JNMS Journal of Nippon Medical School https://www.nms.ac.jp/sh/jnms/

Original

Interferon Regulatory Factor Family Transcription Factor Expression in the Dorsal Root Ganglion of a Rat Model of Neuropathic Pain

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Background: Peripheral nerve injury induces neuroinflammation in the dorsal root ganglion (DRG), which is a major cause of neuropathic pain. Interferon regulatory factors (IRFs) are a family of transcription factors that regulate the expression of inflammatory genes. Although several IRFs affect nociceptive transmission in the spinal cord, their roles in the DRG remain largely unknown.

Methods: Spinal nerve ligation (SNL) was used to develop a rat neuropathic pain model. Pain-related behaviors were assessed by the von Frey test and Plantar test. Gene expression levels of IRF family members were examined using quantitative PCR or immunofluorescence. IRF8 expression was downregulated by intrathecal administration of small interfering RNA (siRNA).

Results: IRF1, IRF5, and IRF8 were upregulated 4 days after nerve injury, but their expression gradually declined thereafter. In contrast, IRF4 and IRF7 expression gradually increased during an observation period of 14 days. No significant changes were observed in the expression of IRF2, IRF3, IRF6, or IRF9 after injury despite a slight increase. IRF8, which exhibited the greatest change in expression, was expressed in DRG neurons of naïve rats, and its distribution was not altered by nerve injury. IRF8 knockdown alleviated mechanical allodynia but not thermal hyperalgesia in neuropathic pain.

Conclusion: To our knowledge, these results are the first to show that multiple IRFs are upregulated in the DRG after peripheral nerve injury. The upregulated members of IRF family in the DRG after nerve injury may be involved in the pathophysiology of neuropathic pain.

(J Nippon Med Sch 2026; 93 (3): 244–251. https://doi.org/10.1272/jnms.JNMS.2026_93-309)

Keywords: dorsal root ganglion, interferon regulatory factor, IRF8, neuropathic pain

Introduction

Peripheral nerve injury to somatosensory neurons causes intractable neuropathic pain, and neuroinflammation in the dorsal root ganglion (DRG) is important in the pathophysiology of neuropathic pain. After nerve injury, DRG neurons recruit and activate various immune and glial cells in the DRG[1–3]. DRG neurons also contribute to neuroinflammation induction in the spinal dorsal horn by releasing proinflammatory cytokines[4,5]. Consistent with the proinflammatory function of DRG neurons, multiple molecular entities, including transcription factors, regulate inflammatory gene expression in DRG neurons[6–8]. However, the molecular mechanisms underlying the inflammatory phenotype of DRG neurons after nerve injury have not been fully elucidated.

Interferon regulatory factors (IRFs) are a family of transcription factors that includes IRF1–9 in mammals[9]. IRFs are important in the transcription of various inflamma-

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https://doi.org/10.1272/jnms.JNMS.2026_93-309
Received: December 2, 2025; Accepted: January 5, 2026

tory genes, thereby orchestrating immune responses. IRF members are preferentially expressed in immune cells, but some are expressed in non-immune cells, including neurons and glial cells. Indeed, expression levels of many IRF members were altered in the spinal cord after peripheral nerve injury. These IRFs induce spinal neuroinflammation and cause hyperalgesia in pain diseases, including neuropathic pain. IRF1 is upregulated in spinal microglia and is responsible for interleukin (IL)-1β induction in neuropathic pain[10]. IRF4 expression was upregulated in the spinal cord in a model of postoperative pain[11]. IRF5 is upregulated in spinal microglia and contributes to neuropathic pain[12–14]. IRF8 upregulation in spinal microglia after peripheral nerve injury results in the development of neuropathic pain by inducing expression of many inflammatory genes[15]. In contrast, IRF7, which is mainly expressed in spinal neurons, is downregulated by intraplantar injection of complete Freund's adjuvant (CFA), resulting in inflammatory pain[16]. Thus, IRFs have a critical role in regulating neuroinflammation in the spinal cord.

However, the contribution of IRFs in the DRG to neuropathic pain remains largely unknown, although upregulation of IRF3 and IRF5 was reported after nerve injury[8] and intraplantar CFA injection[17], respectively. To advance understanding of the molecular mechanisms underlying inflammatory changes in DRG neurons, we used a rat model of neuropathic pain to examine changes in the expression of IRF members after nerve injury.

Materials and Methods

Experimental Animals

All experimental procedures were approved by the President of the Nippon Medical School (approval numbers: 2020-042 and 2025-030) and performed in accordance with the guidelines of the International Association for the Study of Pain[18]. Male and female Sprague Dawley rats (Sankyo Labo Service Corporation, Tokyo, Japan) were used for all experiments. The rats were allowed free cage activity and access to food and water ad libitum. For surgery, all rats were subjected to deep anesthesia with isoflurane inhalation (2%–3%). The neuropathic pain model was produced by spinal nerve ligation (SNL), as previously described[19]. In brief, the left lumbar fifth (L5) spinal nerve was exposed and tightly ligated with 4–0 silk thread at two sites separated by about 1 mm. For sham surgery, the spinal nerve was exposed but not ligated. Naïve rats that did not undergo any treatment or surgical procedure were used as a control. Results from both sexes were combined because no apparent sex differences were observed, although the study was not powered to detect subtle differences between sexes.

Behavioral Tests

Paw withdrawal threshold and latency in hindlimbs in response to mechanical and thermal stimuli, respectively, were measured before and 1, 4, 7, 11, and 14 days after SNL. To evaluate mechanical allodynia, we used the von Frey test. For acclimation, rats were placed individually in plastic enclosures with a mesh floor for at least 15 min before testing. Next, a von Frey filament (Muromachi Kikai, Tokyo, Japan) was applied vertically to the plantar surface of the hind paw until the filament slightly bent. The paw withdrawal threshold was defined as the weakest force (g) that induced hind paw withdrawal at least three times in five trials. To evaluate thermal hyperalgesia, a Plantar test for thermal stimulation (Hargreaves apparatus; Ugo Basile, Comerio, Italy) was used. In brief, rats were placed individually in enclosures with a glass floor for acclimation. Next, a radiant heat generator placed under the glass floor was positioned directly beneath the hind paw, which was stimulated twice, with at least a 5-minute interval between the two stimuli. The mean value of the two trials is referred to as the paw withdrawal latency.

Quantitative PCR (qPCR)

Total RNA was extracted from the L5 DRG using RNAiso Plus according to the manufacturer's protocol (Takara Bio, Shiga, Japan), and a reverse transcription reaction was performed with a random primer using an iScript Select cDNA Synthesis kit (Bio-Rad, Hercules, CA, USA). PCR mixtures were prepared using gene-specific primer pairs (**Supplementary Table 1**) with Power SYBR Green PCR Master Mix (Thermo Fisher Scientific, Waltham, MA, USA), and amplification was performed on a QuantStudio 3 Real-time PCR System (Thermo Fisher Scientific). The PCR conditions consisted of initial denaturation at 95°C for 10 min, followed by 40 cycles of 95°C for 15 s and 60°C for 1 min. All samples were measured in triplicate, and relative expression levels were calculated using the $2^{-\Delta\Delta CT}$ method.

Immunofluorescence

Rats were perfused transcardially with phosphate-buffered saline (PBS) (pH 7.4), followed by perfusion with freshly prepared 4% paraformaldehyde dissolved in PBS. L5 DRGs were postfixed in the same fixative over-

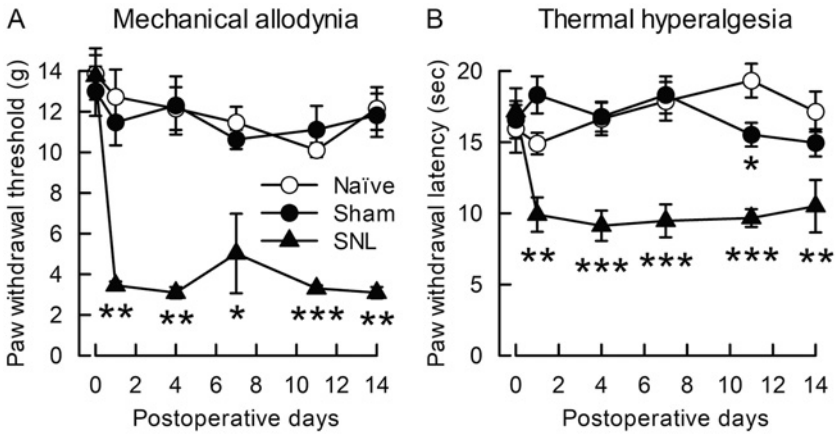

Figure 1 Pain-related behaviors after spinal nerve ligation (SNL)
(A, B) Paw withdrawal threshold (A) and latency (B) to mechanical and thermal stimuli, respectively, were evaluated in naïve, sham, and SNL rats (n = 6–8). *P < 0.05, **P < 0.01, and ***P < 0.001 by the Steel–Dwass test (A) or Dunnett's test (B).

night and cryoprotected in 20% sucrose in PBS at 4°C overnight. The tissues were then rapidly frozen in OCT compound (Sakura Finetek, Tokyo, Japan) using dry ice/acetone. L5 DRGs were sectioned at a thickness of 10 µm using a cryostat (Leica Microsystems, Wetzlar, Germany). The sections were pretreated in PBS containing 5% normal donkey serum and 0.3% Triton X-100 for 30 min, followed by incubation with a mouse anti-IRF8 antibody (1:100; sc-365042, Santa Cruz Biotechnology, Dallas, TX, USA) at 4°C overnight. After three washes in PBS for 5 min each, the sections were incubated with a secondary antibody conjugated to Alexa Fluor 488 (1:1,000; Thermo Fisher Scientific) at room temperature for 1 h. Images were acquired using a high-resolution microscope (BX51, Olympus, Tokyo, Japan). To measure the cell sizes of primary sensory neurons, the area of the cell body was measured in six DRG sections obtained from individual rats by manually tracing the cell-body outlines using ImageJ software (version 1.50b, National Institutes of Health, Bethesda, MD, USA)[20].

Intrathecal Drug Administration

An intrathecal catheter for drug administration was implanted in rats 3 days before injecting small interfering RNA (siRNA), as previously described[21]. In brief, a polyethylene catheter (PE-10) filled with saline was slowly inserted into the spinal subarachnoid space from the cisterna magna to the level of the lumbar enlargement of the spinal cord. Rats without obvious movement disturbances, such as paralysis, were used in further experiments. From the day before SNL surgery, 2 µg/10 µL of predesigned IRF8 siRNA composed of 5′-GCCUAUGAC GCACACCAUU-3′ (sense) and 5′-AAUGGUGUGCGUC AUAGGC-3′ (antisense) (SASI_Rn01_00047868, Sigma-Aldrich, St. Louis, MO, USA) or universal negative control siRNA (SIC-001, Sigma-Aldrich) was administered, followed by 10 µL of saline (flush) through the intrathecal catheter once daily for 5 days.

Statistical Analysis

Analyses were performed using IBM SPSS Statistics for Windows (version 25, IBM Corp., Armonk, NY, USA). Values are presented as the mean ± standard error of the mean. Normality of data was assessed using the Shapiro–Wilk test. For normally distributed datasets, the unpaired t test or Dunnett's test was used. When normality was not assumed, the Mann–Whitney U test or Steel–Dwass test was used. P < 0.05 was considered significant.

Results

Development of Neuropathic Pain in Rats after Nerve Injury

As compared with naïve rats, SNL rats exhibited a significant reduction in paw withdrawal threshold in response to mechanical stimuli and paw withdrawal latency in response to thermal stimuli, both of which persisted for at least 14 days (**Figure 1**). In contrast, sham surgery did not result in a significant reduction in paw withdrawal threshold or latency, except for thermal response on day 11.

Temporal Changes in Gene Expression of IRF Family Transcription Factors

IRF1, IRF5, and IRF8 expression levels, as measured by

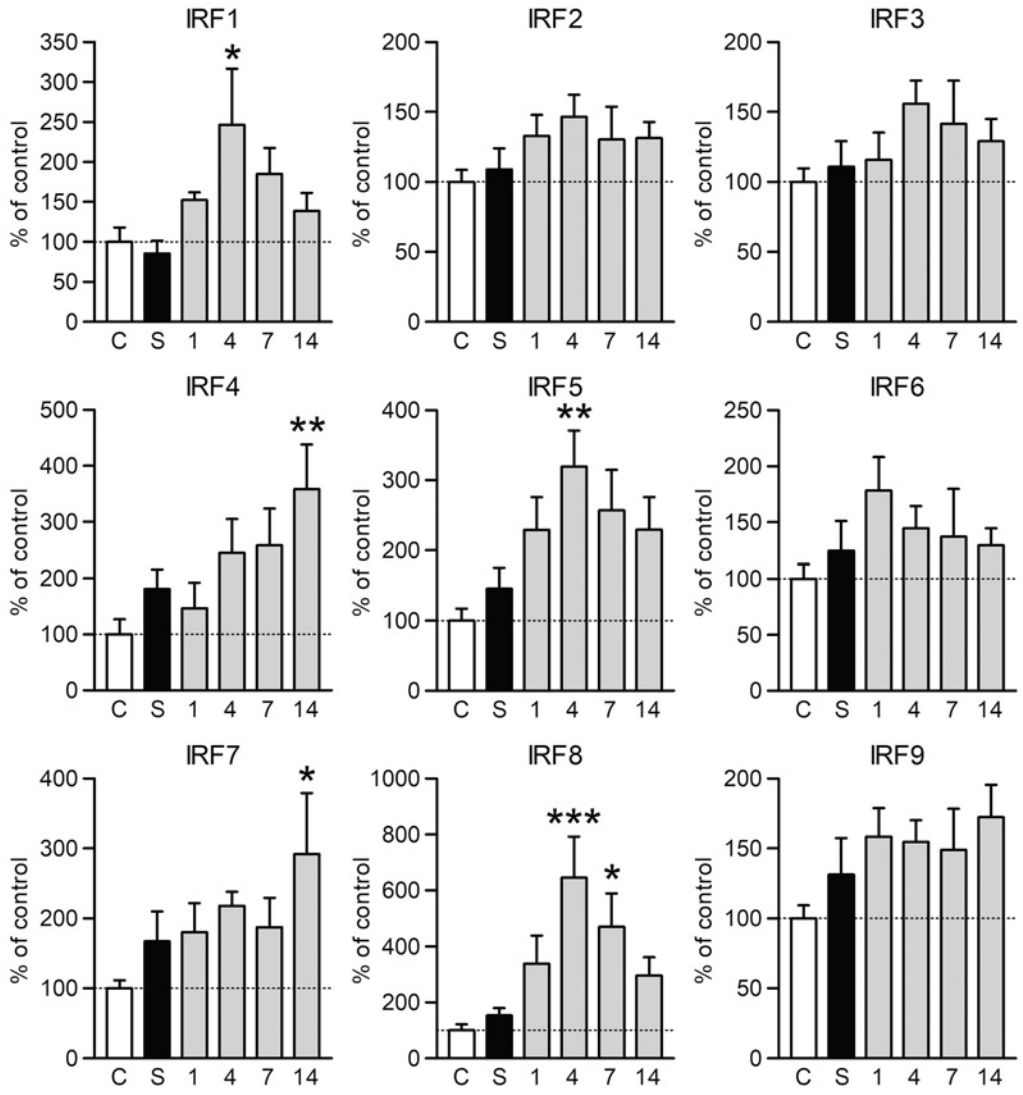

Figure 2 Changes in the expression of interferon regulatory factor (IRF) family transcription factors
Expression levels of IRF family members were analyzed in the dorsal root ganglia (DRGs) of naïve control (indicated as C) and sham-operated (indicated as S) rats at day 14 after the sham operation, as well as SNL rats at days 1, 4, 7, and 14 after SNL using quantitative PCR (n = 5–6). *$P < 0.05$, **$P < 0.01$, and ***$P < 0.001$ by Dunnett's test vs. naïve control rats.

qPCR, were upregulated early after nerve injury (at day 4), followed by a gradual decline (**Figure 2**). In contrast, IRF4 and IRF7 levels showed no significant difference through day 7 and increased expression at day 14. No significant difference was observed in IRF2, IRF3, IRF6, or IRF9 through day 14, although expression levels slightly increased.

IRF8 Is Expressed in DRG Neurons

In naïve rats, immunofluorescence staining detected IRF8 expression in the nuclei of DRG neurons with a wide range of cell-body sizes. IRF8 was preferentially expressed in small (<600 μm^2) and medium-sized (600–1,200 μm^2) DRG neurons (**Figure 3**). This distribution pattern was not changed at day 4 after SNL.

IRF8 Knockdown Alleviates Mechanical Allodynia in Neuropathic Pain

qPCR analysis revealed that IRF8 expression was reduced in the L5 DRG by intrathecal administration of IRF8 siRNA (**Figure 4A**). IRF8 knockdown suppressed the development of mechanical allodynia, but not thermal hyperalgesia, at days 1 and 4 after SNL (**Figure 4B**). IRF8 downregulation had no effect on contralateral-side responses to mechanical and thermal stimuli (**Figure 4C**).

Discussion

The present study revealed that many IRF family mem-

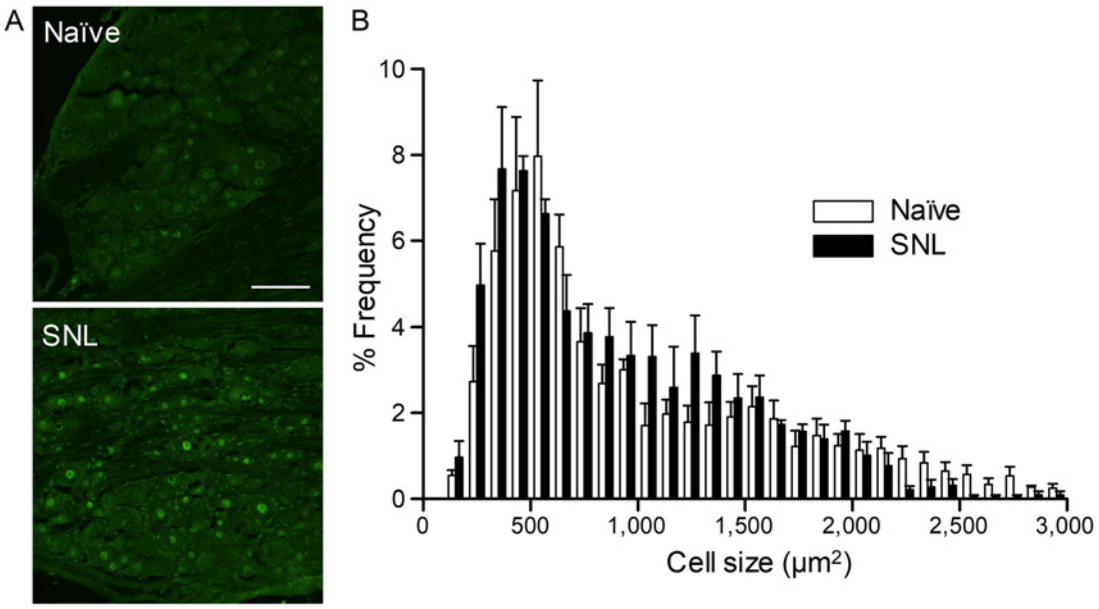

Figure 3 Distribution of interferon regulatory factor 8 (IRF8) expression in the L5 dorsal root ganglia (DRGs) after spinal nerve ligation (SNL)
(A) Representative immunofluorescent images of the lumbar fifth (L5) DRG obtained from naïve rats and SNL rats at day 4. Scale bar, 100 μm. (B) Size distribution of IRF8-immunoreactive DRG neurons (n = 4 animals and n = 5,560 neurons).

bers (IRF1, IRF4, IRF5, IRF7, and IRF8) were significantly upregulated in the DRG after nerve injury. IRF8 showed the greatest expression change and was expressed in DRG neurons. Downregulation of IRF8 alleviated mechanical allodynia in the SNL model of neuropathic pain.

To our knowledge, this is the first study to show that members of the IRF transcription family (IRF1, IRF4, IRF5, IRF7, and IRF8) are upregulated in the DRG after peripheral nerve injury. Although a previous study reported that IRF3 was upregulated in the DRG after peripheral nerve injury[8], the increase in IRF3 expression in the present study was not significant. In the spinal cord, expression levels of IRF1, IRF5, and IRF8 were reported to increase after nerve injury[10,12,15]. In particular, IRFs are responsible for neuroinflammation in the spinal cord, consistent with their role as critical transcription factors mediating inflammatory responses[9]. IRF5 and IRF8 regulate the expression of P2X4 receptor and proinflammatory cytokines in spinal microglia[12,15]. IRF3 is activated in spinal microglia by repeated morphine administration and is involved in morphine torelance[22]. As in the spinal cord, neuroinflammation in the DRG is a critical contributor to neuropathic pain[1,23]. After peripheral nerve injury, various immune cells, such as macrophages and T cells, are mobilized and activated in the DRG to promote or resolve neuroinflammation[23,24]. Activated immune cells in the injured DRG release proinflammatory cytokines, such as IL-1β and tumor necrosis factor-α, which increase the excitability of nociceptive DRG neurons. However, IRFs may also be expressed in non-immune cells, such as neurons and glial cells in the DRG. In fact, IRF8 was expressed in DRG neurons in this study, although it is possible that glial and immune cells are also immunopositive. IRF8 expression and function have been extended to non-hematopoietic cells, despite its high expression in hematopoietic cells[25]. Similarly, IRF1 is observed in neurons of the brainstem and spinal cord[26,27]. Several studies reported that IRF4 is expressed in neurons[28,29]. IRF7 is expressed in epithelial cells, spinal neurons, and astrocytes, as well as in various immune cells, including macrophages[16,30]. Therefore, increased IRF expression may be induced in immune cells, glial cells, or DRG neurons.

In the present study, knockdown of IRF8 attenuated the development of mechanical allodynia induced by nerve injury, without affecting normal nociception. IRF8 regulates the expression of proinflammatory genes, including IL-1β, cathepsin S, and brain-derived neurotrophic factor[15], all of which cause allodynia[4]. Indeed, proinflammatory signals from DRG neurons induce neuroinflammation in the DRG and spinal cord. Therefore, IRF8 upregulation in DRG neurons after nerve injury may cause neuropathic pain by enhancing their proinflammatory capacity. In contrast, IRF8 knockdown did not affect thermal hyperalgesia in the present study.

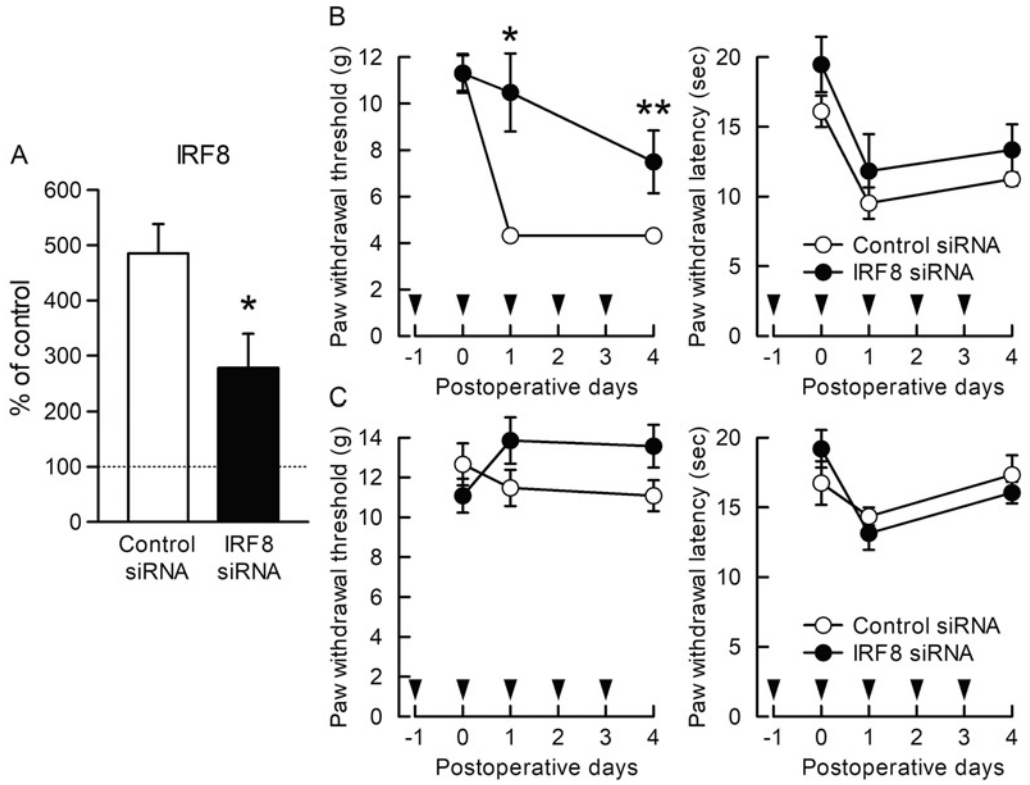

Figure 4 Effects of interferon regulatory factor (IRF8) knockdown on neuropathic pain
(A) IRF8 expression was analyzed in the L5 dorsal root ganglia (DRGs) at day 4 after spinal nerve ligation (SNL), using quantitative PCR. IRF8 or control small interfering (siRNA) was administered intrathecally once daily from 1 day before SNL to 3 days after SNL, as indicated by the arrowheads. (B, C) Paw withdrawal threshold and latency in response to mechanical and thermal stimuli, respectively, were evaluated on the ipsilateral SNL (B) and contralateral intact (C) sides in SNL rats administered siRNA (n = 6–10). *P < 0.05 and **P < 0.01 by the Mann–Whitney U test.

Because responsiveness to mechanical and thermal stimuli varies with the subtype of DRG neurons[31], IRF8 may be specifically upregulated in mechano-sensitive DRG neurons. Alternatively, cytokines induced by IRF8 may specifically regulate mechano-sensitive molecules, such as transient receptor potential channels and Piezo channels. In fact, IL-17A is specifically involved in mechanical hyperalgesia in murine antigen-induced arthritis[32], although the underlying mechanism is poorly understood.

Expression levels of IRF1, IRF5, and IRF8 increased early after nerve injury and then declined through day 14. Because the first 1 week after nerve injury is primarily linked to the onset of neuropathic pain, these IRFs may be involved specifically in the development or chronification of neuropathic pain. Consistent with this, IRF8 knockdown attenuated the development of mechanical allodynia after nerve injury. In addition, IRF1 and IRF5 mediate the induction of proinflammatory cytokines that cause nociceptor sensitization, such as IL-1β and IL-6[10,33], although the involvement of IRF1 and IRF5 in the DRG is unclear. By contrast, IRF4 and IRF7 may contribute to maintenance of neuropathic pain because they were gradually upregulated after nerve injury. Alternatively, their progressive increase may be an adaptive response to suppress the persistent neuroinflammation associated with nerve injury. Notably, IRF4 modulates both pro- and anti-inflammatory processes and, by producing anti-inflammatory cytokines, has a protective role in neurodegenerative diseases[34]. Similarly, IRF7 can promote or suppress inflammation, depending on the cellular microenvironment[30]. IRF7 reduces production of proinflammatory cytokines in the spinal cord and attenuates pain-related behaviors in a model of inflammatory pain induced by intraplantar injection of CFA[16]. Therefore, each member of the IRF family in the DRG may have a distinct role in the development and maintenance of neuropathic pain.

This study has several limitations. First, the sample size was not sufficient to detect sex differences, although no apparent differences were observed. Second, expression levels of IRFs were not assessed at the protein level, which is subject to further post-transcriptional regulation.

Third, off-target effects of IRF8 siRNA cannot be ruled out. Therefore, gene deletion, particularly in specific subtypes of neurons and immune cells, will provide greater insight into the functional role of IRF8 in the DRG in neuropathic pain.

This study demonstrated that IRF1, IRF4, IRF5, IRF7, and IRF8 are upregulated in the DRG after peripheral nerve injury, although the time courses varied. However, their role in neuropathic pain remains unknown. Given that IRF8 contributes to neuropathic pain, future studies of the pathophysiological significance of IRFs in the DRG will likely hasten the development of effective treatments.

Author Contributions: AS designed the study. YW, MM, MY, and AS performed the experiments. YW and AS analyzed the data, prepared the figures, and wrote the manuscript. MM and RA reviewed the manuscript. All authors have read and approved the final manuscript.

Acknowledgments: We thank Mayuri Nakajima for technical assistance, and Robin James Storer, PhD, from Edanz (https://jp.edanz.com/ac) for editing a draft of this manuscript.

Funding: This study was supported by the Japan Society for the Promotion of Science KAKENHI (grant numbers JP19H 03552 and 23K27493 to AS).

Conflict of Interest: The authors declare no competing interests.

Declaration of Generative AI and AI-Assisted Technologies in the Writing Process: No generative AI and AI-assisted technologies were used.

Supplementary Material: Supplementary material associated with this article is available at https://doi.org/10.1272/jnms.JNMS.2026_93-309.

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