Potential therapeutic mechanism of traditional Chinese medicine monomers on neurological recovery after spinal cord injury

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Spinal cord injury (SCI) is a common traumatic disease of the central nervous system; it causes serious physical and psychological harm to patients and a huge economic burden on the entire society.[1] The tough situation of SCI treatment requires further exploration of the mechanism and obtaining a new therapeutic strategy.

Traditional Chinese medicine (TCM) is based on syndrome differentiation and treatment and overall concepts, and TCM compounds are used as the main method to treat diseases. However, its specific molecular mechanism has not been elucidated.

In recent years, with the development and rise of Chinese medicine culture, TCM monomer research has become the main method to study the disease resistance mechanism of TCM. Recent studies have shown that multiple TCM monomers, such as triptolide, curcumin, and ginsenoside, play important roles in the treatment of SCI rats. In the present study, we summarized the TCM monomers related to inflammatory response, apoptosis, neuronal autophagy, oxidative stress, and nerve regeneration after SCI and explained the specific molecular mechanism of each TCM monomer. Combined with the results of our previous experiments,[2] we summarized that (1) TCM monomers inhibit the occurrence and development of inflammatory reactions through the Wnt/β-catenin/nuclear factor-kappa B (NF-κB) signaling pathway in SCI rats and (2) the neuronal inflammatory response regulated by the Wnt/β-catenin/NF-κB signaling pathway has a protective effect on neural function recovery in SCI rats [Figure 1]. This innovative hypothesis provides a new molecular mechanism for the application of related TCM monomers after SCI.

Neural inflammation plays an important role in diseases of the central nervous system. Among the TCM monomers, triptolide, sinomenine, paoniflorin, curcumin, ginsenoside, ginkgolide, baicalin, resveratrol, and saikosaponin exert neuroprotective effect after SCI through anti-inflammatory effects. Their specific molecular mechanisms include inhibiting the activation of microglia and astrocytes, promoting the migration of olfactory ensheathing cells, reducing the release of inflammatory cytokines, regulating microRNA (miRNA) to inhibit the inflammatory response, and mediating the related inflammatory signaling pathways.

After SCI, inflammatory cell infiltration and microglia activation occur at the site of injury, resulting in spinal cord tissue degeneration and neurological dysfunction. Microglia promote inflammatory response by activating and releasing inflammatory cytokines after SCI. Triptolide could inhibit the production of inflammatory factor, tumor necrosis factor (TNF)-α, and interleukin-1β (IL-1β) in the microglia to protect against inflammatory response-mediated neuronal injury and promote spinal cord repair.[3]

Astrocytes could be activated in the body by physical, chemical, and pathological traumas. The activated reactive astrocytes upregulate intermediate filament proteins, which could form obvious glial scar tissues at the injury site, thus affecting neuron-axon regeneration and functional recovery. Triptolide could also inhibit the activation of astrocytes by reducing the expression of intermediate filament proteins and improve the expression of injury-induced mast cells and their cytokolic proteins.[4]

Olfactory ensheathing cells are special glial cells that protect neurons by secreting a neurotrophic factor that inhibits scar formation in the injured spinal cord. They play a crucial role in neuronal protection due to their ability to migrate, proliferate, secrete various neurotrophic factors, and promote axonal regeneration. The TCM monomer ginsenoside Rg1 could promote the migration of olfactory ensheathing cells through the phosphatidylinositol 3 kinase/protein kinase B pathway; reduce the expression of related inflammatory...
cytokines TNF-α, IL-1, and IL-6; and promote the functional repair of SCI in rats.\[5\]

miRNAs regulate the pathology of inflammation after SCI and are a new target for treatment. miR-96 is related to nerve injury. After peripheral nerve injury in rats, the expression of miR-96 in the ipsilateral dorsal root ganglia was downregulated, and an intrathecal injection of miR-96 could reduce the pathological symptoms caused by nerve injury.\[3\] Experiments showed that triptolide could reduce the expression of inflammatory cytokines, such as ionized calcium binding adaptor molecule-1, IKKB, phosphorylated-inhibitory subunit of kappa B alpha, phosphorylated-p65, TNF-α, and IL-1β, by upregulating the expression of miR-96, which promotes exercise recovery in SCI rats.

SCI produces an inflammatory response through the corresponding inflammatory signaling pathway. Among the previously reported TCM monomers, triptolide and ginkgolide regulate the Janus kinase 2/signal transducer and activator of transcription 3 (STAT3) and signal transducer and activator of transcription 1 (STAT1) signaling pathway\[6\]; curcumin acts on the toll like receptors/transforming growth factor-β activated kinase 1/mitogen activated protein kinase kinase and toll/ NF-κB signaling pathway\[7\]; and paeoniflorin participates in regulating the apoptosis signal-regulating kinase 1/phosphorylated-p38/phosphorylated c-Jun N-terminal kinase (ASK1/p-p38/p-JNK) signaling pathway in SCI rats.\[8\] By regulating these inflammatory signaling pathways, TCM monomers could downregulate the expression of pro-inflammatory factors (IL-1β, TNF-α, IL-6, IL-8, and Olig2), upregulate the expression of anti-inflammatory factors (IL-4, IL-10, and transforming growth factor-β), and promote the recovery of SCI rats.

After SCI, the levels of pro-apoptotic factors (caspase and Bax families) significantly increased, whereas those of anti-apoptotic factors (Bcl-2 family) significantly decreased, indicating the activation of neuronal apoptosis. Excessive neuronal apoptosis adversely affected the functional recovery after SCI and inhibited the recovery of tissue morphology and behavior. Therefore, neuronal apoptosis is also a potential target for SCI treatment.

Among the TCM monomers reported above, ginsenoside Rb1\[9\] plays roles in the anti-apoptotic process after spinal cord ischemia-reperfusion injury, and ginkgolide B\[10\] plays roles in the anti-apoptotic process in SCI rats. After these TCM monomers were used to treat SCI, the expression levels of pro-apoptotic proteins caspase-3, caspase-9, and Bax in the body were significantly reduced. The levels of the anti-apoptotic protein Bcl-2 significantly increased, and the ratio of Bax/Bcl-2 was downregulated, which may be related to STAT3 activation. STAT3 could induce the expression of Bcl-2 and inhibit that of Bax.

Autophagy has neuroprotective effects in neurological diseases. For example, simvastatin treated SCI rats by inhibiting the mammalian target of rapamycin (mTOR) signaling pathway and activating autophagy.\[11\] Among the TCM monomers introduced in the present article, curcumin and resveratrol could mediate autophagy response after SCI. Resveratrol could regulate the adenosine monophosphate-activated protein kinase (AMPK)/mTOR signaling pathway, a specific autophagic pathway that causes AMPK phosphorylation during signal transduction. Phosphorylated
Oxidative stress contributes to a cascade of secondary damage following SCI, which results in inflammatory cell infiltration, neuronal and glial cell destruction, neuronal dysfunction, and cell death. Reducing oxidative stress is helpful for the treatment of SCI. The TCM monomers, such as sinomenine, ginsenoside, and resveratrol, could help for the treatment of SCI. The TCM monomer extracts could be converted clinically is it has not been clinically verifi...