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REVIEW PAPER

Curcumin Can Improve Spinal Cord Injury by Inhibiting TGF-β-SOX9 Signaling Pathway

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Abstract

Spinal cord injury (SCI) is a severe nervous system disease with high morbidity and disability rate. Signaling pathways play a key role in the neuronal restorative mechanism following SCI. SRY-related high mobility group (HMG)-box gene 9 (SOX9) affects glial scar formation via Transforming growth factor beta (TGF-β) signaling pathway. Activation of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) is transferred into nucleus to upregulate TGF-β-SOX9. Curcumin exhibits potent anti-inflammatory and anti-oxidant properties. Curcumin can play an important role in SCI recovery by inhibiting the expression of NF-κB and TGF-β-SOX9. Herein, we review the potential mechanism of curcumin-inhibiting SOX9 signaling pathway in SCI treatment. The inhibition of NF-κB and SOX9 signaling pathway by curcumin has the potentiality of serving as neuronal regenerative mechanism following SCI.

Keywords Curcumin · SOX9 signaling pathway · NF-κB signaling pathway · Spinal cord injury · Neuroregeneration · Anti-oxidation · Anti-inflammation

Introduction

Traffic and construction accidents can cause SCI. According to the United States nationwide patient statistics (between the years 1993 and 2012), the average annual incidence rate of acute SCI was about 54 cases per one million, with men being the most injured. The highest SCI incidence rates occur in individuals between the ages of 15 and 24 (Jain et al. 2015). The extent of SCI depends on both primary and secondary mechanisms. The duration of these mechanism could be anywhere from hours, days or years from the start of injury. Primary mechanism refers to the force directly impacted to the spinal cord, which in turn, could disrupt the axons (Sutherland et al. 2016). Secondary mechanism involves a variety of complex pathophysiological processes such as apoptosis, inflammation, formation of free radicals and free radical-induced cell death, scar formation, and edema (Liu and Xu 2012; Zhou et al. 2014). Since primary mechanism is irreversible, current innovative treatments seek to target the secondary mechanism (Hayta and Elden 2018). Primary injury initiates a sequence of events that lead to secondary neuronal cell damage. Secondary injury treatment seeks to target inflammation, scar formation, disruption of the blood spinal cord barrier, and oxidative stress (Ham and Leipzig 2018). Although no effective treatment for SCI currently exists, there is the notion that signaling pathways might play an important role in SCI repair (Yang et al. 2018; Lim et al. 2017; Wang et al. 2017; Irrera et al. 2018; Chen et al. 2015). SOX9 signaling which acts as a key transcriptional factor in SCI was involved in scar formation (Chen et al. 2018; McKillop et al. 2016). Also, curcumin inhibited TGF-β-SOX9 signaling pathway during SCI repair (Yuan et al. 2017).

Relationship Between SOX9 Signaling Pathway and SCI

SOX gene family are part of HMG proteins (Lovell-Badge 2010). SOX proteins could couple with other specific partner proteins to regulate gene transcription.

SOX proteins possess DNA-bending features, which in turn, could assist in their ability to select distinct sites of

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target genes. That said, other elements are involved in choosing the distinct target site. This means that SOX proteins are not the principal element in this selection. In order to exert an effective regulatory function, SOX proteins require both enhancers and second site to bind partner proteins. Some enhancers of SOX9 are collagen type II alpha-1 (Col2a1) minimal enhancer (COL2C2) and splicing factor 1 (SF1). SOX9 does couple with COL2C2 and SF1 to encode CO12a1 and anti-Müllerian hormone (AMH), respectively (Kamachi et al. 1999, 2000).

SOX9 Biological Function

SOX9, a member of the SOXE group, plays an important role in SCI (Xia and Zhu 2015). The relationship between SOX9 and glial scar formation has been evidenced (Xu et al. 2018). In the course of early neuroectodermal development of embryonic stem cells, the upregulation of SOX9 following Notch-1 activation increased and decreased neural stem cells and neurons respectively as well as stimulated both astroglial cell differentiation and neural crest development (Martini et al. 2013). During intrahepatic bile duct development, TGF-β signaling potentially modulated the Jagged-1-Notch-SOX9 signaling axis, and acted as the upstream factor of Notch-SOX9 (Wang et al. 2018). Inflammation has been associated with TGF-β signaling in SCI (Martini et al. 2013; Xun et al. 2017). In a murine model of Osteoarthritis (OA), TGF-β regulated SOX9 via two different ways (Fig. 1); (1) the typical way that required both P38 and serine 211; and (2) the atypical way, which was related to Samds (Coricor and Serra 2016). There are three subtypes of TGF-β, with the subtype I being a significant hindrance to the formation of fibrosis. These functions are activated by the interaction between ligands, specific transmembrane receptors, and intrinsic serine/threonine kinase activity(Wang et al. 2018). SOX9 is essential in the nervous system that could potentially induce glial traits and repress neuronal traits, stimulate SOX9-dependent astrocytes proliferation along with neuronal degeneration, hemorrhage, and breakdown of nervous tissue(Xia and Zhu 2015; Romero-Alemán Mdel et al. 2013).

SOX9 Signaling Promotes Glial Scar Formation

Glial scar consists of extracellular matrix (ECM), which is expressed by reactive astrocytes. Reactive astrocytes include macrophages, microglia, oligodendrocytes, invading Schwann cells, and meningeal fibroblasts (Fan et al. 2016; Wang et al. 2018; Fawcett and Asher 1999). Reactive astrocytes is a potential participant in scar formation (Fawcett and Asher 1999). Chondroitin sulfate proteoglycans (CSPGs), one of the main members of the ECM molecules, sealed wound and inhibited axonal regeneration (Eddleston and Mucke 1993; Schäfer and Tegeder 2018). SOX9 gene has a close relationship with GCPGs and glial fibrillary acidic protein (GFAP). Since the deletion of SOX9 gene did reduce glial scar formation, SOX9 inhibition could be a novel therapeutic strategy for SCI treatment (Gris et al. 2007). The expression of different CSPGs relies on the enzymes, xylosyltransferase-I and -II (XT-I, XT-II) and chondroitin

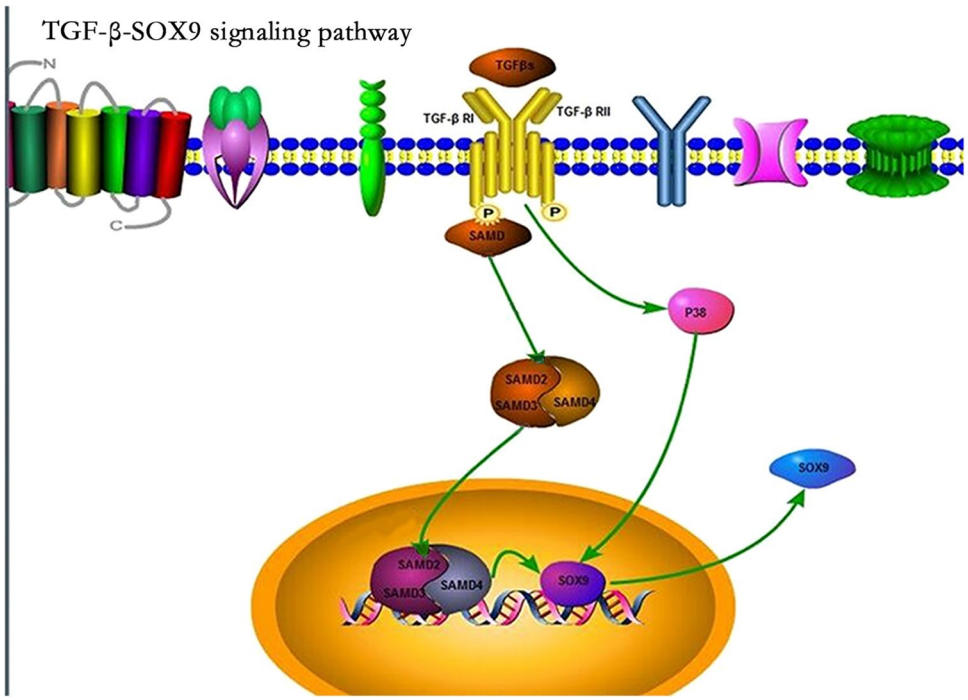

Fig. 1 TGF-β regulated SOX9 via P38 and SAMD two different ways

4-sulfotransferase (C4ST), which acted as part of the CSPG biosynthetic gene (CBG) battery (McKillop et al. 2016). The over-expression of SOX9 significantly stimulated CBG expression, while the knockout of SOX9 gene did the contrary, i.e., reduced CBG expression (McKillop et al. 2016; Gris et al. 2007; Jiansheng et al. 2016).

The Relationship Between NF-κB and TGF-β-SOX9 Signaling Pathways

Secondary injury is activated by inflammation in SCI. NF-κB as a vital nuclear factor in inflammation; the inactive NF-κB combines with IκB (inhibitor kappa B) to form inactive trimer in endochylema. The trimer in NF-κB and IκB covers the nuclear localization sequence of NF-κB that inhibits the activation and nuclear translocation of NF-Kb (Shifera 2010). Thus the degradation of IκB is indispensable to the activation of NF-κB, and IκB degradation is regulated by IκB kinase. Specifically, the degradation signal is phosphorylation of the 42′serine residue in IκB that is catalyzed by the IκB kinase. The rapid degradation of IκB occurs within several minutes, along with the exposure for the nuclear localization sequence of NF-κB (Oeckinghaus and Ghosh 2009). NF-κB binds to κB in the NF-κB reaction gene, and regulates the gene transcription and cellular processes, such as cell growth, differentiation, adhesion, apoptosis, and inflammatory response (Schuliga 2015).

In the Cytokine signaling pathway, which is relevant to SCI, interleukin 1 receptor, type I (IL-1R1), and IL-18Rα are members of the IL-1R/TLR superfamily of receptors that share similar signaling pathways (Dinarello 2009). Once the IL-1α/IL-1β and IL-18 bind to their respective ligands, a second receptor, which is a subunit in the cell membrane is recruited; IL-1 RAcP for IL-1R1 and IL-18Rβ for IL-18Rα(Tsakiri et al. 2008). Subsequent formation of the receptors heterodimers causes the recruitment of MyD88, IRAKs, and TRAF6. The ensuing cellular marks are mediated by NF-κB and MAPK-dependent gene expression (O'Neill 2008). According to the formation of the receptor complexes formed and downstream signaling cascades, a broad spectrum of effects are induced, including regulation of inflammatory gene expression and cell death and survival (Bastien and Lacroix 2014). Relying on the TGF-β RI—TGF-β RII complex, the action of the three TGF-βs promotes the phosphorylation of mothers against decapentaplegic homolog (SMAD) transcription factors. In spinal cord injured rats, chronic inhibition of TGF-ß1 suppressed glial scar formation and upregulated the markers of microglia/macrophage activation (Fig. 2). Thus, TGF-β might shed light on new ideas in improving locomotion after SCI (Kohta et al. 2009).

Curcumin Repairs SCI by Inhibiting TGF-β-SOX9 Signaling Pathway

Traditional Chinese Medicine (TCM) has been widely used for thousands of years. Owing to its medicinal value, it is currently gaining interests in the research community. Curcumin is a rhizome extracted in curcuma longa L (Toda et al. 1985). Curcumin's pharmacological activities have

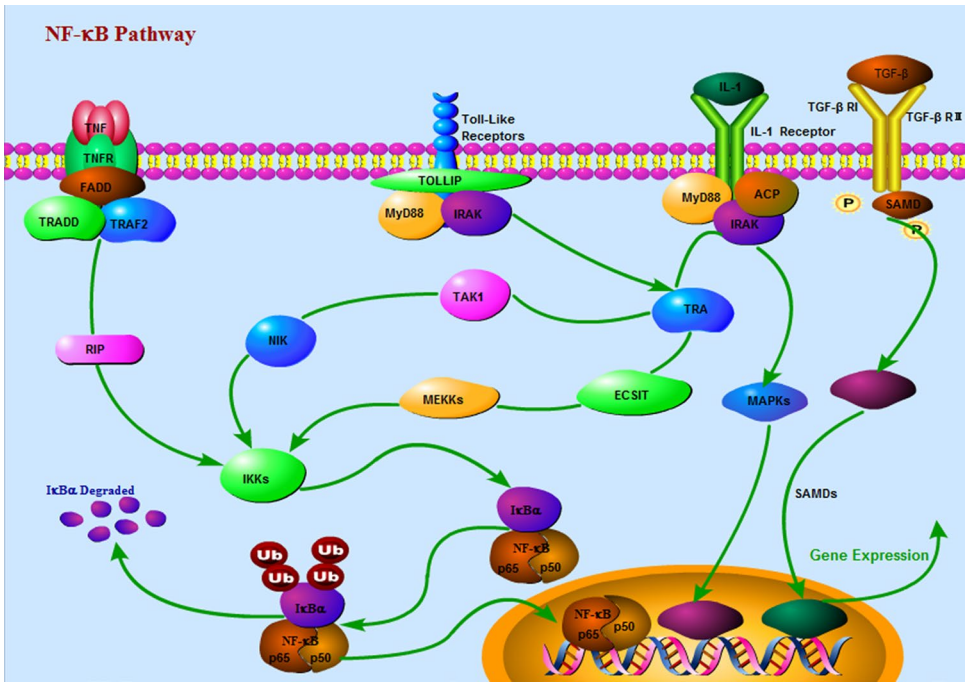

Fig. 2 The relationship between NF-κB and TGF-β-SOX9 signaling pathways

been extensively reported in several diseases such as Alzheimer's disease, with some of its potent pharmacological actions being anti-oxidation and anti-inflammation (Botchway et al. 2018). In atherosclerotic rabbits, curcumin longa supplementation curtailed oxidative stress and impaired fatty streaks formation (Quiles et al. 2002). Curcumin curtails inflammation and oxidative stress by inhibiting NF-κB activation and upregulating nuclear factor-like 2 (Nrf2) expression, respectively. The inhibition of NF-κB activation by curcumin was through p65 translocation while the activation of Nrf2 enhanced the activities of superoxide dismutase (SOD) and catalase (CAT) as well as glutathione levels (Cheng et al. 2018). In cerebral ischemia–reperfusion, curcumin inhibited both autophagic activities and inflammation through the regulation of PI3K/Akt/mTOR and TLR4/p38/MAPK pathways, respectively (Huang et al. 2018). In a Parkinson disease study, curcumin inhibited astrogliosis and significantly suppressed NF-κB activation, while also significantly prevented the release of pro-inflammatory mediators, such as tumor necrosis factor-alpha (TNF-a), IL-1b, and inducible nitric oxide synthase (iNOS). These evidences the neuroprotective effects of curcumin (Sharma and Nehru 2018). The improvement in the stability and systemic bioavailability of curcumin showed ameliorated anti-inflammatory effects through its inhibition of TAK1-NF-κB pathway (Zhang et al. 2018).

Therapeutic Effect of Curcumin Through Suppression of TGF-β-SOX9 Signaling Pathway

Curcumin reduces related inflammatory factors such as TNF-α and IL-1β, thus, providing a better environment for axonal recovery. The inhibition of inflammatory-related factors and NF-κB signaling pathway by curcumin was significant in suppressing secondary injury such as scar formation (Yuan et al. 2015). TGF-β did enhance SOX9 expression in cancer via the c-Jun pathway, with patients manifesting higher SOX9 expression having shorter overall survival (Zhang et al. 2017). During the culturing of nucleus pulposus cells (NPCs) and mesenchymal stem cells (MSCs), TGF-β1 stimulated COL1A1 and SOX9 expressions (Lehmann et al. 2018). SOX9 was also a participant in the downstream target of the TGF-β signaling in renal fibrosis (Li et al. 2018). TGF-β signaling played an important role in CCL4-induced liver fibrosis along with the upregulation of SOX9 (Chen et al. 2017). In Ischemia/reperfusion (IR) liver injured mice, the activation of TGF-β1 promoted inflammation and apoptosis and enhanced SOX9 expressions, with SOX9 subsequently regulating IL-1β, TNF-a, IL-6, and p-NF-kB(Fan et al. 2018). What's more, activation of SOX9 tubular made a great contribution to both acute kidney injury and chronic kidney disease along with renal ischemia, hypoxia, and chronic fibrosis, which were expressed only in renal tubular epithelial cell (Zhu et al. 2017). Also, TGF-β-SOX9 axis promoted proliferation and metastasis of lung cancer cells via C-jun/SMAD3 pathway following the examination of a number of clinical non-small lung cancer samples (Zhang et al. 2017; Wang et al. 2018a, b, c). In oral submucosa fibrosis (OSMF), TGF-β and inducible nitric oxide synthase (iNOS) stimulated the proliferation of fibroblasts and collagen synthesis and downregulated collagenase production (Kale et al. 2013). Fibroblasts potentially forms fibrotic scar, which in turn hinders axonal regeneration and functional recovery in SCI (Xie et al. 2018). Curcumin could inhibit the expressions of TGF-β and iNOS. This, in turn, could potentially curtail the formation of fibrotic scar and improve axonal regeneration and functional recovery in SCI. While it is evident that curcumin decreases the ubiquitination of TGF-β, it also downregulate TGF-β expression and its downstream factor SOX9.

Curcumin did inhibit CSPG-related transcription factors such as TGF-β1,TGF-β2, and SOX9, and downregulated the gene levels of TGF-β and SOX9. Also, curcumin curtailed the GFAP-related inflammatory factors such as TNF-α, IL-1β, and NF-κB, The activation of NF-κB signaling pathway, which is an essential link in SCI, was significantly suppressed by curcumin, with reduction of inflammatory-related factors and recovery of lesion structures (Yuan et al. 2015; Xie et al. 2018; Yu et al. 2013). Curcumin inhibited SOX9 expression in a cancer study where augmented expression of SOX9 was discerned and was correlated with disease progression. Additionally, the downregulation of miR145-SOX9/ADAM17 axis improved the disease treatment (Yu et al. 2013). In promoting functional recovery in SCI, curcumin decreased GFAP and CSPG levels (Bang et al. 2018; Liu et al. 2018a, b).

Curcumin Inhibits TGF-β-SOX9 Signaling Pathway to Reduce Glial Scar Formation in Nervous System Injury

TGF-β and SOX9, both of which contribute to glial scar formation, are significantly inhibited by curcumin. Active astrogloisis plays an important role in SCI by promoting glial scar formation. Also, a study reported type I collagen (Col I) genes (Col1a1 and Col1a2) to be the most significantly expressed (Hara and Kobayakawa 2017). Additionally, astrocyte activation and scar formation were both inhibited through the suppression of miRNA expression in a SCI mice model. Since miRNA is closely related to TGF-β signaling, it could potentially be a downstream factor of TGF-β(Liu et al. 2018). SOX9 protein expression associated to DJ-1 gene was involved in astrogliosis and growth factor production, and inhibited brain injury recovery (Choi et al. 2018). Curcumin inhibited the expression of TGFβ1-induced Nox4, decreased the phosphorylation of Smad3 and eliminated H_2O_2, subsequently

suppressed the release of collagen and prevented fibrotic scarring (Brown et al. 2017). Smad proteins, downstream signaling molecules of TGF-β, were significantly increased, with TGF-β signaling expression being activated following stroke (Li et al. 2017; Doyle et al. 2010). In a stroke study, TGF-β improved astrocytic functions (Cekanaviciute et al. 2014). The transcription factor Olig2, which was regulated by SOX9 + progenitor cells played an important role in the development of oligodendrocytes and gliogenesis (Marsters et al. 2016). SOX9 has been reported to be an astrocytic marker (Sun et al. 2017). The knockdown of SOX9 significantly reduced the levels of GFAP, collagen, and CSPG and promoted locomotor recovery in SCI (Mckillop et al. 2012). Curcumin significantly decreased the inflammatory factors in a SCI mice model, with the expressions of TGF-β and SOX9 both inhibited. The effects of curcumin in this study were dependent on the curcumin (Raghavendra et al. 2016).

Conclusion

Glial scar formation, which ensues in SCI, is activated by inflammation. At the molecular level, TGF-β-SOX9 signaling significantly contributes to this formation. NF-KB, a nuclear factor in inflammation is associated with glial scar formation via TGF-β-SOX9 signaling pathway. Curcumin, possessing both anti-inflammatory and anti-oxidative features, could inhibit the activation of NF-κB and TGF-β-SOX9 signaling pathways, and reduce the expression of GFAP and CSPG along with α-SMA, an important element in glial scar formation. With no issues relating to its safety and having multiple therapeutic effects, curcumin could improve SCI; however, the specific mechanisms regarding its therapeutic effects at the molecular level need to be thoroughly elucidated.

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Compliance with Ethical Standards

Conflict of interest None to declare.

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