Spy1 Protein Mediates Phosphorylation and Degradation of SCG10 Protein in Axonal Degeneration*

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Background: SCG10 is a novel axonal maintenance factor, and rapid SCG10 loss after injury requires JNK activity.

Results: Spy1 mediated SCG10 phosphorylation and degradation, partly in a JNK-dependent manner, and regulated injury-induced axonal degeneration.

Conclusion: Spy1 is an important regulator of SCG10 and axon degeneration.

Significance: Spy1 may be a novel axo-protective therapeutic target for axon loss.

Axon loss is a destructive consequence of a wide range of neurological diseases without a clearly defined mechanism. Recent data demonstrate that SCG10 is a novel axonal maintenance factor and that rapid SCG10 loss after injury requires JNK activity; however, how JNK regulates SCG10 levels in axons following injury is not well known. Here we showed that Spy1, a member of the Speedy/RINGO family protein that regulates microtubule dynamics and protein trafficking in a JNK-dependent manner (14), is an important regulator of SCG10 and can be targeted in future axon degeneration. Taken together, these data suggest that Spy1 is an important regulator of SCG10 and axon degeneration.

SCG10 is a JNK target in the axonal degeneration pathway. The authors offer their sincere apologies for their carelessness and failure to scrupulously preserve the original data.

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Spy1 is a novel regulator of axon degeneration and as such positioning itself as a potential therapeutic target.

Materials and Methods

Expression Plasmid Preparation—SCG10 was isolated by PCR from a human fetal brain complementary DNA library and inserted into pcDNA3.1-Myc vector. The identical method was used for GST-SCG10, His-Spy1, HA-Spy1, and their mutants. SCG10 phosphorylation site mutants S50A, S62A, S73A, and S97A were created from wild-type SCG10. All constructs were verified by sequencing. GFP-tagged lentivirus sh-Spy1 was purchased from GeneChem (Shanghai, China).

Reagents and Antibodies—The following reagents and antibodies were used in this study: rabbit polyclonal anti-Spy1 (Abcam, ab86568), mouse monoclonal anti-SCG10 (Santa Cruz Biotechnology, sc-135620), mouse monoclonal -/H92523-tubulin (Millipore, MAB1637), rabbit polyclonal anti-GAPDH (Abcam, ab9484), mouse monoclonal anti-phosphoserine (Millipore, 05-1000), anti-His, -Myc, and -HA (GenScript Corp., Nanjing, China), JNK inhibitor VII, TAT-TI-JIP153-163 (Calbiochem, 420134), and Cdk2 inhibitor II (Santa Cruz Biotechnology, sc-221409) (24). Z-Leu-Leu-Leu-al (MG132) at 20 /H9262M and SP600125 at 15 /H9262M were purchased from Sigma-Aldrich.

Cell Culture and Transfection—HEK-293 cells were maintained in Dulbecco’s modified Eagle’s medium (Gibco). Medium was supplemented with 10% fetal bovine serum and cultured at 37 °C in a humidified incubator at 5% CO2. Cells were transfected with plasmids using Lipofectamine 2000 (Invitrogen) according to the manufacturer’s instructions.

Dorsal root ganglions (DRGs) from embryonic day 17.5–18.5 rat (Charles River) were cultured in poly-D-lysine-(Sigma) and laminin- (Sigma) coated 24-well plates (Corning). Collected DRGs were trypsinized for 20 min at 37 °C, triturated in medium, and plated as a spot at a density of approximately two DRGs per well in 2 μl of medium. The plates were incubated for 20 min at 37 °C to attach cells to the plastic followed by the addition of Neurobasal medium (Invitrogen) supplemented with 2% (v/v) B27 (Invitrogen), 25 ng/ml nerve growth factor (Promega), and 1 μM 5-fluoro-2′-deoxyuridine and 1 μM uridine (Sigma) to block cell division of nonneuronal cells. Cultures were maintained for 8–9 days before axotomy or drug treatment. We axotomized cultures of DRG neurons with a

FIGURE 1. SCG10 is a binding partner of Spy1. A, Spy1 interacts with SCG10 in vitro. The GST pulldown assay was performed by incubating in vitro-translated His-tagged Spy1 with purified GST-SCG10 immobilized on glutathione-Sepharose beads. GST-SCG10 but not GST was shown to pull down Spy1. Arrows indicate GST and GST-SCG10 bands, and Coomassie Blue staining indicates the loading amounts. WB, Western blot. B, HA-tagged Spy and Myc-tagged SCG10 were co-expressed in HEK-293 cells for immunoprecipitation assays. C, the interaction between endogenous Spy1 and SCG10 in DRG neurons, analyzed by immunoprecipitation using a SCG10-specific antibody. Myc-tagged SCG10 mutants and HA-tagged Spy mutants were co-expressed in HEK-293 cells for immunoprecipitation assays, D and E, the stathmin-like domain (SLD) of SCG10 was required for binding to Spy1. F and G, the Speedy/RINGO domain (S/R) of Spy1 was required for binding to SCG10.

TABLE 1

| Gene name | Gene ID    | Cloning vector | Hybrid vector | Library            | Positive clones |
|-----------|------------|----------------|---------------|--------------------|----------------|
| SPDYA     | NM_182756.3| pcDNA3.1-myc    | pGBK77        | Human fetal brain  | Total 19:      |
|           |            |                |               |                    | 1: CRMP1       |
|           |            |                |               |                    | 2: Homo sapiens chromosome 10 genomic contig, alternate assembly |
|           |            |                |               |                    | 3: MAP15       |
|           |            |                |               |                    | 4: GPRASP1     |
|           |            |                |               |                    | 5: H. sapiens deformed epidermal autoregulatory factor 1 |
|           |            |                |               |                    | 6: FBLN1       |
|           |            |                |               |                    | 7: C12B         |
|           |            |                |               |                    | 8: PLEKHA5     |
|           |            |                |               |                    | 9: DHX36       |
|           |            |                |               |                    | 10: GPSM1      |
|           |            |                |               |                    | 11: TSEN54     |
|           |            |                |               |                    | 12: NDUFS5     |
|           |            |                |               |                    | 13: NDUFB9     |
|           |            |                |               |                    | 14: SENP3      |
|           |            |                |               |                    | 15: TRA2B      |
|           |            |                |               |                    | 16: GPR37      |
|           |            |                |               |                    | 17: KIF3B      |
|           |            |                |               |                    | 18: SCG10      |
|           |            |                |               |                    | 19: UQCRFS1    |
microscalpel. In addition, we added lentivirus to the culture at 4–5 days and allowed 4–5 days for expression. To confirm efficient overexpression or knockdown of a gene, we monitored fluorescence from Venus and performed Western blot analysis to assess the level of the protein of interest.

Western Blot Analysis—Cells were washed and collected from plates in PBS solution, resuspended with 2× H11003 sample buffer, and boiled for 5 min. Proteins were then resolved in an 10% SDS-PAGE gel and transferred to a polyvinylidene difluoride membrane (Millipore).

Rat in Vivo Sciatic Nerve Transection—We used adult Sprague-Dawley rats weighing 220–250 g (Department of Animal Center, Nantong University). We anesthetized animals, made a small incision unilaterally to expose the sciatic nerve, transected the sciatic nerve with surgical scissors, and then sutured the incision. Three hours after transection, rats were euthanized by CO2, and the sciatic nerves were removed for Western blot analysis. From the transected nerve, only distal segments were collected. Rat experiments were performed under the supervision of Division of Comparative Medicine at Nantong University.

Phase-contrast Imaging and Quantifying Axon Degeneration in Vitro—Axon degeneration was analyzed as described previously (14). Briefly, phase-contrast images were obtained on an inverted light microscope (CKX41; Olympus) with a 20× objective. Three nonoverlapping images of each well were taken at each time point and assessed for axon degeneration. Images were processed with the auto-level function in Photoshop (Adobe) for brightness adjustment. We then analyzed the images by using a macro written in ImageJ to calculate the degeneration index (26, 27). After images were binarized, the total axon area was defined by the total number of detected pixels. The area of degenerated axon fragments was calculated.

Results

SCG10 Is a Binding Partner of Spy1—To identify novel Spy1-binding partners, we performed yeast two-hybrid screening using a human fetal brain complementary DNA library with Spy1 as bait and identified SCG10 as a putative binding protein (Table 1). To verify the potential interaction obtained with the yeast two-hybrid screening, we performed an in vitro GST binding assay and showed that in vitro-translated Spy1 interacted with GST-SCG10 but not with GST alone (Fig. 1A). Immunoprecipitation assays were then undertaken to test the intracellular interaction between Spy1 and SCG10. HA-tagged Spy and Myc-tagged SCG10 were co-expressed in HEK-293 cells, and they could pull down each other (Fig. 1B). Importantly, immunoprecipitation of endogenous SCG10 from DRG neurons using a SCG10-specific antibody also pulled down Spy1 protein (Fig. 1C). To determine the protein domains required for the interaction between Spy1 and SCG10, Myc-tagged SCG10 mutants and HA-tagged Spy mutants were co-expressed in HEK-293 cells for immunoprecipitation assays. The data suggested that the stathmin-like domain of SCG10 was required for binding to
Spy1 (Fig. 1, D and E) and that the Speedy/RINGO domain of Spy1 was required for binding to SCG10 (Fig. 1, F and G).

**Spy1 Expression Inversely Correlates with SCG10 during the Early Stage of Axonal Injury**—Previously data showed that SCG10 was a novel axonal maintenance factor (14). Given that our recent data showed that Spy1 participated in the pathological process response to sciatic nerve injury (23), we hypothesized that Spy1 might modulate SCG10 activity and participate in axon regeneration/degeneration. We first examined the expression of both proteins in an *in vitro* model of axonal injury. In DRG neurons, SCG10 expression was lost rapidly from injured distal axons during the first 3 h after axotomy (Fig. 2, A and B), which was in agreement with previous studies (14, 25). Interestingly, Spy1 level was increased in injured distal axons during the same period (Fig. 2, A and B). To further confirm these results, we performed an *in vivo* model of axonal injury of sciatic nerve. Indeed, SCG10 level decreased rapidly in injured distal sciatic nerves at the early stage after transection (Fig. 2, C and D), whereas Spy1 level was increased in parallel (Fig. 2, C and D). Therefore, our data suggested that Spy1 expression was inversely correlated with SCG10 during the early stage of axonal injury.

**Spy1 Mediates SCG10 Phosphorylation and Degradation Partly in a JNK-dependent Manner**—As Spy1 levels showed an inverse correlation with SCG10 after axonal injury, we speculated whether Spy1 could regulate SCG10 level. Forced expression of ectopic Spy1 resulted in a decrease of SCG10 in a dose-dependent manner (Fig. 3, A and B). In contrast, treatment with
the proteasome inhibitor MG132 blocked the loss of SCG10 (Fig. 3, C and D), indicating that Spy1 might impact SCG10 stability rather than its de novo synthesis.

Previous data showed that JNK phosphorylation of SCG10 targeted SCG10 for degradation (14). We then set out to determine whether Spy1 might affect SCG10 phosphorylation in a JNK-dependent manner. Consistent with the observation that Spy1 promoted SCG10 degradation, it also enhanced SCG10 phosphorylation (Fig. 3E). To further identify the specific phosphorylation site(s) of SCG10 by Spy1, four candidate phosphor-
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Discussion

Axon loss is a destructive consequence of a wide range of neurological diseases. Therapies targeting the axon loss process itself are notably absent. Clarifying the mechanism of axon loss may help develop such therapies. Regulated protein degradation promotes the degeneration of injured axons (3), potentially via the degradation of vulnerable axonal maintenance factors. Recent data have demonstrated that SCG10, being similar to NMNAT2 (29), is a novel axonal maintenance factor (14); rapid SCG10 loss after injury requires JNK activity. However, pharmacologically inhibiting JNK activity further slows the degradation of the mutant SCG10 in which two JNK phosphorylation sites (serines 62 and 73) were replaced by alanines, demonstrating that JNK may promote the degradation of SCG10 through other mechanisms, in addition to the phosphorylation of SCG10 (14). Therefore, understanding the mechanisms regulating SCG10 stability may be helpful in finding ways to attenuate axonal destruction, for example, by inhibiting specific degradation machinery targeting SCG10.

Spy1, as a Spy1 family protein, is implicated in mammary gland development and cell cycle regulation. In addition, our work previously showed that Spy1 expression could be detected in the nervous system, including neurons and non-neuronal cells (21). To further investigate the possible role of Spy1 in the nervous system, we performed yeast two-hybrid screening in a human fetal brain complementary DNA library and found that Spy1 was a binding partner of JIP3 (30), a scaffolding protein regulating JNK activity (31). Our results showed that JNK phosphorylation of SCG10 plays an important role in axonal injury, suggesting that Spy1 affects axonal injury in a JNK-dependent manner. Our work further showed Spy1-mediated SCG10 phosphorylation and injury-induced axonal degeneration, which confirmed our hypothesis.

Previous data showed that JNK phosphorylation of SCG10 targeted SCG10 for degradation (14), and our data showed that Spy1 increased JNK kinase activity. These data are in line with previous reports that Spy1 was an activator of CDKs (15, 16), suggesting that Spy1 may exert its pathobiological functions via modulating kinase activities. On the other hand, recent data showed that dual leucine zipper kinase (DLK) regulated stress-induced JNK activity in axons via interaction of dual leucine zipper kinase with the scaffolding protein JIP3 (30, 31). Whether Spy1 has an identical role like dual leucine zipper kinase needs further studies. Furthermore, treatment with JNK kinase inhibitor SP600125 only partially abolished Spy1-mediated phosphorylation of SCG10, suggesting that other mechanisms may take part in the Spy1-mediated phosphorylation of SCI10. Delayed injury-induced axonal degeneration.

Inhibition of Spy1 Attenuates SCG10 Phosphorylation and Delays Injury-induced Axonal Degeneration—Next, we investigated the role of Spy1 in the degeneration of DRG neurons after axotomy. GFP-tagged lentivirus targeting Spy1 was used to infect DRG neurons. Spy1 shRNA #3 resulted in a reduction in Spy1 level when compared with control shRNA (Fig. 3A). Previous data showed that phosphorylated SCG10 appeared at a higher molecular weight than nonphosphorylated SCG10 (Fig. 3B). The ratio of phosphorylated SCG10 to nonphosphorylated SCG10 on JNK kinase, we examined the effect of Spy1 on JNK kinase activity. Our results showed that inhibition of CDK2 had no effect on Spy1-mediated phosphorylation of SCG10 (Fig. 3C). Together, these data suggest that Spy1 mediates SCG10 phosphorylation and degradation partly in a JNK-dependent manner.

Our results showed that inhibition of CDK2 had no effect on Spy1-mediated phosphorylation of SCG10 (Fig. 3C). Previous data showed that JNK phosphorylation of SCG10 induced JNK activity in axons via interaction of dual leucine zipper kinase with the scaffolding protein JIP3 (30, 31). Together, these data suggest that Spy1 mediates SCG10 phosphorylation and degradation partly in a JNK-dependent manner.

Previous studies showed that JNK phosphorylation of SCG10 induced JNK activity in axons via interaction of dual leucine zipper kinase with the scaffolding protein JIP3 (30, 31). Whether Spy1 has an identical role like dual leucine zipper kinase needs further studies. Furthermore, treatment with JNK kinase inhibitor SP600125 only partially abolished Spy1-mediated phosphorylation of SCG10, suggesting that other mechanisms may take part in the Spy1-mediated phosphorylation of SCG10. Delayed injury-induced axonal degeneration. As shown in Fig. 4A, Spy1 knockdown significantly delayed axonal degeneration as quantified by degeneration index, a measurement of fragmented axonal area calculated from phase-contrast images (27, 28). In neurons infected with control virus, axonal fragmentation was apparent by 6 h and robust by 9 h after axotomy (Fig. 4E). In contrast, following knockdown of Spy1, degeneration was significantly delayed (Fig. 4E). Reintroduction of exogenous Spy1 restored axonal degeneration, whereas SP600125 treatment halted axonal degeneration (Fig. 4E). Collectively, these results demonstrated that depletion of Spy1 attenuated SCG10 phosphorylation and delayed injury-induced axonal degeneration.
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SCG10. Clearly, more work is warranted to address this lingering issue.

Most studies show that Spy1 is a cell cycle regulator and that it promotes tumorigenesis (15–21). Here, we demonstrate a cell cycle-independent role for Spy1. Two pieces of evidence may support our data. First, SCG10 binds to the Speedy/RINGO domain of Spy1, but not the CDK-binding domain on the N terminus. Second, the functional interplay between Spy1 and SCG10 is staged in the axons instead of the nucleus where cell cycle regulation takes place. Further investigation is needed to clarify whether SCG10 might modulate Spy1 reciprocally in the nucleus.

In conclusion, our data indicate that Spy1 is an important regulator of axonal maintenance factor SCG10. As such, understanding its regulatory mechanisms may help to find new methods for attenuating axonal degeneration. Spy1 may be a novel axo-protective therapeutic target for axon loss.

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