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Biomarkers in Spinal Cord Injury: from Prognosis to Treatment

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Abstract
Spinal cord injury (SCI) is considered an incurable condition, having a heterogenous recovery and uncertain prognosis. Therefore, a reliable prediction of the improvement in the acute phase could benefit patients. Physicians are unanimous in insisting that at the initial damage of the spinal cord (SC), the patient should be carefully evaluated in order to help selecting an appropriate neuroprotective treatment. However, currently, neurologic impairment after SCI is measured and classified by functional examination. The identification of prognostic biomarkers of SCI would help to designate SC injured patients and correlate to diagnosis and correct treatment. Some proteins have already been identified as good potential biomarkers of central nervous system injury, both in cerebrospinal fluid (CSF) and blood serum. However, the problem for using them as biomarkers is the way they should be collected, as acquiring CSF through a lumbar puncture is significantly invasive. Remarkably, microRNAs (miRNAs) have emerged as interesting biomarker candidates because of their stability in biological fluids and their tissue specificity. Several miRNAs have been identified to have their expressions altered in SCI in many animal models, making them promising candidates as biomarkers after SCI. Moreover, there are yet no effective therapies for SCI. It is already known that altered lysophospholipids (LPs) signaling are involved in the biology of disorders, such as inflammation. Reports have demonstrated that LPs when locally distributed can regulate SCI repair and key secondary injury processes such as apoptosis and inflammation, and so could become in the future new therapeutic approaches for treating SCI.

Keywords Spinal cord injury · Biomarkers · MicroRNAs · Bioactive lipids · Sphingosine-1-phosphate

Introduction

Spinal cord injury (SCI) is considered a cureless condition despite enormous advances in medical and surgical treatments, having devastating physical, psychosocial, and vocational implications for patients and caregivers. Some reports have demonstrated that the incidence of SCI in most countries ranges from 30 to 70 new cases per one million inhabitants per year [1]. Portugal reported an annual incidence rate of 57.8 new cases per million inhabitants between 1989 and 1992, including the pre-hospital phase [2]. In contrast with Portugal and most other countries, Brazil reported 942 new cases/month, meaning 71 new cases per million inhabitants/year [1].

SCI is characterized by a distinct pathophysiological reaction that can be divided into two mechanisms and three phases. It is particularly devastating because of the restricted capacity of the central nervous system (CNS) to fix itself and restore lost cells and fiber tract after injury [3, 4]. The two mechanisms involved after acute SCI are already well characterized and are known as primary mechanical injury and secondary injury. These injuries were induced by several biological processes and include extensive temporal changes in gene expression [3, 5]. According to the patho-mechanism and the postinjury time, the secondary injury process can be split into three characterized phases: acute, subacute (or intermediate), and chronic phase [3, 4, 6].

At the starting moment of the injury, the acute phase is considered to last until the first 48 h after the initial physical insult, which is when numerous pathophysiological processes begin [3], and inflammatory response to injury start. In the acute phase, the major events are caused by ischemia, vascular

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disruption, and hemorrhage, which may be the consequence of the acting inflammatory growth factors. The spinal shock state is induced by the neural tissue that is affected by the inflammatory process [4]. Due to the microcirculation disruption, neurons and glial cells are affected, which induces pathologic changes such as an inflammatory response, ionic deregulation, excessive production of free radicals, and excitotoxicity [7, 8]. The damage to neurons, glial cells, and oligodendrocytes is caused by a unique pathological process that occurs in the CNS and is due the presence of high amounts excitatory neurotransmitters (glutamate, aspartate) [9]. Besides that, another mechanism occurs, which that results in functional neuronal loss or the active and/or passive neurons and glial cell death. At all stages of injury, neurons die due to necrosis; however, apoptotic mechanisms are also related to oligodendrocytes, astrocytes, and neurons' cellular death [10]. When oligodendrocytes are lost, the result is axonal demyelination, which is important for pathological changes associated with clinical impairments [11].

Interestingly, several reports have described that at the end of first 48 h, growth associated molecules start to be delivered, such as extracellular matrix elements, and growth factors, showing an effort of the injured spinal cord to reestablish the neural connections. This has already been described in upregulation of growth factors, such as platelet-derive growth factor (PDGF), inducible nerve growth factor (VGF), brain-derived neurotrophic factor (BDNF), fibroblast-growth-factor (FGF) receptor 1, bone-morphogenetic proteins (BMPs), insulin-like growth factor-I and II (IGF-I and IGF-II), and the neurotrophin NT-3 [12, 13]. Some proteins possibly involved in neuritogenesis were also upregulated, such as dynamin, attractin, and the adhesion molecules (F3 and vascular cell adhesion molecule (VCAM)) [14]. Besides that, nestin and vimentin are also upregulated, probably reflecting the proliferation of neural precursor cells and developing astrocytes, respectively [15], and signaling that regeneration could be on course.

Additionally, during the acute phase, the disturbance of the endothelial cells and the astrocytes become reactive causing the loss of their function due to various inflammatory cytokines, such as tumor necrosis factor (TNF)-α and interleukins (IL-1α, IL-6, and IL-1β), promoting alterations in the blood-spinal cord barrier (BSCB) permeability [16]. Studies in rats have demonstrated that tissue levels of these cytokines peak at 6 to 12 h after injury and remain increased up to 4 days after damage [17]. The major occurring inflammatory reaction are caused by the intrinsic microglia, T cells, astrocytes, macrophages, and neutrophils that infiltrate the injury site as a result of disruption of the BSCB [18]. The disruption of the BSCB causes loss of microenvironment homeostasis and results in intracellular hypercalcemia, which activates calcium-dependent proteases and causes mitochondrial dysfunction that induces mainly oligodendrocyte apoptotic cell death [19].

It is already well established that during all phases of the SCI, some proteins are upregulated and others downregulated at the lesion, making them virtually a possible biomarker of a specific phase. In the first 4 h after the injury, it was observed a high upregulation of genes related to cell death and inflammation that was accompanied with a downregulation of genes that are implicated in neurotransmission and cell excitability [3]. The upregulation of these genes induces the expression of cyclooxygenase 2 (COX2) and from the pro-inflammatory cytokines IL-1β and IL-6 and interleukin receptors (IL-2Rα and IL-4R) [14, 20] that start the inflammatory response at the injury. It was also observed that there was upregulation of some transcription factors such as c-jun, nuclear factor kappa B (NF-kB), and suppressor of cytokine signaling 3 (SOCS-3) that are involved in cell death and damage [20, 21], and from Janus-activated kinase (JAK), and activation and signal transducer of transcription (STAT) family (STAT3 and JAK1), usually involved in repair and regeneration [22, 23]. Studies have demonstrated that in early phases, there is a downregulation of transporters and ion channels involved in cell excitability, such as various ion channels (e.g., K^+, Ca^{2+}, and Na^+ channels), receptors and transporters (e.g., GABA and glutamate transporters) [14, 20] that impair the synaptic transmission.

Several reports have demonstrated that the upregulation and downregulation of some proteins of the acute phase goes on. Those proteins are more enhanced in the following days (72 h), such as IL-1β and COX2 that continue to be upregulated, while the ion channels and neurotransmitter receptors are down-regulated [3]. After the first 12 h of the SCI, the loss of some cytoskeletal proteins such as tau, neurofilament light chain protein (NFL) and heavy neurofilaments (NFH), and microtubule-associated protein 2 (MAP-2) is observed. Furthermore, it is also observed that the expression of myelin-oligodendrocyte glycoprotein (MOG), Nogo-A, and chondroitin sulfate proteoglycans are decreased, indicating impairment of myelin synthesis and probably demyelination, limiting the regenerative attempts [12, 20, 24].

The acute phase is followed by a subacute phase, which is considered to last until 2 weeks following damage and intensify the injury caused by the primary shock. This phase has two main characteristics: the phagocytic response and reactive proliferation of the astrocytes that form the astrocytic glial scar. The phagocytic inflammatory cells usually release reactive oxygen species, which causes DNA oxidative damage, protein oxidation, and lipid peroxidation, which further induces necrosis and apoptosis [25]. The astrocytic glial scar is formed by reactive astrocytes that are proliferating and have processes that are firmly fused, making an inhibitory mesh-like cluster that has an important role acting as a barrier for axonal regeneration, and therefore being considered the major source for the restricted regeneration after a CNS damage [25, 26]. So, the primary self-defense mechanism after SCI is the reactive astrogliosis, when neighboring astrocytes to the injury site suffer morphological hypertrophy, proliferate, and upregulate the expression of glial fibrillary acidic protein

(GFAP), nestin, and vimentin [27–29]. On the other hand, this uncontrolled proliferation of the reactive astrocytes can also have a beneficial role, as it suppresses the formation of aberrant synapses at the injured site and contributes to the rebuilding of the microenvironment homeostasis and re-establishment of the integrity of the BSCB [6, 26]. This process is important for elimination of edema, and it restricts the infiltration of immune cells, helping to diminish the spread of injury [30–32]. Interestingly, it has also been described that astrocytes are additionally responsible for the secretion of a range of cytokines and growth factors such as fibroblast growth factor (FGF)-β, transforming growth factor (TGF)-β, vascular endothelial growth factor (VEGF), and glial cell-derived neurotrophic factor (GDNF), that can, at later stages, promotes oligodendrocyte precursor cell migration, proliferation, and differentiation [6].

There are still some controversies about the characterization of the chronic phase. However, it is commonly accepted that this phase extends from days to years after the shock. At this phase, the cell continues to die from apoptosis, receptor functions, and channel are compromised, and demyelination and scarring accompanies Wallerian degeneration. So, these processes helps to instruct the deficits [33] and are indicators that the lesion has matured. Some studies are focusing on improving regeneration of the injured axons and remyelination employing diverse pharmacological therapies, like methylprednisolone or cell transplantation at this chronic stage, however, none with success [6].

Remarkably, patients with SCI appear to recover differently after an injury, even when they develop similar lesions. As the result of this life-changing condition, recovery occurs with extensive heterogeneity [34, 35]. Actually, the ongoing clinical measures to evaluate patients with acute SCI consist of International Standards for Neurological Classification of Spinal Cord Injury (ISNCSCI) scoring system, the American Spinal Injuries Association (ASIA), and magnetic resonance imaging (MRI) [36]. Conventional MRI is presently the best imaging approach for evaluating SCI during the acute phase [37]. It was already demonstrated that early MRI is important for the evaluation of the patient with SCI without computed tomography evidence of trauma, being a powerful predictor of the lesion length which is important to evaluate the patient prognostic score [38].

On the other hand, conventional MRI could not address satisfactorily the axonal changes that occur in the white matter, being restricted to evaluating macroscopic changes. These changes, such as hemorrhage in the parenchyma, transection, and extended lesion length, could be correlated with poor prognosis, being the findings on clinical neurological examination of the most predictive of outcomes [39]. Therefore, MRI has a restricted success as a prognostic tool, as it is not accurate to evaluate the where the injury is, the degree, and how much white matter is save [39].

Nowadays, the gold standard for the evaluation of a patient in the first 72 h postinjury is combining results of MRI and ASIA examinations which could give better prognosis of recovery of motor scores. However, the initial ISNCSCI evaluation (within 72 h post trauma) can be delayed, due to problems associated with the initial trauma, such as shock, other attendant injuries, drugs, and lack of SCI expertise at the treating hospital [36, 37, 40]. So, sometimes even this evaluation could be unreliable and challenging.

Although all the surgical, medical, and rehabilitative care enhancement have increased the quality of life and extended the lifetime of patients with acute and chronic SCI, much remains to be done to improve the restorative function for individuals with SCI [40]. It is important to note that this improvement of lifespan is crucial for both patients and physicians, to know whether the patient with acute SCI will regain the ability to walk, regardless of neurological conditions, and expect bladder or bowel function improvement. However, it still remains a key concern, since there is still no precise way to predict the outcome [36].

Prevention is the only measure we can take to prevent the primary mechanical damage to the spinal cord [41]. As most of the SCIs are anatomically incomplete, it is known that secondary parenchymal injury helps significantly to the final degree of neural damage, and in this way the extent of the long-term impairment [9]. Remarkably, to attenuate or halt this secondary damage, some neuroprotective intervention candidates have been developed [42]. The quicker and more accurate the diagnoses of the patients, the better the outcome, as patients could be more efficiently recruited to the appropriated clinical trial powered to assess efficacy. Presently, the only way to assess the neurological condition of individuals is by ISNCSCI grading and imaging modalities, for both routine clinical care and clinical trials [36].

Discussion

Proteins: the First Biomarkers Discovered

Although many studies are being conducted on SCI, mainly in rat models, it has not been established yet a corrective approach to a possible clinical application for SCI. SCI is still a severe clinical problem, as standard treatments are presently restricted. However, researches and physicians unanimous agree that the sooner the patients are treated and the extent of the lesion is defined, the better it is. There are already several recent basic research studies and ongoing clinical trials regarding novel therapies for SCI and some studies using cell implantations and various growth factors as treatment [43–45], but none with success.

Nowadays, it is still very difficult to assess damage severity, prognosis, and therapeutic outcomes, as typical neurological

exams are used during evaluation. The variable secondary injury-related symptoms and the recovery variability usually make it difficult to define the severity of SCI based only on the neurological exams [46]. At this moment, unfortunately no laboratory test specific for the diagnosis of SCI is available or drugs for the treatment. In order to make it possible to define the extent of the SCI as soon as possible, it becomes more and more urgent to discover and use biomarkers specific for SCI. This could guide the researchers and physicians to the discovery of new target interventions that can be used to prevent or reduce inability as a result of a SCI.

As defined by Laterza and coworkers in 2009, "An ideal biomarker of tissue injury should be abundant, be preferentially (or exclusively) produced in the tissue of interest, and be typically present at low concentrations in the blood and other body fluids. Upon tissue injury, such biomarkers should be released into the systemic circulation or other body fluids, where they can be detected in a blood-based assay or assay of another accessible body fluid" [47]. Some proteins have already been identified as good potential biomarkers of CNS injury both serum and cerebrospinal fluid (CSF) and in human and animal SCI studies (see Table 1) [46]. These proteins are from astrocytes, neurons, or microglial cells from the injured tissue. Potential protein biomarkers that come from astrocytes are GFAP and calcium-binding protein S100-beta (S100β), both have their levels significantly higher in serum and CSF in SCI patients [48, 59]. When the neuronal damage occurs, it can be detected by modifications of αII-spectrin breakdown products (SBDPs), neurofilament proteins, SBDP150 and UCH-L1, neurofilament light chain (NF-L), phosphorylated form of neurofilament heavy chain (pNF-H), and tau in biofluids (CSF and serum) [49, 50, 60]. The levels of some cytokines are increased in the blood that are related to neuroinflammation, such as IL-6, IL1β, IL12, interferon gamma (IFNγ), and TNFα [61]. However, the problem with using proteins as biomarkers for SCI is that sometimes they should be collected from the CSF in order to define the severity of the injury, and acquiring CSF through a lumbar puncture is significantly invasive [51]. So, the need to define a biomarker that could be detected in the blood or another accessible body fluid would be desirable.

MicroRNA as Biomarkers: the Future?

Emerging studies are pointing at microRNA as a very good candidate to be this biomarker in the blood because they are very stable in fluids, are tissue specific, and have phylogenetic relationship [47]. MiRNAs are endogenously derived, short (usually 18–22 nucleotides in length) that regulate negatively the RNA expression of protein translation by binding the 3′-UTR of their target mRNAs, inducing the mRNA degradation or its translational repression [62]. MiRNAs are present in all systems including the CNS and have tissue-specific or developmental stage-specific expression patterns [63, 64]. There are already some reports using miRNA as biomarkers in some pathologies, such as Alzheimer, ectopic pregnancy, low-grade gliomas, pancreatic adenocarcinomas, ovarian cancer, breast cancers, and many others [65–69]. Therefore, they have attracted huge attention because of their pivotal role in human disease, and have been suggested as promising new therapeutic targets.

One of the first reports concerning the study and identification of miRNAs in SCI was published by Nakanishi and coworkers, in 2010. The study showed for the first time, using the methodology of a miRNA-based array screening from the injured tissue, that the expressions of miR-223 were increased at 12 h and 3 days after SCI, while miR-124a expression was considerably downregulated at 1 through 7 days after SCI [70]. Besides that, they also demonstrated that there was an increase in miR-1, miR-133a, miR-133b, and miR-451 expressions and a decrease in miR-129-3p, miR-342, miR-495, and miR-541 expressions [70]. This work demonstrated for the first time that there is in a mouse model of SCI a time-dependent expression pattern of miR-223 and miR-124a, which may be related to inflammatory responses and cell death, respectively [70].

After this pioneer work, a lot of other works emerged concerning the expression of the miRNAs during the first days after the SCI. The first works were conducted in mouse and rat models and analyzed the expression of miRNAs at the injured tissue. Also, in 2010, Liu and coworkers demonstrated that miR Let-7a, miR-21, miR-15b, and miR-16 are modulated and these changes were correlated with variations in expression of their proapoptotic and antiapoptotic target genes [71]. Two years later, in 2012, the same group demonstrated that variations in miR-21 and miR-199-3p expression are correlated with decreased levels of phosphatase and tensin homolog (PTEN) mRNA and increased levels of mechanistic target of rapamycin (mTOR) mRNA. These two proteins are thought-out to play a crucial role in the regeneration and plasticity and of injured spinal cord [72]. Also in 2012, Yunta and coworkers described the effects of moderate SCI the expression of microRNA 1, 3, and 7 days after the injury at the place of the insult. Interestingly, this pattern changes consists of few microRNAs being upregulated and most being downregulated [4]. In the animals that where operated, the miR-223, miR-21, miR-219-5p, and miR-146a were the ones that were overexpressed, while miR-107 and miR-29c were significantly repressed at 3 days postoperation [4]. What they observed was that there were variations in approximately 20 microRNA expression at 3 and 7 days after SCI. These changes, which are modulating cell death through different pathways, may be stimulated by the apoptosis due to the upregulation of the proapoptotic miR-15b microRNA as well as the downregulation of up to seven protective microRNAs at 3 days after the insult [4].

Table 1 Some protein biomarkers used in traumatic human SCI [48–58]

Biomarker	Sample	Time of sampling (postinjury)	Regulation	Reference
GFAP	Serum/CSF	1–21 days	[↑]	[48, 50–54]
pNF-H	Serum/CSF	48 h	[↑]	[53, 55]
NF-L	Serum/CSF	1–21 days	[↑]	[49, 52, 54]
NSE	Serum	72 h	[↑]	[53, 54, 56]
IL1-β	Serum	2 and 12 weeks postinjury	[↓]	[57]
TNF-α	Serum	22 (2–52 weeks postinjury)	[↑]	[57, 58]
IL-6	Serum/CSF	22 (2–52 weeks postinjury)	[↑]	[51, 58]
IL-8	CSF	3–4 days postinjury	[↑]	[51]
IL 1-RA	Serum	22 (2–52 weeks postinjury)	[↑]	[58]
Anti-GM_1 ganglioside IgG (G and M)	Serum	22 (2–52 weeks postinjury)	[↑]	[58]
Tau	Serum/CSF	= 72 h	[↑]	[48, 51, 54]
S100-β	Serum/CSF	45 h	[↑]	[54]

One of the first studies that identified the miR-9* ("*" tells us that it is found in the cell at lower concentration), miR-84-5p and miR-219, as auspicious biomarkers for judging the severity of SCI in the acute phase was done by Hachisuka and co-workers in 2014. In this work, it was demonstrated that the levels of all three miRNA levels are upregulated relatively to the severity of SCI in the serum of mice within 12 h after injury, suggesting that these miRNAs might be potential biomarkers for anticipating the severity of SCI [73].

Since the first research, concerning miRNA and SCI were published and to this date, more than 400 miRNAs have been identified. It was already demonstrated that nearly 300 kinds of miRNAs had its expression changed in the spinal cord of an adult rat after a SCI. This analysis was done by microarray where a significant variation was noted in 97 miRNAs, of which 60 were hyperexpressed and the remaining 37 had their expressions diminished, making them a possible target for therapy and/or for a biomarker [74, 75].

The major miRNAs described with altered expression in SCI are described in Table 2.

Recently, it was demonstrated that inhibition of miR 486 and miR20a subsequent SCI significantly reduces apoptosis and decreases functional deficits, either by upregulating NeuroD6 expression or by upregulating expression of the major target gene, Ngn1, respectively [76, 82], suggesting for the first time the use of miRNAs as novel drug targets for treating SCI in humans [76]. Another miRNA that was tested as a target after SCI was the miR-210. The miR-210 was injected into spinal cords of mice with SCI, and it induced astrogliosis, angiogenesis, maintenance of myelin and axons, enhanced functional recovery, and impeded apoptosis [83].

Among them, some have developed special interest as possible biomarkers for different phases of the SCI. In a very recent work, Tigchelaar and coworkers analyzed the expression of more than 300 miRNAs from a large animal model (porcine) of thoracic SCI. They provide a complete study of variations that occurs across miRNAs during the early postinjury phase of acute SCI [84]. Here, they describe an amount of 58 significantly upregulated miRNAs in the severe SCI group, 21 in the moderate SCI group, 9 in the mild SCI group, and 7 miRNAs in the SHAM group. Interestingly, there was a global increase in miRNAs in serum that was correlated with injury severity that corresponded to a posttranscriptional regulatory environment considerably modified. This recent work indicates that the miRNAs in the serum could be hopeful candidates as biomarkers in order to evaluate the severity of the damage for SCI or other forms of neurologic injury, even traumatic and/or acute [84].

Perspectives of Biomarkers in SCI

It should be noticed that although there are already some miRNAs identified as biomarkers for some diseases such as glioma, thyroid cancer, and pancreatic cancer in humans [85–87], we did not find any research concerning the identification of miRNAs for SCI biomarkers in human patients. However, we believe that the use of biomarker as a predictive indicator to guide the prognosis, diagnosis, and treatment can help patients with SCI.

During all phases of SCI, there is a modulation of several miRNA expressions, as can be observed in Fig. 2, which could be targets for future therapies. It is not difficult to imagine that with the exploration of miRNAs field and its critical player as regulators in various pathologies, such as cancer and SCI, it is really pertinent to explore and understand the chance of using miRNA as therapeutic agents. There are already some studies that demonstrated the promising use of some anti-miRNA molecules targeting specific miRNAs in vivo and in vitro [125, 126]. A great advantage of using anti-miRNAs for therapeutic applications is that it is easy to administer through local or parenteral injection routes [127].

Table 2 Some miRNAs with altered expression in SCI [4, 5, 70, 76–81]

miRNA	Regulation	Action	Reference
miR-124a	↓	Cell Deth	[70]
miR-223	↑	Inflammatory response	[70]
miR-107	↑	Inflammatory response	[78]
miR-148	↓		[78]
miR-128	↓	Cell death	[79]
miR-219, miR-138, and miR-338	↓	Cell death	[80, 81]
miR-15b	↑	Proapoptotic	[4]
miR-127, miR-181a, miR-411, miR-99a, miR-34a, miR-30b, and miR-30c	↓	Proinflammatory	[4]
miR124, miR129 and miR1	↓		[77]
miR-384-5p miR-30b-5p, miR-486	↓	Proinflammatory	[5, 76]
miR-17 e miR-20	↑	Proinflammatory	[4]
miR-146a, miR-223, miR-221, and miR-1	↑	Anti-inflammatory	[4, 5, 70, 77]

However, the limitation for the use of this technology as a therapeutic tool is the identification of a signature of miRNAs during pathology, their mechanism of action, delivery of anti-miRNAs, and their active form in vivo. Once all this information is available, miRNA could have a brilliant future and has the potential to be a novel therapeutic tool.

Bioactive Lipids: Possible Therapy?

During the SCI, at the secondary injury, the inflammatory process is already well described. There are some molecules described, which are involved in the inflammatory process during the secondary injury, including the lysophospholipids (LPs). The inflammatory process is a two-way road, as it is a major contributor to cell death and loss of neuronal function; it is also responsible for the clearance of cytotoxic cell debris [128, 129]. The biochemical changes involved in SCI are not completely understood; however, recent reports suggest that LPs may play an outstanding role [130, 131].

Sphingosine-1 phosphate (S1P) and lysophosphatidic acid (LPA) are simple LPs that also act as bioactive signaling molecules that play pivotal roles in various biological processes, such as oncogenesis, CNS development, immune function, and wound healing. They have been accepted for decades as simple part in the biosynthesis of cell membranes [132]. LPs were initially identified described as metabolites and precursors in the de novo biosynthesis of phospholipids. However, some 30 years ago, there was a paradigm shift, where it was observed that the LPs have properties similar to signaling molecules or extracellular growth factors. It should be noticed that, for decades, the mechanisms of action for LPs after description of their bioactivities were unknown [132].

Nowadays, it is well established that LPA and S1P regulate the organogenesis and function of several organic systems, such as the reproductive systems, cardiovascular, immune, and nervous. Altered LP signaling is involved in the biology of disorders, such as obesity, inflammation, cancer, autoimmune diseases, atherosclerosis, and neuropathic pain [132]. LPs receptors are expressed by most neural cell types and are involved in several developmental processes within the nervous system including: normal brain development and function, growth and folding of the cerebral cortex, growth cone and process retraction, cell survival, cell migration, cell adhesion, and proliferation [133–139].

So, the LP signaling occurs by binding to its cognate receptors, which coupled to G protein, activates the diverse intracellular messenger systems producing a variety of biological responses [135]. The cellular responses induced by the LPs depend on the cell-surface G protein–coupled receptors (GPCRs) activated to produce the varied downstream cellular responses, developmental stage, on cell type and environment [135] (see Fig. 1).

In 2007, Kimura and coworkers demonstrated that S1P concentration in the spinal cord was considerably elevated in the location of a contusion injury, and that such changes stimulated S1P1-mediatedmigration of in vivo transplanted neural stem/progenitor cells [140]. These progenitor cells then differentiated into neurons and astrocytes, suggesting for the first time an important role for S1P in SCI [140]. Then, some studies were published in rodent models which demonstrated that the administration of FTY720 promotes functional recovery after SCI [141, 142]. FTY720 derivate from the fungal metabolite myriocin, is chemically made and, when phosphorylated, acts as a sphingosine-1-phosphate (S1P) agonist and act on the S1P receptor [143]. The first studies demonstrated that FTY720 can protect neural cell from apoptosis and preserve vascular integrity by acting on endothelial cells, being therefore very effective during SCI [141, 144]. Besides that, FTY720 decreases the astrocyte accumulation in the injured spinal cord reducing the glial scar. It was also reported that the FTY720 can protect oligodendrocyte progenitors from death induced by growth factor depletion and exposure to activated microglia, and it can further enhance remyelination through S1P receptors [144, 145].

The FTY720 was the first drug that modulated S1P receptor approved to treat relapses of multiple sclerosis in 2010 by Food and Drug Administration [146]. Then, the search for more selective S1P receptor modulators with better pharmacokinetic profiles and fewer side effects started. Now, in addition to the FTY720, there are eight more drugs capable of modulating S1P receptors. These drugs are being clinically

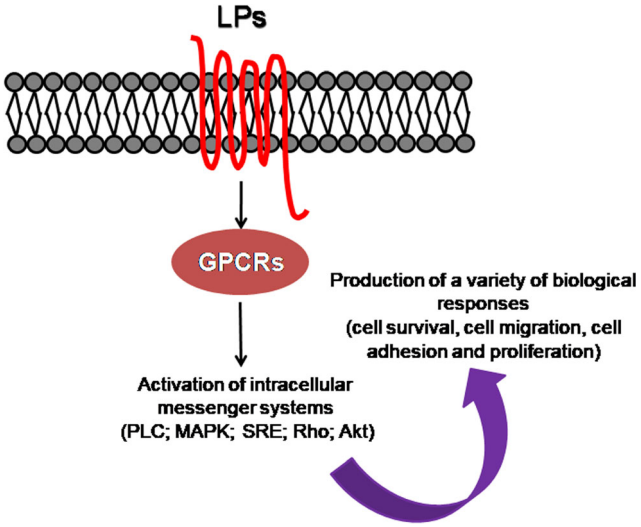

Fig. 1 Scheme of LP receptor coupled to GPCRs. LPA or S1P coupled with the cell-surface G protein–coupled receptors (GPCRs) activated to produce the diverse downstream cellular responses (diagram by Spohr, TCLS)

tested in the contexts of multiple sclerosis and other autoimmune and inflammatory disorders, such as psoriasis, Crohn's disease, ulcerative colitis, polymyositis, dermato myositis, liver failure, renal failure, acute stroke, and transplant rejection [147]. However, we have still not found any clinical trial concerning the use of any of these drugs in spinal cord injury. It is, however, believed that FTY720 could help in multiple sclerosis reducing the lymphocyte egress and in this way contribute to inhibit axon myelin sheath damage [148].

Conclusion

Contrary to the large number of reports applying miRNAs as biomarkers using as animal models rat and mouse predominately, and more recently pig, citing as a model to understand the phenomenon, we did not find any report investigating the role of miRNAs as biomarkers in human spinal cord injury. A small number of studies have already tested the role of some proteins as biomarkers in patients with SCI. But those biomarkers were identified in CSF without precise concentrations [37, 52]. Moreover, none of these studies has correlated the concentrations of the protein biomarkers with the neurological outcome of the patients. So, here we suggest the use of miRNAs as diagnostic tools for predicting outcome after SCI (Fig. 2). Despite the fact that various studies have tried to identify miRNA signature profiles for some pathologies, such as cancers (GBM, breast, bladder) and SCI, unfortunately, a miRNA profile is still far from being well defined for SCI [84, 149–151]. Certainly, more research is mandated in humans, as we believe that miRNAs may point to a future era of customized medicine for individuals with SCIs. There is no doubt that an extensive investigation with high-throughput sequencing of miRNAs in a significantly large group of SCI patients or the analysis of miRNA expression in different phases of the SCI injury is mandatory to the discovery of new therapeutic methods and possible correlations with SCI progression. Nowadays, several methodologies, such as molecular biology and gene expression studies (including PCR arrays, next generation sequencing, in-situ

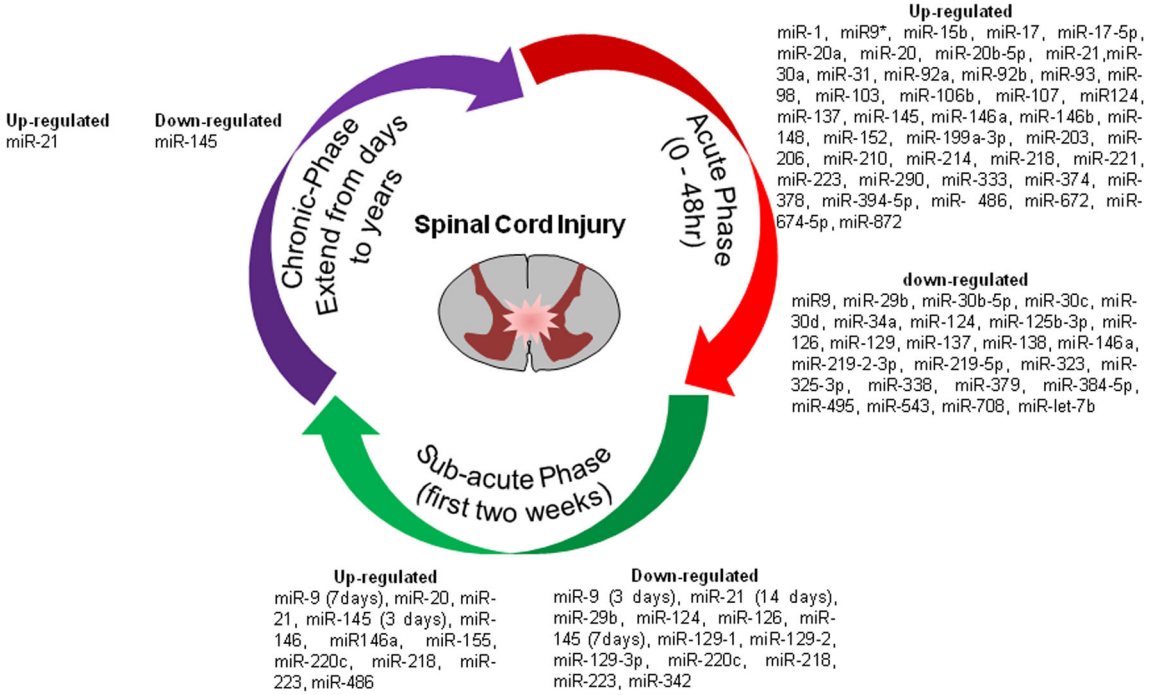

Fig. 2 Schematic representation of the acute phase; subacute phase and chronic phase after a SCI and some miRNA that could be used as biomarkers (diagram by Spohr, TCLS) [4, 5, 72, 75–77, 82, 83, 88–124]

hybridization techniques and microarrays), have made it possible to profile miRNA expression patterns in some pathologies, such as cancer [152], and in animal models, they are already been used in order to identify new signature profiles after SCI [84]. However, these new signatures profiles needs to be screened and validated in human patients with a significant cohort. Recently, it was demonstrated that with a cohort of 46 patients (27 with breast cancer and 19 healthy volunteers), it was possible to identify, using a microRNA array, five miRNAs as novel biomarkers for the detection of breast cancer [150]. So, we believe that a similar cohort may be enough to identify a miRNA profile for SCI. Besides, we believe that in addition to the fact that patients need to be precisely diagnosed, there is not yet efficient treatment for SCI, which must also be developed. Some reports have demonstrated that the bioactive lipids, more specifically S1P could be a promising drug to help SCI patients. Also, FTY720, a modulator of S1P1 receptors that could reduce lymphocyte infiltration into the spinal cord following SCI and enhance the tissue preservation and functional recovery, and it could be a promising drug [141]. We believe that a method for locally distribution of specific S1P1 agonists into injury spinal cord may lead to new therapeutic approaches for treating SCI. This could open a new avenue for the use of bioactive lipids in SCI patients. However, this field still needs much more research.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflicts of interest.

Abbreviations ASIA, American Spinal Injuries Association; BSCB, blood-spinal cord barrier; BMPs, bone morphogenetic proteins; BDNF, brain-derived neurotrophic factor; S100β, calcium-binding protein S100-beta; CNS, central nervous system; CSF, cerebrospinal fluid; COX2, cyclooxygenase 2; FGF-β, fibroblast growth factor beta 1; GPCRs, G protein–coupled receptors; GDNF, glial cell-derived neurotrophic factor; GFAP, glial fibrillary acidic protein; IFNγ, interferon gamma; IGF (I and II), insulin-like growth factor I and II; IL (1β; 1α and 6), interleukin-1β; 1α and 6; IL-4R and IL-2Rα, interleukin receptors; ISNCSCI, International Standards for Neurological Classification of Spinal Cord Injury; JAK, Janus-activated kinase; LPA, Lysophosphatidic acid; LPs, lysophospholipids; MRI, magnetic resonance imaging; mTOR, mechanistic target of rapamycin; miRNA, microRNA; MAP-2, microtubule-associated protein 2; MOG, myelin-oligodendrocyte glycoprotein; NFL and NFH, neurofilament proteins (light and heavy); NF-κB, factor kappa B; PTEN, phosphatase and tensin homolog; PDGF, platelet-derive growth factor; S1P, Sphingosine-1 phosphate; SBDPs, αII-spectrin breakdown products; SC, spinal cord; SCI, spinal cord injury; STAT, signal transducer and activation of transcription family; SOCS-3, suppressor of cytokine signaling 3; TGF-β, transforming growth factor-β; TNF-α, tumor necrosis factor-α; VEGF, vascular endothelial growth factor; VGF, inducible nerve growth factor

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