J Neurology Neuromedicine
www.jneurology.com
Journal of Neurology & Neuromedicine

Commentary Open Access

Commentary: Critical role of JSAP1 and JLP in axonal transport in the cerebellar Purkinje cells of mice

Katsuji Yoshioka*
Division of Molecular Cell Signaling, Cancer Research Institute, Kanazawa University, Kakuma-machi, Kanazawa 920-1192, Japan

Article Info

Article Notes
Received: October 28, 2016
Accepted: November 18, 2016

***Correspondence:**
Dr. Katsuji Yoshioka,
Division of Molecular Cell Signaling, Cancer Research Institute, Kanazawa University, Kakuma-machi, Kanazawa 920-1192, Japan, Telephone: +81-76-234-4532;
Email: katsuji@staff.kanazawa-u.ac.jp

ABSTRACT

Axonal transport is essential for the development, function, and survival of neurons, and impaired axonal transport has been implicated in many neurodegenerative diseases, including Alzheimer's disease and Parkinson's disease. To date, however, how axonal transport is regulated, and how defective transport leads to neurodegeneration, remain largely unknown. This study by Sato et al. shows that the loss of both JSAP1 and JLP in the cerebellar Purkinje cells (PCs) of mice causes axonal dystrophy followed by gradual, progressive PC degeneration. This study also suggests that JSAP1 and JLP regulate kinesin-1-dependent axonal transport in the brain with functional redundancy, which prevents axonal degeneration and subsequent neuronal death. There is increasing evidence that in neurodegenerative diseases, axonal degeneration precedes neuronal cell death. Thus, elucidating the mechanisms of axonal degeneration may provide promising targets for therapeutic intervention. The JSAP1-null, JLP-null mouse generated in this study may provide a useful animal model for studying the molecular basis of axonal degeneration in neurodegenerative diseases, and for developing therapeutic drugs for these diseases.

Commentary

Most neurons have three parts: an axon, a cell body or soma, and dendrites. The axon is usually the longest process of a neuron, and an efficient transport system is required to deliver cargoes such as organelles and proteins along its length. Axonal transport is a complex and highly regulated process that is essential for neuronal development, function, and survival, and defective axonal transport has been implicated in many neurodegenerative diseases, including Alzheimer's disease and Parkinson's disease[1,2]. A mutation in KIF1B, a kinesin-family motor protein, has been reported in patients with Charcot–Marie–Tooth disease type 2A, a progressive neurodegenerative disorder, and specific axonal-transport defects in synaptic-vesicle precursors are observed in the sciatic nerve in heterozygous *Kif1B*-knockout (KO) mice[3]. Falzone et al.[4] showed that deleting the kinesin-1 subunit KLC1 in mice induces early selective axonal-transport defects, which lead to axonopathies with cytoskeletal disorganization and abnormal cargo accumulation. In addition, impaired axonal transport has been observed in neurons from various animal models for neurodegenerative disorders such as amyotrophic lateral sclerosis, Alzheimer's disease, and Parkinson's disease[5,6]. However, the mechanisms that regulate axonal transport, and how defective transport leads to neurodegeneration, remain largely unknown. The authors generated mice with genetic *Jsap1*

or *Jlp* ablations for this study[7], and these mice might serve as a useful animal model for studying the molecular mechanisms of neurodegenerative disorders.

JSAP1 (also known as JIP3 or Sunday Driver 2) and JLP (also known as SPAG9, JIP4, or Sunday Driver 1) were first identified as scaffold proteins for specific JNK and p38 MAP kinase intracellular signaling modules[8-14]. As implied by these many alternate names, these proteins were identified and characterized independently by multiple research groups. Gene KO studies of *Jsap1* and *Jlp* report very different phenotypes in mice: *Jsap1*-KO mice die shortly after birth, most likely due to neural defects[15-17], while *Jlp*-KO mice are viable, grow normally, have a light coat color and pale skin, and exhibit male subfertility[18,19]. Therefore, it has not been asked until recently whether JSAP1 and JLP have redundant functions. This study by Sato et al. demonstrated that JSAP1 and JLP have overlapping functions in the cerebellar Purkinje cells (PCs) of mice. The functional redundancy of JSAP1 and JLP is not likely to be restricted to PCs. In fact, the same research group reported that mice with dorsal-telencephalon-specific double *Jsap1* and *Jlp* deletions, but not those with a single deletion, show neurodegeneration in the postnatal developing brain, have retarded growth, and die before reaching adulthood[20]. Thus, JSAP1 and JLP may play critical and overlapping roles in neurons throughout the brain.

In this study, Sato et al. generated mice with a PC-targeted conditional deletion of *Jsap1*, *Jlp*, or both using loxP-flanked alleles of these genes in combination with the *L7/Pcp2-Cre* transgene, and used these mice to examine the role of JSAP1 and JLP in PCs. Histological analysis of 24-week-old mice revealed the specific loss of PCs and the presence of swollen PC axons in mice with a conditional double KO (cDKO) of *Jsap1* and *Jlp* (*Jsap1:Jlp* cDKO), but not in control mice or those with a single *Jsap1* or *Jlp* cKO. The authors found that the PC counts were comparable in control and *Jsap1:Jlp* cDKO mice at 8 weeks of age; however, after this age, the PC counts decreased in cDKO mice compared to control mice (at all ages examined, up to 40-weeks old). This neuronal loss worsened in the cDKO mice with increasing age. Furthermore, many PC axons were dilated near the PC bodies in cDKO mice at all ages examined, including 8 weeks of age. In addition, hypertrophic PC axons were found in the deep cerebellar nuclei (DCN) of *Jsap1:Jlp* cDKO mice at 8–40 weeks of age, and the number of PC axons in the DCN was noticeably decreased at 16 and 24 weeks of age. Together, the data show that the loss of JSAP1 and JLP in PCs causes axonal dystrophy followed by gradual, progressive PC degeneration.

JSAP1 and JLP are known to interact with components of kinesin-1, specifically the kinesin heavy chain and light chain[21-23], and *in vitro* studies suggested that these proteins act as adaptor proteins linking kinesin-1 to cargoes and as positive regulators of kinesin-1 activity and motility[23-25]. Axonal dystrophy is thought to reflect defective axonal transport; thus, the swollen axons in JSAP1- and JLP-null PCs were likely to be caused by the blockage of kinesin-1–dependent axonal transport in the PCs. Indeed, kinesin-1 cargoes selectively accumulated in the swollen axons of the cDKO mice, which is consistent with an *in vitro* study using *Jsap1*- and *Jlp*-deficient primary cultured hippocampal neurons[20]. This previous *in vitro* study further suggested that JSAP1 and JLP are critical regulators of axonal transport. Altogether, Sato et al.'s *in vivo* study suggests that JSAP1 and JLP regulate kinesin-1-dependent axonal transport in the brain with functional redundancy, thereby preventing axonal degeneration and subsequent neuronal death.

Many neurodegenerative diseases are characterized by slow, progressive neuronal dysfunction and neuron loss. This similarity in pathological features may indicate the existence of common neurodegenerative mechanisms, although distinct neurons are selectively vulnerable to neurodegeneration in these diseases. There is increasing evidence that axonal degeneration, of which impaired axonal transport is an essential cause, precedes neuronal cell death in these diseases[5,6,26]. Therefore, elucidating the mechanisms of axonal degeneration is likely to provide promising targets for therapeutic intervention. Further studies in this area are needed, because current therapies for neurodegenerative diseases generally target non-specific mechanisms and can only relieve symptoms. The JSAP1-null, JLP-null mice generated and analyzed in this study may be a useful animal model for studying the molecular basis of the axonal degeneration accompanying many neurodegenerative diseases, and for developing therapeutic drugs for these diseases.

References

1. Perlson E, Maday S, Fu MM, et al. Retrograde axonal transport: pathways to cell death? Trends Neurosci. 2010; 33(7): 335-344.
2. Millecamps S, Julien JP. Axonal transport deficits and neurodegenerative diseases. Nat Rev Neurosci. 2013; 14(3): 161-176.
3. Zhao C, Takita J, Tanaka Y, et al. Charcot-Marie-Tooth disease type 2A caused by mutation in a microtubule motor KIF1Bbeta. Cell. 2001; 105(5): 587-597.
4. Falzone TL, Stokin GB, Lillo C, et al. Axonal stress kinase activation and tau misbehavior induced by kinesin-1 transport defects. J Neurosci. 2009; 29(18): 5758-5767.
5. De Vos KJ, Grierson AJ, Ackerley S, et al. Role of axonal transport in neurodegenerative diseases. Annu Rev Neurosci. 2008; 31: 151-173.
6. Morfini GA, Burns M, Binder LI, et al. Axonal transport defects in neurodegenerative diseases. J Neurosci. 2009; 29(41): 12776-12786.
7. Sato T, Ishikawa M, Yoshihara T, et al. Critical role of JSAP1 and JLP in axonal transport in the cerebellar Purkinje cells of mice. FEBS Lett. 2015; 589(19 Pt B): 2805-2811.
8. Ito M, Yoshioka K, Akechi M, et al. JSAP1, a novel jun N-terminal protein kinase (JNK)-binding protein that functions as a Scaffold factor in the JNK signaling pathway. Mol Cell Biol. 1999; 19(11): 7539-7548.

9. Kelkar N, Gupta S, Dickens M, et al. Interaction of a mitogen-activated protein kinase signaling module with the neuronal protein JIP3. Mol Cell Biol. 2000; 20(3): 1030-1043.
10. Ito M, Akechi M, Hirose R, et al. Isoforms of JSAP1 scaffold protein generated through alternative splicing. Gene. 2000; 255(2): 229-234.
11. Bowman AB, Kamal A, Ritchings BW, et al. Kinesin-dependent axonal transport is mediated by the sunday driver (SYD) protein. Cell. 2000; 103(4): 583-594.
12. Lee CD, Onésime D, Reddy CD, et al. JLP: A scaffolding protein that tethers JNK/p38MAPK signaling modules and transcription factors. Proc Natl Acad Sci U S A. 2002; 99(22): 14189-14194.
13. Jagadish N, Rana R, Selvi R, et al. Characterization of a novel human sperm-associated antigen 9 (SPAG9) having structural homology with c-Jun N-terminal kinase-interacting protein. Biochem J. 2005; 389(Pt 1): 73-82.
14. Kelkar N, Standen CL, Davis RJ. Role of the JIP4 scaffold protein in the regulation of mitogen-activated protein kinase signaling pathways. Mol Cell Biol. 2005; 25(7): 2733-2743.
15. Kelkar N, Delmotte MH, Weston CR, et al. Morphogenesis of the telencephalic commissure requires scaffold protein JNK-interacting protein 3 (JIP3). Proc Natl Acad Sci U S A. 2003; 100(17): 9843-9848.
16. Ha HY, Cho IH, Lee KW, et al. The axon guidance defect of the telencephalic commissures of the JSAP1-deficient brain was partially rescued by the transgenic expression of JIP1. Dev Biol. 2005;277(1): 184-199.
17. Iwanaga A, Sato T, Sugihara K, et al. Neural-specific ablation of the scaffold protein JSAP1 in mice causes neonatal death. Neurosci Lett. 2007; 429(1):43-48.
18. Iwanaga A, Wang G, Gantulga D, et al. Ablation of the scaffold protein JLP causes reduced fertility in male mice. Transgenic Res. 2008; 17(6): 1045-1058.
19. Enkhtuya R, Sato T, Wakasugi M, et al. The scaffold protein JLP plays a key role in regulating ultraviolet B-induced apoptosis in mice. Genes Cells. 2014; 19(4): 350-358.
20. Sato T, Ishikawa M, Mochizuki M, et al. JSAP1/JIP3 and JLP regulate kinesin-1-dependent axonal transport to prevent neuronal degeneration. Cell Death Differ. 2015; 22(8): 1260-1274.
21. Nguyen Q, Lee CM, Le A, et al. JLP associates with kinesin light chain 1 through a novel leucine zipper-like domain. J Biol Chem. 2005; 280(34): 30185-30191.
22. Verhey KJ, Meyer D, Deehan R, et al. Cargo of kinesin identified as JIP scaffolding proteins and associated signaling molecules. J Cell Biol. 2001; 152(5): 959-970.
23. Sun F, Zhu C, Dixit R, et al. Sunday Driver/JIP3 binds kinesin heavy chain directly and enhances its motility. EMBO J. 2011; 30(16): 3416-3429.
24. Hammond JW, Griffin K, Jih GT, et al. Co-operative versus independent transport of different cargoes by Kinesin-1. Traffic. 2008; 9(5): 725-741.
25. Watt D, Dixit R, Cavalli V. JIP3 Activates Kinesin-1 Motility to Promote Axon Elongation. J Biol Chem. 2015; 290(25): 15512-15525.
26. Lingor P, Koch JC, Tönges L, et al. Axonal degeneration as a therapeutic target in the CNS. Cell Tissue Res. 2012; 349(1): 289-311.