Function of GSK-3 signaling in spinal cord injury (Review)

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Abstract. Spinal cord injury (SCI) is a major social problem with a heavy burden on patient physiology and psychology. Glial scar formation and irreversible neuron loss are the two key points during SCI progression. During the acute phase of spinal cord injury, glial scars form, limiting the progression of inflammation. However, in the subacute or chronic phase, glial scarring inhibits axon regeneration. Following spinal cord injury, irreversible loss of neurons leads to further aggravation of spinal cord injury. Several therapies have been developed to improve either glial scar or neuron loss; however, few therapies reach the stage of clinical trials and there are no mainstream therapies for SCI. Exploring the key mechanism of SCI is crucial for finding further treatments. Glycogen synthase kinase-3 (GSK-3) is a widely expressed kinase with important physiological and pathophysiological functions *in vivo*. Dysfunction of the GSK-3 signaling pathway during SCI has been widely discussed for controlling neurite growth *in vitro* and *in vivo*, improving the proliferation and neuronal differentiation of endogenous neural stem cells and functional recovery from spinal cord injury. SCI can decrease the phosphorylated (p)/total (t)-GSK-3β ratio, which leads to an increase in apoptosis, whereas treatment with GSK-3 inhibitors can promote neurogenesis. In addition, several therapies for the treatment of SCI involve signaling pathways associated with GSK-3. Furthermore, signaling pathways associated with GSK-3 also participate in the pathological process of neuropathic pain that remains following SCI. The present review summarized the roles of GSK-3 signaling in SCI to aid in the understanding of GSK-3 signaling during the pathological processes of SCI and to provide evidence for the development of comprehensive treatments.

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Contents

1. Introduction

The CNS contains the brain and spinal cord from which the peripheral nerves branch and is safeguarded by the spinal cord, which encompasses the meninges, cerebrospinal fluid and spine. The spinal cord exerts important functions, including the regulation of motor and sensory functions (1,2). Spinal cord injury (SCI) is the most common disabling spinal injury; For the last 30 years, its global prevalence has increased from 236 to 1,298 cases per million populations. The estimated global rate of SCI falls between 250,000 and 500,000 individuals every year.

It can damage the normal anatomy of the spinal cord, leading to axonal rupture, neuronal degeneration and necrosis, inflammatory response and demyelination, ultimately leading to severe neurological dysfunction (3,4). SCI frequently results in sensorimotor disorders, autonomic changes and intractable pain; Spinal cord injury can also affect respiratory, urinary, and gastrointestinal functions and is one of the factors leading to the development of infection. After spinal cord injury, a large number of inflammatory substances are released into the blood and cause inflammation throughout the body. Thus seriously affecting the quality of life of patients (5). SCI is categorized into two types: Traumatic and non-traumatic. The former is more common and mainly caused by external physical impacts, such as vehicle accidents, violence and falls (1,6), whereas the latter is usually caused by compression of a tumor; the enlargement of some tumors can compress the spinal cord tissue, resulting in the destruction of the spinal cord tissue, resulting in clinical symptoms, vascular ischemia or congenital disease such as Spinal Bifida (7). The current review mainly focused on traumatic SCI. Following spinal cord injury, axons of the CNS fail to regenerate. By contrast, peripheral nervous system axons regenerate after injury and show restored function. The lack of CNS regeneration after injury may be associated with abnormal expression of specific molecules in myelin and glial scars in the CNS, including Nogo, oligodendroglia-myelin glycoproteins and myelin-associated

glycoproteins (8). A previous study reported that these molecules induce the activity of the Rho-Rho-associated protein containing kinase 2 (ROCKII) and glycogen synthase kinase-3β (GSK-3β) signaling pathways, leading to inhibition of axonal regeneration in the CNS (9). Thus, the Rho-ROCKII and/or GSK-3β signaling pathways may be targets for restoring axon regeneration.

2. Mechanisms involved in SCI

The CNS is composed of neurons and glial cells; glial cells include astrocytes, microglia, oligodendrocytes and Schwann cells, and are crucial for proper CNS development and function (10). The interaction between neurons and glial cells plays an important role in the physiological processes of the central nervous system. The dysfunction of neurons and glial cells is one of the pathogenesis of neuro developmental disorders (11). Glial cells, mainly astrocytes, collaborate with neurons and vasculature to harvest nutrients from the bloodstream, thus providing metabolic sustenance to neurons (12). The myelinating glia of the CNS and the peripheral nervous system, oligodendrocytes and Schwann cells, respectively, contribute to the electrical insulation of axons, thus enabling swift signal transmission (13). Microglial cells are innate immune cells that reside in the CNS; they dynamically monitor the microenvironment of the CNS and contribute to the CNS homeostasis in physiological conditions, and are closely associated with neuroinflammation in pathological conditions (14).

The pathophysiological process of SCI is quite complex, involving the dysfunction of neurons and glial cells, which includes vascular responses, abnormal neuroinflammation, neuronal loss and demyelination (15,16). In addition, traumatic SCI can be divided into two phases: i) Irreversible primary injury, which happens at the moment of injury, and ii) secondary injury, which occurs within minutes following the primary injury (17). Spinal cord compression is the most common pathogenesis of spinal cord injury and persists after injury (18). Bleeding can occur in the early stages of an SCI, followed by disruption of the blood supply. The most common clinical manifestations immediately following injury are disruption of the spinal vascular supply and hypotension/hypoperfusion, resulting in hypovolemia, neurogenic shock and bradycardia due to spinal cord ischemia (19). Disturbance of blood flow following SCI leads to hypoxia and ischemic infarction. Specifically, these two conditions damage the metabolically higher gray matter; white matter and gray matter metabolism show different basic properties, but the responses to neuronal activity are qualitatively similar. The neurons in the damaged area are physically broken and the thickness of the myelin sheath is reduced (20). In addition, edema and macrophage accumulation in the damaged tissue exacerbate the deterioration of neuronal transmission. Secondary injuries can be caused by primary injuries and several pathophysiological mechanisms can come into play hours or days after an SCI occurs (21,22). Energy deficiency caused by ischemia and impaired perfusion at the cellular level is the most influential factor (23). Key changes have been identified, such as bleeding, demyelination, edema, cavity formation with axon and neuron necrosis, and a series of pathological changes such as neuron death and axon breaking in nerve tissue following SCI can further increase infarction (24). Following secondary injury, increased free radical damage and lipid peroxidation in the cell membrane, as well as secondary injury signal cascade in the damaged tissue area, can eventually lead to the death of neurons (25). In addition, during the second injury, released toxic compounds stimulate the differentiation of neural stem/progenitor cells into astrocytes, leading to reactive astrogliosis and the transition from the inflammation phase to glial scar formation (Fig. 1) (26).

The poor prognosis of SCI may be, in large part, due to two critical factors, including glial scar formation and irreversible neuron loss, which work together to interrupt the neural pathway and lead to the damage of axon regeneration (27). In patients with spinal cord injury and in rodent models, obstruction of axon regeneration and its functional recovery has been shown to permanently inhibit regeneration of the spinal cord (28). The central idea of alleviating SCI is preventing, attenuating and reversing secondary injury and improving spinal cord neurological functions (1). Common treatments used in clinical practice include traditional drug therapy (1), surgery (29,30), cell transplantation (31-34), tissue engineering (35), cell therapy and nanomedicine (36). However, these treatments rarely recover SCIs completely and can only improve symptoms and reduce complications.

Glial scar formation. Glial cells of the CNS (mainly astrocytes) are abundant and their roles in sustaining the dynamic balance of the neuronal microenvironment and controlling blood flow are fundamental. Preservation of the blood-brain barrier and the malleability and purpose of the synapses must be regulated (37). Following SCI, the trauma activates resident astrocytes and pericytes, and recruits infiltrating fibroblasts and Schwann cells from the peripheral nervous system, leading to the formation of glial scars in the injured spinal cord (38,39). Fibroblasts and Schwann cells migrate into the epicenter of the lesion and contribute to the production of extracellular matrix (ECM) proteins, such as nestin, glial fibrillary acidic protein and proteins transported by the veins (40,41). The deposition of ECM components and the accumulation and activation of glial cells contribute to the formation of a glial scar around the periphery of the lesion. Other cells such as activated microglia and NG2 glia form a dense boundary that isolates the damaged area (42). The lesion core includes a mixture of mononuclear macrophages, activated fibroblasts and ECM proteins (43,44).

For decades, glial scars have been considered the main factor against spinal cord regeneration (45). The primary inhibitory ECM molecules that are produced by reactive astrocytes during glial scar formation include the chondroitinase enzyme, which acts on chondroitin. In animal models, treatment with chondroitinase following SCI exhibited axonal regeneration and functional recovery (46). In non-mammalian vertebrates such as zebrafish, a restricted amount of glial scarring demonstrated the regeneration of the spinal cord, accompanied by a considerable restoration of motor function (28,47). However, glial scar formation is also an essential event during SCI recovery. In the acute phase of SCI, the formation of a glial scar serves an important role in restricting the size of the primary injury. The glial scar limits excessive inflammation from the lesion to normal tissue, clears debris and repairs the blood-spinal cord barrier, which prevents the spread of toxic

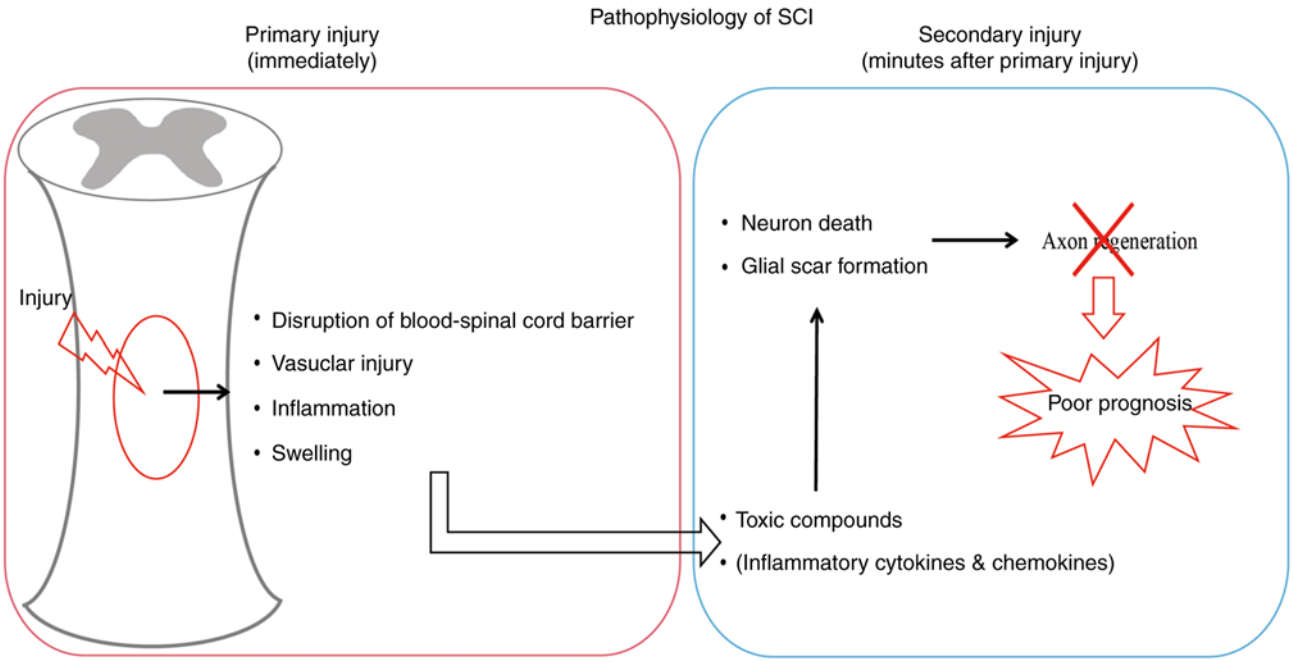

Figure 1. Mechanisms involved in SCI. Traumatic SCI can be divided into two phases, irreversible primary injury that happens immediately at the moment of injury, and secondary injury that occurs within minutes following the primary injury. Irreversible primary injury induced by mechanical injury will lead to the disruption of blood-spinal cord barrier, vascular injury, swelling and inflammation. Subsequently, the damaged neurons and glial cells will release toxic compounds, such as pro-inflammatory cytokines and chemokines, which in turn leads to the second injury with the death of most of cells. In addition, during the second injury, the released toxic compounds will stimulate the differentiation of neural stem/progenitor cells into astrocyte, leading to reactive astrogliosis and the transition from the inflammation phase to glial scar formation, resulting in a poor prognosis. SCI, spinal cord injury.

compounds to the surrounding tissue and the production of neurotrophins (48-50). In the sub-acute or chronic phase, the glial scar inhibits axonal regeneration, which has been shown to be harmful to the regeneration of the spinal cord (45). The dual role of the glial scar (both harmful and protective) during SCI makes it difficult to target the glial scar for therapeutic purposes (Fig. 2) (51).

Neuron loss. Irreversible neuron loss is another crucial part of SCI recovery. A combination of multiple causes, such as direct injury, inflammation, ischemia/reperfusion injury and neurotoxic cells, can lead to neuron loss (52,53). The primary sites of active neurogenesis in the adult brain are the subventricular zone of lateral ventricles and the subgranular zone of the dentate gyrus, which possess the capacity to generate all major neuronal phenotypes (54,55). However, neurons in the spinal cord have low regeneration and proliferation potential, and the vast majority of the adult spinal cord is composed of nerve cells, which mainly produce astrocytes and oligodendrocytes (56). Microglia are resident macrophages of the CNS and are essential in the control of damage repair, brain development and the upkeep of neuronal networks (57). Microglia activation is strongly associated with delayed neuronal loss in the peri-infarct area (58,59). Microglia are found only in the brain, retina and spinal cord (60). They are cells specialized in the phagocytosis and digestion of extracellular matter, including other cells. In normal tissues, microglia are highly differentiated, with elongated processes capable of engulfing smaller objects, such as synapses and fragments, but not larger objects such as neurons (61). However, when microglia are activated by inflammatory stimuli, they increase the expression of opsonins, lysosomes and phagocytic receptors; in addition, the microglia process is retracted, thus producing a large moving cell body capable of phagocytosing neurons (62).

Insufficient neurogenesis in the adult spinal cord is a key challenge in reconstructing original neuronal networks; as such, neural repair and neuroregeneration after nerve repair is a key step in tissue repair following SCI. Various types of stem/progenitor cell therapy have been shown to have great development potential (63,64). Transplantation of cells is considered to be one of the most promising therapies for neuronal regeneration following SCI; this process includes direct injection/transplantation of olfactory ensheathing cells (65), intramedullary Schwann cell (66), embryonic (67) and mesenchymal stem cells (64,68). Although these therapies have demonstrated good therapeutic effects in several preclinical studies, some adverse reactions were found during clinical application. For instance, direct injection of olfactory ensheathing cells had serious side effects, such as syrinx formation, myelomalacia and perioperative morbidity, which limited its clinical application (69); in addition, intramedullary transplantation of Schwann cells can induce unsatisfactory motor and functional improvement (66), and the transplantation of embryonic stem cells also had severe risks such as the formation of teratomas (67), whereas mesenchymal stem cell transplantation could induce tumor formation (70,71). Neuronal reprogramming is a novel technology that can regenerate functional neurons from glial cells by overexpressing neurogenic transcription factors (such as NeuroD1) in several neurodegenerative disorders, including Huntington's and Alzheimer's diseases (72-75). Here, an adeno-associated virus is used to overexpress NeuroD1 to the convert reactive

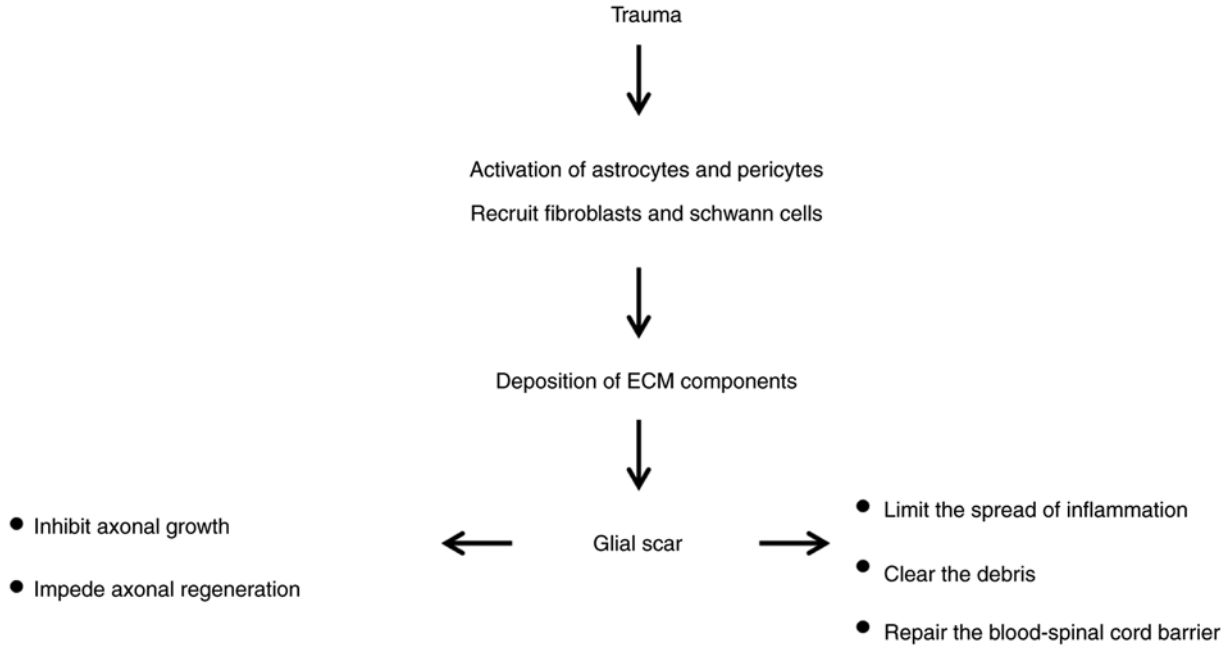

Figure 2. A schematic representation of glial scar formation and its double-sided effects. Following SCI, trauma activates resident astrocytes and pericytes, and recruits infiltrating fibroblasts and Schwann cells from periphery. Fibroblasts and Schwann cells migrate into the lesion epicenter and contribute to the deposition of ECM proteins, such as GFAP, nestin and vimentin. The deposition of ECM components and the accumulation and activation of glial cells work together in the formation of a glial scar around the periphery of the lesion. The formation of glial scars can limit the spread of inflammation, remove debris and repair the blood-spinal barrier, but can also inhibit axon growth and hinder axon regeneration. ECM, extracellular matrix; GFAP, glial fibrillary acidic protein; SCI, spinal cord injury.

astrocytes into neurons in the dorsal horn of the injured spinal cord, thus providing a novel possibility for the treatment of SCI.

3. GSK-3

GSK-1, GSK-2 and GSK-3 are highly conserved serine/threonine kinases in the GSK protein family; they were initially identified as negative regulators of glycogen metabolism (76). Among them, GSK-3 is the most studied as it has pivotal roles in numerous cellular functions, including regulating gene expression, cell survival and neuronal polarity (77). GSK-3 has two isoforms, GSK-3α and GSK-3β, and one splice variant (GSK-3β2), which is expressed specifically in the nervous system (78). These two isoforms share ~95% amino acid identity, thus, GSK-3α and GSK-3β have unique and overlapping functions (79). GSK-3 has a large number of interacting substrates, including CREB (80), the Nfat family of proteins (81), neurogenin 2 (82), SMAD1 (83) and β-catenin (84), all of which are part of the cyclic AMP response element-binding protein family. Among the two isoforms, GSK-3β may have more predicted substrates than GSK-3α, so GSK-3β has traditionally received more attention (85).

GSK-3 is mainly localized in the cytoplasm where it regulates transcription factors by regulating their protein concentrations, DNA attachment capabilities and/or nuclear positioning (86). Most kinases are inactive in resting cells and become active after phosphorylation. In contrast with other kinases, GSK-3 is highly active in unstimulated cells and it is rendered inactive after phosphorylation following stimulation from various sources, including growth factors (87). Growth factor-mediated phosphorylation of GSK-3 inhibits its activation and leads to the activation of its downstream substrates.

GSK-3 is ubiquitously expressed in the human body, and its dysfunction has been confirmed in several disorders such as cancer, cardiovascular diseases, diabetes and inflammatory conditions. GSK-3 is also expressed in the CNS and participates in several physiological and pathological functions (88). There is evidence of a close association between the disruption of GSK-3 signaling and the emergence of neuroinflammation, neurodegenerative illnesses and psychiatric disorders. For example, GSK-3 is a key role in the pathogenesis of Alzheimer's disease, as it participates in the abnormal phosphorylation of τ protein and the production of amyloid-β (89-92). Dysfunction of the GSK-3β signaling pathway has also been demonstrated in neuropsychiatric disorders, such as schizophrenia (93). In postmortem tissues of patients with schizophrenia, GSK-3β mRNA expression was reduced in the active frontal cortex and dorsolateral prefrontal cortex, although there was no difference in occipital cortical protein expression (93,94). GSK-3 also regulates rhythms in hippocampal clock gene expression and synaptic plasticity (95). During brain development, GSK-3 and its upstream and downstream regulators serve key roles in the fundamental processes of neurodevelopment, and the disruption of GSK-3 signaling is associated with several neurodevelopmental disorders such as delayed development and intellectual disability (78).

Along with its role in neurodegenerative and neurodevelopmental diseases, GSK-3 also serves an important role in neurogenesis. Behavioral deficits and neuroprogenitor cell proliferation in schizophrenia are regulated by the GSK-3/β-catenin signaling pathway (96). The hippocampal neurons of adults display heightened neurogenesis, as well

as migration, differentiation, proliferation and neurophenotypic formation, which are linked to the inhibition of GSK-3 in rats (97). A correlation between GSK-3 inhibition and an increase in neurogenesis was established *in vitro* and *in vivo* in adult mouse neural progenitors (97-99). Neurogenesis in the dentate gyrus of the hippocampus of adult rats can be induced by the small molecule NP03112 or lithium-induced inhibition of GSK-3 (97,100). Conditional deletion of GSK-3 in mouse neural progenitors increases proliferation (101). Considering the close relationship between GSK-3 and neurogenesis, the role of GSK-3 signaling pathway in SCI is further discussed below.

4. Function and role of GSK-3 in SCI

SCI decreases the ratio of p-GSK-3β/t-GSK-3β and increases the number of apoptotic cells in the spinal dorsal horn. Increasing this ratio may be a useful strategy for reducing apoptosis and subsequent neuropathic pain associated with SCI (102). PI3K-mediated activation of GSK-3β can reduce dorsal root ganglia neurite outgrowth associated with excitotoxic spinal cord injury dysesthesias (103). The development of GSK-3 signaling pathway in spinal cord injury is shown in Fig. 3.

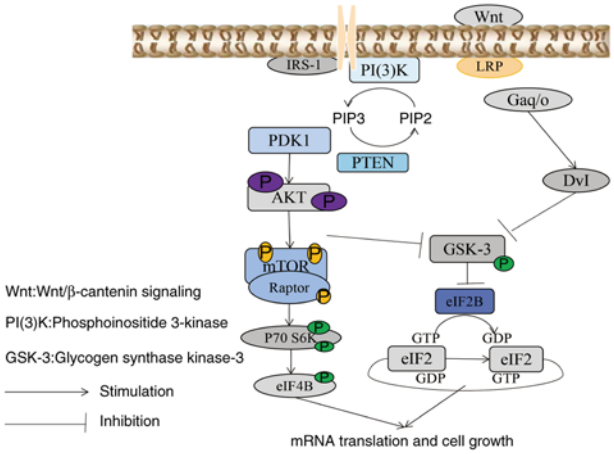

Figure 3. The main lipid substrate of PTEN is PIP3, and PTEN is a negative regulator of PI3K/AKT signaling. In the upstream signaling network, The activation of mTOR by AKT leads to phospholipid activation of GSK-3, which transduces signals from various growth factors and cytokines into intracellular information. PTEN, phosphatase and tensin homolog; PIP3, phosphatidylinositol-3,4,5-trisphosphate; GSK-3, glycogen synthase kinase-3.

Role of GSK-3 inhibitors in SCI. The aforementioned hypothesis, that GSK-3 regulates SCI, can first be demonstrated using GSK-3 inhibitors. The function of several GSK-3 inhibitors in spinal cord injury has been extensively studied. For example, GSK-3 inhibitor Ro3303544 was demonstrated to stimulate neurogenesis in cultured multipotent stem cells and in SCI rat model (104), as also demonstrated using 4-benzyl-2-methyl-1,2,4-thiadiazolidine-3 (TDZD-8). GSK-3 is most effectively and precisely inhibited by a 5-dione non-ATP inhibitor. Treatment with TDZD-8, one of these inhibitors, following SCI could significantly inhibit neuronal apoptosis and increases the density of cortical spinal tract fibers around the injured area (105). Combination therapy with TDZD-8 and Y27632 (a Rho-associated coiled-coil kinase 2 inhibitor) could improve the protective effect on axonal regeneration in a rat SCI model (106). Lithium, a traditional inhibitor of GSK-3β, has been extensively utilized in the treatment of mood disorders, particularly manic depression (107). Neurotrophic factors, such as nerve growth factor, neurotrophic factor-3, brain-derived neurotrophic factor (BDNF) and receptors in the brain are all involved in the increase in the concentration and amount of lithium in animals (108). Lithium also stimulates stem cells proliferation, including neural stem cells in the subventricular area, striatum, spinal cord and forebrain (103). Animal models of stroke and brain injury, as well as Huntington's, Alzheimer's, Parkinson's and amyotrophic lateral sclerosis diseases, show that lithium (107) increases the incidence of these diseases. Li *et al* (109) showed that in spinal cord neurons, lithium inhibits GSK-3 activity through two different signaling pathways; lithium activates phosphorylation of AKT in the acute phase and upregulates the expression of Na^+/K^+-ATPase α1 in the chronic phase (109). A hypoxic environment is often generated around the SCI tissue, so that single therapy with gene or stem cells becomes inefficient. Combination treatment with the GSK-3 inhibitor, CHIR99021, and a histone deacetylase inhibitor, such as valproic acid, can significantly boost gene expression through hypoxia/neuron-inducible gene expression system and human-induced neural therapy such as additive stimulus induction. SCI tends to damage nerve tissue and create a hypoxic environment (110). A previous study (56) confirmed that gene or stem cell therapy alone is inefficient, but studies of combination stem cell and gene therapy to treat tissue damage have begun to overcome associated limitations, including inefficient gene delivery and poor treatment effectiveness. Therefore, the combination of stem cells, gene therapy and hypoxia-specific systems may contribute to the reconstruction of SCI (104). Endoplasmic reticulum (ER) stress-induced apoptosis serves an important role in SCI. The AKT/GSK-3β signaling pathway was demonstrated to be able to reduce ER stress-induced apoptosis in SH-SY5Y cells when valproate, a well-known medication for treating epilepsy and mania in clinics, is administered (111). Table I outlines the dosage and effects of GSK-3 inhibitors.

Treatments through GSK-3 in SCI. Alongside the inhibitors, the therapeutic effects of several other treatments in SCI that also target GSK-3 signaling pathways have been investigated. Basic fibroblast growth factor (bFGF) is a potential neuroprotective factor that can promote regeneration and repair of SCI, especially in the early stage of the injury (112-114). Adrenomedullin (AM) is highly expressed in the spinal cord; it can increase p-AKT, p-GSK-3β, p-CREB and BDNF expression levels and promote cAMP accumulation in dorsal root ganglion, which indicates the possible beneficial role of AM in the protection, survival and regeneration of sensory neurons during SCI (115). The potential neuroprotective effects of astaxanthin, a powerful antioxidant and anti-inflammatory agent, on spinal cord ischemia-reperfusion injury may be due to activation of the PI3K/Akt/GSK-3β pathway (116), although the mechanism remains to be elucidated. Loureirin B is a constituent of Traditional Chinese Medicine that is extracted from Dragon's blood tree and has been shown to

Table I. A summary of doses and effects of GSK-3 inhibitors.

First author/s, year	GSK-3 inhibitor	Dose	Effects	(Refs.)
Rodriguez-Jimenez *et al*, 2021	Ro3303544[a]	1 μM, 24 h	Promotes ependymal stem/progenitor cells and human embryonic stemcell-derived neural progenitor differentiation to mature neurons; enhances neurogenesis in ependymal stem/progenitor cells.	(104)
Lei *et al*, 2019	TDZD-8[b]	1 mg/kg/d, 3 weeks	Promotes neuronal cell regeneration and functional recovery in SCI model rats	(105)
Zhang *et al*, 2016	Y27632 + TDZD-8[c]	Y27632 1.6 mg/kg, 2 weeks; TDZD-8 1 mg/kg, 3 weeks	Protects against secondary SCI by inhibiting apoptosis in SCI rats	(106)
Burgess *et al*, 2001	Lithium[d]	1 mM, 1-48 h, *in vitro*; 20 mg/kg/d, 3 days, *in vivo*	Activates phosphorylation of AKT in the acute phase, and upregulates the expression of Na^+/K^+-ATPase α1 in the chronic phase in primarily cell cultured spinal cord neurons	(107)

[a]Ro3303544 can promote the neurogenesis in both cultured multipotent stem cells and in SCI model. [b]TDZD-8 is the most effective and specific non-ATP-competitive inhibitor of GSK-3; treatment with TDZD-8 following SCI can significantly inhibited neuronal apoptosis and increased density of cortical spinal tract fibers around areas of injury. [c]Y27632 + TDZD-8; a combination therapy of TDZD-8 and Y27632 (a ROCKII inhibitor) can improve the protective effect on axonal regeneration in rats SCI models. [d]Lithium is a traditional inhibitor of GSK-3β, which has been widely used to treat mood disorders, especially manic depression; in animals, lithium upregulates neurotrophins, including brain-derived neurotrophic factor and nerve growth factor, neurotrophin-3, as well as receptors to these growth factors in brain. Lithium also stimulates proliferation of stem cells, including bone marrow and neural stem cells in the subventricular zone, striatum and forebrain. GSK-3, glycogen synthase kinase-3; SCI, spinal cord injury; TDZD-8, 4-benzyl-2-methyl-1,2,4-thiadiazolidine-3,5-dione.

affect insulin secretion stimulation, blood glucose reduction and immune suppression (117,118). In addition to these functions, Loureirin B also promotes neuron polarization and axon regeneration by regulating the Akt/GSK-3β pathway following SCI (119). Analysis of gene expression profiles can reveal several essential pathways and genes linked to neuropathic pain in those suffering from spinal cord injury. Among them, GSK-3β is identified in human umbilical cord-derived mesenchymal stem cell (HUCMSC) transplantation has been confirmed to be an effective therapy to alleviate the symptoms of neuropathic pain and to improve motor recovery following SCI (120). Stable bFGF-overexpressing HUCMSC transplantation exhibited improved therapeutic outcomes, such as reduction of glial scar formation, improvement of nerve regeneration and proliferation of endogenous neural stem cells and increased locomotion functional recovery of posterior limbs in a mouse SCI model (121). In addition, the promotion of the proliferation and neuronal differentiation of neural stem cells was demonstrated to operate through the PI3K-Akt-GSK-3β pathway (116). Neuropathic pain is a common complication following SCI experienced by 75-80% of patients with SCI (121,122). GSK-3B protein is in the protein-protein interaction network (123). Furthermore, the signaling pathways of GSK-3β have been reported to closely participate in nerve injuries, such as neurodegenerative diseases, inflammation and neuropathic pain (102). Therefore, GSK-3 signaling pathways may also participate in the pathological process of neuropathic pain following SCI.

Relationship between neuropathic pain and GSK-3 in SCI. Intrathecal injection of ghrelin can significantly suppress the activation of GSK-3β in the spinal dorsal horn and alleviate neuropathic pain (124). Activation of the GSK-3 signaling pathway significantly enhances motor function, as well as reducing SCI-induced allodynia and hyperalgesia when laser treatment and human adipose-derived stem cell transplantation are combined (125). Intrathecal injection of SB216763, a selective GSK-3β inhibitor, has been shown to increase the level of p-GSK-3β in the dorsal lumbar sections of the spinal cord and to completely inhibit the tolerance to morphine analgesia in rats (126).

Neuroinflammation has been identified to be crucial in the development of neuropathic pain (127). Chemokine CXCL5, which participates in the inflammatory process of CNS, regulates neuropathic pain after injury by modulating GSK-3β phosphorylation and activity in rats (128). Valproate can inhibit pAKT/pGSK-3β-mediated neuronal death induced by neuropathic pain (129). Spinal nerve ligation could induce

mechanical allodynia and thermal hyperalgesia (130). The administration of GSK-3β selective inhibitor AR-014418 decreased mechanical allodynia by increasing the p-/t-GSK-3β ratio and decreasing apoptosis in spinal nerve ligation model rats; however, it did not affect thermal hyperalgesia (101). However, there are also reports (98) showing that GSK-3β activity was enhanced in the hippocampus but reduced in the spinal dorsal horn following spared nerve injury. Induced neuropathic pain can cause short-term memory deficits and treatment with selective GSK-3β inhibitors, such as SB216763 and AR-A014418, can prevent short-term memory deficits but does not affect neuropathic pain (131). These discrepancies may be due to the use of different animal models, although they all lead to neuropathic pain.

5. Conclusion

The pathophysiological process of SCI is quite complex; nonetheless, the poor prognosis of patients with SCI may mainly be due to glial scar formation and irreversible neuron loss. Glial scar formation and concomitant inflammatory responses, on the one hand, inhibit the spread of lesions; on the other hand, they limit the injury repair. The dual role of glial scars makes it difficult to be used as a therapeutic target (46). In addition, irreversible neuron loss is another critical part of SCI recovery. The importance of neuron loss has led researchers to develop corresponding treatments; therefore, several stem/progenitor cells therapies have been developed (57-59). Unfortunately, only a few therapies reach the clinical trial stage, and their therapeutic effects are debatable. Exploring the key mechanism of SCI is crucial for finding improved treatments.

The dysfunction of GSK-3 signaling pathway during SCI has been widely investigated. SCI decreases the ratio of p-/t-GSK-3β. Treatment with GSK-3 inhibitors can promote neurogenesis; in addition, several therapies for the treatment of SCI also act through GSK-3 signaling pathways. In addition, GSK-3 signaling pathways also participate in the pathological process of neuropathic pain, which is one of the common complications of SCI. Based on the current body of evidence, GSK-3 signaling can be considered a potential therapeutic target for SCI. However, the data of GSK-3 inhibitors promoting neurogenesis in SCI are mainly generated from *in vitro* experiments. The development of therapies based on GSK-3 still needs further study. Nonetheless, the present review summarized the participation of GSK-3 signaling in SCI and may help understand the role GSK-3 signaling during the pathological processes of SCI.

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Availability of data and materials

Not applicable.

Authors' contributions

XD and HH were responsible for the literature search and discussion. ZC made substantial contributions to conception and design, conducted a thorough review of the manuscript for its significant intellectual content and gave his approval to the final version. Data authentication is not applicable. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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