



The Repression of the HMGB1-TLR4-NF- κ B Signaling Pathway by Safflower Yellow May Improve Spinal Cord Injury

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Spinal cord injury (SCI) often results in abnormal sensory and motor functions. Current interventions for SCI in the clinical setting are not effective partly due to the complexity concerning its pathophysiological mechanism. In the wake of SCI, considerable inflammatory cells assemble around the injured area that induces a series of inflammatory reactions and aggravates tissue lesions, thereby affecting the recovery of the damaged nerve tissue. Therefore, the inhibition of inflammatory responses can improve the repair of the injured spinal cord tissue. Safflower Yellow (SY) is the main active ingredient of *Carthamus tinctorius*. SY has anti-inflammatory effect, as it can inhibit $\text{I}\kappa\text{B}\alpha$ phosphorylation to impede the NF- κ B signaling pathway and p53 nuclear translocation. Besides, SY can limit the release of pro-inflammatory factors, which in turn may alleviate secondary SCI and prevent further complications. In this report, we analyze the pathophysiological mechanism of SCI, the role of inflammatory responses, and how SY interferes with the HMGB1-TLR4-NF- κ B signaling pathway to attenuate inflammatory responses in SCI.

Keywords: safflower yellow, spinal cord injury, inflammatory reaction, glial scar, the HMGB1-TLR4-NF- κ B signaling pathway

INTRODUCTION

Spinal cord injury (SCI) is a serious central nervous system injury (Ahuja et al., 2017; Hodgetts and Harvey, 2017). In the past decade, significant number of people have suffered from SCI, with its incidence rate still on the rise. According to the National Spinal Cord Injury Statistical Center, there are about 12,500 new SCI cases each year in the North America (Alizadeh et al., 2019). SCI impairs sensorimotor circuits, culminating in motor and sensory dysfunctions (Hilton and Tetzlaff, 2018; Ganzer et al., 2020). SCI considerably affects an individual's quality of life, and causes an immense social and economic burden (Schattling et al., 2019). To date, the neuron-regenerative repair of SCI continues to be a challenge in the clinical setting (Lindsay et al., 2020). Although several factors could be attributed to this problem, the two main factors concerning the ineffective treatment of SCI are persistent neuro-inflammation and glial scar formation (Yoshizaki et al., 2021). After SCI, astrocytes around the lesion are activated under the action of inflammatory factors. These reactive astrocytes aggregate around the lesion and form glial scars to protect undamaged spinal cord tissue that impedes axonal regeneration (Okada et al., 2018).

Physical trauma can cause the rupture of blood vessels of the spinal cord, damage the blood spinal cord barrier, and result in local bleeding and ischemia, edema, and inflammation, and cell-death (Tran et al., 2018). SCI has two phases: primary SCI and secondary SCI (Hachem et al., 2017). Primary SCI is usually a mechanical damage that causes the destruction of the blood spinal cord barrier and induces local inflammatory responses (Stahel et al., 2012). Secondary injury occurs several hours, days or weeks after the primary SCI. This happens under the action of inflammatory factors, with secondary injury aggravating the damage to the spinal cord tissue (Fan et al., 2013; Tran et al., 2018). Cells within the lesion sites release ATP, DNA, glutamate and free radicals, leading to the formation of a post-damaged cytotoxic environment (Ahuja and Fehlings, 2016). In view of this, inflammatory responses are significant players in secondary SCI (Bethea and Dietrich, 2002).

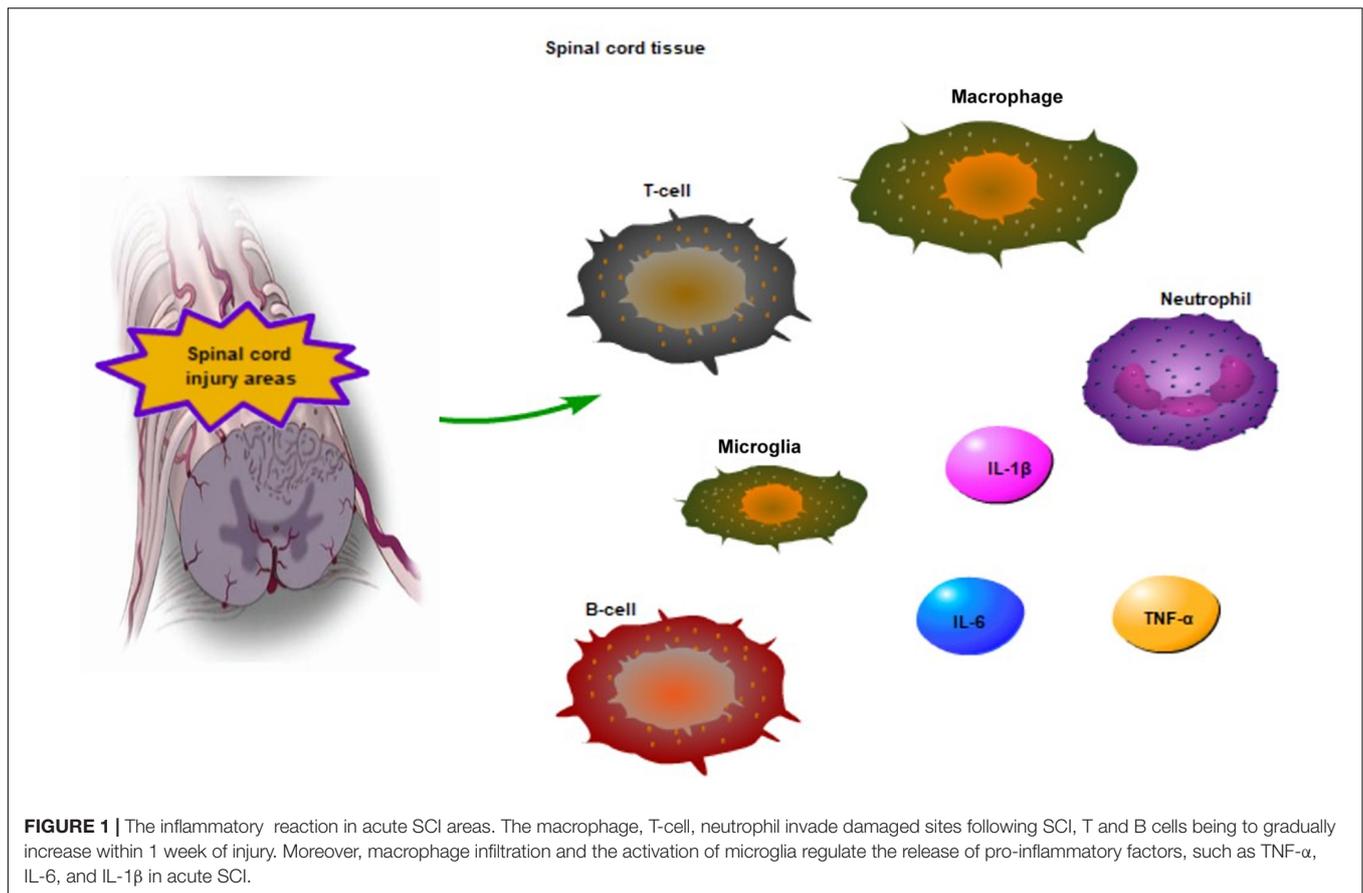
THE ROLE OF INFLAMMATORY REACTION IN SCI PROGRESSION

Inflammatory reaction is a protective mechanism of the body. However, excessive and persistent inflammatory microenvironment can hinder spinal cord repair (Li X. et al., 2020). In the wake of SCI, myelin debris are formed, which triggers complement-mediated inflammatory reaction (Kopper and Gensel, 2018). A distinctive consequence of SCI is the upregulation of multiple families of inflammatory molecules that involve cytokines and chemokines (Rice et al., 2007). Inflammatory reaction may aggravate SCI, and cause neuronal cell death, neurodegeneration, and neuroinflammation (Polcyn et al., 2020). Neuroinflammation is one of the key factors that drives secondary SCI (Gaojian et al., 2020). SCI can give rise to a comprehensive inflammatory cascade response induced by the activation of innate immune cells (microglia and astrocyte), leukocytes (neutrophil and macrophage), and neuronal cell death. These cells release pro-inflammatory cytokines, chemokines, free radicals, excitatory toxic amino acids, and nitric oxide (NO) (Hausmann, 2003; Anwar et al., 2016). The pro-inflammatory macrophage and the anti-inflammatory phenotype of the immune cells aggregate at the damage sites to initiate an immune inflammatory response following SCI (Rice et al., 2007; Fan et al., 2020). After SCI, astrocytes play a vital role in SCI pathology through a phenotypic change called reactive cells (Hara et al., 2017). Reactive astrocytes are commonly divided into A1 and A2 types, which are analogous to macrophages M1 and M2 (Liddelow and Barres, 2017; Liddelow et al., 2017; Vismara et al., 2020). Microglia refers to macrophage in the central nervous system (CNS) (Yu et al., 2021). Noteworthy is that invasive macrophages have different functions from microglia (Milich et al., 2019). Classical activated neuro-inflammatory microglia can induce the production of A1 reactive astrocytes (Liddelow et al., 2017). Activated macrophage/microglia are polarized into M1 and M2 sub-types, exhibiting pro-inflammatory and anti-inflammatory effects following SCI (Ransohoff, 2016; Lin et al., 2020). For instance, M1 phenotype generate pro-inflammatory cytokines

(such as TNF- α and IL-1 β), while M2 phenotype may curtail inflammation via IL-4 and IL-10 cytokines (Jiang et al., 2017). The ratio of M1 to M2 influences the microenvironment of the spinal cord tissue after injury, as the augmentation of M1 phenotype after SCI will negatively affect the injury repair (Fan et al., 2018). Besides, reactive oxygen species (ROS) can lead to cell and tissue dysfunction through the oxidation of DNA and cell membranes, which further causes inflammation (Hervera et al., 2018; Kertmen et al., 2018). SCI comprises of three stages; acute stage, acute secondary stage, and chronic stage (Nukolova et al., 2018).

The Role of Inflammatory Reaction in Acute Spinal Cord Injury

Acute SCI is one of the stages of SCI. At this stage, cell fragments are formed and intracellular proteins are released as potent inflammatory stimuli. These injury-exposed fragment signals, also known as damage-associated molecular patterns (DAMPs), activate pattern recognition receptors (PRRs) on inflammatory cells after SCI (Orr and Gensel, 2018). The acute SCI includes primary and secondary injuries. Oxidative stress leads to the release of cytoplasmic components and mitochondrial dysfunction in primary SCI. Secondary injury begins as early as minutes after the primary SCI, and involves spinal cord ischemia and free radical-mediated peroxidation (Albayar et al., 2019; Pinchi et al., 2019). Oxidative stress is the main cause of neuronal tissue damage, as it can initiate cytotoxicity by enhancing lipid peroxidation in damaged neuronal tissue (Guan et al., 2020). In particular, lipid peroxidation is extremely important in acute SCI (Kwon et al., 2004). Secondary SCI has inflammatory reaction that leads to edema and hemorrhage, which in turn aggravates the injured area. Macrophages, neutrophils and T-cells invade damaged sites, leading to blood-brain barrier disruption (Lambrechts and Cook, 2021; **Figure 1**). The first infiltrated inflammatory cells are neutrophils, which peak around day 1 after acute SCI. Neutrophils decrease within 1 week of injury, while monocytes increase in the spinal cord. Similarly, T and B-lymphocytes being to gradually increase during the first week after injury (Wu et al., 2019; **Figure 1**). Subsequent to acute SCI, ischemia leads to the formation of an acidic environment. Moreover, macrophage infiltration and the activation of microglia further promote the release of pro-inflammatory factors, including TNF- α , IL-1 β , and interleukin 6 (IL-6) (Xi et al., 2021; **Figure 1**). The microglia are the key immune cell type in CNS (DiSabato et al., 2016). Under normal circumstances, microglia perform immune defense mechanisms, regulate neuronal and synaptic activities, secrete nutritional factors and support neuronal survival and axon growth in CNS (DiSabato et al., 2016; Gaudet and Fonken, 2018). The microglia can be strongly activated and carry out double-edged tasks following SCI (Gaudet and Fonken, 2018). The microglial and macrophages can have beneficial roles in acute SCI. A large number of macrophages and microglia are recruited in the lesion epicenter within 7 days after SCI (Stirling and Yong, 2008). Activated microglial and macrophages secrete products that promote



axon growth. Zymosan-activated macrophages create a growth-microenvironment to increase the density of axons *in vivo* (Gensel et al., 2009). A study has showed that M1 phenotype cells can produce proteases and oxidative metabolites to kill neurons and glia, conversely, M2 phenotype cells can contribute to tissue repair via downregulating inflammatory responses in SCI (Kigerl et al., 2009). Acute SCI leads to chronic SCI, and chronic complications after acute SCI are detrimental (Chen et al., 2020).

The Role of Inflammatory Reaction in Chronic Spinal Cord Injury

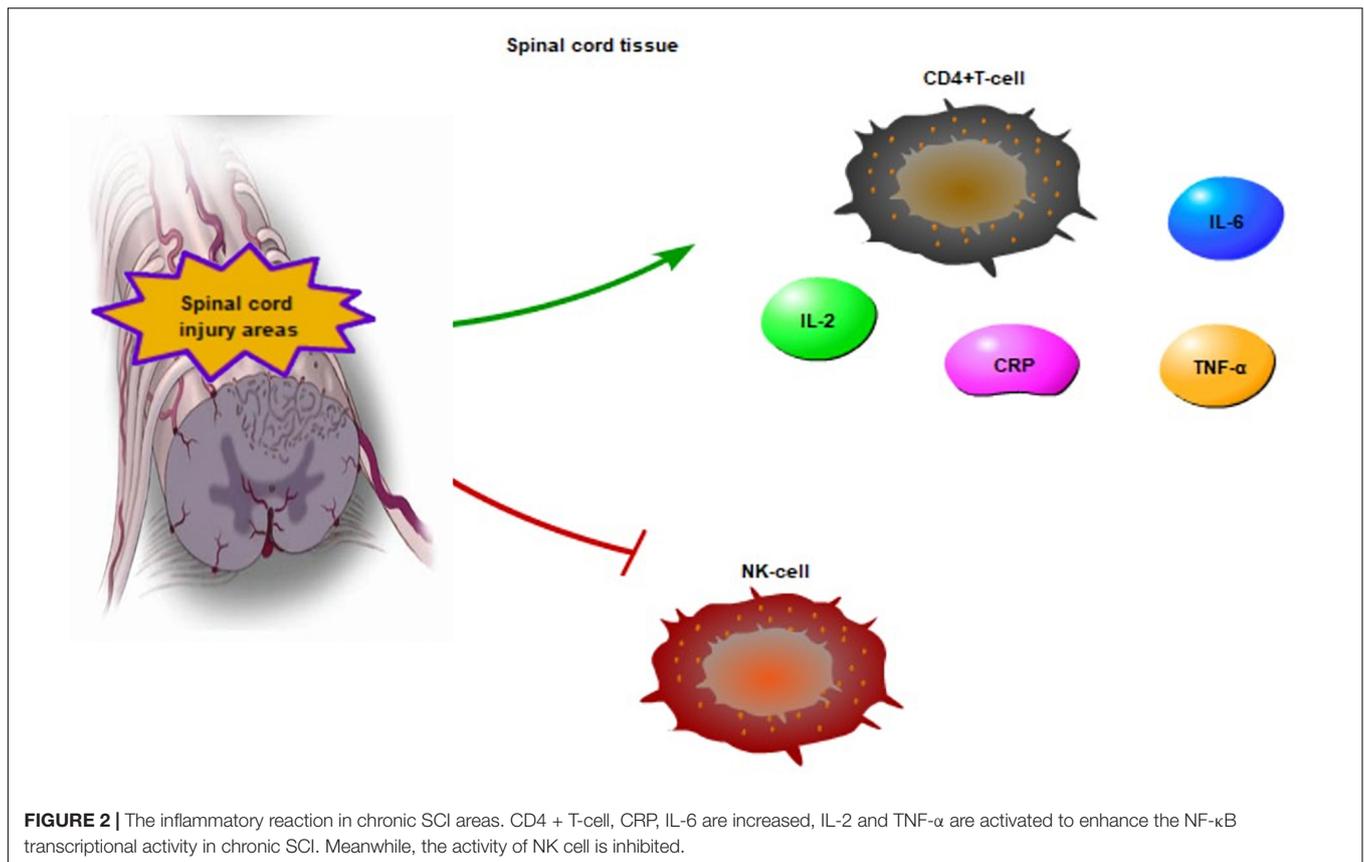
Systemic inflammation is key to chronic SCI (Diaz et al., 2021). Systemic inflammatory markers, such as c-reactive protein (CRP) and IL-6, are increased after chronic SCI (Hart et al., 2016; Lynch et al., 2017; Dugan et al., 2021). Chronic SCI can intensify IL-2 and TNF- α levels to upregulate the NF- κ B transcriptional activity (Yarar-Fisher et al., 2016). Microglia appears to be strongly related to chronic neuroinflammation after SCI, and microglial cells expressing TNF- α may transform the polarization of astrocytes to neurotoxic phenotypes (Yoshizaki et al., 2021). Besides, natural killer cell numbers, cytotoxic activity levels, and T-lymphocytes in patients with chronic SCI exhibit abnormal function (Figure 2). There are indications that CD4⁺ T cells are increased in the spinal tissue (Monahan et al., 2015;

Herman et al., 2018). Therefore, several factors such as IL-2, IL-6, CRP, TNF- α and CD4⁺T cells can be activated, however, NK cells can be inhibited in chronic SCI (Figure 2). Chronic SCI is a period of stabilization and low activity, where the nerve function around the injured areas gradually decreases (Rodríguez-Barrera et al., 2017).

SAFFLOWER YELLOW CAN INHIBIT INFLAMMATORY REACTION

The Biological Role of Safflower Yellow

Carthamus tinctorius is a plant of Compositae or Asteraceae family (Delshad et al., 2018). Safflower is the dry flower of *Carthamus tinctorius*, a commonly used traditional Chinese medicine that has been reported to improve trauma, gynecological disease, cardiovascular conditions, blood circulation, and remove blood stasis (Wang et al., 2011). SY is the effective component of safflower water-soluble extract, with its main component being hydroxysafflower yellow (Asgarpanah and Kazemivash, 2013; Li H. et al., 2020; Wang et al., 2020). The molecular formula of SY is C₆₀H₇₄O₃₈, contains hydroxyl groups, carbonyl groups, aromatic rings and conjugated carbonyl groups. Hydroxysafflower yellow A-4'-O-b-D-glucopyranoside and 3'-hydroxyhydroxysafflower yellow A are separated from the SY (Zhang et al., 2020). SY has anti-infection and anti-inflammatory



properties, and has been used for the clinical treatment of patients who suffer from severe sepsis and septic shock (Li et al., 2016). Furthermore, SY has anti-fibrotic (Wang et al., 2011), anti-oxidative (Wang et al., 2020), anti-coagulative (Sun et al., 2010), anti-obesity (Yan et al., 2020), anti-calcium-antagonist (Du et al., 2019), and neuroprotective effects (Pang et al., 2020). In recent times, the mediation of SY in inflammation has attracted significant attention.

Safflower Yellow Inhibits the HMGB1-TLR4-NF- κ B Signaling Pathway

High mobility group box 1 protein (HMGB1) is a nuclear non-histone DNA-binding protein expressed in all nuclear animal cells, and can be used as a potent inflammatory late mediator when passively secreted during inflammatory response (Scaffidi et al., 2010; Li et al., 2015). HMGB1, which can stimulate neuroinflammatory responses under deleterious conditions, is a damage-associated molecular pattern (DAMP) molecule (Yu et al., 2019). HMGB1 can induce intracellular signaling pathway by interacting with at least three pattern recognition receptors: Toll-like receptor-2 (TLR-2) and TLR-4, and the receptor for advanced glycation products (PAGE) (van Zoelen et al., 2009). Among them, TLR-2 and TLR-4 are key players, while PAGE has a minimal role (Park et al., 2004). The migration ability of breast cancer cells is closely related to HMGB1 (Lv et al., 2016). HMGB1 can be released from the nucleus to the cytoplasm

under damage conditions to activate TLR4 signaling pathway and play a biological role (Lv et al., 2016; Antón et al., 2017; Xu et al., 2020). HMGB1 and TLR-4 interactions may lead to NF- κ B upregulation, which results in producing and releasing inflammatory cytokines, such as IL-1 β , TNF- α and IL-6 (Zhang et al., 2007; Kang et al., 2015; Wang et al., 2015; Xu et al., 2020; **Figure 3**). The HMGB1-TLR4-NF- κ B signaling pathway is an inflammatory signaling pathway that mediates multiple inflammation-related pathways (Sun et al., 2019). NF- κ B is a well-established inflammatory transcription factors produced by almost all animal cells. More importantly, the NF- κ B signaling pathway has a significant number of target genes that can regulate a variety of biological functions, including inflammation, apoptosis, cell adhesion, cell stress response, and immunity (Jing and Lee, 2014). More importantly, the NF- κ B signaling pathway is instrumental in inflammation (Ma and Hottiger, 2016). There is a positive feedback mechanism between inflammation and the NF- κ B signaling pathway after SCI (Károva et al., 2019). Exposing neutrophils or macrophages to HMGB1 can lead to enhanced NF- κ B signaling pathway and pro-inflammatory cytokine expression (Park et al., 2004). Interestingly, SY can improve inflammatory response and exert effect on inflammatory factors, like TNF- α , IL-1(IL-1 β), and IL-6 (Zhou et al., 2018; Du et al., 2019; **Figure 3**). Furthermore, SY can inhibit the activation of the NF- κ B signaling pathway by suppressing I κ B α phosphorylation and cell nucleus translocation of p65 (Li et al., 2013; **Figure 3**). Moreover, SY may suppress the NF- κ B signaling

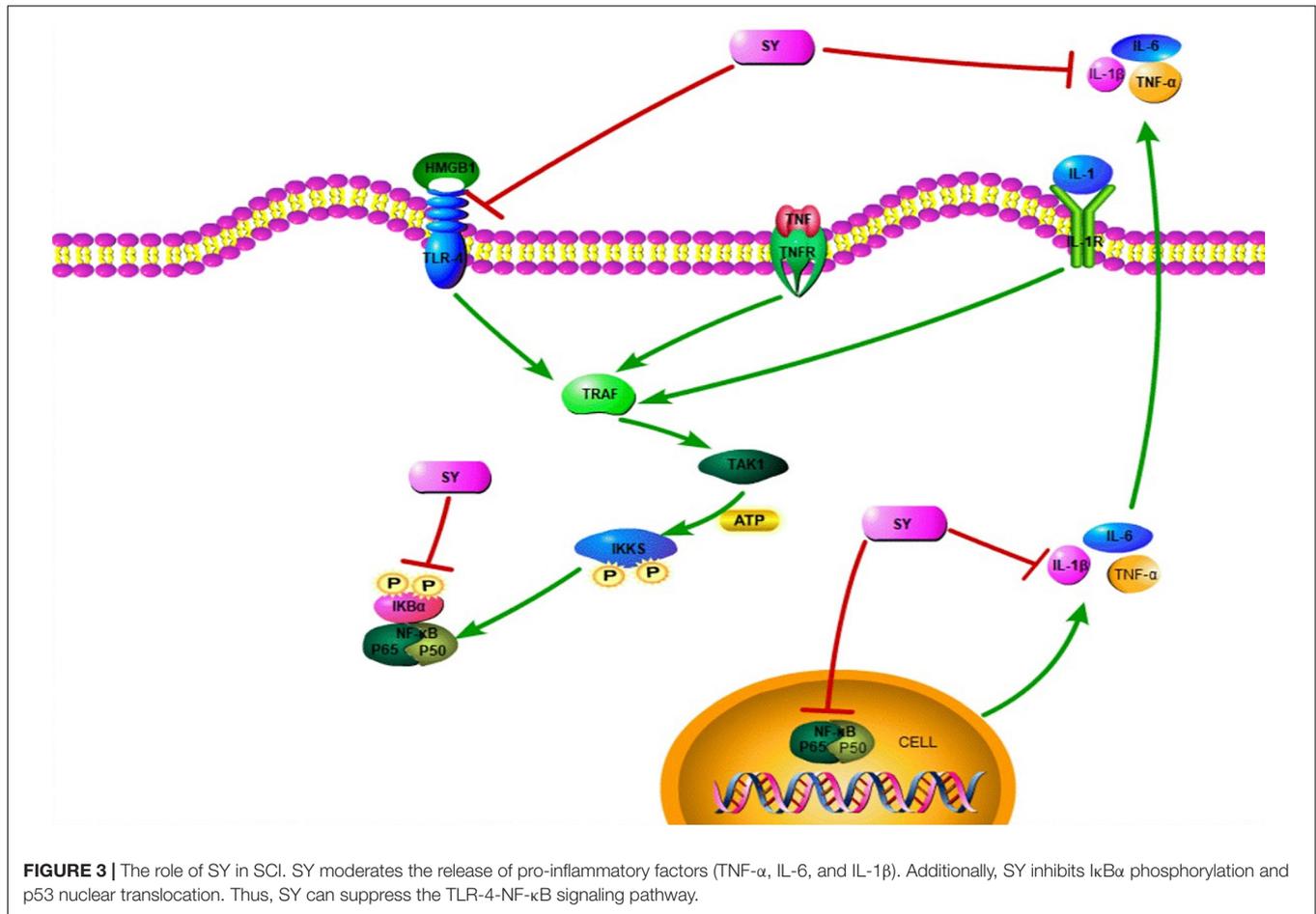


FIGURE 3 | The role of SY in SCI. SY moderates the release of pro-inflammatory factors (TNF- α , IL-6, and IL-1 β). Additionally, SY inhibits I κ B α phosphorylation and p53 nuclear translocation. Thus, SY can suppress the TLR-4-NF- κ B signaling pathway.

TABLE 1 | Beneficial effects of SY in diseases.

Diseases	Species	Doses	Outcome	References
Pulmonary fibrosis	Rats	0.25 mg/ml	SY can inhibit α -SMA mRNA expression in lung fibroblast.	Wang et al., 2011
Osteoarthritis	Rats	50 μ g/ml	SY can regulate NF- κ B/SIRT1/AMPK signaling pathway, and prevent inflammation.	Wang et al., 2020
Focal cerebral	Rats	8 mg/kg	HSYA suppresses thrombin formation and inflammatory responses.	Sun et al., 2010
Obesity	Mice	120 mg/kg	SY may improve insulin sensitivity.	Yan et al., 2020
Cerebral ischemia	Rats	8 mg/kg	SYB can activate AMPK and reduce NF- κ B mediated inflammation.	Du et al., 2019
Alzheimer's disease (AD)	Mice	30 mg/kg	SY can improve learning and memory functions.	Pang et al., 2020
CNS	Cell	80 μ g/ml	SY can inhibit inflammatory response.	Yang et al., 2016
AD	Mice	100 mg/kg	SY can improve AD by decreasing the expression of proteins related to β -amyloid formation.	Shi et al., 2018
ROS	Cell	/	SYB can effectively reduce ROS generation by decreasing NADPH oxidase activity.	Wang et al., 2013
Bone fracture	Cell	18 μ g/ml	SY can promote angiogenesis to improve bone fracture.	Tang et al., 2018
Obesity/diabetic	Mice	80 μ g/ml	SY can reduce body fat mass and improve insulin sensitivity.	Zhu et al., 2016
Cardiovascular disease (CVD)	Mice	25 μ g/ml	SY has an effect on angiotensin II-induced adventitial fibroblast proliferation.	Liu et al., 2014
CVD	Cell	20 μ g/ml	HSYA can decrease PDGF-BB-induced proliferation, migration, and Akt signaling pathway.	Song et al., 2014
AD	Cell	10 μ g/ml	HSYA can inhibit neuroinflammation by reducing A β 1-42-induced cytotoxicity in BV-2 cells.	Zhang et al., 2014
SCI	Rabbits	90 μ g/ml	SY can improve SCI by enhancing Bcl-2 expression and inhibiting Bax and caspase-3 activation.	Zhou et al., 2013

pathway by restricting the TNF- α (Wang et al., 2020). SY has a significant role in the minimization of ROS level (Lu et al., 2019). Also, SY can downregulate the TLR-4 expression (Yang et al., 2015; **Figure 3**). Besides, SY can transform microglia from inflammatory M1 to anti-inflammatory M2, which then plays an anti-inflammatory role by hindering the TLR-4-NF- κ B signaling pathway (Yang et al., 2016). SY has been widely studied in various diseases, most especially, SCI (**Table 1**).

CONCLUDING REMARKS

Inflammation plays an important role in SCI, which have been expounded in this report. The NF- κ B is a central transcription factor of inflammatory mediators, and the neuroinflammatory response caused by activated microglia through the NF- κ B pathway is a consequential contributing factor to secondary injury (Chen et al., 2018). The HMGB1-TLR-4-NF- κ B signaling is an inflammatory pathway upregulated during SCI. Particularly, HMGB1 and TLR-4 interactions can lead to NF- κ B upregulation, which in turn results in the formation and release of inflammatory cytokines at increasing levels in secondary SCI (Zhang et al., 2007;

Wang et al., 2015). SY has several pharmacological effects, such as anti-inflammation and anti-oxidation. SY may mitigate the release of pro-inflammatory factors, TNF- α , IL-1 β , and IL-6. Far more, SY can inhibit the HMGB1-TLR-4-NF- κ B signaling pathway to ameliorate inflammatory response and offer protection to the spinal cord in the event of an injury. Notwithstanding, the specific molecular mechanism of HMGB1-TLR-4-NF- κ B following SCI are presently unclear, and warrants further thorough investigations using appropriate experimental models.

AUTHOR CONTRIBUTIONS

XL designed the study. LW, BOAB, and XL prepared the first draft of the manuscript and revised the manuscript. All authors approved the final manuscript.

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