a new basis for SCI treatment.

5.5.1.3. MiR-130a. MiR-130a expression is higher in M1 macrophages than in M2 macrophages, and overexpression of miR-130a promotes the M1 phenotype of macrophages, prevents polarization of macrophages toward the M2 phenotype, and acts as a molecular switch during the development of macrophages [136]. Furthermore, miR-130a-3p drastically reduced the expression of M2 markers in human macrophages and collaborated with miR-142-5p to regulate the expression of pro-fibrotic genes in macrophages during chronic inflammation [137]. MiR-130a is also important in neuronal development. MiR-130a reduces neurite development and the creation of dendritic secondary and tertiary branches by targeting Recombinant Human Methyl-CpG-binding protein 2 (MeCP2) control [138]. Additionally, there is evidence to suggest that miR-130a-3p may indirectly regulate vascular endothelial growth factor-2 (VEGFR-2) expression in the peripheral nervous system (PNS), impacting axon development and neurogenic cell survival [139]. Yao et al. investigated the role of miR-130a-3p after SCI, finding that it was significantly up-regulated in the lesion site of SCI rats compared to the sham operation group, and that inhibiting the expression of miR-130a-3p could reduce the production of inflammatory factors and neuron apoptosis, thereby alleviating neuropathic pain caused by injury [140]. However, additional mechanistic studies and long-term effects are required to fully assess if miR-130 might be employed as a potential therapeutic target for reducing post-SCI

neuropathic pain.

5.5.2. M2 polarization-related miRNAs in SCI

5.5.2.1. MiR-22. MiR-22 has recently been shown to be effective in the treatment of a variety of neurological diseases [141]. MiR-22-3p promotes intrinsic neuronal regeneration through CBL/p-EGFR/p-STAT3/GAP43/p-GAP43 axis and restores sensory transmission in the spinal cord after injury [142]. Liu et al. used microarray analysis to detect miRNA expression profiles in rats 24 and 48 h after spinal cord ischemia-reperfusion injury (SCIRI) and built an altered miRNA-TF regulatory pattern, discovering that miR-22-3p may affect apoptosis and inflammation following SCIRI by regulating the MAPK pathway. However, the experiment only provides a preliminary examination of the function of the hypothesized miRNA-TF regulation mode, which needs to be verified by functional tests [143]. The following year, Fang et al. identified miR-22-3p as a new target for the therapy of SCIRI by proving through additional in vivo and in vitro experiments that it may reduce SCIRI by inhibiting interferon regulatory factor 5 (IRF5) to increase M2 macrophage polarization [144].

5.5.2.2. MiR-124. MiR-124 is more than 100 times more abundant in the mammalian CNS than in other organs, and microarray analysis has revealed that miR-124 is also one of the most strongly expressed miRNA groups in the spinal cord [145]. Numerous studies have shown that MiR-124 plays a crucial role in neural regeneration and may one day be used to treat SCI. MiR-124 can regulate the differentiation of neural stem cells into neurons via the Neat1-Wnt/-catenin signaling axis, which assisting in neural regeneration and promoting the restoration of motor function [146]. Furthermore, Song et al. initially investigated how miR-124 affected the transplantation of bone marrow-derived stem cells (BMSCs) for the treatment of SCI in a rat SCI model and showed that miR-124 promotes the differentiation of BMSCs into neuronal cells for SCI repair, with PDXK being a potential mechanism [147]. However, additional research is required to target its downstream signaling pathways. Additionally, miR-124 is a very sensitive and specific diagnostic marker that can be utilized to promptly identify patients with acute SCI (within 24 h) and start treatment right away [148].

It has also attracted a lot of attention for its function in post-injury inflammation and neuropathic pain. MiR-124 not only inactivates macrophages, but it also polarizes them from M1 to M2 phenotype. At the same time, polarization of M2-type macrophages enhanced miR-124 expression, which aided in the formation and maintenance of the M2 phenotype. It is an essential regulator of microglia/macrophages in the CNS [149,150]. Hanneke et al. proposed that intravenous injection of miR-124 could restore the M1:M2 ratio to normal levels following injury and alleviate chronic pain caused by microglia activation [151]. Katharina et al. used further validation in the spinal cords of mice using a formalin model to show that miR-124a alleviates post-injury pain by regulating the target protein MECP2 and reducing the expression of pro-inflammatory genes, thereby alleviating post-injury pain [152]. Small Extracellular Vesicles (sEV) have received a great deal of attention in recent years. sEV are a broad term for a type of vesicle with a bilayer lipid membrane structure that cells secrete. It is widely assumed in recent years that extracellular vesicles play an important role in intercellular communication by wrapping mRNAs, miRNAs, and plasmids to specifically recognize target cells for signaling. Using miRNA microarray hybridization, a study discovered that miR-124-3p, one of the miRNAs essential for neuronal growth and function, was substantially expressed in released neuronal exosomes [153]. Furthermore, Jiang et al. found that the interaction of miR-124-3p with neuron-derived exosomes could prevent M1 microglia activation via the MYH9/PI3K/AKT/NF-κB signaling pathway, hence enhancing functional recovery after SCI [11].

MiR-124, a nerve-specific miRNA, can be used to prevent and treat persistent inflammation and neuropathic pain following SCI, and it is highly expressed as a miRNA in neuronal exosomes via multiple pathways to aid SCI recovery. However, more research is needed to identify the mechanisms that promote recovery as well as potential side effects.

5.5.2.3. MiR-146a. Taganov et al. were the first to propose a role for miR-146a/b in innate immune response modulation and identified this miRNA as a regulator of classical NF-κB activation [111]. MiR-146a has recently been demonstrated to modulate innate immune responses and decrease macrophage inflammation in human neurological illnesses by targeting the proteins tumor necrosis factor receptor-associated factor 6 (TRAF6), interleukin receptor-associated kinase 1 (IRAK1), and IRAK2 [154]. MiR-146a-5p inhibits LPS-induced TRAF6 upregulation in the spinal cord via c-Jun NH2-terminal kinase (JNK)/C–C motif chemokine ligand 2 (CCL2) signaling, thereby lowering inflammatory responses and alleviating neuroinflammation [155]. Furthermore, Zuo et al. revealed that miR-146a can suppress inflammatory responses and promote SCI repair by activating the TLR/NF-κB signaling pathway [156]. However, more in vitro testing is necessary to verify this result regarding SCI repair.

5.5.2.4. The dual role of MiR-21. MiR-21, a highly expressed anti-inflammatory miRNA in numerous mammalian cells, has emerged as a crucial switch in the inflammatory response, controlling the balance and transition between pro- and anti-inflammatory states. Identifying miR-21 targets has aided in understanding its mechanisms of action in the immune response. MiR-21 targets the pro-inflammatory tumor suppressor Programmed Cell Death 4 (PDCD4) after LPS stimulation, regulating IL-10 induction, and the miR-21/PDCD4 axis also is a key target in various immunological diseases [157,158]. MiR-21 has a role in the pathophysiology of SCI, and its expression increased following the damage, peaking on the first day and then declining [159]. Several studies have shown that miR-21 promotes post-injury repair by lowering apoptosis and inflammation following SCI and protecting neurons [160,161].

However, other research has found that miR-21 deficiency suppresses macrophage M1 expression while increasing M2 markers. This is because miR-21 deficiency silences STAT3, preventing the expression of prostaglandin E2 (PGE2) genes in M2 macrophages [113]. Xie et al. demonstrated that miR-21 knockdown significantly reduced inflammatory responses at the injury site and increased

brain-derived neurotrophic factor (BDNF) expression and basso mouse scale (BMS) score at postoperative day 14, promoting neurological recovery after SCI, and the AKT signaling pathway is involved in this process [162].

Furthermore, miR-21 is a pro-fibrotic miRNA in many organs [163]. Wang et al. demonstrated that miR-21-5p activates the TGF signaling pathway to promote fibrotic scar formation after SCI, inhibiting axonal regeneration and thus negatively impacting SCI recovery [164]. As a universal anti-inflammatory miRNA, miR-21, in general, plays an active role in a range of features following SCI, including decreasing apoptosis and supporting neuronal regeneration. However, it may also have negative effects by causing fibrotic scar formation after injury. As a result, we must emphasize the role of potential miR-21 therapies throughout the post-SCI process, as well as the combined effects of their actions on various aspects.

5.5.2.5. MiR-223. MiR-223 reduces inflammation by inhibiting the expression of the NLRP3 inflammasome and IL-1 [165,166]. MiR-223 is a critical inflammatory factor in the interaction of macrophages and inflammatory diseases; it directly targets IKKα and regulates its expression during macrophage differentiation to regulate the NF-kB pathway. This process prevents new macrophages from becoming overly activated, but it also prepares macrophages for future pro-inflammatory responses [167]. The previous evidence came from adipose tissue inflammation, where it was shown to be a critical regulator of macrophage polarization, targeting Pknox1 and thereby boosting M2 polarization to regulate tissue inflammation [168]. Furthermore, Zhang et al. demonstrated that miR-233 inhibits the TLR-induced inflammatory response in macrophages by targeting RhoB and downstream IL-6 expression [169].

MiR-223 expression increased following SCI in the SD rat model and was linked to disease progression [159]. Previous research found that injecting Antagomir-223 to inhibit miR-223 increased anti-apoptotic protein expression, promoted angiogenesis, and improved functional recovery [170]. While the evidence described above implies that miR-223 has a negative influence on SCI, some research have discovered a beneficial effect. Wang et al. discovered that miR-223-3p inhibited Recombinant Polyclonal Antibody3 (RIP3)-mediated necroptosis and inflammatory factor secretion, alleviating SCI [171]. More research is needed to investigate MiR-223's combined impact on many elements of post-injury inflammation and apoptosis as a viable therapeutic target for SCI.

5.5.2.6. MiR-34a. Three members of the miR-34 family, miR-34a, miR-34b, and miR-34c, are all potential tumor suppressors. The best researched of these is MiR-34a, which is also a novel inflammatory regulator [172]. Pei et al. first investigated the regulatory role of miR-34a in inflammation and discovered that miR-34a inhibits LPS-induced activation of NF-κB and production of TNF-α and IL-7 inflammatory factors by targeting Notch1, implying a negative regulatory feedback role in the inflammatory process [109]. MiR-34a and miR-34c differ in expression in both the post-SCI acute and sub-acute periods, and miR-34a participates in various physiological processes, including post-SCI cell death, inflammatory responses, and others, by regulating the target gene Notch1 and candidate target genes Colony-stimulating factor 1receptor (Csf1r) and platelet derived growth factor receptor alpha (PDGFRa) [173]. Additionally, M2 macrophage polarization after SCI is driven by two pathways: STAT6 combines with the miR-34a initiator to activate its transcript; and LncGBP9 sponges miR-34a to counteract the inhibition of SOCS3 expression and transmits this via the STAT1/STAT6 signal, which facilitates post-damaged repair [174].

5.5.2.7. MiR-93. MiR-93 is involved in inflammatory illnesses, and studies have demonstrated that it reduces inflammatory responses in mice with acute lung damage and osteoarthritis by targeting a key anti-inflammatory immunological mechanism, the TLR4/NF-κB signaling pathway [175,176]. Xu et al. discovered that miR-93 expression was considerably reduced in LPS-stimulated macrophages and prevented the synthesis of pro-inflammatory cytokines via targeting IRAK4 and so established the now recognized role of miR-93 in macrophages [177]. Ganta et al. went on to investigate the role of miR-93 in regulating macrophage polarization in peripheral artery disease, hypothesizing that miR-93 reduced the production of Immunoresponsive Gene-1 (IRG1) and Itaconic Acid in macrophages and induced the polarization of M2 macrophages, promoting the development of blood vessels and arteries [178]. In addition, miR-93 can inhibit neuroinflammation and play a neuroprotective role after SCI [179]. There is evidence that the lncRNA GAS5 stimulates PTEN expression by targeting miR-93 and increases apoptosis and inflammatory factor expression after SCI. However, there are some flaws in this study. First, the cell model was produced in a neuronal cell line rather than primary neuronal cells, which may have an effect on the experimental outcomes. Secondly, long-term effects should be evaluated to determine the feasibility of the GAS5/miR-93/PTEN axis as a new therapeutic target for SCI [180].

5.5.2.8. MiR-132. MiR-132 has been demonstrated to be one of the most elevated miRNAs during the inflammatory phase of human skin wound healing, and its overexpression in keratinocytes may be important in facilitating the transition from the inflammatory to the proliferative phase [181]. Furthermore, neuropathic pain was associated with a higher expression of miR-132-3p in inflammatory neuropathy, about 1.1 times higher than in the control group, whereas pain was not associated with miR-132-3p expression in non-inflammatory neuropathy, which was confirmed in animal models. Intriguingly, intrathecal injection of miR-132-3p activated microglia in the spinal cord, demonstrating that miR-132 was implicated in the inflammatory cascade and immune cell infiltration [182]. Fang et al. investigated the function of miR-132 in the SCI inflammatory response and discovered that overexpression of miR-132-3p might prevent M1 polarization of macrophages and limit the activation of the MEKK3-mediated inflammatory signaling pathway, thereby minimizing SCIRI damage. However, other downstream targets of miR-132-3p need to be considered to determine the feasibility of miR-132-3p for the treatment of SCIRI as a whole [183].

6. Advances and challenges in clinical miRNA treatment

RNA interference (RNAi) technology targets and degrades certain mRNA molecules, effectively silencing or lowering the expression of target genes, mostly through the interaction of siRNA and miRNA. This technology's advancement eventually brings gene regulation into clinical practice [184,185]. Four siRNA drugs have been approved by the US Food and Drug Administration (FDA): Patisiran，Givosiran，Lumasiran，Inclisiran, Several more siRNA therapeutics have also entered clinical trials, including five that have entered crucial phase III trials [186]. We concentrated on the article's mention of ongoing clinical studies miR-122 for inflammation-related functions. Miravirsen (SPC3649) - An anti-Mir-122 targeted medication made of LNAs ribonucleotides in several phase 2 clinical trials for the treatment of hepatitis C virus (HCV) infection [187]. Furthermore, another anti-miR-122 oligotropic acid product created for HCV:RG-101 has proven reliable therapeutic success in clinical trials, but the development of the second phase of clinical investigations has recently been halted due to significant side effects such as jaundice [188]. In comparison to siRNA therapy, only roughly 20 miR therapies advanced to the clinical trial stage, and none advanced to the phase III clinical trial stage. Zhang et al. evaluated the drug targets of the two medications and discovered that the number of targets of endogenous miR was between 30 and 250, whereas the number of targets of exogenous siRNA was around 1–3. He called it the "too many targets for miRNA effect" (TMTME), and it could be one of the reasons for the delayed development of miR treatments in clinical trials [189]. Additionally, the first human phase 1 clinical study of a cancer treatment based on MRX34 (a miR-34a mimic) had extremely detrimental outcomes, which were ended prematurely due to unexpectedly significant immune-mediated toxicity, even resulting in the deaths of four patients [190]. Although the exact explanation of this is still unknown, it is evident that miRNA therapies are currently confronting a number of unique difficulties.

First, the most prevalent barrier to miRNA therapy is that nuclease in plasma or tissue degrades unmodified siRNA within 1 h, necessitating proper chemical modifications [191]. 2′-O modifications in siRNA, especially 2′-Ome and 2′-F, have been used to improve the nuclease and heat stability of siRNA [192,193]. SiRNA modified with 2′-OMe-4′-thioribonucleoside, namely four 4 ′-thioribonucleosides at both ends of the sensory chain and four residues at the 3′ end of the antisense chain, exhibits significant resistance to nuclease degradation [194]. Furthermore, the phosphorothioate group (PS) is chiral and has a Rp or Sp structure, which boosts serum stability when siRNA is modified [195]. Jahns et al. demonstrated that raising the Rp/Sp ratio in PS bonds in complete oligoribonucleotides (ORN) increased cell activity and nuclease resistance in serum [196]. Boranophosphate (BP) modification is also possible. Compared to double-stranded siRNA (ds-siRNA), single-stranded siRNA (ss-siRNA) has less off-target and pro-inflammatory side effects, but it cannot effectively induce RNAi due to poor activity. BP-induced ss-siRNA can suppress gene expression at low doses, last a long time, and boost nuclease resistance to a degree [197]. However, while chemical modifications can alleviate the problem of siRNA degradation by nucleases to some extent, repeated injection or infusion may be required to avoid its short half-life.

The blood-spinal barrier (BSCB) is a crucial physical barrier for preserving chemical equilibrium in the spinal environment. It prevents the diffusion of physiological and metabolic chemicals between spinal cord tissue and blood circulation. After SCI, BSCB repair can lessen its pathogenic development [198]. However, it also prevents most chemicals from entering the spinal cord tissue. We summarize numerous approaches to delivering miRNA-based medicines to SCI damage locations. Intrathecal injection into the subarachnoid space is currently the most commonly used method for delivering miRNA drugs to SCI, such as miR-182 [199], miR-21a-5p [200], miR-223 [201], miR-129-5p [202]，miR-139-5p [203], etc. Lentiviral vector-mediated gene expression or RNAi interference is long-lasting and stable, and epidural injection of miR-34c overexpression vector in SCI rats promotes neuronal recovery by reducing CXCL14 expression and JAK2/STAT3 signaling [204]. Moreover, intrathecal administration of the miRNA-124 antagonist carrier inhibited SCIRI [205]. sEV are carriers of intercellular communication, which can cross the blood-brain barrier (BBB), which almost 98 % of drugs cannot pass, and mediate the communication between neurons and astrocytes in the CNS. Meanwhile, miRNAs loaded into exosomes can also obtain better therapeutic effects and are potential targeted drug delivery tools [153,206]. MiR-146a-5p and miRNA-22 modified mesenchymal stem cell-derived exosomes can both improve nerve function recovery after damage[207,208]。

Off-target side effects are now a key barrier to the clinical transition of miRNA therapeutics, and because both exogenous siRNA and endogenous miRNA contain the same downstream effector-Ago, this problem is unavoidable [209]. However, this off-target action might not only produce misleading positive result [210], but also have negative repercussions, such as limiting cell development [211], causing cell death [212], causing rat liver poisoning [213], and so on. Researchers have worked hard to solve this challenge. MiRNA-like off-target is specific to a single sequence. Reduced siRNA concentration can reduce off-target effects and increase target specificity, therefore it is recommended to reduce siRNA concentration to maintain sufficient targeting activity [214]. Another technique to lower concentration and get rid of off-target effects is to use siRNA pools, innovative siRNA libraries that chemically created from more than 60 distinct low-concentration siRNAs targeting a single target by a highly intricate enzymatic procedure [215]. Second, perfect sequence matching between the siRNA guide chain and the target mRNA is necessary because the efficiency of the siRNA-based off-target effect is heavily dependent on the thermodynamic stability of the seed double-stranded body formed between the seed and the target [216]. Chemical modification is another, more direct approach to lowering off-target effects. The key to modification is the substitution of 2′-O-methylribosyl at position 2 in the guide chain, which decreased off-target transcript silencing by 66 % and correspondingly reduced the false-positive phenotype that may be associated with it [217]. Locked nucleic acid (LNA), which forms methylene bridges between 2′-O and 4′-C atoms on the ribose through different shrinkage, is another frequently used chemical modification. It can improve the stability of nuclease and double-stranded structure and reduce off-target effects after siRNA modification [218,219]. However, there is less overlap and is species-specific when comparing miRNA-like off-target transcription from human and mouse liver tumor cells, which makes clinical studies much more challenging [220].

MiRNA-based therapeutics have become a potential SCI treatment option, however there are still numerous obstacles to overcome. Recent years have seen the other development of numerous promising treatment approaches for controlling macrophage polarization

following SCI.

Mesenchymal stem cells (MSC) have emerged as a significant source of stem cells for the cell transplantation therapy used to treat SCI due to their easy availability, low immunogenicity, multi-differentiation, and anti-inflammatory properties [221], Additionally, a substantial number of clinical trials are in the exploratory stage [222]. Mesenchymal stem cell treatment does, however, have several drawbacks, such as poor in vivo survival and heterogeneity. Small extracellular vesicles made from mesenchymal stem cells (MSC-sEV) have steadily emerged as a possible future therapy option for SCI in order to address these drawbacks [223]. The Kocsis team created a rat SCI model with IV-infused MSCs and discovered that they target M2 macrophages at the site of damage [224]. Later, Kocsis et al. further investigated the internal mechanism and discovered that transforming growth factor-beta (TGF-β) expression was not only increased after infused but also upregulated and activated the TGF-β signaling pathway. It reduces the permeability of the BSCB and finally promotes the recovery of motor function following injury [225]. Currently, the common sEV that promotes the polarization of macrophages M2: M1 after SCI and improves the functional recovery after loss is mainly derived from BMSCs [226], umbilical cord mesenchymal stem cells (UCB-MSCs) [227] and adipose stem cells [228]. Additionally, research has demonstrated that sEV obtained from dental pulp mesenchymal stem cells (DPSC) is more immunosuppressive than sEV derived from BMSC [229], and has potential as a medication for the treatment of SCI [230].

SCI is a severe central nervous system disorder, and there are currently just a few medications that have been shown to be successful in treating it. Chinese medicine extracts have been found in studies to be an effective treatment for SCI. Salidroside (Sal) [231] and Quercetin [46] can enhance functional recovery after injury by suppressing the polarization of M1 macrophages. Berberine (Ber) loaded its drug carrier, M2 macrophage exosomes (Exos), to target drug delivery to the location of SCI, lower the expression of inflammation and apoptotic factors, and enhance the motor function of SCI mice [232]. Human endogenous active compounds may also make promising SCI therapeutic candidates. TUDCA is a hydrophilic, non-toxic bile acid generated in people and bears in low amounts. Sohn et al. discovered that it could inhibit the inflammatory response of RAW 264.7 macrophages as well as the expression of inflammatory factors at the injured site after SCI [233], and TUDCA-induced M2 macrophages were transplanted to the injured site to promote anti-inflammatory effect and motor function recovery in rats after SCI [55]. Melatonin, an antioxidant released by the pineal gland during the dark periods of the circadian cycle, has been demonstrated in recent research to protect tissues from secondary damage caused by SCI [234]. This protection may be due to melatonin's ability to suppress the inflammatory response and promote M2 macrophage polarization in the early stages of SCI [235]. Azithromycin (AZM), minocycline, and other antibiotics are also effective anti-inflammatory medications. AZM is an immunomodulatory macrolide antibiotic that can polarize macrophages into the M2 phenotype [236]. In order to further analyze its role in SCI, Gensel et al. gave AZM treatment before and after the construction of a mouse SCI model. They discovered that administering AZM before and after SCI could successfully stimulate the polarization of M2 macrophages. Additionally, in the experiment of post-SCI administration, a small-scale gene array was used to determine the phenotype of macrophages at the injured site. It was discovered that a dose of 160 mg/kg could significantly increase the ratio of macrophages M2:M1, highlighting the fact that AZM is a potential ideal medication for the treatment of SCI [237,238]. Furthermore, opioids such as morphine are among the most efficient pain relievers after SCI. However, studies have shown that morphine use can increase inflammation and mortality at the injured site, and minocycline pretreatment can not only reduce the number of macrophages at the lesion site, particularly pro-inflammatory macrophages, but also block the negative effects of morphine on functional recovery after injury [239]. However, the author's further studies demonstrated that minocycline could only prevent the harmful effects of a single intrathecal morphine injection but could not prevent the adverse effects of repeated morphine injections [240]. More research is needed to determine the viability of using it in conjunction with opioids to treat SCI.

7. Conclusion

The M1 and M2 phenotypes of macrophages represent different responses to inflammation after SCI, and the M1 phenotype's long-term dominance after SCI is detrimental to recovery. On this basis, we found that some miRNA can regulate the polarization direction of M1 and M2 macrophages in SCI, reduce the number of M1-type macrophages, and increase the number, duration of presence, and distribution of M2-type macrophages, providing a therapeutic option for SCI recovery. But there is still much work to be done. For starters, a better understanding of the biological functions and targets of macrophage-associated miRNAs is required. Many miRNA functions are still unknown, and more research into the specific pathogenesis of miRNA-induced macrophage polarization is needed. Second, combining lncRNA, circRNA, and miRNA research can provide new ideas and clues for the study of macrophage polarization, as well as identify new therapeutic targets and treatments for SCI. Third, the immune response following SCI is a dynamic process, and the interaction of various immune cells should be thoroughly considered. Finally, because the majority of preclinical studies of miRNAs in SCI have been conducted in animals, more human studies are required to successfully complete clinical translation. Despite the difficulties, miRNA-based therapy has emerged as a promising strategy for future SCI treatment.

Funding

My research was supported by the following projects, The central government guides local science and technology development fund projects (YDZJSX2022A056); National Natural Science Foundation of China (82001326); Basic Research Project of Shanxi Province (201901D211319, 20210302124172, 202203021212373).

Data availability statement

The data associated with our study have not been deposited in a publicly available repository. Data will be made available on request.

CRediT authorship contribution statement

Jiawei Wang: Writing - original draft, Writing - review & editing. **Feng Tian:** Writing - original draft, Writing - review & editing. **Lili Cao:** Project administration. **Ruochen Du:** Project administration. **Jiahui Tong:** Visualization. **Xueting Ding:** Visualization. **Yitong Yuan:** Funding acquisition. **Chunfang Wang:** Funding acquisition.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] M. Khorasanizadeh, M. Yousefifard, M. Eskian, Y. Lu, M. Chalangari, J.S. Harrop, S.B. Jazayeri, S. Seyedpour, B. Khodaei, M. Hosseini, V. Rahimi-Movaghar, Neurological recovery following traumatic spinal cord injury: a systematic review and meta-analysis, J. Neurosurg. Spine (2019) 1–17, https://doi.org/10.3171/2018.10.Spine18802.
[2] GBD 2016 Traumatic Brain Injury and Spinal Cord Injury Collaborators.Global, regional, and national burden of traumatic brain injury and spinal cord injury, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016, Lancet Neurol. 18 (2019) 56–87, https://doi.org/10.1016/s1474-4422(18)30415-0.
[3] P. Jendelova, Therapeutic strategies for spinal cord injury, Int. J. Mol. Sci. 19 (2018), https://doi.org/10.3390/ijms19103200.
[4] M. Locati, G. Curtale, A. Mantovani, Diversity, mechanisms, and significance of macrophage plasticity, Annu. Rev. Pathol. 15 (2020) 123–147, https://doi.org/10.1146/annurev-pathmechdis-012418-012718.
[5] T.X. Lu, M.E. Rothenberg, MicroRNA, J. Allergy Clin. Immunol. 141 (2018) 1202–1207, https://doi.org/10.1016/j.jaci.2017.08.034.
[6] R.C. Lee, R.L. Feinbaum, V. Ambros, The C. elegans heterochronic gene lin-4 encodes small RNAs with antisense complementarity to lin-14, Cell 75 (1993) 843–854, https://doi.org/10.1016/0092-8674(93)90529-y.
[7] B.J. Reinhart, F.J. Slack, M. Basson, A.E. Pasquinelli, J.C. Bettinger, A.E. Rougvie, H.R. Horvitz, G. Ruvkun, The 21-nucleotide let-7 RNA regulates developmental timing in Caenorhabditis elegans, Nature 403 (2000) 901–906, https://doi.org/10.1038/35002607.
[8] P. Sun, D.Z. Liu, G.C. Jickling, F.R. Sharp, K.J. Yin, MicroRNA-based therapeutics in central nervous system injuries, J. Cerebr. Blood Flow Metabol. 38 (2018) 1125–1148, https://doi.org/10.1177/0271678x18773871.
[9] L. Zou, J. He, L. Gu, R.A. Shahror, Y. Li, T. Cao, S. Wang, J. Zhu, H. Huang, F. Chen, X. Fan, J. Wu, W. Chao, Brain innate immune response via miRNA-TLR7 sensing in polymicrobial sepsis, Brain Behav. Immun. 100 (2022) 10–24, https://doi.org/10.1016/j.bbi.2021.11.007.
[10] S. Ghafouri-Fard, A. Abak, S. Tavakkoli Avval, H. Shoorei, M. Taheri, M. Samadian, The impact of non-coding RNAs on macrophage polarization, Biomed. Pharmacother. 142 (2021), 112112, https://doi.org/10.1016/j.biopha.2021.112112.
[11] D. Jiang, F. Gong, X. Ge, C. Lv, C. Huang, S. Feng, Z. Zhou, Y. Rong, J. Wang, C. Ji, J. Chen, W. Zhao, J. Fan, W. Liu, W. Cai, Neuron-derived exosomes-transmitted miR-124-3p protect traumatically injured spinal cord by suppressing the activation of neurotoxic microglia and astrocytes, J. Nanobiotechnol. 18 (2020) 105, https://doi.org/10.1186/s12951-020-00665-8.
[12] J. Rhodes, C. Zipfel, J.D.G. Jones, B.P.M. Ngou, Concerted actions of PRR- and NLR-mediated immunity, Essays Biochem. 66 (2022) 501–511, https://doi.org/10.1042/ebc20220067.
[13] J. Kipnis, S. Gadani, N.C. Derecki, Pro-cognitive properties of T cells, Nat. Rev. Immunol. 12 (2012) 663–669, https://doi.org/10.1038/nri3280.
[14] L. Leng, Z. Yuan, R. Pan, X. Su, H. Wang, J. Xue, K. Zhuang, J. Gao, Z. Chen, H. Lin, W. Xie, H. Li, Z. Chen, K. Ren, X. Zhang, W. Wang, Z.B. Jin, S. Wu, X. Wang, Z. Yuan, H. Xu, H.M. Chow, J. Zhang, Microglial hexokinase 2 deficiency increases ATP generation through lipid metabolism leading to β-amyloid clearance, Nat. Metab. 4 (2022) 1287–1305, https://doi.org/10.1038/s42255-022-00643-4.
[15] I. Pineau, S. Lacroix, Proinflammatory cytokine synthesis in the injured mouse spinal cord: multiphasic expression pattern and identification of the cell types involved, J. Comp. Neurol. 500 (2007) 267–285, https://doi.org/10.1002/cne.21149.
[16] A.T. Stammers, J. Liu, B.K. Kwon, Expression of inflammatory cytokines following acute spinal cord injury in a rodent model, J. Neurosci. Res. 90 (2012) 782–790, https://doi.org/10.1002/jnr.22820.
[17] Y.O. Mukhamedshina, E.R. Akhmetzyanova, E.V. Martynova, S.F. Khaiboullina, L.R. Galieva, A.A. Rizvanov, Systemic and local cytokine profile following spinal cord injury in rats: a multiplex analysis, Front. Neurol. 8 (2017) 581, https://doi.org/10.3389/fneur.2017.00581.
[18] Y. Taoka, K. Okajima, M. Uchiba, K. Murakami, S. Kushimoto, M. Johno, M. Naruo, H. Okabe, K. Takatsuki, Role of neutrophils in spinal cord injury in the rat, Neuroscience 79 (1997) 1177–1182, https://doi.org/10.1016/s0306-4522(97)00011-0.
[19] R.A. Dorschner, J. Lee, O. Cohen, T. Costantini, A. Baird, B.P. Eliceiri, ECRG4 regulates neutrophil recruitment and CD44 expression during the inflammatory response to injury, Sci. Adv. 6 (2020), eaay0518, https://doi.org/10.1126/sciadv.aay0518.
[20] D.P. Stirling, S. Liu, P. Kubes, V.W. Yong, Depletion of Ly6G/Gr-1 leukocytes after spinal cord injury in mice alters wound healing and worsens neurological outcome, J. Neurosci. 29 (2009) 753–764, https://doi.org/10.1523/jneurosci.4918-08.2009.
[21] K. Ley, H.M. Hoffman, P. Kubes, M.A. Cassatella, A. Zychlinsky, C.C. Hedrick, S.D. Catz, Neutrophils: new insights and open questions, Sci. Immunol. 3 (2018), https://doi.org/10.1126/sciimmunol.aat4579.
[22] S. Zivkovic, M. Ayazi, G. Hammel, Y. Ren, For better or for worse: a look into neutrophils in traumatic spinal cord injury, Front. Cell. Neurosci. 15 (2021), 648076, https://doi.org/10.3389/fncel.2021.648076.
[23] H. Kumar, H. Choi, M.J. Jo, H.P. Joshi, M. Muttigi, D. Bonanomi, S.B. Kim, E. Ban, A. Kim, S.H. Lee, K.T. Kim, S. Sohn, X. Zeng, I. Han, Neutrophil elastase inhibition effectively rescued angiopoietin-1 decrease and inhibits glial scar after spinal cord injury, Acta Neuropathol. Commun. 6 (2018) 73, https://doi.org/10.1186/s40478-018-0576-3.
[24] K. Kubota, H. Saiwai, H. Kumamaru, T. Maeda, Y. Ohkawa, Y. Aratani, T. Nagano, Y. Iwamoto, S. Okada, Myeloperoxidase exacerbates secondary injury by generating highly reactive oxygen species and mediating neutrophil recruitment in experimental spinal cord injury, Spine (Phila Pa 1976 37 (2012) 1363–1369, https://doi.org/10.1097/BRS.0b013e31824b9e77.
[25] K.D. Beck, H.X. Nguyen, M.D. Galvan, D.L. Salazar, T.M. Woodruff, A.J. Anderson, Quantitative analysis of cellular inflammation after traumatic spinal cord injury: evidence for a multiphasic inflammatory response in the acute to chronic environment, Brain 133 (2010) 433–447, https://doi.org/10.1093/brain/awp322.

[26] J. Chen, Z. Wang, Z. Zheng, Y. Chen, S. Khor, K. Shi, Z. He, Q. Wang, Y. Zhao, H. Zhang, X. Li, J. Li, J. Yin, X. Wang, J. Xiao, Neuron and microglia/macrophage-derived FGF10 activate neuronal FGFR2/PI3K/Akt signaling and inhibit microglia/macrophages TLR4/NF-κB-dependent neuroinflammation to improve functional recovery after spinal cord injury, Cell Death Dis. 8 (2017), e3090, https://doi.org/10.1038/cddis.2017.490.

[27] S.A. Liddelow, K.A. Guttenplan, L.E. Clarke, F.C. Bennett, C.J. Bohlen, L. Schirmer, M.L. Bennett, A.E. Münch, W.S. Chung, T.C. Peterson, D.K. Wilton, A. Frouin, B.A. Napier, N. Panicker, M. Kumar, M.S. Buckwalter, D.H. Rowitch, V.L. Dawson, T.M. Dawson, B. Stevens, B.A. Barres, Neurotoxic reactive astrocytes are induced by activated microglia, Nature 541 (2017) 481–487, https://doi.org/10.1038/nature21029.

[28] V. Bellver-Landete, F. Bretheau, B. Mailhot, N. Vallières, M. Lessard, M.E. Janelle, N. Vernoux, M. Tremblay, T. Fuehrmann, M.S. Shoichet, S. Lacroix, Microglia are an essential component of the neuroprotective scar that forms after spinal cord injury, Nat. Commun. 10 (2019) 518, https://doi.org/10.1038/s41467-019-08446-0.

[29] Y. Li, X. He, R. Kawaguchi, Y. Zhang, Q. Wang, A. Monavarfeshani, Z. Yang, B. Chen, Z. Shi, H. Meng, S. Zhou, J. Zhu, A. Jacobi, V. Swarup, P.G. Popovich, D. H. Geschwind, Z. He, Microglia-organized scar-free spinal cord repair in neonatal mice, Nature 587 (2020) 613–618, https://doi.org/10.1038/s41586-020-2795-6.

[30] D.J. Hellenbrand, K.A. Reichl, B.J. Travis, M.E. Filipp, A.S. Khalil, D.J. Pulito, A.V. Gavigan, E.R. Maginot, M.T. Arnold, A.G. Adler, W.L. Murphy, A.S. Hanna, Sustained interleukin-10 delivery reduces inflammation and improves motor function after spinal cord injury, J. Neuroinflammation 16 (2019) 93, https://doi.org/10.1186/s12974-019-1479-3.

[31] R. Shechter, A. London, C. Varol, C. Raposo, M. Cusimano, G. Yovel, A. Rolls, M. Mack, S. Pluchino, G. Martino, S. Jung, M. Schwartz, Infiltrating blood-derived macrophages are vital cells playing an anti-inflammatory role in recovery from spinal cord injury in mice, PLoS Med. 6 (2009), e1000113, https://doi.org/10.1371/journal.pmed.1000113.

[32] S. David, A. Kroner, Repertoire of microglial and macrophage responses after spinal cord injury, Nat. Rev. Neurosci. 12 (2011) 388–399, https://doi.org/10.1038/nrn3053.

[33] J. Rueda-Carrasco, M.J. Martin-Bermejo, G. Pereyra, M.I. Mateo, A. Borroto, F. Brosseron, M.P. Kummer, S. Schwartz, J.P. López-Atalaya, B. Alarcon, P. Esteve, M.T. Heneka, P. Bovolenta, SFRP1 modulates astrocyte-to-microglia crosstalk in acute and chronic neuroinflammation, EMBO Rep. 22 (2021), e51696, https://doi.org/10.15252/embr.202051696.

[34] D.M. Norden, A.M. Fenn, A. Dugan, J.P. Godbout, TGFβ produced by IL-10 redirected astrocytes attenuates microglial activation, Glia 62 (2014) 881–895, https://doi.org/10.1002/glia.22647.

[35] S.C. Funes, M. Rios, J. Escobar-Vera, A.M. Kalergis, Implications of macrophage polarization in autoimmunity, Immunology 154 (2018) 186–195, https://doi.org/10.1111/imm.12910.

[36] C.D. Mills, K. Kincaid, J.M. Alt, M.J. Heilman, A.M. Hill, M-1/M-2 macrophages and the Th1/Th2 paradigm, J. Immunol. 164 (2000) 6166–6173, https://doi.org/10.4049/jimmunol.164.12.6166.

[37] D. Dooley, E. Lemmens, T. Vangansewinkel, D. Le Blon, C. Hoornaert, P. Ponsaerts, S. Hendrix, Cell-based delivery of interleukin-13 directs alternative activation of macrophages resulting in improved functional outcome after spinal cord injury, Stem Cell Rep. 7 (2016) 1099–1115, https://doi.org/10.1016/j.stemcr.2016.11.005.

[38] A. Aderem, R.J. Ulevitch, Toll-like receptors in the induction of the innate immune response, Nature 406 (2000) 782–787, https://doi.org/10.1038/35021228.

[39] E.A. Ross, A. Devitt, J.R. Johnson, Macrophages: the good, the bad, and the gluttony, Front. Immunol. 12 (2021), 708186, https://doi.org/10.3389/fimmu.2021.708186.

[40] P.J. Murray, J.E. Allen, S.K. Biswas, E.A. Fisher, D.W. Gilroy, S. Goerdt, S. Gordon, J.A. Hamilton, L.B. Ivashkiv, T. Lawrence, M. Locati, A. Mantovani, F. O. Martinez, J.L. Mege, D.M. Mosser, G. Natoli, J.P. Saeij, J.L. Schultze, K.A. Shirey, A. Sica, J. Suttles, I. Udalova, J.A. van Ginderachter, S.N. Vogel, T. A. Wynn, Macrophage activation and polarization: nomenclature and experimental guidelines, Immunity 41 (2014) 14–20, https://doi.org/10.1016/j.immuni.2014.06.008.

[41] P. Loke, M.G. Nair, J. Parkinson, D. Guiliano, M. Blaxter, J.E. Allen, IL-4 dependent alternatively-activated macrophages have a distinctive in vivo gene expression phenotype, BMC Immunol. 3 (2002) 7, https://doi.org/10.1186/1471-2172-3-7.

[42] A. Mantovani, A. Sica, S. Sozzani, P. Allavena, A. Vecchi, M. Locati, The chemokine system in diverse forms of macrophage activation and polarization, Trends Immunol. 25 (2004) 677–686, https://doi.org/10.1016/j.it.2004.09.015.

[43] C. Atri, F.Z. Guerfali, D. Laouini, Role of human macrophage polarization in inflammation during infectious diseases, Int. J. Mol. Sci. 19 (2018), https://doi.org/10.3390/ijms19061801.

[44] K.M. Sheu, A. Hoffmann, Functional hallmarks of healthy macrophage responses: their regulatory basis and disease relevance, Annu. Rev. Immunol. 40 (2022) 295–321, https://doi.org/10.1146/annurev-immunol-101320-031555.

[45] K.A. Kigerl, J.C. Gensel, D.P. Ankeny, J.K. Alexander, D.J. Donnelly, P.G. Popovich, Identification of two distinct macrophage subsets with divergent effects causing either neurotoxicity or regeneration in the injured mouse spinal cord, J. Neurosci. 29 (2009) 13435–13444, https://doi.org/10.1523/jneurosci.3257-09.2009.

[46] H. Fan, H.B. Tang, L.Q. Shan, S.C. Liu, D.G. Huang, X. Chen, Z. Chen, M. Yang, X.H. Yin, H. Yang, D.J. Hao, Quercetin prevents necroptosis of oligodendrocytes by inhibiting macrophages/microglia polarization to M1 phenotype after spinal cord injury in rats, J. Neuroinflammation 16 (2019) 206, https://doi.org/10.1186/s12974-019-1613-2.

[47] J.Y. Hong, Y. Seo, G. Davaa, H.W. Kim, S.H. Kim, J.K. Hyun, Decellularized brain matrix enhances macrophage polarization and functional improvements in rat spinal cord injury, Acta Biomater. 101 (2020) 357–371, https://doi.org/10.1016/j.actbio.2019.11.012.

[48] J.C. Fleming, M.D. Norenberg, D.A. Ramsay, G.A. Dekaban, A.E. Marcillo, A.D. Saenz, M. Pasquale-Styles, W.D. Dietrich, L.C. Weaver, The cellular inflammatory response in human spinal cords after injury, Brain 129 (2006) 3249–3269, https://doi.org/10.1093/brain/awl296.

[49] J.J. Wang, G. Ye, H. Ren, C.R. An, L. Huang, H. Chen, H. Zhang, J.X. Lin, X. Shen, B.C. Heng, J. Zhou, Molecular expression profile of changes in rat acute spinal cord injury, Front. Cell. Neurosci. 15 (2021), 720271, https://doi.org/10.3389/fncel.2021.720271.

[50] T. Zrzavy, C. Schwaiger, I. Wimmer, T. Berger, J. Bauer, O. Butovsky, J.M. Schwab, H. Lassmann, R. Höftberger, Acute and non-resolving inflammation associate with oxidative injury after human spinal cord injury, Brain 144 (2021) 144–161, https://doi.org/10.1093/brain/awaa360.

[51] G. Sun, S. Yang, G. Cao, Q. Wang, J. Hao, Q. Wen, Z. Li, K.F. So, Z. Liu, S. Zhou, Y. Zhao, H. Yang, L. Zhou, Z. Yin, γδ T cells provide the early source of IFN-γ to aggravate lesions in spinal cord injury, J. Exp. Med. 215 (2018) 521–535, https://doi.org/10.1084/jem.20170686.

[52] T. Fujiyoshi, T. Kubo, C.C. Chan, M. Koda, A. Okawa, K. Takahashi, M. Yamazaki, Interferon-γ decreases chondroitin sulfate proteoglycan expression and enhances hindlimb function after spinal cord injury in mice, J. Neurotrauma 27 (2010) 2283–2294, https://doi.org/10.1089/neu.2009.1144.

[53] M. Yaguchi, S. Ohta, Y. Toyama, Y. Kawakami, M. Toda, Functional recovery after spinal cord injury in mice through activation of microglia and dendritic cells after IL-12 administration, J. Neurosci. Res. 86 (2008) 1972–1980, https://doi.org/10.1002/jnr.21658.

[54] S. Kobashi, T. Terashima, M. Katagi, Y. Nakae, J. Okano, Y. Suzuki, M. Urushitani, H. Kojima, Transplantation of M2-deviated microglia promotes recovery of motor function after spinal cord injury in mice, Mol. Ther. 28 (2020) 254–265, https://doi.org/10.1016/j.ymthe.2019.09.004.

[55] G.H. Han, S.J. Kim, W.K. Ko, D. Lee, I.B. Han, S.H. Sheen, J.B. Hong, S. Sohn, Transplantation of tauroursodeoxycholic acid-inducing M2-phenotype macrophages promotes an anti-neuroinflammatory effect and functional recovery after spinal cord injury in rats, Cell Prolif. 54 (2021), e13050, https://doi.org/10.1111/cpr.13050.

[56] G. Song, R. Yang, Q. Zhang, L. Chen, D. Huang, J. Zeng, C. Yang, T. Zhang, TGF-β secretion by M2 macrophages induces glial scar formation by activating astrocytes in vitro, J. Mol. Neurosci. 69 (2019) 324–332, https://doi.org/10.1007/s12031-019-01361-5.

[57] M.S. Hayden, S. Ghosh, Shared principles in NF-kappaB signaling, Cell 132 (2008) 344–362, https://doi.org/10.1016/j.cell.2008.01.020.

[58] S. Wang, M. Lu, W. Wang, S. Yu, R. Yu, C. Cai, Y. Li, Z. Shi, J. Zou, M. He, W. Xie, D. Yu, H. Jin, H. Li, W. Xiao, C. Fan, F. Wu, Y. Li, S. Liu, Macrophage polarization modulated by NF-κB in polylactide membranes-treated peritendinous adhesion, Small 18 (2022), e2104112, https://doi.org/10.1002/smll.202104112.

[59] M.A. Lauterbach, J.E. Hanke, M. Serefidou, M.S.J. Mangan, C.C. Kolbe, T. Hess, M. Rothe, R. Kaiser, F. Hoss, J. Gehlen, G. Engels, M. Kreutzenbeck, S. V. Schmidt, A. Christ, A. Imhof, K. Hiller, E. Latz, Toll-like receptor signaling rewires macrophage metabolism and promotes histone acetylation via ATP-citrate lyase, Immunity 51 (2019) 997–1011.e7, https://doi.org/10.1016/j.immuni.2019.11.009.

[60] C.H. Fong, M. Bebien, A. Didierlaurent, R. Nebauer, T. Hussell, D. Broide, M. Karin, T. Lawrence, An antiinflammatory role for IKKbeta through the inhibition of "classical" macrophage activation, J. Exp. Med. 205 (2008) 1269–1276, https://doi.org/10.1084/jem.20080124.

[61] L.V. Webb, S. Ventura, S.C. Ley, ABIN-2, of the TPL-2 signaling complex, modulates mammalian inflammation, Trends Immunol. 40 (2019) 799–808, https://doi.org/10.1016/j.it.2019.07.001.

[62] F. Kaiser, D. Cook, S. Papoutsopoulou, R. Rajsbaum, X. Wu, H.T. Yang, S. Grant, P. Ricciardi-Castagnoli, P.N. Tsichlis, S.C. Ley, A. O'Garra, TPL-2 negatively regulates interferon-beta production in macrophages and myeloid dendritic cells, J. Exp. Med. 206 (2009) 1863–1871, https://doi.org/10.1084/jem.20091059.

[63] C. Porta, M. Rimoldi, G. Raes, L. Brys, P. Ghezzi, D. Di Liberto, F. Dieli, S. Ghisletti, G. Natoli, P. De Baetselier, A. Mantovani, A. Sica, Tolerance and M2 (alternative) macrophage polarization are related processes orchestrated by p50 nuclear factor kappaB, Proc. Natl. Acad. Sci. U. S. A. 106 (2009) 14978–14983, https://doi.org/10.1073/pnas.0809784106.

[64] F. Li, H. Liang, H. You, J. Xiao, H. Xia, X. Chen, M. Huang, Z. Cheng, C. Yang, W. Liu, H. Zhang, L. Zeng, Y. Wu, F. Ge, Z. Li, W. Zhou, Y. Wen, Z. Zhou, R. Liu, D. Jiang, N. Xie, B. Liang, Z. Liu, Y. Kong, C. Chen, Targeting HECTD3-IKKα axis inhibits inflammation-related metastasis, Signal Transduct. Targeted Ther. 7 (2022) 264, https://doi.org/10.1038/s41392-022-01057-0.

[65] B. Liu, Y. Yang, V. Chernishof, R.R. Loo, H. Jang, S. Tahk, R. Yang, S. Mink, D. Shultz, C.J. Bellone, J.A. Loo, K. Shuai, Proinflammatory stimuli induce IKKalpha-mediated phosphorylation of PIAS1 to restrict inflammation and immunity, Cell 129 (2007) 903–914, https://doi.org/10.1016/j.cell.2007.03.056.

[66] F. Wang, S. Zhang, R. Jeon, I. Vuckovic, X. Jiang, A. Lerman, C.D. Folmes, P.D. Dzeja, J. Herrmann, Interferon gamma induces reversible metabolic reprogramming of M1 macrophages to sustain cell viability and pro-inflammatory activity, EBioMedicine 30 (2018) 303–316, https://doi.org/10.1016/j.ebiom.2018.02.009.

[67] H.H. Lee, E. Jang, S.Y. Kang, J.S. Shin, H.S. Han, T.W. Kim, D.H. Lee, J.H. Lee, D.S. Jang, K.T. Lee, Anti-inflammatory potential of Patrineolignan B isolated from Patrinia scabra in LPS-stimulated macrophages via inhibition of NF-κB, AP-1, and JAK/STAT pathways, Int. Immunopharm. 86 (2020), 106726, https://doi.org/10.1016/j.intimp.2020.106726.

[68] A. Al Mamun, A. Chauhan, S. Qi, C. Ngwa, Y. Xu, R. Sharmeen, A.L. Hazen, J. Li, J.A. Aronowski, L.D. McCullough, F. Liu, Microglial IRF5-IRF4 regulatory axis regulates neuroinflammation after cerebral ischemia and impacts stroke outcomes, Proc. Natl. Acad. Sci. U. S. A. 117 (2020) 1742–1752, https://doi.org/10.1073/pnas.1914742117.

[69] J. Xu, Z. Chen, F. Yu, H. Liu, C. Ma, D. Xie, X. Hu, R.K. Leak, S.H.Y. Chou, R.A. Stetler, Y. Shi, J. Chen, M.V.L. Bennett, G. Chen, IL-4/STAT6 signaling facilitates innate hematoma resolution and neurological recovery after hemorrhagic stroke in mice, Proc. Natl. Acad. Sci. U. S. A. 117 (2020) 32679–32690, https://doi.org/10.1073/pnas.2018497117.

[70] A. Bhattacharjee, M. Shukla, V.P. Yakubenko, A. Mulya, S. Kundu, M.K. Cathcart, IL-4 and IL-13 employ discrete signaling pathways for target gene expression in alternatively activated monocytes/macrophages, Free Radic. Biol. Med. 54 (2013) 1–16, https://doi.org/10.1016/j.freeradbiomed.2012.10.553.

[71] H. Jeong, H. Yoon, Y. Lee, J.T. Kim, M. Yang, G. Kim, B. Jung, S.H. Park, C.E. Lee, SOCS3 attenuates dexamethasone-induced M2 polarization by down-regulation of GILZ via ROS- and p38 MAPK-dependent pathways, Immune Netw. 22 (2022) e33, https://doi.org/10.4110/in.2022.22.e33.

[72] Z.W. Hu, Y.H. Wen, R.Q. Ma, L. Chen, X.L. Zeng, W.P. Wen, W. Sun, Ferroptosis driver SOCS1 and suppressor FTH1 independently correlate with M1 and M2 macrophage infiltration in head and neck squamous cell carcinoma, Front. Cell Dev. Biol. 9 (2021), 727762, https://doi.org/10.3389/fcell.2021.727762.

[73] L. Zhu, H. Wu, Z. Ma, D. Dong, Z. Yang, J. Tian, Astaxanthin ameliorates lipopolysaccharide-induced acute lung injury via inhibition of inflammatory reactions and modulation of the SOCS3/JAK2/STAT3 signaling pathways in mice, Food Funct. 13 (2022) 11638–11651, https://doi.org/10.1039/d2fo02182j.

[74] F.P.R. Santana, R.C. da Silva, V. Ponci, A. Pinheiro, C.R. Olivo, L.C. Caperuto, F.M. Arantes-Costa, S.R. Claudio, D.A. Ribeiro, I. Tibério, L.G. Lima-Neto, J.H. G. Lago, C.M. Prado, Dehydrodieugenol improved lung inflammation in an asthma model by inhibiting the STAT3/SOCS3 and MAPK pathways, Biochem. Pharmacol. 180 (2020), 114175, https://doi.org/10.1016/j.bcp.2020.114175.

[75] H. Qin, A.T. Holdbrooks, Y. Liu, S.L. Reynolds, L.L. Yanagisawa, E.N. Benveniste, SOCS3 deficiency promotes M1 macrophage polarization and inflammation, J. Immunol. 189 (2012) 3439–3448, https://doi.org/10.4049/jimmunol.1201168.

[76] H. Dickensheets, N. Vazquez, F. Sheikh, S. Gingras, P.J. Murray, J.J. Ryan, R.P. Donnelly, Suppressor of cytokine signaling-1 is an IL-4-inducible gene in macrophages and feedback inhibits IL-4 signaling, Gene Immun. 8 (2007) 21–27, https://doi.org/10.1038/sj.gene.6364352.

[77] C.L. Xiao, W.C. Yin, Y.C. Zhong, J.Q. Luo, L.L. Liu, W.Y. Liu, K. Zhao, The role of PI3K/Akt signalling pathway in spinal cord injury, Biomed. Pharmacother. 156 (2022), 113881, https://doi.org/10.1016/j.biopha.2022.113881.

[78] C. Lin, Y. Shao, C. Zeng, C. Zhao, H. Fang, L. Wang, J. Pan, L. Liu, W. Qi, X. Feng, H. Qiu, H. Zhang, Y. Chen, H. Wang, D. Cai, C.J. Xian, Blocking PI3K/AKT signaling inhibits bone sclerosis in subchondral bone and attenuates post-traumatic osteoarthritis, J. Cell. Physiol. 233 (2018) 6135–6147, https://doi.org/10.1002/jcp.26460.

[79] W.C. Chou, E. Rampanelli, X. Li, J.P. Ting, Impact of intracellular innate immune receptors on immunometabolism, Cell. Mol. Immunol. 19 (2022) 337–351, https://doi.org/10.1038/s41423-021-00780-y.

[80] T. Fukao, S. Koyasu, PI3K and negative regulation of TLR signaling, Trends Immunol. 24 (2003) 358–363, https://doi.org/10.1016/s1471-4906(03)00139-x.

[81] A. Androulidaki, D. Iliopoulos, A. Arranz, C. Doxaki, S. Schworer, V. Zacharioudaki, A.N. Margioris, P.N. Tsichlis, C. Tsatsanis, The kinase Akt1 controls macrophage response to lipopolysaccharide by regulating microRNAs, Immunity 31 (2009) 220–231, https://doi.org/10.1016/j.immuni.2009.06.024.

[82] A. Arranz, C. Doxaki, E. Vergadi, Y. Martinez de la Torre, K. Vaporidi, E.D. Lagoudaki, E. Ieronymaki, A. Androulidaki, M. Venihaki, A.N. Margioris, E. N. Stathopoulos, P.N. Tsichlis, C. Tsatsanis, Akt1 and Akt2 protein kinases differentially contribute to macrophage polarization, Proc. Natl. Acad. Sci. U. S. A. 109 (2012) 9517–9522, https://doi.org/10.1073/pnas.1119038109.

[83] D.T. Graves, T.N. Milovanova, Mucosal immunity and the FOXO1 transcription factors, Front. Immunol. 10 (2019) 2530, https://doi.org/10.3389/fimmu.2019.02530.

[84] T. Weichhart, G. Costantino, M. Poglitsch, M. Rosner, M. Zeyda, K.M. Stuhlmeier, T. Kolbe, T.M. Stulnig, W.H. Hörl, M. Hengstschläger, M. Müller, M. D. Säemann, The TSC-mTOR signaling pathway regulates the innate inflammatory response, Immunity 29 (2008) 565–577, https://doi.org/10.1016/j.immuni.2008.08.012.

[85] A.J. Covarrubias, H.I. Aksoylar, T. Horng, Control of macrophage metabolism and activation by mTOR and Akt signaling, Semin. Immunol. 27 (2015) 286–296, https://doi.org/10.1016/j.smim.2015.08.001.

[86] E. Vergadi, E. Ieronymaki, K. Lyroni, K. Vaporidi, C. Tsatsanis, Akt signaling pathway in macrophage activation and M1/M2 polarization, J. Immunol. 198 (2017) 1006–1014, https://doi.org/10.4049/jimmunol.1601515.

[87] E. Fung, S.M. Tang, J.P. Canner, K. Morishige, J.F. Arboleda-Velasquez, A.A. Cardoso, N. Carlesso, J.C. Aster, M. Aikawa, Delta-like 4 induces notch signaling in macrophages: implications for inflammation, Circulation 115 (2007) 2948–2956, https://doi.org/10.1161/circulationaha.106.675462.

[88] T.V. Arumugam, S.H. Baik, P. Balaganapathy, C.G. Sobey, M.P. Mattson, D.G. Jo, Notch signaling and neuronal death in stroke, Prog. Neurobiol. 165–167 (2018) 103–116, https://doi.org/10.1016/j.pneurobio.2018.03.002.

[89] J.C. Lin, J.Q. Wu, F. Wang, F.Y. Tang, J. Sun, B. Xu, M. Jiang, Y. Chu, D. Chen, X. Li, S. Su, Y. Zhang, N. Wu, S. Yang, K. Wu, J. Liang, QingBai decoction regulates intestinal permeability of dextran sulphate sodium-induced colitis through the modulation of notch and NF-κB signalling, Cell Prolif. 52 (2019), e12547, https://doi.org/10.1111/cpr.12547.

[90] J. Gamrekelashvili, T. Kapanadze, S. Sablotny, C. Ratiu, K. Dastagir, M. Lochner, S. Karbach, P. Wenzel, A. Sitnow, S. Fleig, T. Sparwasser, U. Kalinke, B. Holzmann, H. Haller, F.P. Limbourg, Notch and TLR signaling coordinate monocyte cell fate and inflammation, Elife 9 (2020), https://doi.org/10.7554/eLife.57007.

[91] H. Xu, J. Zhu, S. Smith, J. Foldi, B. Zhao, A.Y. Chung, H. Outtz, J. Kitajewski, C. Shi, S. Weber, P. Saftig, Y. Li, K. Ozato, C.P. Blobel, L.B. Ivashkiv, X. Hu, Notch-RBP-J signaling regulates the transcription factor IRF8 to promote inflammatory macrophage polarization, Nat. Immunol. 13 (2012) 642–650, https://doi.org/10.1038/ni.2304.

[92] D.P. Bartel, Metazoan MicroRNAs, Cell 173 (2018) 20–51, https://doi.org/10.1016/j.cell.2018.03.006.

[93] M. Ha, V.N. Kim, Regulation of microRNA biogenesis, Nat. Rev. Mol. Cell Biol. 15 (2014) 509–524, https://doi.org/10.1038/nrm3838.

[94] V.M. Ruiz-Arroyo, Y. Nam, Dynamic Protein-RNA recognition in primary MicroRNA processing, Curr. Opin. Struct. Biol. 76 (2022), 102442, https://doi.org/10.1016/j.sbi.2022.102442.

[95] Z. Lou, Z. Cheng, H. Li, Z. Teng, Y. Liu, Z. Tian, Predicting miRNA-disease associations via learning multimodal networks and fusing mixed neighborhood information, Briefings Bioinf. 23 (2022), https://doi.org/10.1093/bib/bbac159.

[96] J.A. Vidigal, A. Ventura, The biological functions of miRNAs: lessons from in vivo studies, Trends Cell Biol. 25 (2015) 137–147, https://doi.org/10.1016/j.tcb.2014.11.004.

[97] W. Yu, S. Wang, Y. Wang, H. Chen, H. Nie, L. Liu, X. Zou, Q. Gong, B. Zheng, MicroRNA: role in macrophage polarization and the pathogenesis of the liver fibrosis, Front. Immunol. 14 (2023), 1147710, https://doi.org/10.3389/fimmu.2023.1147710.

[98] V. Cobos Jiménez, E.J. Bradley, A.M. Willemsen, A.H. van Kampen, F. Baas, N.A. Kootstra, Next-generation sequencing of microRNAs uncovers expression signatures in polarized macrophages, Physiol. Genom. 46 (2014) 91–103, https://doi.org/10.1152/physiolgenomics.00140.2013.

[99] J.W. Graff, A.M. Dickson, G. Clay, A.P. McCaffrey, M.E. Wilson, Identifying functional microRNAs in macrophages with polarized phenotypes, J. Biol. Chem. 287 (2012) 21816–21825, https://doi.org/10.1074/jbc.M111.327031.

[100] Y. Zhang, M. Zhang, M. Zhong, Q. Suo, K. Lv, Expression profiles of miRNAs in polarized macrophages, Int. J. Mol. Med. 31 (2013) 797–802, https://doi.org/10.3892/ijmm.2013.1260.

[101] C.E. Monk, G. Hutvagner, J.S. Arthur, Regulation of miRNA transcription in macrophages in response to Candida albicans, PLoS One 5 (2010), e13669, https://doi.org/10.1371/journal.pone.0013669.

[102] L. Lu, S. McCurdy, S. Huang, X. Zhu, K. Peplowska, M. Tiirikainen, W.A. Boisvert, L.X. Garmire, Time Series miRNA-mRNA integrated analysis reveals critical miRNAs and targets in macrophage polarization, Sci. Rep. 6 (2016), 37446, https://doi.org/10.1038/srep37446.

[103] D.W. Melton, X. Lei, J.A. Gelfond, P.K. Shireman, Dynamic macrophage polarization-specific miRNA patterns reveal increased soluble VEGF receptor 1 by miR-125a-5p inhibition, Physiol. Genom. 48 (2016) 345–360, https://doi.org/10.1152/physiolgenomics.00098.2015.

[104] P. Thulin, T. Wei, O. Werngren, L. Cheung, R.M. Fisher, D. Grandér, M. Corcoran, E. Ehrenborg, MicroRNA-9 regulates the expression of peroxisome proliferator-activated receptor δ in human monocytes during the inflammatory response, Int. J. Mol. Med. 31 (2013) 1003–1010, https://doi.org/10.3892/ijmm.2013.1311.

[105] S. Pasca, A. Jurj, B. Petrushev, C. Tomuleasa, D. Matei, MicroRNA-155 implication in M1 polarization and the impact in inflammatory diseases, Front. Immunol. 11 (2020) 625, https://doi.org/10.3389/fimmu.2020.00625.

[106] S. Banerjee, N. Xie, H. Cui, Z. Tan, S. Yang, M. Icyuz, E. Abraham, G. Liu, MicroRNA let-7c regulates macrophage polarization, J. Immunol. 190 (2013) 6542–6549, https://doi.org/10.4049/jimmunol.1202496.

[107] W. Zhang, H. Liu, W. Liu, Y. Liu, J. Xu, Polycomb-mediated loss of microRNA let-7c determines inflammatory macrophage polarization via PAK1-dependent NF-κB pathway, Cell Death Differ. 22 (2015) 287–297, https://doi.org/10.1038/cdd.2014.142.

[108] H. Ying, Y. Kang, H. Zhang, D. Zhao, J. Xia, Z. Lu, H. Wang, F. Xu, L. Shi, MiR-127 modulates macrophage polarization and promotes lung inflammation and injury by activating the JNK pathway, J. Immunol. 194 (2015) 1239–1251, https://doi.org/10.4049/jimmunol.1402088.

[109] P. Jiang, R. Liu, Y. Zheng, X. Liu, L. Chang, S. Xiong, Y. Chu, MiR-34a inhibits lipopolysaccharide-induced inflammatory response through targeting Notch1 in murine macrophages, Exp. Cell Res. 318 (2012) 1175–1184, https://doi.org/10.1016/j.yexcr.2012.03.018.

[110] Y. Sun, Q. Li, H. Gui, D.P. Xu, Y.L. Yang, D.F. Su, X. Liu, MicroRNA-124 mediates the cholinergic anti-inflammatory action through inhibiting the production of pro-inflammatory cytokines, Cell Res. 23 (2013) 1270–1283, https://doi.org/10.1038/cr.2013.116.

[111] K.D. Taganov, M.P. Boldin, K.J. Chang, D. Baltimore, NF-kappaB-dependent induction of microRNA miR-146, an inhibitor targeted to signaling proteins of innate immune responses, Proc. Natl. Acad. Sci. U. S. A. 103 (2006) 12481–12486, https://doi.org/10.1073/pnas.0605298103.

[112] C.I. Caescu, X. Guo, L. Tesfa, T.D. Bhagat, A. Verma, D. Zheng, E.R. Stanley, Colony stimulating factor-1 receptor signaling networks inhibit mouse macrophage inflammatory responses by induction of microRNA-21, Blood 125 (2015) e1–e13, https://doi.org/10.1182/blood-2014-10-608000.

[113] Z. Wang, S. Brandt, A. Medeiros, S. Wang, H. Wu, A. Dent, C.H. Serezani, MicroRNA 21 is a homeostatic regulator of macrophage polarization and prevents prostaglandin E2-mediated M2 generation, PLoS One 10 (2015), e0115855, https://doi.org/10.1371/journal.pone.0115855.

[114] Q. Chen, H. Wang, Y. Liu, Y. Song, L. Lai, Q. Han, X. Cao, Q. Wang, Inducible microRNA-223 down-regulation promotes TLR-triggered IL-6 and IL-1β production in macrophages by targeting STAT3, PLoS One 7 (2012), e42971, https://doi.org/10.1371/journal.pone.0042971.

[115] M. Rajman, G. Schratt, MicroRNAs in neural development: from master regulators to fine-tuners, Development 144 (2017) 2310–2322, https://doi.org/10.1242/dev.144337.

[116] M.A. Mori, R.G. Ludwig, R. Garcia-Martin, B.B. Brandão, C.R. Kahn, Extracellular miRNAs: from biomarkers to mediators of physiology and disease, Cell Metab. 30 (2019) 656–673, https://doi.org/10.1016/j.cmet.2019.07.011.

[117] M.F. Schmidt, Drug target miRNAs: chances and challenges, Trends Biotechnol. 32 (2014) 578–585, https://doi.org/10.1016/j.tibtech.2014.09.002.

[118] L. Guo, Q. Zhang, X. Ma, J. Wang, T. Liang, miRNA and mRNA expression analysis reveals potential sex-biased miRNA expression, Sci. Rep. 7 (2017), 39812, https://doi.org/10.1038/srep39812.

[119] N.K. Liu, X.F. Wang, Q.B. Lu, X.M. Xu, Altered microRNA expression following traumatic spinal cord injury, Exp. Neurol. 219 (2009) 424–429, https://doi.org/10.1016/j.expneurol.2009.06.015.

[120] M. Yunta, M. Nieto-Díaz, F.J. Esteban, M. Caballero-López, R. Navarro-Ruíz, D. Reigada, D.W. Pita-Thomas, A. del Águila, T. Muñoz-Galdeano, R.M. Maza, MicroRNA dysregulation in the spinal cord following traumatic injury, PLoS One 7 (2012), e34534, https://doi.org/10.1371/journal.pone.0034534.

[121] E.R. Strickland, M.A. Hook, S. Balaraman, J.R. Huie, J.W. Grau, R.C. Miranda, MicroRNA dysregulation following spinal cord contusion: implications for neural plasticity and repair, Neuroscience 186 (2011) 146–160, https://doi.org/10.1016/j.neuroscience.2011.03.063.

[122] A. De Biase, S.M. Knoblach, S. Di Giovanni, C. Fan, A. Molon, E.P. Hoffman, A.I. Faden, Gene expression profiling of experimental traumatic spinal cord injury as a function of distance from impact site and injury severity, Physiol. Genom. 22 (2005) 368–381, https://doi.org/10.1152/physiolgenomics.00081.2005.

[123] S. Tigchelaar, F. Streijger, S. Sinha, S. Flibotte, N. Manouchehri, K. So, K. Shortt, E. Okon, M.A. Rizzuto, I. Malenica, A. Courtright-Lim, A. Eisen, K.V. Keuren-Jensen, C. Nislow, B.K. Kwon, Serum MicroRNAs reflect injury severity in a large animal model of thoracic spinal cord injury, Sci. Rep. 7 (2017) 1376, https://doi.org/10.1038/s41598-017-01299-x.

[124] S. Tigchelaar, R. Gupta, C.P. Shannon, F. Streijger, S. Sinha, S. Flibotte, M.A. Rizzuto, J. Street, S. Paquette, T. Ailon, R. Charest-Morin, N. Dea, C. Fisher, M. F. Dvorak, S. Dhall, J.M. Mac-Thiong, S. Parent, C. Bailey, S. Christie, K. Van Keuren-Jensen, C. Nislow, B.K. Kwon, MicroRNA biomarkers in cerebrospinal fluid and serum reflect injury severity in human acute traumatic spinal cord injury, J. Neurotrauma 36 (2019) 2358–2371, https://doi.org/10.1089/neu.2018.6256.

[125] P.S. Eis, W. Tam, L. Sun, A. Chadburn, Z. Li, M.F. Gomez, E. Lund, J.E. Dahlberg, Accumulation of miR-155 and BIC RNA in human B cell lymphomas, Proc. Natl. Acad. Sci. U. S. A. 102 (2005) 3627–3632, https://doi.org/10.1073/pnas.0500613102.

[126] K.A. Jablonski, A.D. Gaudet, S.A. Amici, P.G. Popovich, M. Guerau-de-Arellano, Control of the inflammatory macrophage transcriptional signature by miR-155, PLoS One 11 (2016), e0159724, https://doi.org/10.1371/journal.pone.0159724.

[127] W. Chen, L. Wang, Z. Liu, MicroRNA-155 influences cell damage in ischemic stroke via TLR4/MYD88 signaling pathway, Bioengineered 12 (2021) 2449–2458, https://doi.org/10.1080/21655979.2021.1935066.

[128] Q. Wen, Y. Wang, Q. Pan, R. Tian, D. Zhang, G. Qin, J. Zhou, L. Chen, MicroRNA-155-5p promotes neuroinflammation and central sensitization via inhibiting SIRT1 in a nitroglycerin-induced chronic migraine mouse model, J. Neuroinflammation 18 (2021) 287, https://doi.org/10.1186/s12974-021-02342-5.

[129] A.D. Gaudet, S. Mandrekar-Colucci, J.C. Hall, D.R. Sweet, P.J. Schmitt, X. Xu, Z. Guan, X. Mo, M. Guerau-de-Arellano, P.G. Popovich, miR-155 deletion in mice overcomes neuron-intrinsic and neuron-extrinsic barriers to spinal cord repair, J. Neurosci. 36 (2016) 8516–8532, https://doi.org/10.1523/jneurosci.0735-16.2016.
[130] C.F. Hu, S.P. Wu, G.J. Lin, C.C. Shieh, C.S. Hsu, J.W. Chen, S.H. Chen, J.S. Hong, S.J. Chen, Microglial Nox2 plays a key role in the pathogenesis of experimental autoimmune encephalomyelitis, Front. Immunol. 12 (2021), 638381, https://doi.org/10.3389/fimmu.2021.638381.
[131] G. Khayrullina, S. Bermudez, K.R. Byrnes, Inhibition of NOX2 reduces locomotor impairment, inflammation, and oxidative stress after spinal cord injury, J. Neuroinflammation 12 (2015) 172, https://doi.org/10.1186/s12974-015-0391-8.
[132] B. Sabirzhanov, Y. Li, M. Coll-Miro, J.J. Matyas, J. He, A. Kumar, N. Ward, J. Yu, A.I. Faden, J. Wu, Inhibition of NOX2 signaling limits pain-related behavior and improves motor function in male mice after spinal cord injury: participation of IL-10/miR-155 pathways, Brain Behav. Immun. 80 (2019) 73–87, https://doi.org/10.1016/j.bbi.2019.02.024.
[133] Z.Y. Zou, J. Liu, C. Chang, J.J. Li, J. Luo, Y. Jin, Z. Ma, T.H. Wang, J.L. Shao, Biliverdin administration regulates the microRNA-mRNA expressional network associated with neuroprotection in cerebral ischemia reperfusion injury in rats, Int. J. Mol. Med. 43 (2019) 1356–1372, https://doi.org/10.3892/ijmm.2019.4064.
[134] D. Wang, S. He, B. Liu, C. Liu, MiR-27-3p regulates TLR2/4-dependent mouse alveolar macrophage activation by targetting PPARγ, Clin. Sci. (Lond.) 132 (2018) 943–958, https://doi.org/10.1042/cs20180083.
[135] Z. Ye, J. Hu, H. Xu, B. Sun, Y. Jin, Y. Zhang, J. Zhang, Serum exosomal microRNA-27-3p aggravates cerebral injury and inflammation in patients with acute cerebral infarction by targeting PPARγ, Inflammation 44 (2021) 1035–1048, https://doi.org/10.1007/s10753-020-01399-3.
[136] L. Lin, H. Lin, L. Wang, B. Wang, X. Hao, Y. Shi, miR-130a regulates macrophage polarization and is associated with non-small cell lung cancer, Oncol. Rep. 34 (2015) 3088–3096, https://doi.org/10.3892/or.2015.4301.
[137] S. Su, Q. Zhao, C. He, D. Huang, J. Liu, F. Chen, J. Chen, J.Y. Liao, X. Cui, Y. Zeng, H. Yao, F. Su, Q. Liu, S. Jiang, E. Song, miR-142-5p and miR-130a-3p are regulated by IL-4 and IL-13 and control profibrogenic macrophage program, Nat. Commun. 6 (2015) 8523, https://doi.org/10.1038/ncomms9523.
[138] Y. Zhang, M. Chen, Z. Qiu, K. Hu, W. McGee, X. Chen, J. Liu, L. Zhu, J.Y. Wu, MiR-130a regulates neurite outgrowth and dendritic spine density by targeting MeCP2, Protein Cell 7 (2016) 489–500, https://doi.org/10.1007/s13238-016-0272-7.
[139] K. Glaesel, C. May, K. Marcus, V. Matschke, C. Theiss, V. Theis, miR-129-5p and miR-130a-3p regulate VEGFR-2 expression in sensory and motor neurons during development, Int. J. Mol. Sci. 21 (2020), https://doi.org/10.3390/ijms21113839.
[140] L. Yao, Y. Guo, L. Wang, G. Li, X. Qian, J. Zhang, H. Liu, G. Liu, Knockdown of miR-130a-3p alleviates spinal cord injury induced neuropathic pain by activating IGF-1/IGF-1R pathway, J. Neuroimmunol. 351 (2021), 577458, https://doi.org/10.1016/j.jneuroim.2020.577458.
[141] S.H. Rastegar-Moghaddam, A. Ebrahimzadeh-Bideskan, S. Shahba, A.M. Malvandi, A. Mohammadipour, MicroRNA-22: a novel and potent biological therapeutics in neurological disorders, Mol. Neurobiol. 59 (2022) 2694–2701, https://doi.org/10.1007/s12035-022-02769-8.
[142] B. Li, Z. Wang, M. Yu, X. Wang, X. Wang, C. Chen, Z. Zhang, M. Zhang, C. Sun, C. Zhao, Q. Li, W. Wang, T. Wang, L. Zhang, G. Ning, S. Feng, miR-22-3p enhances the intrinsic regenerative abilities of primary sensory neurons via the CBL/p-EGFR/p-STAT3/GAP43/p-GAP43 axis, J. Cell. Physiol. 235 (2020) 4605–4617, https://doi.org/10.1002/jcp.29338.
[143] Z.G. Liu, Y. Li, J.H. Jiao, H. Long, Z.Y. Xin, X.Y. Yang, MicroRNA regulatory pattern in spinal cord ischemia-reperfusion injury, Neural. Regen. Res. 15 (2020) 2123–2130, https://doi.org/10.4103/1673-5374.280323.
[144] H. Fang, M. Yang, Q. Pan, H.L. Jin, H.F. Li, R.R. Wang, Q.Y. Wang, J.P. Zhang, MicroRNA-22-3p alleviates spinal cord ischemia/reperfusion injury by modulating M2 macrophage polarization via IRF5, J. Neurochem. 156 (2021) 106–120, https://doi.org/10.1111/jnc.15042.
[145] T. Brandenburger, M. Castoldi, M. Brendel, H. Grievink, L. Schlösser, R. Werdehausen, I. Bauer, H. Hermanns, Expression of spinal cord microRNAs in a rat model of chronic neuropathic pain, Neurosci. Lett. 506 (2012) 281–286, https://doi.org/10.1016/j.neulet.2011.11.023.
[146] Y. Cui, Y. Yin, Z. Xiao, Y. Zhao, B. Chen, B. Yang, B. Xu, H. Song, Y. Zou, X. Ma, J. Dai, LncRNA Neat1 mediates miR-124-induced activation of Wnt/β-catenin signaling in spinal cord neural progenitor cells, Stem Cell Res. Ther. 10 (2019) 400, https://doi.org/10.1186/s13287-019-1487-3.
[147] J.L. Song, W. Zheng, W. Chen, Y. Qian, Y.M. Ouyang, C.Y. Fan, Lentivirus-mediated microRNA-124 gene-modified bone marrow mesenchymal stem cell transplantation promotes the repair of spinal cord injury in rats, Exp. Mol. Med. 49 (2017) e332, https://doi.org/10.1038/emm.2017.48.
[148] X. Ma, T. Ma, L. Chang, X. Chen, G. Xia, C. Li, H. Liu, Correlation between miRNA-124, miRNA-544a, and TNF-α levels in acute spinal cord injury, Spinal Cord 60 (2022) 779–783, https://doi.org/10.1038/s41393-022-00763-4.
[149] E.D. Ponomarev, T. Veremeyko, N. Barteneva, A.M. Krichevsky, H.L. Weiner, MicroRNA-124 promotes microglia quiescence and suppresses EAE by deactivating macrophages via the C/EBP-α-PU.1 pathway, Nat. Med. 17 (2011) 64–70, https://doi.org/10.1038/nm.2266.
[150] T. Veremeyko, S. Siddiqui, I. Sotnikov, A. Yung, E.D. Ponomarev, IL-4/IL-13-dependent and independent expression of miR-124 and its contribution to M2 phenotype of monocytic cells in normal conditions and during allergic inflammation, PLoS One 8 (2013), e81774, https://doi.org/10.1371/journal.pone.0081774.
[151] H.L. Willemen, X.J. Huo, Q.L. Mao-Ying, J. Zijlstra, C.J. Heijnen, A. Kavelaars, MicroRNA-124 as a novel treatment for persistent hyperalgesia, J. Neuroinflammation 9 (2012) 143, https://doi.org/10.1186/1742-2094-9-143.
[152] K.L. Kynast, O.Q. Russe, C.V. Möser, G. Geisslinger, E. Niederberger, Modulation of central nervous system-specific microRNA-124a alters the inflammatory response in the formalin test in mice, Pain 154 (2013) 368–376, https://doi.org/10.1016/j.pain.2012.11.010.
[153] Y. Men, J. Yelick, S. Jin, Y. Tian, M.S.R. Chiang, H. Higashimori, E. Brown, R. Jarvis, Y. Yang, Exosome reporter mice reveal the involvement of exosomes in mediating neuron to astroglia communication in the CNS, Nat. Commun. 10 (2019) 4136, https://doi.org/10.1038/s41467-019-11534-w.
[154] L. Chen, R. Dong, Y. Lu, Y. Zhou, K. Li, Z. Zhang, M. Peng, MicroRNA-146a protects against cognitive decline induced by surgical trauma by suppressing hippocampal neuroinflammation in mice, Brain Behav. Immun. 78 (2019) 188–201, https://doi.org/10.1016/j.bbi.2019.01.020.
[155] Y. Lu, D.L. Cao, B.C. Jiang, T. Yang, Y.J. Gao, MicroRNA-146a-5p attenuates neuropathic pain via suppressing TRAF6 signaling in the spinal cord, Brain Behav. Immun. 49 (2015) 119–129, https://doi.org/10.1016/j.bbi.2015.04.018.
[156] Z.C. Lv, X.Y. Cao, Y.X. Guo, X.D. Zhang, J. Ding, J. Geng, K. Feng, H. Niu, Effects of MiR-146a on repair and inflammation in rats with spinal cord injury through the TLR/NF-κB signaling pathway, Eur. Rev. Med. Pharmacol. Sci. 23 (2019) 4558–4563, https://doi.org/10.26355/eurrev_201906_18031.
[157] H.D. Brahmbhatt, R. Gupta, A. Gupta, S. Rastogi, D. Subramani, A. Mobeen, V.V. Batra, A. Singh, Differential regulation of miR-21-5p delays wound healing of melanocyte-deprived vitiligo skin by modulating the expression of tumor-suppressors PDCD4 and Maspin, J. Cell. Physiol. 237 (2022) 1429–1439, https://doi.org/10.1002/jcp.30614.
[158] R. Li, Y.X. Wen, Y.Q. Geng, Y.J. Zhou, Y. Zhang, Y.B. Ding, X.M. Chen, R.F. Gao, J.L. He, Y.X. Wang, X.Q. Liu, miR-21a inhibits decidual cell apoptosis by targeting Pdcd4, Genes Dis. 8 (2021) 171–180, https://doi.org/10.1016/j.gendis.2019.09.013.
[159] H.J. Chung, W.H. Chung, S.H. Do, J.H. Lee, H.Y. Kim, Up-regulation of MicroRNAs-21 and -223 in a sprague-dawley rat model of traumatic spinal cord injury, Brain Sci. 10 (2020), https://doi.org/10.3390/brainsci10030141.
[160] X. Lv, J. Liang, Z. Wang, MiR-21-5p reduces apoptosis and inflammation in rats with spinal cord injury through PI3K/AKT pathway, Panminerva Med. (2020), https://doi.org/10.23736/s0031-0808.20.03974-9.
[161] T. Zhang, S. Ni, Z. Luo, Y. Lang, J. Hu, H. Lu, The protective effect of microRNA-21 in neurons after spinal cord injury, Spinal Cord 57 (2019) 141–149, https://doi.org/10.1038/s41393-018-0180-1.
[162] W. Xie, S.Y. Yang, Q. Zhang, Y. Zhou, Y. Wang, R. Liu, W. Wang, J. Shi, B. Ning, T. Jia, Knockdown of MicroRNA-21 promotes neurological recovery after acute spinal cord injury, Neurochem. Res. 43 (2018) 1641–1649, https://doi.org/10.1007/s11064-018-2580-1.
[163] D. Ramanujam, A.P. Schön, C. Beck, P. Vaccarello, G. Felician, A. Dueck, D. Esfandyari, G. Meister, T. Meitinger, C. Schulz, S. Engelhardt, MicroRNA-21-Dependent macrophage-to-fibroblast signaling determines the cardiac response to pressure overload, Circulation 143 (2021) 1513–1525, https://doi.org/10.1161/circulationaha.120.050682.
[164] W. Wang, R. Liu, Y. Su, H. Li, W. Xie, B. Ning, MicroRNA-21-5p mediates TGF-β-regulated fibrogenic activation of spinal fibroblasts and the formation of fibrotic scars after spinal cord injury, Int. J. Biol. Sci. 14 (2018) 178–188, https://doi.org/10.7150/ijbs.24074.

[165] V. Neudecker, M. Haneklaus, O. Jensen, L. Khailova, J.C. Masterson, H. Tye, K. Biette, P. Jedlicka, K.S. Brodsky, M.E. Gerich, M. Mack, A.A.B. Robertson, M. A. Cooper, G.T. Furuta, C.A. Dinarello, L.A. O'Neill, H.K. Eltzschig, S.L. Masters, E.N. McNamee, Myeloid-derived miR-223 regulates intestinal inflammation via repression of the NLRP3 inflammasome, J. Exp. Med. 214 (2017) 1737–1752, https://doi.org/10.1084/jem.20160462.
[166] G. Zhao, K. Jiang, Y. Yang, T. Zhang, H. Wu, A. Shaukat, C. Qiu, G. Deng, The potential therapeutic role of miR-223 in bovine endometritis by targeting the NLRP3 inflammasome, Front. Immunol. 9 (2018) 1916, https://doi.org/10.3389/fimmu.2018.01916.
[167] T. Li, M.J. Morgan, S. Choksi, Y. Zhang, Y.S. Kim, Z.G. Liu, MicroRNAs modulate the noncanonical transcription factor NF-kappaB pathway by regulating expression of the kinase IKKalpha during macrophage differentiation, Nat. Immunol. 11 (2010) 799–805, https://doi.org/10.1038/ni.1918.
[168] G. Zhuang, C. Meng, X. Guo, P.S. Cheruku, L. Shi, H. Xu, H. Li, G. Wang, A.R. Evans, S. Safe, C. Wu, B. Zhou, A novel regulator of macrophage activation: miR-223 in obesity-associated adipose tissue inflammation, Circulation 125 (2012) 2892–2903, https://doi.org/10.1161/circulationaha.111.087817.
[169] N. Zhang, L. Fu, Y. Bu, Y. Yao, Y. Wang, Downregulated expression of miR-223 promotes Toll-like receptor-activated inflammatory responses in macrophages by targeting RhoB, Mol. Immunol. 91 (2017) 42–48, https://doi.org/10.1016/j.molimm.2017.08.026.
[170] D. Liu, Y. Huang, C. Jia, Y. Li, F. Liang, Q. Fu, Administration of antagomir-223 inhibits apoptosis, promotes angiogenesis and functional recovery in rats with spinal cord injury, Cell. Mol. Neurobiol. 35 (2015) 483–491, https://doi.org/10.1007/s10571-014-0142-x.
[171] Y. Wang, J. Jiao, P. Ren, M. Wu, Upregulation of miRNA-223-3p ameliorates RIP3-mediated necroptosis and inflammatory responses via targeting RIP3 after spinal cord injury, J. Cell. Biochem. (2019), https://doi.org/10.1002/jcb.28438.
[172] X. Wu, Y.L. Cheng, M. Matthen, A. Yoon, G.K. Schwartz, S. Bala, A.M. Taylor, F. Momen-Heravi, Down-regulation of the tumor suppressor miR-34a contributes to head and neck cancer by up-regulating the MET oncogene and modulating tumor immune evasion, J. Exp. Clin. Cancer Res. 40 (2021) 70, https://doi.org/10.1186/s13046-021-01865-2.
[173] Y. Chen, S. Cao, P. Xu, W. Han, T. Shan, J. Pan, W. Lin, X. Chen, X. Wang, Changes in the expression of miR-34a and its target genes following spinal cord injury in rats, Med Sci Mon. 22 (2016) 3981–3993, https://doi.org/10.12659/msm.900893.
[174] J. Zhou, Z. Li, T. Wu, Q. Zhao, Q. Zhao, Y. Cao, LncGBP9/miR-34a axis drives macrophages toward a phenotype conducive for spinal cord injury repair via STAT1/STAT6 and SOCS3, J. Neuroinflammation 17 (2020) 134, https://doi.org/10.1186/s12974-020-01805-5.
[175] H. Gao, D. Xiao, L. Gao, X. Li, MicroRNA-93 contributes to the suppression of lung inflammatory responses in LPS-induced acute lung injury in mice via the TLR4/MyD88/NF-κB signaling pathway, Int. J. Mol. Med. 46 (2020) 561–570, https://doi.org/10.3892/ijmm.2020.4610.
[176] Y. Ding, L. Wang, Q. Zhao, Z. Wu, L. Kong, MicroRNA-93 inhibits chondrocyte apoptosis and inflammation in osteoarthritis by targeting the TLR4/NF-κB signaling pathway, Int. J. Mol. Med. 43 (2019) 779–790, https://doi.org/10.3892/ijmm.2018.4033.
[177] Y. Xu, H. Jin, X. Yang, L. Wang, L. Su, K. Liu, Q. Gu, X. Xu, MicroRNA-93 inhibits inflammatory cytokine production in LPS-stimulated murine macrophages by targeting IRAK4, FEBS Lett. 588 (2014) 1692–1698, https://doi.org/10.1016/j.febslet.2014.03.013.
[178] V.C. Ganta, M.H. Choi, A. Kutateladze, T.E. Fox, C.R. Farber, B.H. Annex, A MicroRNA93-interferon regulatory factor-9-immunoresponsive gene-1-itaconic acid pathway modulates M2-like macrophage polarization to revascularize ischemic muscle, Circulation 135 (2017) 2403–2425, https://doi.org/10.1161/circulationaha.116.025490.
[179] X.T. Yan, L.J. Ji, Z. Wang, X. Wu, Q. Wang, S. Sun, J.M. Lu, Y. Zhang, MicroRNA-93 alleviates neuropathic pain through targeting signal transducer and activator of transcription 3, Int. Immunopharm. 46 (2017) 156–162, https://doi.org/10.1016/j.intimp.2017.01.027.
[180] Y. Cao, C. Jiang, H. Lin, Z. Chen, Silencing of long noncoding RNA growth arrest-specific 5 alleviates neuronal cell apoptosis and inflammatory responses through sponging microRNA-93 to repress PTEN expression in spinal cord injury, Front. Cell. Neurosci. 15 (2021), 646788, https://doi.org/10.3389/fncel.2021.646788.
[181] D. Li, A. Wang, X. Liu, F. Meisgen, J. Grünler, I.R. Botusan, S. Narayanan, E. Erikci, X. Li, L. Blomqvist, L. Du, A. Pivarcsi, E. Sonkoly, K. Chowdhury, S. B. Catrina, M. Ståhle, N.X. Landén, MicroRNA-132 enhances transition from inflammation to proliferation during wound healing, J. Clin. Invest. 125 (2015) 3008–3026, https://doi.org/10.1172/jci79052.
[182] M. Leinders, N. Üçeyler, R.A. Pritchard, C. Sommer, L.S. Sorkin, Increased miR-132-3p expression is associated with chronic neuropathic pain, Exp. Neurol. 283 (2016) 276–286, https://doi.org/10.1016/j.expneurol.2016.06.025.
[183] H. Fang, H.F. Li, Q. Pan, H.L. Jin, M. Yang, R.R. Wang, Q.Y. Wang, J.P. Zhang, MiR-132-3p modulates MEKK3-dependent NF-κB and p38/JNK signaling pathways to alleviate spinal cord ischemia-reperfusion injury by hindering M1 polarization of macrophages, Front. Cell Dev. Biol. 9 (2021), 570451, https://doi.org/10.3389/fcell.2021.570451.
[184] A. Fire, S. Xu, M.K. Montgomery, S.A. Kostas, S.E. Driver, C.C. Mello, Potent and specific genetic interference by double-stranded RNA in Caenorhabditis elegans, Nature 391 (1998) 806–811, https://doi.org/10.1038/35888.
[185] R.L. Setten, J.J. Rossi, S.P. Han, The current state and future directions of RNAi-based therapeutics, Nat. Rev. Drug Discov. 18 (2019) 421–446, https://doi.org/10.1038/s41573-019-0017-4.
[186] G.M. Traber, A.M. Yu, RNAi-based therapeutics and novel RNA bioengineering technologies, J. Pharmacol. Exp. Therapeut. 384 (2023) 133–154, https://doi.org/10.1124/jpet.122.001234.
[187] L.F. Gebert, M.A. Rebhan, S.E. Crivelli, R. Denzler, M. Stoffel, J. Hall, Miravirsen (SPC3649) can inhibit the biogenesis of miR-122, Nucleic Acids Res. 42 (2014) 609–621, https://doi.org/10.1093/nar/gkt852.
[188] M.H. van der Ree, J.M. de Vree, F. Stelma, S. Willemse, M. van der Valk, S. Rietdijk, R. Molenkamp, J. Schinkel, A.C. van Nuenen, U. Beuers, S. Hadi, M. Harbers, E. van der Veer, K. Liu, J. Grundy, A.K. Patick, A. Pavlicek, J. Blem, M. Huang, P. Grint, S. Neben, N.W. Gibson, N.A. Kootstra, H.W. Reesink, Safety, tolerability, and antiviral effect of RG-101 in patients with chronic hepatitis C: a phase 1B, double-blind, randomised controlled trial, Lancet (London, England) 389 (2017) 709–717, https://doi.org/10.1016/s0140-6736(16)31715-9.
[189] S. Zhang, Z. Cheng, Y. Wang, T. Han, The risks of miRNA therapeutics: in a drug target perspective, Drug Des. Dev. Ther. 15 (2021) 721–733, https://doi.org/10.2147/dddt.S288859.
[190] D.S. Hong, Y.K. Kang, M. Borad, J. Sachdev, S. Ejadi, H.Y. Lim, A.J. Brenner, K. Park, J.L. Lee, T.Y. Kim, S. Shin, C.R. Becerra, G. Falchook, J. Stoudemire, D. Martin, K. Kelnar, H. Peltier, V. Bonato, A.G. Bader, S. Smith, S. Kim, V. O'Neill, M.S. Beg, Phase 1 study of MRX34, a liposomal miR-34a mimic, in patients with advanced solid tumours, Br. J. Cancer 122 (2020) 1630–1637, https://doi.org/10.1038/s41416-020-0802-1.
[191] S.S. Kim, H. Garg, A. Joshi, N. Manjunath, Strategies for targeted nonviral delivery of siRNAs in vivo, Trends Mol. Med. 15 (2009) 491–500, https://doi.org/10.1016/j.molmed.2009.09.001.
[192] B.A. Kraynack, B.F. Baker, Small interfering RNAs containing full 2'-O-methylribonucleotide-modified sense strands display Argonaute2/eIF2C2-dependent activity, RNA 12 (2006) 163–176, https://doi.org/10.1261/rna.2150806.
[193] M. Manoharan, A. Akinc, R.K. Pandey, J. Qin, P. Hadwiger, M. John, K. Mills, K. Charisse, M.A. Maier, L. Nechev, E.M. Greene, P.S. Pallan, E. Rozners, K. G. Rajeev, M. Egli, Unique gene-silencing and structural properties of 2'-fluoro-modified siRNAs, Angew Chem. Int. Ed. Engl. 50 (2011) 2284–2288, https://doi.org/10.1002/anie.201006519.
[194] M. Takahashi, C. Nagai, H. Hatakeyama, N. Minakawa, H. Harashima, A. Matsuda, Intracellular stability of 2'-OMe-4'-thioribonucleoside modified siRNA leads to long-term RNAi effect, Nucleic Acids Res. 40 (2012) 5787–5793, https://doi.org/10.1093/nar/gks204.
[195] X. Yang, M. Sierant, M. Janicka, L. Peczek, C. Martinez, T. Hassell, N. Li, X. Li, T. Wang, B. Nawrot, Gene silencing activity of siRNA molecules containing phosphorodithioate substitutions, ACS Chem. Biol. 7 (2012) 1214–1220, https://doi.org/10.1021/cb300078e.
[196] H. Jahns, M. Roos, J. Imig, F. Baumann, Y. Wang, R. Gilmour, J. Hall, Stereochemical bias introduced during RNA synthesis modulates the activity of phosphorothioate siRNAs, Nat. Commun. 6 (2015) 6317, https://doi.org/10.1038/ncomms7317.
[197] A.H. Hall, J. Wan, A. Spesock, Z. Sergueeva, B.R. Shaw, K.A. Alexander, High potency silencing by single-stranded boranophosphate siRNA, Nucleic Acids Res. 34 (2006) 2773–2781, https://doi.org/10.1093/nar/gkl339.
[198] L.Y. Jin, J. Li, K.F. Wang, W.W. Xia, Z.Q. Zhu, C.R. Wang, X.F. Li, H.Y. Liu, Blood-spinal cord barrier in spinal cord injury: a review, J. Neurotrauma 38 (2021) 1203–1224, https://doi.org/10.1089/neu.2020.7413.

[199] M. Fei, Z. Li, Y. Cao, C. Jiang, H. Lin, Z. Chen, MicroRNA-182 improves spinal cord injury in mice by modulating apoptosis and the inflammatory response via IKKβ/NF-κB, Lab. Invest. 101 (2021) 1238–1253, https://doi.org/10.1038/s41374-021-00606-5.

[200] Y. Zhang, T. Meng, J. Chen, Y. Zhang, J. Kang, X. Li, G. Yu, L. Tian, Z. Jin, H. Dong, X. Zhang, B. Ning, miR-21a-5p promotes inflammation following traumatic spinal cord injury through upregulation of neurotoxic reactive astrocyte (A1) polarization by inhibiting the CNTF/STAT3/Nkrf pathway, Int. J. Biol. Sci. 17 (2021) 2795–2810, https://doi.org/10.7150/ijbs.60509.

[201] M. Zhang, L. Wang, S. Huang, X. He, MicroRNA-223 targets NLRP3 to relieve inflammation and alleviate spinal cord injury, Life Sci. 254 (2020), 117796, https://doi.org/10.1016/j.lfs.2020.117796.

[202] G. Wan, Y. An, J. Tao, Y. Wang, Q. Zhou, R. Yang, Q. Liang, MicroRNA-129-5p alleviates spinal cord injury in mice via suppressing the apoptosis and inflammatory response through HMGB1/TLR4/NF-κB pathway, Biosci. Rep. 40 (2020), https://doi.org/10.1042/bsr20193315.

[203] P. Wang, Y. Zhang, Y. Xia, D. Xu, H. Wang, D. Liu, S. Xu, Y. Sun, MicroRNA-139-5p promotes functional recovery and reduces pain hypersensitivity in mice with spinal cord injury by targeting mammalian sterile 20-like kinase 1, Neurochem. Res. 46 (2021) 349–357, https://doi.org/10.1007/s11064-020-03170-4.

[204] J. Shen, F. Gao, L. Zhao, Q. Hao, Y.L. Yang, MicroRNA-34c promotes neuronal recovery in rats with spinal cord injury through the C-X-C motif ligand 14/Janus kinase 2/signal transducer and activator of transcription-3 axis, Chin. Med. J. (Engl). 133 (2020) 2177–2185, https://doi.org/10.1097/cm9.0000000000001022.

[205] K. Liu, L. Yan, X. Jiang, Y. Yu, H. Liu, T. Gu, E. Shi, Acquired inhibition of microRNA-124 protects against spinal cord ischemia-reperfusion injury partially through a mitophagy-dependent pathway, J. Thorac. Cardiovasc. Surg. 154 (2017) 1498–1508, https://doi.org/10.1016/j.jtcvs.2017.05.046.

[206] J. Feng, Y. Zhang, Z. Zhu, C. Gu, A. Waqas, L. Chen, Emerging exosomes and exosomal MiRNAs in spinal cord injury, Front. Cell Dev. Biol. 9 (2021), 703989, https://doi.org/10.3389/fcell.2021.703989.

[207] X. Lai, Y. Wang, X. Wang, B. Liu, L. Rong, miR-146a-5p-modified hUCMSC-derived exosomes facilitate spinal cord function recovery by targeting neurotoxic astrocytes, Stem Cell Res. Ther. 13 (2022) 487, https://doi.org/10.1186/s13287-022-03116-3.

[208] Y. Sheng, X. Zhou, J. Wang, H. Shen, S. Wu, W. Guo, Y. Yang, MSC derived EV loaded with miRNA-22 inhibits the inflammatory response and nerve function recovery after spinal cord injury in rats, J. Cell Mol. Med. 25 (2021) 10268–10278, https://doi.org/10.1111/jcmm.16965.

[209] A.L. Jackson, P.S. Linsley, Recognizing and avoiding siRNA off-target effects for target identification and therapeutic application, Nat. Rev. Drug Discov. 9 (2010) 57–67, https://doi.org/10.1038/nrd3010.

[210] C.J. Echeverri, P.A. Beachy, B. Baum, M. Boutros, F. Buchholz, S.K. Chanda, J. Downward, J. Ellenberg, A.G. Fraser, N. Hacohen, W.C. Hahn, A.L. Jackson, A. Kiger, P.S. Linsley, L. Lum, Y. Ma, B. Mathey-Prévôt, D.E. Root, D.M. Sabatini, J. Taipale, N. Perrimon, R. Bernards, Minimizing the risk of reporting false positives in large-scale RNAi screens, Nat. Methods 3 (2006) 777–779, https://doi.org/10.1038/nmeth1006-777.

[211] N. Daga, S. Eicher, A. Kannan, A. Casanova, S.H. Low, S. Kreibich, D. Andritschke, M. Emmenlauer, J.L. Jenkins, W.D. Hardt, U.F. Greber, C. Dehio, C. von Mering, Growth-restricting effects of siRNA transfections: a largely deterministic combination of off-target binding and hybridization-independent competition, Nucleic Acids Res. 46 (2018) 9309–9320, https://doi.org/10.1093/nar/gky798.

[212] Y. Fedorov, E.M. Anderson, A. Birmingham, A. Reynolds, J. Karpilow, K. Robinson, D. Leake, W.S. Marshall, A. Khvorova, Off-target effects by siRNA can induce toxic phenotype, RNA 12 (2006) 1188–1196, https://doi.org/10.1261/rna.28106.

[213] M.M. Janas, M.K. Schlegel, C.E. Harbison, V.O. Yilmaz, Y. Jiang, R. Parmar, I. Zlatev, A. Castoreno, H. Xu, S. Shulga-Morskaya, K.G. Rajeev, M. Manoharan, N. D. Keirstead, M.A. Maier, V. Jadhav, Selection of GalNAc-conjugated siRNAs with limited off-target-driven rat hepatotoxicity, Nat. Commun. 9 (2018) 723, https://doi.org/10.1038/s41467-018-02989-4.

[214] S.P. Persengiev, X. Zhu, M.R. Green, Nonspecific, concentration-dependent stimulation and repression of mammalian gene expression by small interfering RNAs (siRNAs), RNA 10 (2004) 12–18, https://doi.org/10.1261/rna5160904.

[215] M. Hannus, M. Beitzinger, J.C. Engelmann, M.T. Weickert, R. Spang, S. Hannus, G. Meister, siPools: Highly complex but accurately defined siRNA pools eliminate off-target effects, Nucleic Acids Res. 42 (2014) 8049–8061, https://doi.org/10.1093/nar/gku480.

[216] K. Ui-Tei, Y. Naito, K. Nishi, A. Juni, K. Saigo, Thermodynamic stability and Watson-Crick base pairing in the seed duplex are major determinants of the efficiency of the siRNA-based off-target effect, Nucleic Acids Res. 36 (2008) 7100–7109, https://doi.org/10.1093/nar/gkn902.

[217] A.L. Jackson, J. Burchard, D. Leake, A. Reynolds, J. Schelter, J. Guo, J.M. Johnson, L. Lim, J. Karpilow, K. Nichols, W. Marshall, A. Khvorova, P.S. Linsley, Position-specific chemical modification of siRNAs reduces "off-target" transcript silencing, RNA 12 (2006) 1197–1205, https://doi.org/10.1261/rna.30706.

[218] J. Elmén, H. Thonberg, K. Ljungberg, M. Frieden, M. Westergaard, Y. Xu, B. Wahren, Z. Liang, H. Ørum, T. Koch, C. Wahlestedt, Locked nucleic acid (LNA) mediated improvements in siRNA stability and functionality, Nucleic Acids Res. 33 (2005) 439–447, https://doi.org/10.1093/nar/gki193.

[219] C.H. Lai, R.Y. Chen, H.P. Hsieh, S.J. Tsai, K.C. Chang, C.J. Yen, Y.C. Huang, Y.W. Liu, J.C. Lee, Y.C. Lai, L.Y. Hung, B.W. Lin, A selective Aurora-A 5'-UTR siRNA inhibits tumor growth and metastasis, Cancer Lett. 472 (2020) 97–107, https://doi.org/10.1016/j.canlet.2019.12.031.

[220] J. Burchard, A.L. Jackson, V. Malkov, R.H. Needham, Y. Tan, S.R. Bartz, H. Dai, A.B. Sachs, P.S. Linsley, MicroRNA-like off-target transcript regulation by siRNAs is species specific, RNA 15 (2009) 308–315, https://doi.org/10.1261/rna.1326809.

[221] W.C. Chen, W.F. Liu, Y.Y. Bai, Y.Y. Zhou, Y. Zhang, C.M. Wang, S. Lin, H.F. He, Transplantation of mesenchymal stem cells for spinal cord injury: a systematic review and network meta-analysis, J. Transl. Med. 19 (2021) 178, https://doi.org/10.1186/s12967-021-02843-0.

[222] A. Trounson, C. McDonald, Stem cell therapies in clinical trials: progress and challenges, Cell Stem Cell 17 (2015) 11–22, https://doi.org/10.1016/j.stem.2015.06.007.

[223] G.U. Kim, S.E. Sung, K.K. Kang, J.H. Choi, S. Lee, M. Sung, S.Y. Yang, S.K. Kim, Y.I. Kim, J.H. Lim, M.S. Seo, G.W. Lee, Therapeutic potential of mesenchymal stem cells (MSCs) and MSC-derived extracellular vesicles for the treatment of spinal cord injury, Int. J. Mol. Sci. 22 (2021), https://doi.org/10.3390/ijms222413672.

[224] K.L. Lankford, E.J. Arroyo, K. Nazimek, K. Bryniarski, P.W. Askenase, J.D. Kocsis, Intravenously delivered mesenchymal stem cell-derived exosomes target M2-type macrophages in the injured spinal cord, PLoS One 13 (2018), e0190358, https://doi.org/10.1371/journal.pone.0190358.

[225] M. Nakazaki, T. Morita, K.L. Lankford, P.W. Askenase, J.D. Kocsis, Small extracellular vesicles released by infused mesenchymal stromal cells target M2 macrophages and promote TGF-β upregulation, microvascular stabilization and functional recovery in a rodent model of severe spinal cord injury, J. Extracell. Vesicles 10 (2021), e12137, https://doi.org/10.1002/jev2.12137.

[226] R. Li, K. Zhao, Q. Ruan, C. Meng, F. Yin, Bone marrow mesenchymal stem cell-derived exosomal microRNA-124-3p attenuates neurological damage in spinal cord ischemia-reperfusion injury by downregulating Ern1 and promoting M2 macrophage polarization, Arthritis Res. Ther. 22 (2020) 75, https://doi.org/10.1186/s13075-020-2146-x.

[227] X. Zhai, K. Chen, H. Yang, B. Li, T. Zhou, H. Wang, H. Zhou, S. Chen, X. Zhou, X. Wei, Y. Bai, M. Li, Extracellular vesicles derived from CD73 modified human umbilical cord mesenchymal stem cells ameliorate inflammation after spinal cord injury, J. Nanobiotechnol. 19 (2021) 274, https://doi.org/10.1186/s12951-021-01022-z.

[228] K. Shen, Y. Jia, X. Wang, J. Zhang, K. Liu, J. Wang, W. Cai, J. Li, S. Li, M. Zhao, Y. Wang, D. Hu, Exosomes from adipose-derived stem cells alleviate the inflammation and oxidative stress via regulating Nrf2/HO-1 axis in macrophages, Free Radic. Biol. Med. 165 (2021) 54–66, https://doi.org/10.1016/j.freeradbiomed.2021.01.023.

[229] L. Ji, L. Bao, Z. Gu, Q. Zhou, Y. Liang, Y. Zheng, Y. Xu, X. Zhang, X. Feng, Comparison of immunomodulatory properties of exosomes derived from bone marrow mesenchymal stem cells and dental pulp stem cells, Immunol. Res. 67 (2019) 432–442, https://doi.org/10.1007/s12026-019-09088-6.

[230] C. Liu, F. Hu, G. Jiao, Y. Guo, P. Zhou, Y. Zhang, Z. Zhang, J. Yi, Y. You, Z. Li, H. Wang, X. Zhang, Dental pulp stem cell-derived exosomes suppress M1 macrophage polarization through the ROS-MAPK-NFκB P65 signaling pathway after spinal cord injury, J. Nanobiotechnol. 20 (2022) 65, https://doi.org/10.1186/s12951-022-01273-4.

[231] C. Wang, Q. Wang, Y. Lou, J. Xu, Z. Feng, Y. Chen, Q. Tang, G. Zheng, Z. Zhang, Y. Wu, N. Tian, Y. Zhou, H. Xu, X. Zhang, Salidroside attenuates neuroinflammation and improves functional recovery after spinal cord injury through microglia polarization regulation, J. Cell Mol. Med. 22 (2018) 1148–1166, https://doi.org/10.1111/jcmm.13368.

[232] Z.S. Gao, C.J. Zhang, N. Xia, H. Tian, D.Y. Li, J.Q. Lin, X.F. Mei, C. Wu, Berberine-loaded M2 macrophage-derived exosomes for spinal cord injury therapy, Acta Biomater. 126 (2021) 211–223, https://doi.org/10.1016/j.actbio.2021.03.018.
[233] S.J. Kim, W.K. Ko, M.J. Jo, Y. Arai, H. Choi, H. Kumar, I.B. Han, S. Sohn, Anti-inflammatory effect of Tauroursodeoxycholic acid in RAW 264.7 macrophages, Bone marrow-derived macrophages, BV2 microglial cells, and spinal cord injury, Sci. Rep. 8 (2018) 3176, https://doi.org/10.1038/s41598-018-21621-5.
[234] Y. Zhang, W.X. Zhang, Y.J. Zhang, Y.D. Liu, Z.J. Liu, Q.C. Wu, Y. Guan, X.M. Chen, Melatonin for the treatment of spinal cord injury, Neural. Regen. Res. 13 (2018) 1685–1692, https://doi.org/10.4103/1673-5374.238603.
[235] Y. Zhang, Z. Liu, W. Zhang, Q. Wu, Y. Zhang, Y. Liu, Y. Guan, X. Chen, Melatonin improves functional recovery in female rats after acute spinal cord injury by modulating polarization of spinal microglial/macrophages, J. Neurosci. Res. 97 (2019) 733–743, https://doi.org/10.1002/jnr.24409.
[236] B.S. Murphy, V. Sundareshan, T.J. Cory, D. Hayes Jr., M.I. Anstead, D.J. Feola, Azithromycin alters macrophage phenotype, J. Antimicrob. Chemother. 61 (2008) 554–560, https://doi.org/10.1093/jac/dkn007.
[237] J.C. Gensel, T.J. Kopper, B. Zhang, M.B. Orr, W.M. Bailey, Predictive screening of M1 and M2 macrophages reveals the immunomodulatory effectiveness of post spinal cord injury azithromycin treatment, Sci. Rep. 7 (2017), 40144, https://doi.org/10.1038/srep40144.
[238] B. Zhang, W.M. Bailey, T.J. Kopper, M.B. Orr, D.J. Feola, J.C. Gensel, Azithromycin drives alternative macrophage activation and improves recovery and tissue sparing in contusion spinal cord injury, J. Neuroinflammation 12 (2015) 218, https://doi.org/10.1186/s12974-015-0440-3.
[239] M. Aceves, M.N. Terminel, A. Okoreeh, A.R. Aceves, Y.M. Gong, A. Polanco, F. Sohrabji, M.A. Hook, Morphine increases macrophages at the lesion site following spinal cord injury: protective effects of minocycline, Brain Behav. Immun. 79 (2019) 125–138, https://doi.org/10.1016/j.bbi.2019.01.023.
[240] J. Rau, L. Weise, R. Moore, M. Terminel, K. Brakel, R. Cunningham, J. Bryan, A. Stefanov, M.A. Hook, Intrathecal minocycline does not block the adverse effects of repeated, intravenous morphine administration on recovery of function after, Sci. Exp Neurol. 359 (2023), 114255, https://doi.org/10.1016/j.expneurol.2022.114255.