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Region-Specific Effects of Weight-Bearing and Non-Weight-Bearing Exercise on Schwann Cell Transcription Factors and Functional Recovery Following Sciatic Nerve Injury

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Abstract

This study aimed to investigate the region-specific effects of weight-bearing and non-weight-bearing exercise on Schwann cell transcriptional activity and functional recovery following sciatic nerve injury. Five-week-old male Sprague-Dawley (SD) rats were randomly assigned to four groups: normal control (CONT), sedentary after injury (SED), treadmill exercise (TEX), and swimming exercise (SWIM). All groups except CONT underwent sciatic nerve crush injury. TEX and SWIM groups received daily exercise interventions, while SED remained inactive. The expression levels of Sox10 and Krox20 were analyzed in proximal, injury, and distal (P-I-D) nerve segments at 3 and 21 days post-crush through both qualitative and quantitative Western blot analysis. Functional recovery was assessed via forelimb grip strength and the sciatic functional index (SFI). At 3 days post-crush (dpc), Sox10 expression in the distal segment was significantly upregulated in both TEX and SWIM groups compared to SED ($P<0.001$), with TEX higher than SWIM ($P<0.05$). At 21 dpc, Sox10 expression remained significantly elevated in the TEX group compared to both the SED ($P<0.01$) and SWIM ($P<0.05$) groups. Krox20 expression at 3 dpc showed a similar trend, with higher levels in TEX and SWIM than SED ($P<0.001$ and $P<0.05$), and TEX showing greater expression than SWIM ($P<0.01$). However, differences disappeared by 21 dpc ($P>0.05$). Functionally, TEX showed greater grip strength ($P<0.001$) and improved SFI ($P<0.05$) at 21 dpc. The CONT group maintained baseline values throughout. These findings suggest that early moderate-intensity treadmill exercise promotes Schwann cell-mediated regeneration through region-specific transcriptional activation and enhances functional recovery more effectively than non-weight- bearing exercise.

Key words: Sciatic nerve injury, Weight-bearing and non-weight-bearing exercise, Peripheral nerve regeneration

Introduction

The sciatic nerve, the longest and thickest peripheral nerve in the human body, originates from the L4–L5 lumbar and S1–S3 sacral spinal roots, and is primarily responsible for transmitting motor and sensory signals to and from the lower extremities (Standring et al., 2005). Damage to this nerve—referred to as sciatic nerve injury (SNI)—can lead to profound neuromuscular dysfunction, including impaired gait, sensory disturbances, neuropathic pain, and muscle weakness, all of which significantly compromise functional independence and quality of life (Ropper & Zafonte, 2015). Common causes of SNI include mechanical trauma, iatrogenic injury, and metabolic neuropathies such as those seen in diabetes, where concurrent

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inflammation and microvascular compromise further impede nerve regeneration (Beydoun, 2003).

While peripheral nerves exhibit a degree of spontaneous regeneration, the process is frequently incomplete due to inflammation, axonal degeneration, fibrotic scarring, and limited remyelination (Chen et al., 2007). Schwann cells are essential for axonal repair and remyelination. Upon injury, they dedifferentiate, remove debris, and secrete neurotrophic factors such as BDNF and NGF to support axonal regrowth, followed by redifferentiation to restore the myelin sheath (Decker et al., 2006; Liao et al., 2017).

Among the transcriptional regulators of Schwann cell function, Krox20 and Sox10 are central; Sox10 controls early Schwann cell differentiation and regulates Krox20, which in turn activates genes like MPZ and PMP22 necessary for remyelination (Britsch et al., 2001; Finzsch et al., 2010; Topilko et al., 1994). Previous studies have emphasized that protein expression patterns differ spatially and temporally between the proximal, injury, and distal segments of the nerve, and these regional variations significantly influence regenerative success (Bryan et al., 2012; Chato-Astrain et al., 2023). Therefore, it is critical to understand how Schwann cells modulate Krox20 and Sox10 expression in a region-specific manner during regeneration, to develop targeted therapeutic strategies for enhancing functional recovery.

Exercise has emerged as a promising non-pharmacological intervention that facilitates peripheral nerve regeneration. Treadmill and swimming exercises have been shown to increase the expression of neurotrophic factors and improve electrophysiological and morphological outcomes after SNI in rodent models (Fralish et al., 2021; Park & Höke, 2014). A comparison between weight-bearing (e.g., treadmill) and non-weight-bearing (e.g., swimming) exercise modalities may provide important insights in peripheral nerve rehabilitation, as they differentially influence mechanical loading, joint pressure, and systemic circulation, which in turn affect neurotrophic signalling and Schwann cell activity (Kim et al., 2015; Yu & Seo, 2024). For example, weight- bearing exercise provides proprioceptive stimulation and enhances neuromuscular engagement, while non-weight-bearing exercise minimizes mechanical stress while still improving circulation and anti- inflammatory responses (Liu et al., 2024; Özocak et al., 2023). Recent evidence indicates that these distinct loading environments may lead to different patterns of axonal regeneration and myelin repair, suggesting the need to investigate their respective molecular mechanisms by region and modality using standardized experimental models (Kumar et al., 2021; Teodori et al., 2011). Moreover, it has been hypothesized that exercise-induced Schwann cell activation may modulate the expression of Sox10 and Krox20, promoting myelin repair and axonal integrity (Maugeri et al., 2021; Klimaschewski, 2024; Zhou and Notterpek, 2016).

Although exercise has shown beneficial effects on peripheral nerve regeneration, the region-specific responses of key Schwann cell transcription factors such as Krox20 and Sox10 to different exercise modalities remain to be fully elucidated. Therefore, this study aims to investigate the spatiotemporal expression patterns of Krox20 and Sox10 following sciatic nerve injury. In particular, the effects of treadmill (weight-bearing) and swimming (non-weight-bearing) exercise will be compared across the proximal, injury, and distal segments of the affected nerve.

Methods

Experimental Animals

Male Sprague-Dawley rats (5 weeks old) were used in this experiment. All animals were housed under standard laboratory conditions with a constant room temperature of 22–24°C, relative humidity of 60%, and a 12/12-hr light/dark cycle. Commercial rat chow (Samyang Co., Seoul, Korea) and water were provided ad libitum.

Animals were randomly assigned to four experimental groups (n = 10 per group) as follows: the normal control group (CONT) did not undergo any surgical procedures or exercise; the sedentary group after sciatic nerve injury (SED) was subjected to sciatic nerve crush injury without exercise; the treadmill exercise group (TEX)

underwent sciatic nerve injury followed by daily treadmill training; and the swimming exercise group (SWIM) underwent sciatic nerve injury followed by daily swimming exercise.

Each group was further subdivided by time point, with tissues collected at 3 and 21 days post-crush (dpc). Sciatic nerve segments from the proximal (P), injury (I), and distal (D) regions were harvested for molecular analysis. To evaluate regional changes in protein expression, the sciatic nerve was dissected into three segments: proximal (P), injury (I), and distal (D) regions. These segments were obtained by cutting the nerve into 0.5 cm lengths relative to the crush injury site, with the injury region centered at the crush point. This approach has been previously described in studies of peripheral nerve regeneration and myelination (Seo et al., 2009; Zhu et al., 2025).

Sciatic Nerve Injury

Rats assigned to the injury groups (SED, TEX, and SWIM) were anesthetized using an inhalation anesthesia system (Jeungdo Bio & Plant, Seoul, Korea). Anesthesia was induced with 2.0–2.5% isoflurane and maintained at 1.5–1.8% during the surgical procedure. After shaving and sterilizing the left thigh region, the sciatic nerve was carefully exposed and crushed using fine forceps for 1 minute and 30 seconds with constant pressure, as previously described (Cho et al., 2021). Immediately following the procedure, the rats were placed on a heating pad maintained at 37°C until full recovery from anesthesia and then returned to their cages. Sciatic nerve injury was induced prior to the initiation of exercise in all experimental groups (SED, TEX, and SWIM). Exercise protocols—treadmill or swimming—were initiated from 3 days post-crush and continued until tissue collection. Sciatic nerve samples were harvested at 3- or 21-days post-injury for analysis.

Treadmill and Swim Exercise Protocols

To adapt to the treadmill environment, all rats underwent a low-intensity pretraining session for 5–7 days before the initiation of the main experiment. The treadmill device (Jeungdo Bio & Plant, Seoul, Korea) was used exclusively for rat locomotion. For the exercise groups, treadmill (TEX) and swimming (SWIM) training began at 3 days post-injury and continued once daily for 14 consecutive days. Rats in the TEX group walked on the treadmill at a speed of 8 m/min for 30 minutes per session without inclination. Rats in the SWIM group performed swimming exercise in a cylindrical tank (height: 45 cm, diameter: 130 cm, water depth: ~40 cm, water temperature: 32 ± 1°C) for 30 minutes per session. SED group remained in their home cages without any physical intervention during the same period. All animals were sacrificed 2 days after the final exercise session, either at 3- or 21-days post-crush depending on the group allocation.

Western Blot Analysis

The extracted sciatic nerve segments from the proximal, injury, and distal regions were homogenized and lysed in RIPA buffer containing protease and phosphatase inhibitors. After centrifugation, the supernatant was collected, and protein concentration was determined using a BCA assay. Equal amounts of protein (20 μg) from each sample were denatured by boiling in sample buffer and separated by SDS-polyacrylamide gel electrophoresis (SDS-PAGE), followed by transfer onto a polyvinylidene difluoride (PVDF) membrane (Millipore, Billerica, MA, USA) using a wet transfer system at a constant current200 mA for 2 hours at 4°C. Membranes were blocked in Tris-buffered saline with 0.1% Tween-20 (TBST) containing 5% non-fat dry milk for 1 hour at room temperature and then incubated overnight at 4°C with the following primary antibodies: anti-Krox20 rabbit polyclonal antibody (1:1000, Cell Signaling Technology, Danvers, MA, USA), anti-Sox10 rabbit polyclonal antibody (1:1000, Cell Signaling Technology, Danvers, MA, USA),and anti-β-actin mouse monoclonal antibody (1:5000, Santa Cruz Biotechnology, Santa Cruz, CA, USA) as the internal loading control. After washing with TBST, the membranes were incubated with horseradish peroxidase

(HRP)-conjugated secondary antibodies (anti-rabbit or anti-mouse IgG, 1:2000; GeneTex Inc., Irvine, CA, USA) for 1 hour at room temperature. Immunoreactive bands were visualized using an enhanced chemiluminescence detection reagent (Westar ECL substrates, Cyanagen, Bologna, Italy), and images were captured and quantified using the Chemidoc imaging system and Image Lab software (Bio-Rad, Hercules, CA, USA).

Sciatic Functional Index (SFI) Measurement

To evaluate functional recovery of the sciatic nerve following injury, the Sciatic Functional Index (SFI) was measured on days 0 (baseline), 7, 14, and 21 post-injury in all experimental (SED, TEX, and SWIM) and control groups. The SFI is a widely used quantitative method for assessing hindlimb motor function after peripheral nerve damage (Bain et al., 1989). Rats were allowed to walk freely along a narrow corridor (8 × 100 cm) lined with white paper. The plantar surface of the hind paws was dipped in non-toxic black ink, and footprints were recorded during straight walking. Only continuous steps with clearly distinguishable toe and heel prints were included for analysis. The following measurements were taken from each footprint: print length (PL), toe spread (TS; distance between the first and fifth toes), and intermediary toe spread (ITS; distance between the second and fourth toes). These parameters were measured for both the injured (E) and uninjured (N) limbs. The SFI was calculated using the Bain formula as follows: SFI = -38.3 × (EPL - NPL)/NPL + 109.5 × (ETS - NTS)/NTS + 13.3 × (EITS - NITS)/NITS - 8.8

An SFI value of 0 indicates normal function, whereas a value of –100 represents complete impairment. Each rat underwent at least three valid footprint recordings per time point, and the average was used for analysis. All behavioral assessments were conducted by an investigator blinded to group allocation to ensure objectivity.

Grip Strength Measurement

To assess neuromuscular function and muscular strength, forelimb grip strength was measured on days 0, 7, 14, and 21 post-injury using a grip strength meter (BIO-GS4, Bioseb, Vitrolles, France). The apparatus comprises a stainless-steel trapezoidal grip connected to a high-precision force transducer with a sampling rate of 1000 Hz, ensuring accurate detection of peak force values. During the test, each rat was gently lifted by the base of its tail and allowed to grasp the grip bar with its forepaws. Once a firm grip was established, the rat was steadily pulled backward in a horizontal plane until it released the grip. The peak force exerted immediately before release was recorded. Each rat underwent three consecutive trials per session, with at least a one-minute rest interval between trials to prevent muscle fatigue. The average of the three trials was calculated and normalized to the animal's body weight to account for inter-individual variability. This method is widely recognized for its reliability in evaluating motor function in rodent models (Meyer et al., 1979; Takeshita et al., 2017).

Statistics

All data are expressed as mean ± standard deviation (SD). Prior to conducting statistical tests, data were assessed for normality using the Shapiro–Wilk test. Since the data were normally distributed, one-way analysis of variance (ANOVA) was performed for group comparisons at each time point, followed by Duncan’s post hoc test to determine intergroup differences. The level of statistical significance was set at $P < 0.05$. All statistical analyses and graphical representations were conducted using GraphPad Prism version 6.0 (GraphPad Software, La Jolla, CA, USA).

Results

Early Upregulation of Krox20 Expression in Response to Exercise at 3 Days Post-Injury

The expression of Krox20 protein was analyzed at 3 days post-crush (3 dpc) in the proximal (P), injury (I), and distal (D) segments of the sciatic nerve in

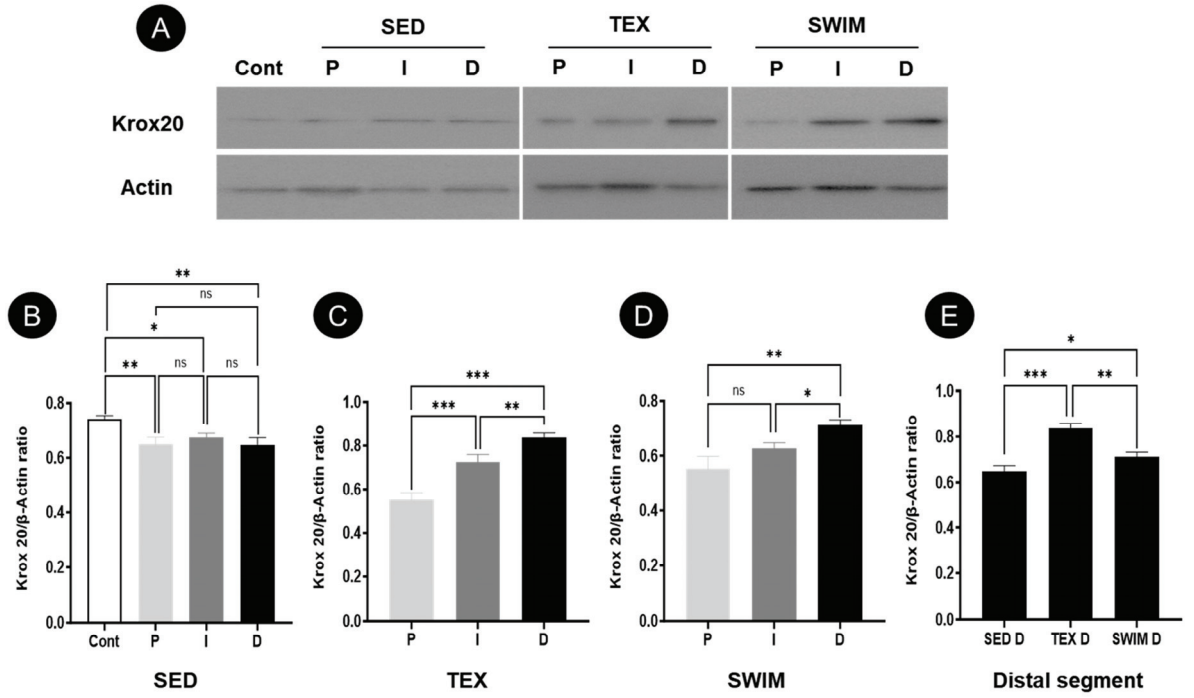

Figure 1. Expression of Krox20 protein in the proximal (P), injury (I), and distal (D) segments of the sciatic nerve across sedentary (SED), treadmill exercise (TEX), and swimming exercise (SWIM) groups at 3dpc. (A) Representative Western blot images showing Krox20 expression in each segment and group, with β-actin used as a loading control. (B–D) Quantitative analysis of Krox20 protein levels in the P, I, and D segments, respectively within each group. (E) Comparison of Krox20 expression among the three groups specifically in the distal segment. *P<0.05, **P<0.01, ***P<0.001.

the sedentary (SED), treadmill exercise (TEX), and swimming exercise (SWIM) groups (Figure 1). In the SED group, Krox20 expression was not significantly different among the three segments (P>0.05) (Figure 1B). In the TEX group, expression was significantly elevated in both the injury and distal segments compared to the proximal segment (P<0.01, P<0.001, respectively) (Figure 1C). Similarly, in the SWIM group, the distal segment showed significantly higher expression than the proximal and injury segments (P<0.05) (Figure 1D). When comparing the distal segments among the groups, both the TEX (P<0.001) and SWIM (P<0.05) groups exhibited significantly higher Krox20 expression than the SED group (P<0.05), and the TEX group showed significantly higher expression than the SWIM group (P<0.01) (Figure 1E).

Sustained Krox20 Expression Following Exercise at 21 Days After Sciatic Nerve Injury

To evaluate the sustained effects of exercise on Schwann cell activity, Krox20 expression was examined in the proximal (P), injury (I), and distal (D) segments of the sciatic nerve at 21 days post-crush (21 dpc) (Figure 2). Representative Western blot images are shown in Figure 2A, with β-actin used as a loading control. In the SED group, Krox20 expression was significantly lower in the proximal segment compared to the distal segment (P<0.05) (Figure 2B). In the TEX group, Krox20 expression was significantly higher in the distal segment than in the proximal segment (P<0.01) (Figure 2C). However, in the SWIM group, no significant differences were observed among the segments (P>0.05) (Figure 2D). Comparison of the

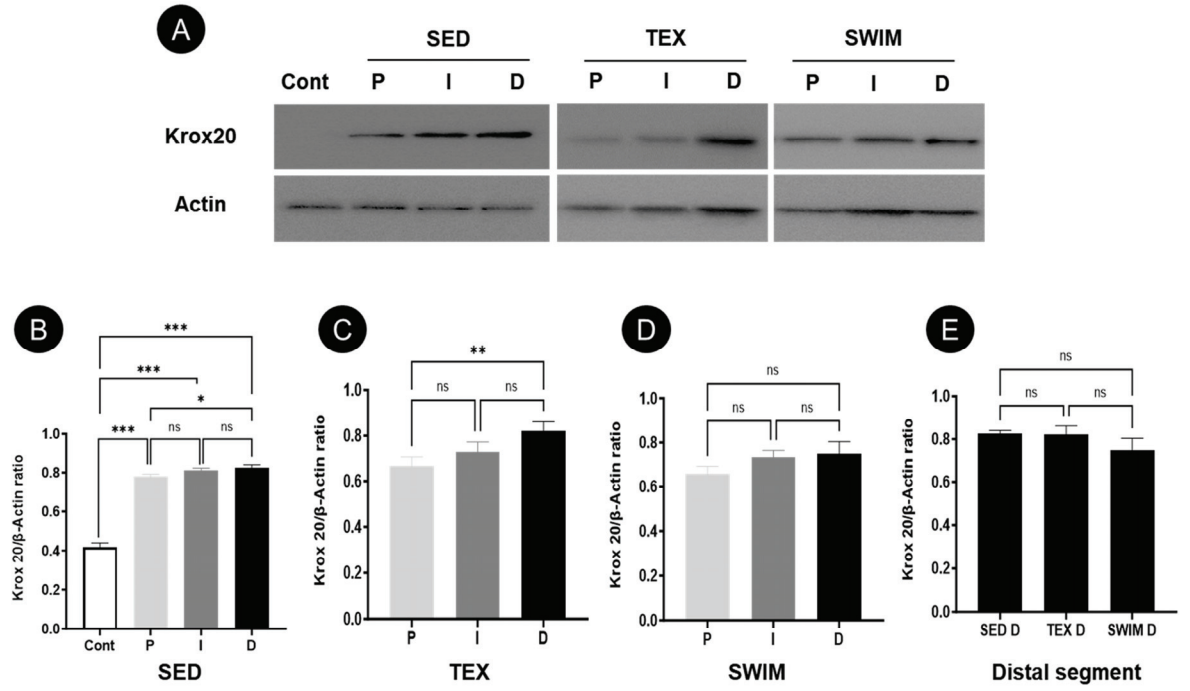

Figure 2. Expression of Krox20 protein in the proximal (P), injury (I), and distal (D) segments of the sciatic nerve across sedentary (SED), treadmill exercise (TEX), and swimming exercise (SWIM) groups at 21dpc. (A) Representative Western blot images showing Krox20 expression in each segment and group, with β-actin used as a loading control. (B–D) Quantitative analysis of Krox20 protein levels in the P, I, and D segments, respectively within each group. (E) Comparison of Krox20 expression among the three groups specifically in the distal segment. *P<0.05, **P<0.01, ***P<0.001.

distal segments among the three groups revealed no significant differences in Krox20 expression levels (Figure 2E).

Sox10 Upregulation in Response to Exercise at 3 Days Post-Injury

Sox10, an upstream regulator of Krox20, plays a critical role in Schwann cell lineage commitment and the early response to nerve injury. To assess early Schwann cell activation, Sox10 expression was evaluated at 3 days post-crush (3 dpc) in the proximal (P), injury (I), and distal (D) segments of the sciatic nerve (Figure 3). In the SED, TEX, and SWIM groups, Sox10 expression did not differ significantly among the three segments (P>0.05) (Figure 3B–D). When comparing the distal segments among the groups, both the TEX and SWIM groups exhibited significantly higher expression than the SED group (TEX: P<0.001; SWIM: P<0.001), notably Sox10 expression in the TEX group was also significantly higher than in the SWIM group (P<0.05) (Figure 3E).

Sox10 Expression Sustained by Exercise at 21 Days Post-Injury

Sox10, a transcription factor involved in Schwann cell lineage maintenance and remyelination, was analyzed at 21 days post-crush (21 dpc) in the proximal (P), injury (I), and distal (D) segments of the sciatic nerve in sedentary (SED), treadmill exercise (TEX), and swimming exercise (SWIM) groups (Figure 4). In the SED, TEX, and SWIM groups, Sox10 expression was not significantly different among the three segments (P>0.05) (Figure 4B–D). When comparing the distal segments among the groups, the TEX group

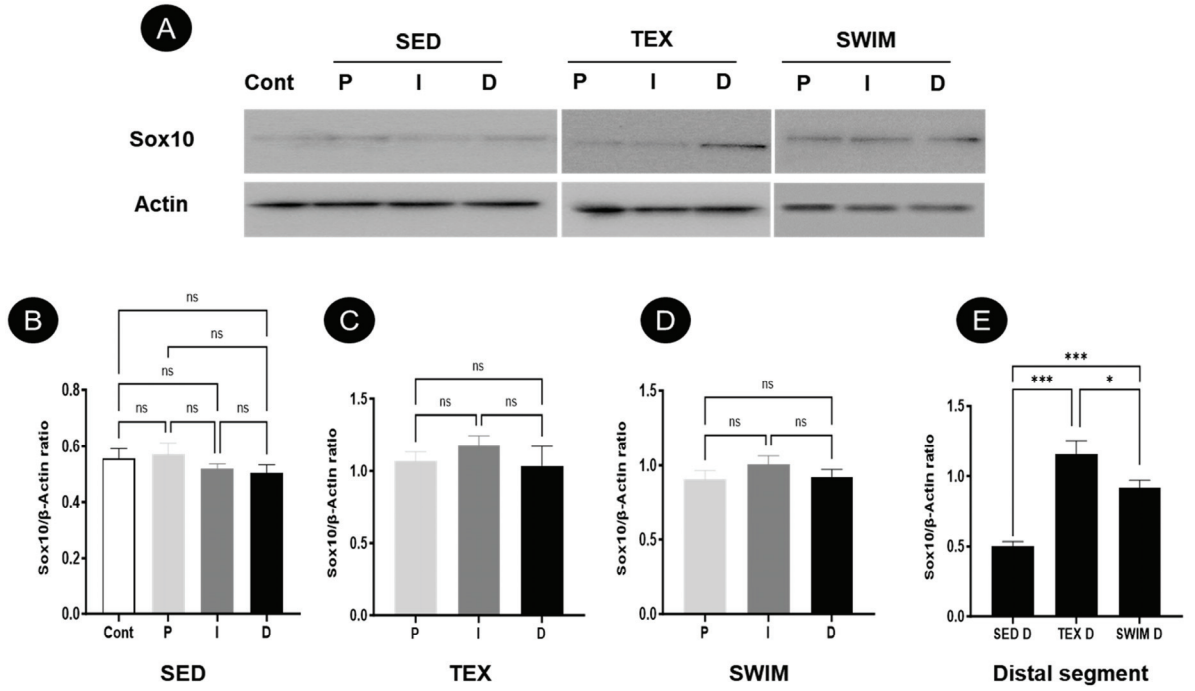

Figure 3. Expression of Sox10 protein in the proximal (P), injury (I), and distal (D) segments of the sciatic nerve across sedentary (SED), treadmill exercise (TEX), and swimming exercise (SWIM) groups at 3dpc. (A) Representative Western blot images showing Sox10 expression in each segment and group, with β-actin used as a loading control. (B-D) Quantitative analysis of Sox10 protein levels in the P, I, and D segments, respectively within each group. (E) Comparison of Sox10 expression among the three groups specifically in the distal segment. *P<0.05, **P<0.01 *** P<0.001.

exhibited significantly higher Sox10 expression than both the SED (P<0.01) and SWIM (P<0.05) groups (Figure 4E).

Grip Strength Recovery Induced by Exercise After Sciatic Nerve Injury

Forelimb grip strength was evaluated on days 0, 7, 14, and 21 following sciatic nerve crush injury to assess functional motor recovery in the control (CONT), sedentary (SED), treadmill exercise (TEX), and swimming exercise (SWIM) groups (Figure 5).

At day 0, all groups exhibited similar baseline grip strength levels. On day 7, all injured groups (SED, TEX, SWIM) showed a significant reduction in grip strength compared to baseline values, while the CONT group maintained stable strength throughout the period. From day 14 onward, both the TEX and SWIM groups demonstrated significantly greater grip strength than the SED group (P<0.001), and this improvement persisted through day 21. No significant differences were observed between the TEX and SWIM groups at any time point.

Time-Course Recovery of Sciatic Functional Index (SFI) Following Exercise Intervention

Sciatic functional index (SFI) was assessed on days 0, 7, 14, and 21 post-crush (DPC) in the control (CONT), sedentary (SED), treadmill exercise (TEX), and swimming exercise (SWIM) groups to evaluate functional recovery after sciatic nerve injury (Figure 6).

At baseline (day 0), all groups showed similar SFI values. By day 7, all injured groups (SED, TEX, SWIM) exhibited a marked decrease in SFI, indicating severe

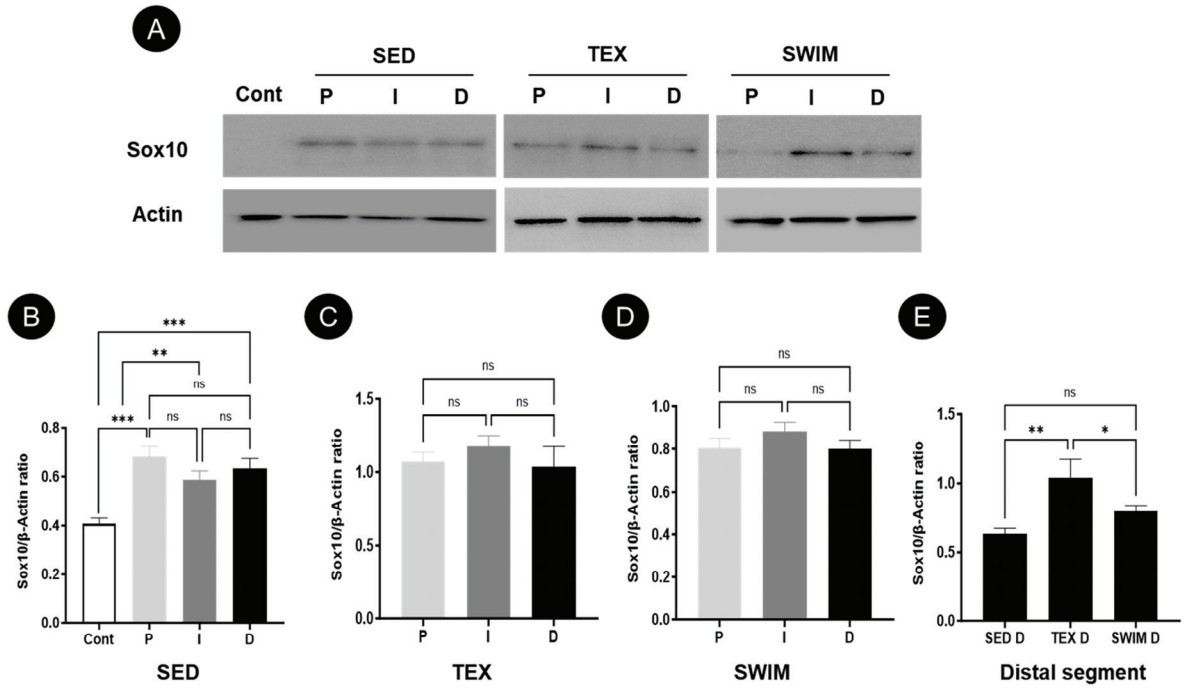

Figure 4. Expression of Sox10 protein in the proximal (P), injury (I), and distal (D) segments of the sciatic nerve across sedentary (SED), treadmill exercise (TEX), and swimming exercise (SWIM) groups at 21dpc. (A) Representative Western blot images showing Sox10 expression in each segment and group, with β-actin used as a loading control. (B-D) Quantitative analysis of Sox10 protein levels in the P, I, and D segments, respectively within each group. (E) Comparison of Sox10 expression among the three groups specifically in the distal segment. *P<0.05, **P<0.01 *** P<0.001.

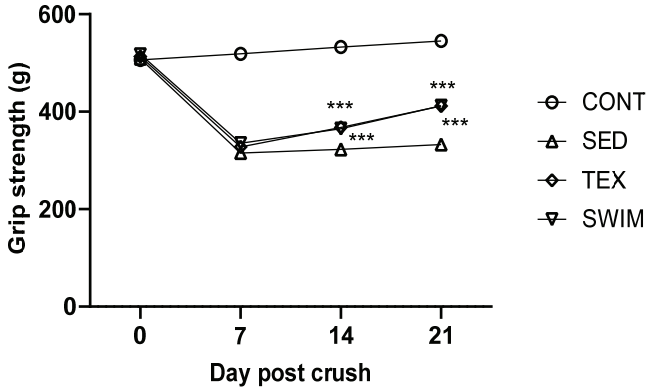

Figure 5. Changes in forelimb grip strength following sciatic nerve crush injury. Grip strength was measured in grams (g) on days 0, 7, 14, and 21 post-crush in control (CONT), sedentary (SED), treadmill exercise (TEX), and swimming exercise (SWIM) groups. All injured groups (SED, TEX, SWIM) exhibited a marked decrease in grip strength at day 7 compared to baseline. From day 14 onward, the TEX and SWIM groups showed significantly improved grip strength compared to the SED group. The CONT group maintained stable grip strength throughout the experimental period. ***P<0.001 vs. SED.

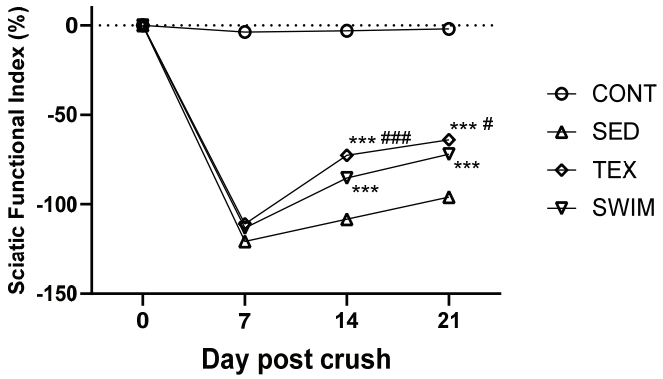

Figure 6. Changes in sciatic functional index (SFI) following sciatic nerve crush injury. SFI was measured on days 0, 7, 14, and 21 post-crush (DPC) in control (CONT), sedentary (SED), treadmill exercise (TEX), and swimming exercise (SWIM) groups. The CONT group maintained stable SFI values across all time points. In contrast, all injured groups (SED, TEX, SWIM) exhibited a sharp decline in SFI at day 7. From day 14 onward, both TEX and SWIM groups showed significantly improved SFI values compared to the SED group. Notably, the TEX group exhibited significantly greater recovery than the SWIM group at days 14 and 21. ***P<0.001 vs. SED; #P<0.05, ###P<0.001vs.SWIM.

functional impairment, while the CONT group maintained stable values throughout the experimental period. From day 14 onward, both the TEX and SWIM groups demonstrated significantly improved SFI values compared to the SED group (P<0.001). Furthermore, the TEX group exhibited significantly greater recovery than the SWIM group at day 14 (P<0.001) and day 21 (P<0.05), suggesting a stronger effect of treadmill exercise on functional regeneration.

Discussion

This study investigated the differential effects of weight-bearing (treadmill) and non-weight-bearing (swimming) exercise on Krox20 expression following sciatic nerve injury. Our findings revealed that both exercise modalities significantly increased Krox20 expression in the injury and distal segments at 3 days post-crush compared to sedentary conditions. Notably, the treadmill exercise (TEX) group exhibited the highest expression in the distal segment. At 21 days post-injury, the TEX group maintained elevated Krox20 expression in the distal region, whereas the swimming (SWIM) group showed no regional differences, and the sedentary (SED) group exhibited persistently low expression levels.

These results align with previous studies suggesting that sustained mechanical stimulation contributes to the maintenance of Schwann cell transcriptional identity and regenerative signalling (English et al., 2009; Gordon and English, 2016). While our data demonstrate sustained Krox20 upregulation in the TEX group, the underlying mechanisms remain to be fully elucidated. One possible explanation, supported by previous literature, is epigenetic regulation such as histone acetylation and chromatin remodelling (Gomez-Sanchez et al., 2022; McGee et al., 2009). However, these interpretations are speculative and were not directly assessed in this study.. In contrast, while swimming exercise may improve circulation and reduce inflammation, it appears insufficient to support sustained transcriptional activation due to the absence of mechanical loading and proprioceptive input. These findings indicate that differences in biomechanical and biochemical stimuli, depending on exercise modality, play a crucial role in modulating Schwann cell activity during peripheral nerve regeneration. In conclusion, this study experimentally demonstrates that weight-bearing

exercise creates a more favorable microenvironment for maintaining long-term Schwann cell transcriptional activity and promoting peripheral nerve regeneration. Nevertheless, due to the complexity of the regenerative process, further studies incorporating additional molecular markers and functional recovery outcomes are necessary to fully elucidate the underlying mechanisms.

This study examined the impact of treadmill (TEX) and swimming (SWIM) exercise on Sox10 expression during early and subacute phases following sciatic nerve injury. At 3 days post-crush (dpc), both TEX and SWIM groups showed significantly increased Sox10 expression in the distal segment compared to the sedentary (SED) group, with the TEX group exhibiting a greater upregulation. This early induction suggests that physical activity facilitates Schwann cell reprogramming during the acute regenerative phase. Sox10 is a master regulator of Schwann cell identity and plasticity, critical for initiating the repair phenotype, including dedifferentiation, proliferation, and debris clearance (Finzsch et al., 2010). The marked upregulation observed in the distal segment is consistent with the initiation of Wallerian degeneration and the increased need for Schwann cell activation within the distal nerve stump (LeBlanc et al., 2007; Wilcox et al., 2020). Treadmill exercise induced stronger Sox10 expression than swimming, likely due to its greater neuromechanical input and proprioceptive stimulation—factors known to promote calcium-dependent transcriptional activation in glial cells (Klimaschewski, 2024). While swimming improved early Sox10 activation, its non-weight-bearing nature may limit the extent of mechanosensory signaling required for sustained transcriptional drive. At 21 dpc, Sox10 expression remained significantly elevated in the TEX group compared to both SED and SWIM groups, though regional differences diminished. This indicates a shift toward normalization as regeneration progresses but also underscores the sustained influence of treadmill training in maintaining Schwann cell transcriptional identity. Sox10 remains essential not only in early reprogramming but also in long-term remyelination and axonal organization (Duman et al., 2020; Finzsch et al., 2010).

Furthermore, treadmill exercise is known to increase systemic and local neurotrophic factors such as BDNF, GDNF, and IGF-1, which can synergistically sustain Sox10 expression via transcriptional and epigenetic regulation (Liu et al., 2010; Xu et al., 2023). Swimming, in contrast, appears insufficient to maintain this prolonged activation in the absence of mechanical loading (Fletcher et al., 2024). These results parallel our findings on Krox20, a downstream effector of Schwann cell redifferentiation that drives myelin gene expression. The preferential upregulation of Krox20 in the distal segment and its higher levels in the TEX group suggest that weight-bearing exercise more effectively accelerates the transition toward remyelination (Chen et al., 2007; Finzsch et al., 2010; Topilko et al., 1994). In sum, while both treadmill and swimming promote early Schwann cell activation, treadmill exercise uniquely sustains Sox10 and Krox20 expression into the subacute phase. These findings support the role of early, moderate weight-bearing activity in enhancing the molecular cascade of peripheral nerve regeneration.

Both forelimb grip strength and sciatic functional index (SFI) measurements demonstrated that exercise interventions significantly promote functional recovery following sciatic nerve injury. From day 14 onward, the treadmill (TEX) and swimming (SWIM) groups exhibited marked improvements in grip strength compared to the sedentary group (SED), with effects sustained through day 21. This indicates enhanced neuromuscular function likely driven by improved axonal regeneration and reinnervation at the neuromuscular junction. Similarly, SFI analysis revealed that both TEX and SWIM groups recovered locomotor function over time, but treadmill exercise consistently resulted in superior outcomes at both day 14 and 21, underscoring the critical role of weight-bearing activity in gait restoration. Grip strength reflects distal motor unit recruitment and muscle force transmission, while SFI captures complex hindlimb coordination involving spinal reflex arcs and peripheral afferents (Goulart et al., 2014). The convergence of improvements in both metrics suggests that exercise facilitates not only morphological regeneration but also

the re-establishment of functional motor circuits. Treadmill training provides mechanical loading and proprioceptive input that enhance Schwann cell-mediated repair and central pattern generator (CPG) activation, thereby accelerating the reinstatement of coordinated movement patterns (Archer and Garcia, 2015). While swimming was also effective in promoting grip strength and partially restoring SFI, its non-weight-bearing nature may limit engagement of key mechanosensory pathways and reduce feedback-driven neuroplasticity. This aligns with previous reports suggesting that proprioceptive stimulation during rehabilitation is essential for optimizing motor output after peripheral nerve injury (Liu et al., 2024; Xia et al., 2021). Together, these findings emphasize that early exercise—particularly treadmill-based locomotion—supports comprehensive functional recovery by targeting both muscular strength and gait control systems. These insights highlight the need to consider loading characteristics when designing rehabilitation protocols for peripheral nerve injuries.

Conclusion

This study demonstrates that early exercise intervention, particularly weight-bearing treadmill training, effectively enhances molecular and functional recovery following sciatic nerve injury. Treadmill exercise induced sustained upregulation of key Schwann cell transcription factors—Sox10 and Krox20—in the distal segment, supporting both early dedifferentiation and subsequent remyelination. These molecular changes were accompanied by improvements in grip strength and sciatic functional index (SFI), indicating restoration of neuromuscular performance and coordinated locomotion. In contrast, swimming exercise, while beneficial in the early phase, failed to sustain long-term transcriptional activity or achieve comparable functional outcomes. These findings highlight the importance of exercise modality in peripheral nerve rehabilitation and suggest that moderate, weight-bearing activity may provide a more favorable microenvironment for Schwann cell-mediated regeneration.

However, this study has several limitations. First, the sample size was relatively small, which may limit the generalizability of the findings. Second, the focus was limited to the expression of Sox10 and Krox20, and other key signaling molecules and pathways involved in nerve regeneration were not assessed.

Further research should explore additional molecular targets and pathways involved in Schwann cell dynamics and examine long-term outcomes beyond the acute and subacute phases. In addition, comparative studies using different intensities and durations of exercise may help refine rehabilitation strategies tailored to specific injury types and recovery timelines.

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Writing-original draft preparation: Yeong-Hyun, Cho
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Conflict of Interest

The author declare no conflict of interest.

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