Neuroprotective role of Noggin in spinal cord injury

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Abstract
Spinal cord injury is one of the leading causes of morbidity and mortality among young adults in many countries including the United States. Difficulty in the regeneration of neurons is one of the main obstacles that leave spinal cord injury patients with permanent paralysis in most instances. Recent research has found that preventing acute and subacute secondary cellular damages to the neurons and supporting glial cells can help slow the progression of spinal cord injury pathogenesis, in part by reactivating endogenous regenerative proteins including Noggin that are normally present during spinal cord development. Noggin is a complex protein and natural inhibitor of the multifunctional bone morphogenetic proteins, and its expression is high during spinal cord development and after induction of spinal cord injury. In this review article, we first discuss the change in expression of Noggin during pathogenesis in spinal cord injury. Second, we discuss the current research knowledge about the neuroprotective role of Noggin in preclinical models of spinal cord injury. Lastly, we explain the gap in the knowledge for the use of Noggin in the treatment of spinal cord injury. The results from extensive in vitro and in vivo research have revealed that the therapeutic efficacy of Noggin treatment remains debatable due to its neuroprotective effects observed only in early phases of spinal cord injury but little to no effect on altering pathogenesis and functional recovery observed in the chronic phase of spinal cord injury. Furthermore, clinical information regarding the role of Noggin in the alleviation of progression of pathogenesis, its therapeutic efficacy, bioavailability, and safety in human spinal cord injury is still lacking and therefore needs further investigation.

Key Words: apoptosis; astrocyte differentiation; axon myelination; axon regeneration; bone morphogenetic protein; glial scar; heterotrophic ossification; neurogenesis; neuropathic pain; Noggin; spinal cord injury

Introduction
Spinal cord injury (SCI) occurs mostly due to motor vehicle accidents followed by other severely traumatic events including gun violence, sport-related injuries, accidental falls, and work-related injuries (Raghava et al., 2017; Merritt et al., 2019). The occurrence of SCI is associated with serious health and mental problems and an enormous economic burden on the patients, their families, and the society at large (Raghava et al., 2017; Merritt et al., 2019). SCI is more common in the United States than the other countries around the world, with an incidence of approximately 40 new cases per million per year (Farace and Alves, 2000; Devivo et al., 2012; Chan et al., 2013; Roach et al., 2018). SCI mostly affects young adults (teens to early twenties), and it is 3 to 4 times more common in males than in females (Farace and Alves, 2000; Devivo, 2012; Chan et al., 2013; Roach et al., 2018). SCI in the males mostly occurs in early life due to road traffic accidents or sports-related injuries, whereas SCI in the females mostly occurs in late life (Farace and Alves, 2000; Devivo, 2012; Chan et al., 2013; Roach et al., 2018). Penetrating SCI tends to be more severe with complete damage to the spinal cord resulting in poor functional recovery of motor function (Farace and Alves, 2000; Devivo, 2012; Chan et al., 2013; Roach et al., 2018). In contrast, patients with blunt SCI tend to have incomplete damage to the spinal cord with a relatively better outcome (Farace and Alves, 2000; Devivo, 2012; Chan et al., 2013; Roach et al., 2018).

SCI occurs most frequently in the cervical region followed by the thoracic region and then the lumbar region. Temporary or persistent impairment in the locomotor and sensory functions in the body portion innervated by the injured spinal segment may be experienced by the patients with SCI. Additionally, allodynia, heterotrophic ossifications, skin ulcers, diabetes, and other long-term effects may occur in patients with SCI (Menon and Tan, 1992; Ditunno et al., 1994; McKinley et al., 2002; Wuermsers et al., 2007).

SCI comprises three overlapping phases at the cellular level: acute, subacute, and chronic phases (Witw and Fehlings, 2015; Anjum et al., 2020). Loss of neurons and glial cells, swelling, bleeding, edema, and infiltration of inflammatory cells characterize the acute phase, which occurs within the first 48 hours after the induction of injury (Witw and Fehlings, 2015; Anjum et al., 2020). The subacute phase begins within 2 weeks after the damage and is marked by the formation of glial scar and axon sprouting (Witw and Fehlings, 2015; Anjum et al., 2020). The chronic phase of SCI is characterized by more glial scar deposition, apoptosis, necrosis, demyelination, and Wallerian axon degeneration, and it can last for months or years (Witw and Fehlings, 2015; Anjum et al., 2020). Even though these stages have been widely reported in the literature, there is no consensus, and these stages of damage are likely to differ by individual case and depending on the severity of the initial lesion.

Multiple spine traumas are prevalent in SCI patients, resulting in spinal cord compression, laceration, or transection damage (Warburton et al., 2007; Rabinstein, 2018; Wang et al., 2021). Even though the initial injury is irreversible, SCI treatment seeks to stabilize the spine, prevent further damage, and enhance functional recovery (Warburton et al., 2007; Rabinstein, 2018; Wang et al., 2021). The current management of patients with SCI includes surgical interventions for stabilization or decompression, medical treatment for respiratory, cardiovascular, and other organ complications, and rehabilitation to control metabolic changes, bowel problems, urinary tract complications, and prevent deep vein thrombosis (Warburton et al., 2007; Rabinstein, 2018; Wang et al., 2021).

Despite advances in SCI therapy, patients have a high mortality rate, roughly three times that of the general population, with respiratory issues, cardiac problems, cancer, infection, septicemia, and unintentional accidents being the most prevalent reasons of death (Devivo et al., 2022). As a result, recent research has focused on preclinical models of SCI with the goal of using novel therapeutics to target molecular pathways involved in the regulation of early pathogenic changes in SCI, particularly the acute and subacute phases, to improve neuronal survival, reduce astrogial scar formation, enhance axonal regeneration, and remyelination (Ray et al., 2011).}

Noggin is an endogenous inhibitor of a collection of multifunctional bone morphogenetic proteins (BMPs), a subgroup of the transforming growth factor-beta family of proteins that are involved in the spinal cord development and homeostasis (Al-Sammarraie and Ray, 2021). In this review article,}

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we focused on the neuroprotective role of Noggin in preclinical models of SCI, doses, route of administration, and duration of treatment. Further, we discussed the results for the neuroprotective effects of Noggin in promoting functional recovery in preclinical models of SCI following exogenous treatment with recombinant Noggin in cell culture models of SCI (Table 1) as well as in animal models of SCI (Table 2). Similarly, we discussed the results for the neuroprotective effects of Noggin after engrafting the engineered cells expressing Noggin protein to the injured site of the spinal cord (Table 3). The major finding from these studies is that the neuroprotective effect is noticeable in an early phase of SCI in both in vitro and in vivo models following exogenous Noggin treatment (Figure 1) as well as in SCI in vivo models following therapy with the engineered Noggin expressing cells or implants (Figure 2). It needs to be noted that the molecular mechanisms for the neuroprotective effect of Noggin in the early phase of SCI occur mostly via the p-Smad1/5/8 pathway and/or the p-signal transducer and activator of transcription 3 (p-STAT3) pathway (Figure 3), but the long-term neuroprotective effect of Noggin in SCI remains debatable to date.

### Table 1 | Noggin treatment in cell culture models of spinal cord injury

| Cell type                        | Noggin treatment         | Dose          | Duration | References   |
|----------------------------------|--------------------------|---------------|----------|--------------|
| Astrocytes derived from spinal cord of postnatal rat pups | Recombinant human Noggin protein | 1.5 µg/mL | 6 d | Fuller et al., 2007 |
| Neural progenitor cells isolated from adult YFP mice | Recombinant human Noggin protein | 50–150 ng/mL | 5 d | Hart et al., 2020 |
| Gliial cells isolated from rat pup cortices | Recombinant human Noggin protein | 150 ng/mL | 3 d | Hart et al., 2020 |
| Oligodendrocyte precursors isolated from rat pup cortices | Recombinant human Noggin protein | 150 ng/mL | 24 h | Hart et al., 2020 |
| Primary cortical neurons isolated from rat embryo cortices | Recombinant human Noggin protein | 150 ng/mL | 3 d | Hart et al., 2020 |
| Neurospheres cultured from spinal cords of adult female mice | Recombinant mouse Noggin protein | 200 ng/mL | 3 d | Xiao et al., 2010 |

### Table 2 | Noggin treatment in animal models of spinal cord injury

| Animal model | Mode of spinal cord injury | Noggin treatment | Dose and route of administration | Duration | References   |
|--------------|---------------------------|------------------|---------------------------------|----------|--------------|
| Sprague-Dawley rats (female) | Contusion injury at T7 | Recombinant human Noggin protein | 1.2–2.4 µg/d intrathecal injections | 3 d to 10 wk | Hart et al., 2020 |
| Mice (female) | Contusion injury at T8 and T9 | Recombinant mouse Noggin protein | 15 ng/kg/d intrathecal injection with osmotic minipump | 1 wk | Xiao et al., 2010 |
| Sprague-Dawley rats (female) | Transection injury at T10 | Recombinant Noggin protein | 1 µg/kg noggin injection | 1 to 7 d | Cui et al., 2015 |
| Sprague-Dawley rats (female) | Contusion injury at T9–T10 | Recombinant mouse Noggin protein | 17.8 µg/kg/d intrathecal injection with osmotic minipump | 2 wk | Matsuura et al., 2008 |
| Adult Sprague-Dawley rats (male) | Ligation of spinal nerve ligation at L5 (an animal model of neuropathic pain) | Recombinant Noggin protein | 5 µg/mL intrathecal injection | 1 to 7 d | Yang et al., 2019 |

### Table 3 | Noggin expressing cells or implants engrafted in animal models of spinal cord injury

| Animal model | Type of spinal cord injury | Noggin expressing cells or implant | Duration | References   |
|--------------|---------------------------|----------------------------------|----------|--------------|
| Adult C57BL/6 mice (female) | Transection (hemisection) T9–T10 | Biomaterial bridge implants loaded with plenti-CMV-Noggin | 8 wk | Smith et al., 2019 |
| Adult Fischer 344 rats (female) | Contusion injury at T9 | Noggin-expressing oligodendrocyte precursor cells derived from Fischer rat embryos | 5 wk | Enzmann et al., 2005 |
| Adult Fischer 344 rats (female) | Focal ischemic injury at C7 | Noggin-expressing neuronal restricted cells derived from Fischer rat embryos | 5 wk | Enzmann et al., 2005 |
| Adult Fischer 344 rats (female) | Focal ischemic injury at C7 | Noggin-expressing neural stem cells derived from Fischer rat embryos | 5 wk | Enzmann et al., 2005 |
| Adult C57BL/6 mice (female) | Achilles tenotomy (heterotopic ossification animal model) | Noggin-expressing mouse muscle-derived stem cells | 10 wk | Hannallah et al., 2004 |
| Adult ICR mice (male) | Contusion injury at T8 and T9 | Noggin-expressing neural progenitor cells derived from ICR mice | 3 wk | Setoguchi et al., 2004 |

Figure 1 | Neuroprotective effect of exogenous Noggin treatment in SCI. Both in vitro and in vivo models of SCI following Noggin treatments show enhancement of neuronal survival, axon remyelination, synaptic plasticity, and functional recovery. SCI: Spinal cord injury.

Figure 2 | Neuroprotective effects of engineered Noggin expressing cells or implants in SCI. Noggin expressing cells or implants modulate the fate of differentiation of the precursor cells into myelin-producing oligodendrocytes, improve functional recovery following SCI, and attenuate secondary complications of allodynia and heterotopic ossification. SCI: Spinal cord injury.

Figure 3 | Molecular mechanisms of the neuroprotective effect of Noggin in SCI. Noggin binds to BMP ligand (most likely BMP4) and prevents its binding with BMP receptor (BMPR) 1 and 2. Noggin treatment inhibits BMP-mediated phosphorylation of Smad 1/5/8 and/or STAT3, which can lead to inhibition of astrocyte differentiation, glial scar formation, and neuronal and glial cell apoptosis. BMP: Bone morphogenetic protein; GFAP: glial fibrillary acidic protein; p-STAT3: p-signal transducer and activator of transcription 3; SCI: spinal cord injury.
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Structure, Function, and Expression of Noggin during Development and Spinal Cord Injury

Noggin gene (NOG) encodes for Noggin protein and NOG is located on human chromosome 17q21 (Valenzuela et al., 1995; Gong et al., 1999; Diano et al., 2001). Human Noggin following expression of NOG is secreted as a homotrimeric protein, involving two distinct ends: a carboxy terminal (acidic) and a carboxy terminal (cysteine-rich). In addition, Noggin has a heparin-binding region that holds the protein to the cell surface. Noggin is a specific endogenous antagonist of BMP, a multifunctional protein belonging to the transforming growth factor-beta family. Noggin binds to BMP receptor 1 and 2 binding sites on the surface of BMP ligands, with higher affinity to BMP4 compared to BMP7, and impedes their interactions with BMP receptors (Groppi et al., 2002).

Noggin is highly expressed in dorsal somite and notochord and prechordal mesoderm, which are important for the development of neural plate and neural tube during spinal cord development (Smith and Harland, 1992; Setoguchi et al., 2004). Mutation in the human homolog of the NOG has been associated with multiple synostosis syndrome and syringalagia deafness syndrome in humans (Edwards et al., 2000).

Noggin expression is further reactivated during SCI, and it is particularly expressed in the glial scar at the injury site and in the white matter. This high expression data implied that reactivating endogenous Noggin in the acute and subacute phases of SCI could be beneficial in reducing glial scar formation at the injury site and away from the impeding glial scar (Darian-Smith, 2009; Liu et al., 2012). Reorganization of synapses involves a change in the morphology of dendrites and an increase in dendritic spines (Darian-Smith, 2009; Liu et al., 2012). Regulation of neural plasticity at the molecular level involves reactivation of the signaling molecules and growth factors that are normally downregulated in the chronic phase of SCI, and their role in neural plasticity is currently under investigation (Bartlett et al., 2005). Noggin expression is further reactivated during SCI, and it is particularly expressed in the white matter and glial scar formation (Setoguchi et al., 2004). Intrathecal administration of Noggin in a rat model of contusion SCI enhanced regeneration following SCI is not observed in humans, a study in an animal model of SCI has shown evidence of regeneration due to Noggin treatment. Intrathecal administration of Noggin in a rat model of contusion SCI enhanced regeneration following SCI is not observed in humans, a study in an animal model of SCI has shown evidence of regeneration due to Noggin treatment. Intrathecal administration of Noggin in a rat model of contusion SCI enhanced regeneration following SCI is not observed in humans, a study in an animal model of SCI has shown evidence of regeneration due to Noggin treatment.
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in amounts of autophagy, apoptosis, and necrosis that lead to demyelination of axons ultimately impairing neuronal conductivity (Wang et al., 2017). Remyelination of neurons is an important function of the glial cells during spinal cord injury development and regeneration. Damage to the glial cells, particularly oligodendrocytes, is an important factor that impairs axonal remyelination in neurons (Monje, 2021).

Oligodendrocytes are one of the most important glial cells responsible for the myelination of axons. Damage to the spinal cord causes severe damage in the oligodendrocyte populations due to significant amounts of apoptosis and necrosis. Disruption of differentiation in OPCs in course of SCI helps replenish some of the lost cells and promote remyelination of axons following injury (Almad et al., 2011). Overexpression of platelet-derived growth factor-AA and Noggin treatment increased number of oligodendrocytes and oligodendrocyte progenitors, allowing remyelination of neurons following SCI in mice (Smith et al., 2019). This combination therapy, which acts to enroll and differentiate endogenous progenitors to aid remyelination following injury, represents a promising translatable treatment for SCI.

In addition, a study showed that low doses of intrathecal Noggin treatment in a rat model of contusion SCI with high BMP4 expression were able to increase oligodendrogenesis and oligodendrocyte differentiation, and high doses were able to sustain the number of mature oligodendrocytes following injury (Hart et al., 2020). In contrast, Noggin treatment and histological analysis of spinal cord tissue obtained from the rats with contusion SCI had no significant effect on axonal density and thickness of myelin sheet compared to untreated control, suggesting no effect of Noggin treatment on remyelination of axon on a long-term (Hart et al., 2020).

These results implied that long-term Noggin treatment would be effective in increasing the number of myelin-producing oligodendroglia cells that would help promote the remyelination of axons following injury.

Noggin Reduces Caspase-Mediated Apoptosis in Spinal Cord Injury

Apoptotic, necrotic, and autophagic cell deaths are found throughout the progressive pathogenesis of SCI. The cell death processes involve both neurons and glial cells, particularly the myelin-producing oligodendrocytes. In vitro treatment of Noggin was able to inhibit caspase-3-induced apoptotic cell death in both neuronal and oligodendrocytes exposed to a high concentration of BMP4 (Hart et al., 2020). Similarly, in vivo study showed that Noggin treatment reduced active caspase-3-mediated apoptotic cell death in a rat model of contusion SCI. However, BMP inhibition was cell-type specific and only protective in asymptotic phase of SCI; it did not affect cell death in late SCI (Almad et al., 2011). These results from both in vitro and in vivo studies strongly suggest the neuroprotective effect of Noggin in preventing early neuronal loss following injury.

Noggin Improves Functional Recovery following Spinal Cord Injury

Functional recovery is impaired temporarily or permanently following SCI due to primary and secondary loss of neurons, glial cells, demyelination of neuronal pathways, and glial scar formation. The effects of Noggin on functional recovery following SCI remains controversial. Intrathecal administration of Noggin in a rat model of transection SCI showed 8 folds improvement in the Basso, Beattie and Bresnahan score assessed 7 days post-injury (Cui et al., 2015). Similarly, intrathecal administration of Noggin in a rat model of contusion SCI and high BMP2/4 signaling showed improvement of locomotor recovery, as the Basso, Beattie and Bresnahan score assessed at 10 weeks following injury (Matsuura et al., 2008). In addition, engrafting Noggin expressing NPCs in a mouse model of contusion SCI resulted in significant partial improvement in locomotor function (Setoguchi et al., 2004).

In contrast, histological literature review and locomotor assessment 10 weeks following contusion SCI injury in a rat model with augmented BMP4 signaling showed no significant protective effect of Noggin on functional recovery, reduction in glial scar formation, or tissue preservation following injury (Hart et al., 2020).

These results also suggested that Noggin treatment could have a transient neuroprotective effect in improving functional recovery in acute and subacute phases of SCI. This effect diminished in chronic phase of SCI. It also implies that Noggin inhibition of BMP signaling has a minor effect on long-term tissue healing post-injury and it is inefficient for preventing chronic damage and glial scar formation in the late phase of SCI, suggesting the involvement of other factors and pathways that play the major roles in the pathogenesis during the late phase of SCI, requiring further investigation.

References

In vivo study showed that Noggin reduces allodynia, as evidenced by alleviation of the decrease in paw-withdrawal threshold in response to stimuli. It also inhibited BMP4-mediated GFAP expression and astrocyte activation as well. Also, it inhibits phosphorylation of the STAT3, a downstream target of BMP4 and important glial activation marker, over the course of 7 days (Yang et al., 2019).

Noggin Reduces Heterotopic Ossification following Spinal Cord Injury

Heterotopic ossification (HO) is another long-term complication following SCI (Franz et al., 2022). It also occurs in patients with mutations in BMP receptors without injury (Agarwal et al., 2017). HO is characterized by the development of painful bone growth in muscle, tendon, and tissues below the injury site (Xu et al., 2022). Although the causes of HO are largely unknown, evidence from animal studies suggests the involvement of BMP-Noggin signaling in its pathogenesis. BMP4 was correlated with induction of HO in mice, while engrafting Noggin expressing muscle-derived stem cells in mice model of HO was able to inhibit HO and enhanced demineralization of the formed bone matrix (Hannallah et al., 2004).

Conclusions and Future Directions

Noggin, which is a secreted endogenous inhibitor of BMP signaling, is differentially expressed during acute and subacute phases of SCI. Noggin is mainly expressed by the glial cells, particularly astrocytes. Many in vitro studies show neuroprotective effects of Noggin by enhancing oligodendrocyte differentiation, which is important for axonal remyelination in neurons. Similarly, in vivo studies have shown the potential of Noggin treatment in preventing early neuronal loss following injury, represents a promising translatable treatment for SCI.

Overall, there is clear evidence that Noggin treatment has neuroprotective effects of SCI, preventing early neuronal loss following injury. Further preclinical investigations to make it translational to the clinics and to determine whether it is a potential therapy to improve patient outcomes following SCI.

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