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SHORT COMMUNICATION

Expression profile of aminoacyl-tRNA synthetases in dorsal root ganglion neurons after peripheral nerve injury

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Abstract Aminoacyl-tRNA synthetases (AminoARSs) are essential enzymes involved in acylating tRNA with amino acids. In addition to the typical functions of AminoARSs, various non-canonical functions have been reported, such as involvement in cellular regulatory processes and signal transduction. Here, to explore the cellular changes in sensory neurons after nerve injury, we evaluated AARS mRNA expression in rat dorsal root ganglia (DRG) neurons using AminoARS-specific primers. Of 20 AminoARSs, we found that expression of lysyl-tRNA synthetase (KARS) and glutaminyl-tRNA synthetase (QARS) was decreased in the DRG injured side. We observed decreased KARS and QARS expression in DRG neuronal cell bodies, but not in satellite cells. Therefore, we suggest the possibility that KARS and QARS may act as signaling molecules to transfer abnormal sensory signals to the spinal dorsal horn after peripheral nerve damage. Therefore, KARS and QARS may represent powerful pharmaceutical targets via control of their non-canonical functions.

Keywords Aminoacyl tRNA synthetases · Neuron · Dorsal root ganglion · Peripheral nerve injury

Introduction

Aminoacyl-tRNA synthetases (AminoARSs) are housekeeping enzymes that acylate tRNA with amino acids and are ubiquitously expressed in living cells. Therefore, the first step in translation is attaching the correct amino acid such that the tRNA charge is appropriate. AminoARSs have multiple functions in various biological processes beyond translation (i.e., non-canonical functions). For instance, AminoARSs are involved in RNA splicing and trafficking, rRNA synthesis, apoptosis, inflammation and angiogenesis (Han et al. 2003; Ko et al. 2002). Secreted lysyl-tRNA synthetase (KARS) induces the proinflammatory response (Park et al. 2005b). The nuclear localization of methionyl-tRNA synthetase (MARS) stimulates rRNA synthesis in proliferative cells (Ko et al. 2000). Glutaminyl-tRNA synthase (QARS) negatively regulates apoptosis signal-regulating kinase 1 (ASK1) to block apoptosis (Ko et al. 2001). Tyrosyl-tRNA synthetase (YARS) is split into two fragments that act as two distinct cytokines (Kleeman et al. 1997; Wakasugi and Schimmel 1999). A truncated form of tryptophanyl-tRNA synthetase (WARS) is linked to angiogenesis regulation (Tolstrup et al. 1995; Wakasugi et al. 2002).

In the nervous system, AminoARS dysfunction contributes to various neuronal diseases. Inherited peripheral neuropathies, such as Charcot-Marie-Tooth disease (CMT), are caused by heritable mutations in glycyl-tRNA synthetase (GARS) or YARS (Antonellis et al. 2003; Jordanova et al. 2006). An abnormal interaction between KARS and Cu/Zn superoxide dismutase 1 (SOD1) mutations was observed in an animal model of amyotrophic lateral sclerosis (ALS), a motor neuron disease caused by a SOD1 mutation (Kunst et al. 1997). However, there have been no studies examining AminoARS non-canonical functions in the sensory nervous system after peripheral nerve injury.

Peripheral nerve injury often results in spontaneous pain, hyperalgesia and allodynia. After peripheral nerve injury, multiple pathophysiological changes, including

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generic changes in ion channels, receptors, neuropeptides, signal transmitters and so forth, occur in the peripheral nervous system (PNS) (Wang et al. 2013; Cao et al. 2013; Zhu et al. 2014) and the central nervous system (CNS) (Scholz and Woolf 2002; Ji and Strichartz 2004). These changes in the injured primary sensory neurons influence the activity of the innervated spinal dorsal horn (Hökfelt et al. 1994; Alvares and Fitzgerald 1999) and subsequently lead to pain initiation, as well as its development and maintenance (Zimmermann 2001).

In this study, we assessed the expression profiles of AminoARSs in the dorsal root ganglia (DRG) following peripheral nerve injury. In situ hybridization (ISH) was performed to identify the location of AminoARS mRNA expression in the DRG. Our data demonstrated that KARS and QARS expression was altered in the DRG after peripheral nerve injury. Thus, our findings illustrate how AminoARSs expression is regulated in adult DRG by peripheral nerve injury and suggest a new therapeutic strategy for peripheral nerve injury-related diseases.

Materials and Methods

Animals

Adult male Wistar rats were used (body weight, 200–250 g). The rats were housed with food and water ad libitum on a 12-h light/dark cycle, and cages were changed weekly. All animal experiments were performed in accordance with standard guidelines for animal experiments determined by the Kyung Hee University School of Medicine. All efforts were made to minimize the number of rats used and their suffering.

Tissue processing

Seven days after sciatic nerve transection, fourth and fifth lumbar vertebrae (L4 and L5) DRGs were collected and stored as appropriate for each experiment. For immunohistochemistry (IHC) and ISH, tissues were perfused with saline, followed by 4 % paraformaldehyde (PFA) in 0.1 M phosphate buffer (PB, pH 7.4). DRGs were sectioned at 16 μm using a cryostat. To analyze mRNA expression and for Western blotting, unfixed DRGs at the L4–L6 segment were immersed into liquid nitrogen quickly.

The tissue samples were subjected to semi-quantitative reverse transcription polymerase chain reaction (RT-PCR) analysis. In brief, total DRG RNA was extracted using the acid guanidinium thiocyanate–phenol–chloroform extraction method and then reverse-transcribed using oligo dT and SuperScript® III (Invitrogen Corporation, Carlsbad, CA, USA). RT-PCR was conducted using specific primers for AminoARS. Each acronym and the designed primer sets are described in Table 1. RT-PCR was conducted using 35 PCR cycles depending on the target gene, with an annealing temperature of 60 °C. Each reaction was conducted in triplicate. The products were separated through an agarose gel and visualized using GelRed™ (Biotium, Hayward, CA, USA). The AARS expression levels were normalized to glyceraldehyde 3-phosphate dehydrogenase (GAPDH) values.

In situ hybridization

Rat AminoARSs cDNA fragments were amplified by RT-PCR, and subcloned into the pGEM®-T Easy Vector (Promega, Madison, WI, USA). Digoxigenin (DIG)-labeled cRNA riboprobes were generated by in vitro transcription using T7 RNA Polymerase (Promega) and SP6 RNA Polymerase (Promega). DRG sections were fixed in 4 % PFA in PB for 20 min at room temperature (RT). After three rinses in phosphate-buffered saline (PBS) for 15 min each with 0.1 % active diethylpyrocarbonate (DEPC), the slides were pre-hybridized in 50 % formamide, 5X saline sodium citrate (SSC) and 40 μg/mL salmon sperm DNA for 2 h at 55 °C. Prehybridization buffer was substituted with hybridization buffer (400 ng/mL of DIG-labeled probe in 50 % formamide, 5X SSC and 40 μg/mL salmon sperm DNA) overnight at 55 °C. To remove excess probe, sections were rinsed in 2X SSC for 30 min at RT and then washed in 2X SSC for 2 h at 65 °C and subsequently in 0.1X SSC at 65 °C. After washing, the sections were equilibrated in Buffer 1 (100 mM Tris–HCl, 150 mM NaCl, pH 7.5) for 5 min and then incubated in Buffer 2 (Buffer 1 with 0.3 % blocking reagent; Roche, Mannheim, Germany) with 1:5,000 diluted alkaline phosphatase (AP)-coupled anti-DIG antibody (Roche) for 2 h at RT. After two 15-min rinses in Buffer 1, the sections were incubated in Buffer 3 (100 mM Tris–HCl, 100 mM NaCl, 50 mM $MgCl_2$, pH 9.5). Sections were incubated in 200 μL nitro-blue tetrazolium and 5-bromo-4-chloro-3′-indolyphosphate (NBT/BCIP) mix (Roche) in Buffer 3. The sections were then rinsed with PBS and mounted. Images were captured using a microscope (Axioskop2; Carl Zeiss, Oberkochen, Germany).

Immunohistochemistry

For IHC combined with ISH, the sections were immunostained with the appropriate antibodies. The slides were fixed in 4 % PFA for 10 min. After three washes in PBS, the samples were washed with PBS containing 0.3 % Triton X-100 (PBST; Biosesang, Sungnam, Korea) for 10 min, treated with 10 % fetal bovine serum (FBS; Hyclone, Logan, UT, USA) for 1 h and incubated with mouse

Table 1 PCR primers and product sizes

cDNA target	Symbol	Gene bank ID	Forward primer sequence (5′–3′)	Reverse primer sequence(5′–3′)	Product size (bp)
Alanyl-tRNA snthetase	AARS	NM_001100517.1	ACATGGCCTACAGGGTTCTG	ATCTACCACCAGGCCCTTCT	436
Cysteinyl-tRNA snthetase	CARS	NM_001106319.1	TGTGAAGCTTGCCACAGAA	TTGGGAGAGCGTTTCTCACT	479
Aspartyl-tRNA snthetase	DARS	NM_053799.2	CGGCGGAAGATTATGCTAA	CTCTCCCGTCCTCTTCTCCT	456
Glutamyl-prolyl-tRNA snthetase	EPRS	NM_001024238.1	AATCCTGCGCTACTTGGCT	TGCATGCCCAATGTGTAAGT	487
Phenylalanyl-tRNA snthetase alpha subunit	FARSa	NM_001024237.1	GATAATCCCGTCTTGGAGCA	ATCACTTCGGTCAGCAGCTT	501
Phenylalanyl-tRNA snthetase beta subunit	FARSb	NM_001004252.1	GACAGCAATGGAGTGGTCCT	GTCCTCCACAATGTCACACG	429
Glycyl-tRNA snthetase	GARS	NM_001271139.1	ATCGGAAGCTCTGACTCGAA	AAGCAGCCACTGAGGAAAAA	426
Histidyl-tRNA snthetase	HARS	NM_001025414.1	TGTCATCAAGCTCCGTTCAG	TTTTTAGCGGCAGAGACGTT	493
Isoleucine-tRNA snthetase	IARS	NM_001100572.1	TCATTGCGTTCTTTGAGACG	CAAGAGCTTCTGGGTCTTGG	473
Lysyl-tRNA snthetase	KARS	NM_001006967.1	CTACCACAACGAGCTGGACA	TTTGCGAGTTTCTTCGGTCT	410
Leucyl-tRNA snthetase	LARS	NM_001009637.1	TCAGGGAAGAGTGCTGTCCT	GACTTTTCCGTTTGCATGGT	409
Methionine-tRNA snthetase	MARS	NM_001127659.1	GCTGTCAGCAATGAACCTGA	TCTGCAGAGGAGTGGTTGTG	445
Asparaginyl-tRNA snthetase	NARS	NM_001025635.2	TGACAAAGATGCTGGAGTCG	AGTACAGCCCATCGGAACAC	422
Glutaminyl-tRNA snthetase	QARS	XM_003752229.2	GTGGTGGAGAACGGTGAAGT	CCTTTGAGCTCTTCCCCTCT	482
Arginyl-tRNA snthetase	RARS	NM_001105777.2	TATGAGCCGCCTCTTTGAGT	AGGCACGAACACAATTTTCC	442
Seryl-tRNA snthetase	SARS	NM_001007606.1	CCGTGAGTTGGTTTCCTGTT	CTCTCTGTTCCAGGGCAGAC	445
Threonyl-tRNA snthetase	TARS	NM_001006976.1	TTTGTCTCTCAGCGGTCCTT	TTGGAGGGCCGTAACATAAG	474
Valyl-tRNA snthetase	VARS	NM_053292.1	GGACAACATCCGAGACTGGT	TGACATTGCCGAGAGACTTG	474
Tryptophanyl-tRNA snthetase	WARS	NM_001013170.2	AAGTGACACCGTGGAGGAAC	TCCATCTGACCACACGACAT	482
Tyrosyl-tRNA snthetase	YARS	NM_001025696.1	TACCAAAGGCACCGACTACC	AGGAAAGAGGACGTGCTTGA	460
Glyceraldehyde-3phosphate dehydrogenase	GAPDH	NM_008084	CTACATGGTCTACATGTTCCAGTATG	AGTTGTCATGGATGACCTTGG	380

anti-neuronal nuclear antigen (NeuN; 1:1,000; Millipore, Billerica, MA, USA) and mouse anti-S100 (S100; 1:1,000; Sigma, St. Louis, MO, USA) primary antibodies for 1 h at RT. After three 10-min washes with PBS, the slides were incubated for 2 h at RT with Alexa Fluor® 488 and 594 (1:1,000; Invitrogen, Carlsbad, CA, USA) secondary antibodies. The slides were in aqueous mounting medium (Biomeda, Foster City, CA, USA) and analyzed using a laser scanning confocal microscope (LSM700; Carl Zeiss, Oberkochen, Germany).

Western blotting

L4 and L5 DRG tissue samples were lysed by homogenization in modified radioimmunoprecipitation assay buffer [RIPA; 50 mmol/L Tris–HCl (pH 7.4), 150 mmol/L NaCl, 0.5 % deoxycholic acid, 0.5 % Triton X-100, 1 mmol/L phenylmethylsulfonyl fluoride, 1 mmol/L sodium o-vanadate, 1X protease inhibitor cocktail tablet (Roche Molecular Biochemicals, Nutley, NJ, USA)]. Samples with equal amounts of protein (15 μg) were separated by 10 % sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE), and the resolved proteins were electrotransferred onto a nitrocellulose membrane (Hybond-C; GE Healthcare, Little Chalfont, UK). Membranes were incubated with 5 % non-fat milk in Tris-buffered saline (TBS) containing 0.05 % Tween 20 (TBST) overnight and incubated with polyclonal primary antibodies against isoleucyl-tRNA synthetase (IARS) (1:200; Neomics, Seoul, Korea), KARS (1:200; Neomics, Seoul, Korea) and QARS (1:200; Neomics, Seoul, Korea) and with a monoclonal primary antibody against β-actin (1:5,000; Sigma, St. Louis, MO, USA) for 1 h at RT. Membranes were then washed three time with TBST and probed with the appropriate horseradish

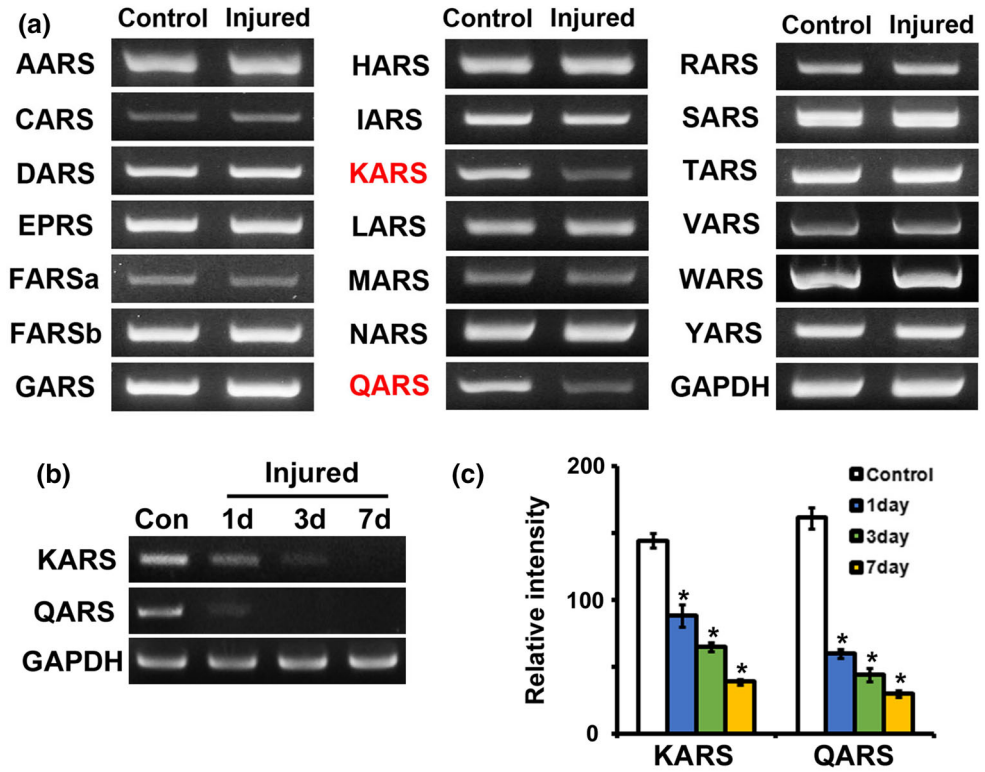

Fig. 1 Expression profile of aminoacyl-tRNA synthetase (AminoARS) mRNA in dorsal root ganglia (DRG). **a** Altered AminoARS mRNA expression in DRG 7 day after peripheral nerve transection, as determined by reverse transcription polymerase chain reaction (RT-PCR). RNA (5 μg) extracted from rat DRG was analyzed by RT-PCR. Lysyl-tRNA synthetase (KARS) and glutaminyl-tRNA synthetase (QARS) mRNA expression was decreased in the injured DRG. Glyceraldehyde 3-phosphate dehydrogenase (GAPDH) was used as a loading control. **b** Time course of KARS and QARS mRNA expression in the L4/5 spinal dorsal horn at control, day 1, day 3 and day 7 after nerve injury. **c** Semi-quantification of the relative intensities of KARS and QARS mRNA levels in DRG at the time course. *Bars* represent the means ± standard deviations (SD). $*p < 0.001$ (n = 6)

peroxidase (HRP)-conjugated secondary antibodies (1:2,000; Invitrogen, Carlsbad, CA, USA) for 1 h at RT. Signals were visualized using enhanced chemiluminescence (ECL; Amersham, Buckinghamshire, England). All experiments were repeated three times.

Statistical analysis

Data are expressed as means ± standard deviations (SD). Differences in values over time for each group were analyzed statistically using analysis of variance (ANOVA) followed by Bonferroni's post hoc tests. A *P* value of <0.001 was considered to be statistically significant.

Results

To determine the effect of peripheral nerve injury on AminoARS expression in rat DRG, we designed a total of 20 PCR primers (Table 1) and amplified the rat AminoARSs. PCR analysis using cDNA reverse transcribed from total RNA was performed in L4/L5 DRG. Of the 20 AminoARSs examined, KARS and QARS were altered in expression in DRG after peripheral nerve injury. Seven days after sciatic nerve injury, KARS and QARS expression levels were decreased significantly in the ipsilateral portion of the L4/L5 DRG compared with the control side of the L4/L5 regions (Fig. 1a). The 18 remaining AminoARSs showed similar mRNA expression patterns in both control and injured samples (Fig. 1a). Around 7 day after nerve injury is the time to maintain the neuropathic pain after the initiation of the pain. Because one of the causes of neuropathic pain is to transfer abnormal sensory signals from DRG to spinal dorsal after nerve injury, we choose 7 day after nerve injury to assess the relationship between AminoARSs expression and neuropathic pain. Next, we performed the time course analysis to confirm the expression of KARS and QARS at time points, control, day 1, day 3 and day 7, using semi-quantitative RT-PCR. The expression of KARS and QARS in DRG at day 1 after nerve injury was significantly decreased and their decreases were maintained until 7 days after nerve injury (Fig. 1b). Semi-quantitative analysis of relative AminoARS intensities also showed decreased KARS and QARS

mRNA expression in the injured DRG at 7 days after nerve injury compared with the control (Fig. 1c).

To investigate the expression of KARS and QARS at the protein level, we performed Western blot analysis. Significantly decreased KARS and QARS bands were observed in tissue harvested from the injured DRG compared with the control side (Fig. 2a, b).

To estimate these changes and further identify the cell types expressing KARS and QARS, ISH and IHC were performed using DIG-labeled probes and antibodies. First, we assessed KARS and QARS mRNA expression patterns in DRG using ISH. Similar to the RT-PCR and Western blot data (Figs. 1, 2), KARS (Fig. 3a) and QARS (Fig. 3c) expression was decreased significantly on the injured side

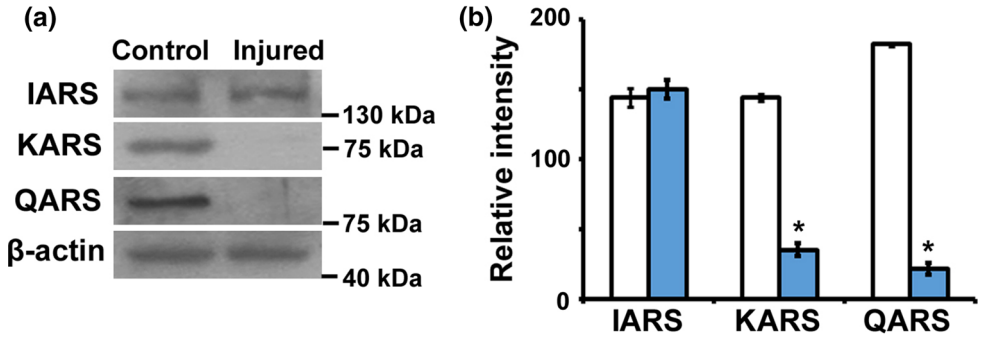

Fig. 2 KARS and QARS protein expression levels in DRG after sciatic nerve transection. **a** Western blot analysis of isoleucyl-tRNA synthetase (IARS), KARS and QARS proteins after sciatic nerve transection. Proteins extracted from control and injured DRG on day 7 after transection were subjected to Western blot analysis. β-actin was used as a loading control. **b** Quantification of IARS, KARS and QARS protein expression levels in L4/5 DRG. $*p < 0.001$ (n = 5)

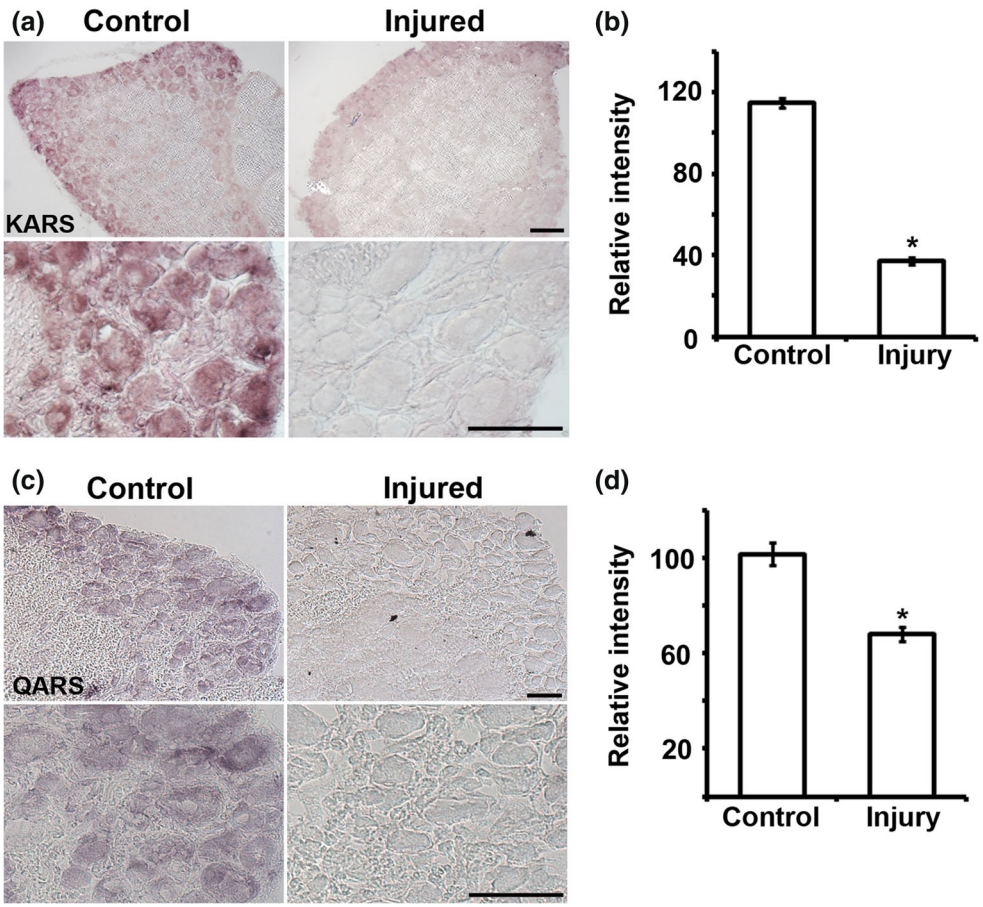

Fig. 3 Distribution of KARS and QARS mRNA in response to transection. **a, c** KARS and QARS mRNA detected by digoxigenin (DIG)-labeled probes in DRG after unilateral transection. KARS and QARS hybridization signals were decreased on the injured side. *Lower panels* represent high-magnification representations of the *left panels*. *Scale bar*, 100 μm. **b, d** Quantitative analysis of the relative DIG-positive intensities of KARS and QARS mRNA levels in DRG. The DIG-positive intensity was measured in a randomly selected area (100 × 100 μm). *Bar* represents mean ± SD. $*p < 0.001$ (n = 6)

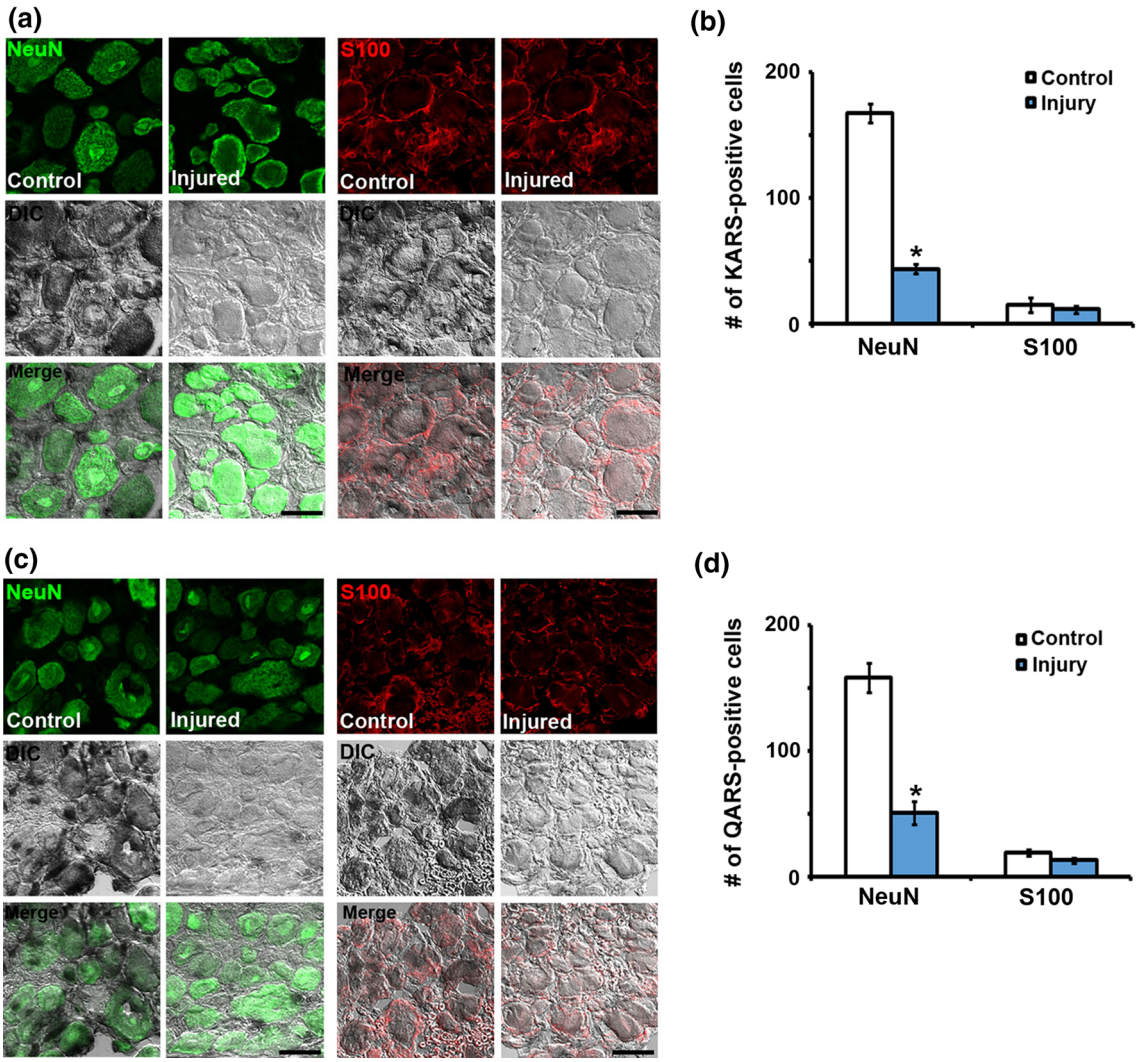

Fig. 4 In situ hybridization (ISH) demonstrating KARS and QARS mRNA localization after transection. **a**, **c** Double labeling of KARS and QARS mRNA by ISH and fluorescence immunohistochemistry (IHC) for neuronal nuclear antigen (NeuN*; green*) and S100 protein (S100; *red*). All KARS and QARS mRNA-expressing cells in DRG were NeuN-positive (*arrows*). *Scale bar*, 40 μm. **b, d** Quantitative analysis of DIG-positive cells in DRG. The number of DIG-positive cells among 100 cell marker-positive cells was measured in a randomly selected area (300 × 300 μm). $*p < 0.001$ (n = 5). Based on their immunohistochemical profile, KARS and QARS mRNA-expressing cells were identified as neurons. (Color figure online)

compared with the control side. Quantitative analysis of relative KARS (Fig. 3b) and QARS (Fig. 3d) intensities also revealed decreased KARS and QARS mRNA expression in the injured DRG compared with the control side.

To identify the cell types that expressed KARS and QARS, we immunostained ISH samples with antibodies against anti-NeuN and anti-S100, markers of neuronal cell bodies and satellite cells, respectively. According to ISH, using KARS and QARS probes, DIG-positive signals for both KARS (Fig. 4a) and QARS (Fig. 4c) were co-localized with NeuN, but not S100, on the DRG control side. However, on the injured DRG side, decreased DIG-positive KARS (Fig. 4a) and QARS (Fig. 4c) signals were observed. These findings indicate that expression of KARS and QARS mRNA was decreased in the cell body of DRG primary sensory neurons. Quantitative analysis of the DIG-labeled intensities showed decreased KARS (Fig. 4b) and QARS (Fig. 4d) mRNA expression in neuronal cell bodies and, to a lesser extent, in satellite cells.

Discussion

In the present study, we screened 20 rat AminoARS genes using semi-quantitative RT-PCR to compare gene expression between control and injured DRG (Fig. 1). We found decreased expression of KARS and QARS on the injured

side. In addition, we conducted further evaluation to determine the morphological patterns of KARS and QARS expression and to determine KARS- or QARS-expressing cell types using ISH and IHC. After peripheral nerve injury, KARS and QARS mRNA expression was decreased in neuronal cell bodies of the injured DRG (Fig. 4). Thus, pharmacological modulation of KARS and QARS expression may be a useful approach for the treatment of sensory neuron dysfunction caused by peripheral nerve injury. It is therefore important to determine AminoARS gene expression profiles in the DRG after peripheral nerve injury. In this study, we described for the first time AminoARS mRNA and protein expression patterns and AminoARS mRNA cell type localization in the DRG.

Why does KARS and QARS expression decrease in DRG neuronal cell bodies after nerve injury? Previous studies showed that AminoARSs have several non-canonical functions that involve a large number of molecular events in living cells beyond their original function of translation (Son et al. 2014; Park et al. 2005a, 2008). KARS is secreted from human cells through tumor necrosis factor alpha (TNF-α) stimulation, and secreted KARS induces the immune response through the activation of immune cells (Park et al. 2005b). GARS is also secreted from macrophages via the Fas ligand and is involved in defense against tumorigenesis (Park et al. 2012). Previous studies suggested the possibility that some AminoARSs act as signaling molecules. Based on our results demonstrating that KARS and QARS mRNA are decreased in the injured DRG neuronal cell body, KARS and QARS may be secreted from primary sensory neurons in the injured DRG after nerve injury. Secreted KARS and QARS may act as neurotransmitters to induce plastic changes in the spinal cord and CNS through synaptic transmission. The peripheral nerve damage-induced changes may also be linked to neuropathic pain. Further evaluation is necessary to identify the functions of decreased KARS and QARS in DRG neurons after peripheral nerve injury.

Second, the decreased KARS and QARS may exert neuroprotective action. Following peripheral nerve injury damages to primary DRG neurons, the mRNA expression levels of many genes change in DRG (Kim et al. 2009). Macrophages are also recruited to the area surrounding damaged DRG neurons (Ton et al. 2013; Laast et al. 2011). Our data showed that KARS and QARS were decreased in injured DRG neurons. Based on previous studies and our results, it seems likely that decreased KARS and QARS expression may affect macrophage recruitment to injured DRG neurons and gene expression changes in injured DRGs. In other words, KARS and QARS may inhibit abnormal genetic changes and maintain molecular homeostasis in normal DRG neurons. Thus, further evaluation of decreased KARS and QARS expression in injured neurons is needed to demonstrate their potential neuroprotective effects.

In summary, our data represent the first morphological and molecular characterizations of AminoARSs in DRGs. We showed that the expression of KARS and QARS mRNA was decreased in injured DRG after peripheral nerve injury, but not in satellite cells. To date, information regarding AminoARSs in the DRG after nerve injury has been scarce. Thus, a detailed understanding of these genes could aid in elucidation of the nature and mechanism of abnormal changes in primary sensory neuronal gene expression after peripheral nerve damage. Because neuropathic pain is related to abnormal sensory signal transduction, regulation of KARS and QARS expression may provide a new therapeutic target for neuropathic pain.

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Conflicts of interest The authors claim no conflicts of interest.

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