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## 2025

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**Design by** Yuko Tonohira

**On the cover:**
Confocal image illustrating a structured array of lamina synapses, reflecting the *Drosophila* compound eye organization using membrane reporter CD8-GFP (green) and synaptic active zone marker Bruchpilot (BRP, magenta). This highlights both the organization of photoreceptor axons R1-R8 and their synapses with lamina monopolar cells. Image © 2025 Ortiz-Vega et al. See "Regulation of proteostasis by sleep in Alzheimer's disease" on page 14.

Rockefeller University Press

# NEUROSCIENCE SPECIAL COLLECTIONS 2025

The editors of the *Journal of Cell Biology* (*JCB*), *Journal of Experimental Medicine* (*JEM*), *Journal of General Physiology* (*JGP*), and *Life Science Alliance* (*LSA*) present special collections of recently published articles that elucidate new advances within the field of neuroscience. If you enjoy the selected abstracts included in this magazine, we encourage you to scan the QR codes to view the full online collections and sign up for email alerts to receive the latest research.

# $Ca^{2+}$ regulates ER-PM MCS density via Esyt

Membrane contact sites (MCS) between the plasma membrane (PM) and endoplasmic reticulum (ER) regulate $Ca^{2+}$ influx. However, the mechanisms by which cells modulate ER–PM MCS density are not understood, and the role of $Ca^{2+}$, if any, in regulating these is unknown.

We report that in *Drosophila* photoreceptors, MCS density is regulated by the $Ca^{2+}$ channels TRP and TRPL. Regulation of MCS density by $Ca^{2+}$ is mediated by *Drosophila* extended synaptotagmin (dEsyt), a protein localized to ER–PM MCS and previously shown to regulate MCS density. We find that the $Ca^{2+}$-binding activity of dEsyt is required for its function in vivo. $dEsyt^{CaBM}$, a $Ca^{2+}$ non-binding mutant of dEsyt, is unable to modulate MCS structure. Further, reconstitution of dEsyt null photoreceptors with $dEsyt^{CaBM}$ is unable to rescue ER–PM MCS density and other key phenotypes.

Thus, our data support a role for $Ca^{2+}$ binding to dEsyt in regulating ER–PM MCS density in photoreceptors, thus tuning signal transduction during light-activated $Ca^{2+}$ influx.

**ORIGINAL PAPER**

Nath, V.R., H. Krishnan, S. Mishra, and P. Raghu. 2025. $Ca^{2+}$ binding to Esyt modulates membrane contact site density in *Drosophila* photoreceptors. *J. Cell Biol.* 224 (5): e202407190. https://doi.org/10.1083/jcb.202407190

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# Persistent endolysosomal perforations in neurons

Endocytosis, required for the uptake of receptors and their ligands, can also introduce pathological aggregates such as α-synuclein (α-syn) in Parkinson's Disease. We show here the unexpected presence of intrinsically perforated endolysosomes in neurons, suggesting involvement in the genesis of toxic α-syn aggregates induced by internalized preformed fibrils (PFFs).

Aggregation of endogenous α-syn in late endosomes and lysosomes of human iPSC-derived neurons (iNs), seeded by internalized α-syn PFFs, caused the death of the iNs but not of the parental iPSCs and non-neuronal cells. Live-cell imaging of iNs showed constitutive perforations in ~5% of their endolysosomes. These perforations, identified by 3D electron microscopy in iNs and CA1 pyramidal neurons and absent in non-neuronal cells, may facilitate cytosolic access of endogenous α-syn to PFFs in the lumen of endolysosomes, triggering aggregation.

Inhibiting the PIKfyve phosphoinositol kinase reduced α-syn aggregation and associated iN death, even with ongoing PFF endolysosomal entry, suggesting that maintaining endolysosomal integrity might afford a therapeutic strategy to counteract synucleinopathies.

**ORIGINAL PAPER**

Sanyal, A., G. Scanavachi, E. Somerville, A. Saminathan, A. Nair, R.F. Bango Da Cunha Correia, B. Aylan, E. Sitarska, A. Oikonomou, N.S. Hatzakis, and T. Kirchhausen. 2025. Neuronal constitutive endolysosomal perforations enable α-synuclein aggregation by internalized PFFs. *J. Cell Biol.* 224 (2): e202401136. https://doi.org/10.1083/jcb.202401136

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JCB Journal of Cell Biology

# KNL-1 modulates actin dynamics to control dendrite branching

The function of the nervous system is intimately tied to its complex and highly interconnected architecture. Precise control of dendritic branching in individual neurons is central to building the complex structure of the nervous system. Here, we show that the kinetochore protein KNL-1 and its associated KMN (Knl1/Mis12/Ndc80 complex) network partners, typically known for their role in chromosome–microtubule coupling during mitosis, control dendrite branching in the *Caenorhabditis elegans* mechanosensory PVD neuron.

KNL-1 restrains excess dendritic branching and promotes contact-dependent repulsion events, ensuring robust sensory behavior and preventing premature neurodegeneration. Unexpectedly, KNL-1 loss resulted in significant alterations of the actin cytoskeleton alongside changes in microtubule dynamics within dendrites. We show that KNL-1 modulates F-actin dynamics to generate proper dendrite architecture and that its N terminus can initiate F-actin assembly.

These findings reveal that the postmitotic neuronal KMN network acts to shape the developing nervous system by regulating the actin cytoskeleton and provide new insight into the mechanisms controlling dendrite architecture.

**ORIGINAL PAPER**

Alves Domingos, H., M. Green, V.R. Ouzounidis, C. Finlayson, B. Prevo, and D.K. Cheerambathur. 2025. The kinetochore protein KNL-1 regulates the actin cytoskeleton to control dendrite branching. *J. Cell Biol.* 224 (2): e202311147. https://doi.org/10.1083/jcb.202311147

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# Local glycolysis supports axonal regeneration

Successful axonal regeneration following injury requires the effective allocation of energy. How axons withstand the initial disruption in mitochondrial energy production caused by the injury and subsequently initiate regrowth is poorly understood.

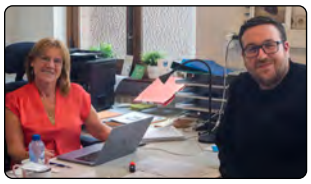
Transcriptomic data showed increased expression of glycolytic genes after optic nerve crush in retinal ganglion cells with the co-deletion of *Pten* and *Socs3*. Using retinal cultures in a multicompartment microfluidic device, we observed increased regrowth and enhanced mitochondrial trafficking in the axons of *Pten* and *Socs3* co-deleted neurons. While wild-type axons relied on mitochondrial metabolism, after injury, in the absence of *Pten* and *Socs3*, energy production was supported by local glycolysis. Specific inhibition of lactate production hindered injury survival and the initiation of regrowth while slowing down glycolysis upstream impaired regrowth initiation, axonal elongation, and energy production.

Together, these observations reveal that glycolytic ATP, combined with sustained mitochondrial transport, is essential for injury-induced axonal regrowth, providing new insights into the metabolic underpinnings of axonal regeneration.

**ORIGINAL PAPER**

Masin, L., S. Bergmans, A. Van Dyck, K. Farrow, L. De Groef, and L. Moons. 2024. Local glycolysis supports injury-induced axonal regeneration. *J. Cell Biol.* 223 (12): e202402133. https://doi.org/10.1083/jcb.202402133

**RESEARCHER DETAILS**



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# Drp1 controls astrocyte morphology and organization

Dysfunctional mitochondrial dynamics are a hallmark of devastating neurodevelopmental disorders such as childhood refractory epilepsy. However, the role of glial mitochondria in proper brain development is not well understood.

We show that astrocyte mitochondria undergo extensive fission while populating astrocyte distal branches during postnatal cortical development. Loss of mitochondrial fission regulator, dynamin-related protein 1 (Drp1), decreases mitochondrial localization to distal astrocyte processes, and this mitochondrial mislocalization reduces astrocyte morphological complexity.

Functionally, astrocyte-specific conditional deletion of Drp1 induces astrocyte reactivity and disrupts astrocyte organization in the cortex. These morphological and organizational deficits are accompanied by loss of perisynaptic astrocyte process proteins such as gap junction protein connexin 43.

These findings uncover a crucial role for mitochondrial fission in coordinating astrocytic morphogenesis and organization, revealing the regulation of astrocytic mitochondrial dynamics as a critical step in neurodevelopment.

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Rodriguez Salazar, M.P., S. Kolanukuduru, V. Ramirez, B. Lyu, G. Manigault, G. Sejourne, H. Sesaki, G. Yu, and C. Eroglu. 2025. Mitochondrial fission controls astrocyte morphogenesis and organization in the cortex. *J. Cell Biol.* 224 (10): e202410130. https://doi.org/10.1083/jcb.202410130

JEM Journal of Experimental Medicine

# ILC2s promote angiogenic sprouting after stroke

Group 2 innate lymphoid cells (ILC2s) regulate immunity and tissue repair but are rarely found in the brain. Whether ILC2s can infiltrate the brain from the bloodstream and the underlying mechanisms involved remain unclear. While ILC2s have recently been identified as key immunosuppressive players in neuroinflammation, their role in brain tissue repair remains promising but underexplored.

Here, using in vivo and in vitro expansion of ILC2s, we demonstrate that ILC2s can enter the brain parenchyma from the blood circulation early after ischemic stroke in a CXCR1-dependent manner. Once in the brain, ILC2s improve long-term recovery of sensory motor functions by promoting initiation of angiogenesis, namely angiogenic sprouting.

Mechanistically, ILC2s produce α-calcitonin gene-related peptide (α-CGRP) to enhance angiogenic sprouting. ILC2s depleted of α-CGRP infiltrate the brain but fail to initiate angiogenesis. Impaired function of CGRP receptors on cerebrovascular endothelial cells abolishes the angiogenic effect of ILC2s.

These findings highlight ILC2s as a promising target for promoting therapeutic angiogenesis in stroke recovery.


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**ORIGINAL PAPER**
Ping, A., F. Yang, L. Lu, X. Zhang, J. Lu, H. Li, Y. Gu, Z. Jin, J. Zhang, and L. Shi. 2025. Brain-infiltrating ILC2s boost poststroke angiogenic initiation through α-CGRP production. *J. Exp. Med.* 222 (11): e20241830. https://doi.org/10.1084/jem.20241830


# STING mediates NGLY1 deficiency

The STING pathway is increasingly recognized as a key regulator of neuroinflammation in neurodegenerative disease, but its role in noninflammatory conditions remains unclear. We generated a postnatal inducible whole-body *Ngly1* knockout mouse (i*Ngly1*$^{-/-}$) to model NGLY1 deficiency, an early-onset neurodegenerative disorder.

i*Ngly1*$^{-/-}$ mice exhibit progressive motor deficits, Purkinje cell loss, and shortened lifespan without evidence of gliosis or immune activation. Cell type–specific deletion of *Ngly1* in Purkinje cells or microglia failed to induce disease, suggesting multiple cell-intrinsic and cell-extrinsic signals are required. Genetic ablation of Sting1 in i*Ngly1*$^{-/-}$ mice rescues Purkinje cell loss, improves motor function, and extends lifespan. Single-nucleus RNA sequencing reveals proteostasis disruption in Purkinje cells, altered cerebellar granule cell subpopulations, and STING-dependent suppression of cholesterol biosynthesis in glia. Pharmacological inhibition of STING with an orally bioactive antagonist, VS-X4, significantly mitigates neuropathology and motor disease.

These findings identify STING as a key mediator of neuropathology in NGLY1 deficiency and implicate a role of STING in noninflammatory neurological disease.

This work is supported by Grace Science Foundation (www.gracescience.org), a non-profit organization that supports patients and scientists to find a cure for NGLY1 deficiency.


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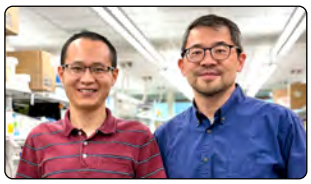

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**ORIGINAL PAPER**
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# Gut microbiota–derived TMAVA reduces CNS-aGVHD

Acute graft-versus-host disease (aGVHD) can affect the central nervous system (CNS) through microglial activation and T cell infiltration, but the role of gut microbiota in CNS-aGVHD remains unclear. Here, we investigated the role of microbiota in microglial activation during aGVHD using antibiotic-treated specific pathogen–free (SPF), germ-free (GF), and wildling mice.

Antibiotic-mediated microbiota depletion led to infiltration of IFN-γ–producing T cells in the brain, activation of microglia via the TLR4/p38 MAPK pathway, and neurocognitive deficits in SPF aGVHD mice. Microglial depletion reversed the neurocognitive deficits. GF and wildling mice treated with antibiotics exhibited similar microglial activation after allogeneic hematopoietic cell transplantation (allo-HCT).

Mechanistically, the bacteria-derived metabolite N,N,N-trimethyl-5-aminovaleric acid (TMAVA) was decreased in microglia following antibiotic treatment. TMAVA administration suppressed TLR4/p38 MAPK pathway activity in microglia and alleviated gut microbiota depletion–mediated neurocognitive deficits. Additionally, TMAVA abundance decreased in patient blood after allo-HCT and after GVHD onset.

In summary, we identify TMAVA loss as a central causative factor for CNS-aGVHD, opening new perspectives for a metabolite-based therapy.

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**ORIGINAL PAPER**
Chatterjee, S., T. Rückert, I. Martin, E. Michaeli, J. Buescher, P. Apostolova, D. Erny, M.-E. Lalioti, F. Biavasco, A. Hartmann, S. Runge, L.M. Braun, N. Talvard-Balland, R.C. Adams, A. Schmitt-Graeff, J. Cook, V. Wenger, D. Athanassopoulos, D. Hasavci, A.P. Vallejo-Janeta, T. Blank, P. Schaible, J.M. Vinnakota, A. Zähringer, S.C. Ganal-Vonarburg, W. Melchinger, D. Pfeifer, N. Köhler, S.P. Rosshart, D. Michonneau, G. Socié, G. Andrieux, N. Cabezas-Wallscheid, M. Boerries, M. Prinz, and R. Zeiser. 2025. Gut microbiota–derived TMAVA is a modulator of acute CNS-GVHD. *J. Exp. Med*. 222 (9): e20242180. https://doi.org/10.1084/jem.20242180

# Increased disease-associated microglia and CD8⁺ T cells in Spg15-deficiency

In central nervous system (CNS) diseases characterized by late-onset neurodegeneration, the interplay between innate and adaptive immune responses remains poorly understood. This knowledge gap is exacerbated by the prolonged protracted disease course as it complicates the delineation of brain-resident and infiltrating cells.

Here, we conducted comprehensive profiling of innate and adaptive immune cells in a murine model of spastic paraplegia 15 (SPG15), a complicated form of hereditary spastic paraplegia. Using fate-mapping of bone marrow–derived cells, we identified microgliosis accompanied by infiltration and local expansion of T cells in the CNS of *Spg15*$^{-/-}$ mice. Single-cell analysis revealed an expansion of disease-associated microglia (DAM) and effector CD8⁺ T cells prior to neuronal loss. Analysis of potential cell–cell communication pathways suggested bidirectional interactions between DAM and effector CD8⁺ T cells, potentially contributing to disease progression in *Spg15*$^{-/-}$ mice.

In summary, we identified a shift in microglial phenotypes associated with the recruitment and expansion of T cells as a new characteristic of *Spg15*-driven neuropathology.

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**ORIGINAL PAPER**
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JEM Journal of Experimental Medicine

# USP5 mutation and congenital insensitivity to pain

Cav3.2 T-type calcium channels and their dysregulation by the deubiquitinase USP5 contribute to development of inflammatory and neuropathic pain. We report on a pediatric patient with a de novo heterozygous missense mutation R24W in USP5 who exhibits pain insensitivity.

We created a CRISPR knock-in mouse harboring this mutation and performed detailed behavioral analyses in acute and chronic pain models. Heterozygous R24W mice of both sexes are resistant to acute pain and to thermal hypersensitivity in chronic inflammatory and neuropathic pain models. In contrast, only male R24W mice confer resistance to development of mechanical hypersensitivity. R24W mice lack upregulation of Cav3.2 and USP5 that is normally observed with CFA-induced inflammation. Moreover, mutant USP5 exhibits a dramatic reduction in enzymatic activity but stronger interactions with Cav3.2.

Hence, R24W mutant USP5 is a critical regulator of chronic and acute pain states in humans by acting as a dominant-negative regulator of Cav3.2. Our data validate USP5 as a potential therapeutic target for chronic pain in humans.

**ORIGINAL PAPER**

Antunes, F.T.T., M.A. Gandini, A. Garcia-Caballero, S. Huang, M.Y. Ali, E. Gambeta, I.A. Souza, E.K. Harding, L. Ferron, A. Stray-Pedersen, V.M. Gadotti, and G.W. Zamponi. 2025. A pathological missense mutation in the deubiquitinase USP5 leads to insensitivity to pain. *J. Exp. Med.* 222 (8): e20241877. https://doi.org/10.1084/jem.20241877

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# Glutamate release at invaginating rod synapses

Synapses of retinal rod photoreceptors involve deep invaginations occupied by second-order rod bipolar cell (RBP) and horizontal cell (HC) dendrites. Synaptic vesicles are released into this invagination at multiple sites beneath an elongated presynaptic ribbon.

To study the impact of this architecture on glutamate diffusion and receptor activity, we reconstructed four rod terminals and their postsynaptic dendrites from serial electron micrographs of the mouse retina. We incorporated these structures into anatomically realistic Monte Carlo simulations of neurotransmitter diffusion and receptor activation. By comparing passive diffusion of glutamate in realistic structures with geometrically simplified models, we found that glutamate exits anatomically realistic synapses 10-fold more slowly than previously predicted.

Constraining simulations with physiological data, we modeled activity of EAAT5 glutamate transporters in rods, AMPA receptors on HC dendrites, and metabotropic glutamate receptors (mGluR6) on RBP dendrites. Simulations suggested that ~3,000 EAAT5 populate rod membranes. While uptake by surrounding glial Müller cells retrieves most glutamate released by rods, binding and uptake by EAAT5 influence RBP kinetics. Glutamate persistence allows mGluR6 on RBP dendrites to integrate the stream of vesicles released by rods in darkness. Glutamate's tortuous diffusional path confers quantal variability, as release from nearby ribbon sites exerts larger effects on RBP and HC receptors than release from more distant sites. Temporal integration supports slower sustained release rates, but additional quantal variability can impede postsynaptic detection of changes in release produced by rod light responses.

These results show an example of the profound impact that synaptic architecture can have on postsynaptic responses.

**ORIGINAL PAPER**
Thoreson, W.B., T.M. Bartol, N.H. Conoan, and J.S. Diamond. 2025. The architecture of invaginating rod synapses slows glutamate diffusion and shapes synaptic responses. *J. Gen. Physiol.* 157 (3): e202413746. https://doi.org/10.1085/jgp.202413746

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# FAT3 deficiency impairs high-frequency flicker ERG

Vision is initiated by the reception of light by photoreceptors and subsequent processing via downstream retinal neurons. Proper circuit organization depends on the multifunctional tissue polarity protein FAT3, which is required for amacrine cell connectivity and retinal lamination.

Here, we investigated the retinal function of *Fat3* mutant mice and found decreases in both electroretinography and perceptual responses to high-frequency flashes. These defects did not correlate with abnormal amacrine cell wiring, pointing instead to a role in bipolar cell subtypes that also express FAT3. The role of FAT3 in the response to high temporal frequency flashes depends upon its ability to transduce an intracellular signal. Mechanistically, FAT3 binds to the synaptic protein PTPσ intracellularly and is required to localize GRIK1 to OFF-cone bipolar cell synapses with cone photoreceptors.

These findings expand the repertoire of FAT3's functions and reveal its importance in bipolar cells for high-frequency light response.

**ORIGINAL PAPER**
Avilés, E.C., S.K. Wang, S. Patel, S. Cordero, S. Shi, L. Lin, V.J. Kefalov, L.V. Goodrich, C.L. Cepko, and Y. Xue. 2025. ERG responses to high-frequency flickers require FAT3 signaling in mouse retinal bipolar cells. *J. Gen. Physiol.* 157 (2): e202413642. https://doi.org/10.1085/jgp.202413642

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JGP Journal of General Physiology

# Sodium channel gating in vitro and in silico

Voltage-gated sodium channels (VGSCs) in the peripheral nervous system shape action potentials (APs) and thereby support the detection of sensory stimuli. Most of the nine mammalian VGSC subtypes are expressed in nociceptors, but predominantly, three are linked to several human pain syndromes: while $Na_v1.7$ is suggested to be a (sub-)threshold channel, $Na_v1.8$ is thought to support the fast AP upstroke. $Na_v1.9$, as it produces large persistent currents, is attributed a role in determining the resting membrane potential.

We characterized the gating of $Na_v1.1$–$Na_v1.3$ and $Na_v1.5$–$Na_v1.9$ in manual patch clamp with a focus on the AP subthreshold depolarization phase. $Na_v1.9$ exhibited the most hyperpolarized activation, while its fast inactivation resembled the depolarized inactivation of $Na_v1.8$. For some VGSCs (e.g., $Na_v1.1$ and $Na_v1.2$), a positive correlation between ramp current and window current was detected. Using a modified Hodgkin–Huxley model that accounts for the time needed for inactivation to occur, we used the acquired data to simulate two nociceptive nerve fiber types (an Aδ- and a mechano-insensitive C-nociceptor) containing VGSC conductances according to published human RNAseq data. Our simulations suggest that $Na_v1.9$ is supporting both the AP upstroke and its shoulder. A reduced threshold for AP generation was induced by enhancing $Na_v1.7$ conductivity or shifting its activation to more hyperpolarized potentials, as observed in $Na_v1.7$-related pain disorders.

Here, we provide a comprehensive, comparative functional characterization of VGSCs relevant in nociception and describe their gating with Hodgkin–Huxley–like models, which can serve as a tool to study their specific contributions to AP shape and sodium channel–related diseases.

## ORIGINAL PAPER

Köster, P.A., E. Leipold, J. Tigerholm, A. Maxion, B. Namer, T. Stiehl, and A. Lampert. 2025. Nociceptor sodium channels shape subthreshold phase, upstroke, and shoulder of action potentials. *J. Gen. Physiol.* 157 (2): e202313526. https://doi.org/10.1085/jgp.202313526

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# Adaptive plasticity in sensory neurons

In response to changes in activity induced by environmental cues, neurons in the central nervous system undergo homeostatic plasticity to sustain overall network function during abrupt changes in synaptic strengths. Homeostatic plasticity involves changes in synaptic scaling and regulation of intrinsic excitability. Increases in spontaneous firing and excitability of sensory neurons are evident in some forms of chronic pain in animal models and human patients. However, whether mechanisms of homeostatic plasticity are engaged in sensory neurons of the peripheral nervous system (PNS) is unknown.

Here, we show that sustained depolarization (induced by 24-h incubation in 30 mM KCl) induces compensatory changes that decrease the excitability of mouse and human sensory neurons without directly opposing membrane depolarization. Voltage-clamp recordings show that sustained depolarization produces no significant alteration in voltage-gated potassium currents, but a robust reduction in voltage-gated sodium currents, likely contributing to the overall decrease in neuronal excitability. The compensatory decrease in neuronal excitability and reduction in voltage-gated sodium currents reversed completely following a 24-h recovery period in a normal medium. Similar adaptive changes were not observed in response to 24 h of sustained action potential firing induced by optogenetic stimulation at 1 Hz, indicating the need for prolonged depolarization to drive engagement of this adaptive mechanism in sensory neurons.

Our findings show that mouse and human sensory neurons are capable of engaging adaptive mechanisms to regulate intrinsic excitability in response to sustained depolarization in a manner similar to that described in neurons in the central nervous system.

## ORIGINAL PAPER

McIlvried, L.A., J.S. Del Rosario, M.Y. Pullen, A. Wangzhou, T.D. Sheahan, A.J. Shepherd, R.A. Slivicki, J.A. Lemen, T.J. Price, B.A. Copits, and R.W. Gereau. 2025. Intrinsic adaptive plasticity in mouse and human sensory neurons. *J. Gen. Physiol.* 157 (1): e202313488. https://doi.org/10.1085/jgp.202313488

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# $Na_v1.8$ and $Na_v1.7$ interplay in a model of inherited erythromelalgia pain

While voltage-gated sodium channels $Na_v1.7$ and $Na_v1.8$ both contribute to electrogenesis in dorsal root ganglion (DRG) neurons, details of their interactions have remained unexplored. Here, we studied the functional contribution of $Na_v1.8$ in DRG neurons using a dynamic clamp to express $Na_v1.7$L848H, a gain-of-function $Na_v1.7$ mutation that causes inherited erythromelalgia (IEM), a human genetic model of neuropathic pain, and demonstrate a profound functional interaction of $Na_v1.8$ with $Na_v1.7$ close to the threshold for AP generation.

At the voltage threshold of −21.9 mV, we observed that $Na_v1.8$ channel open-probability exceeded $Na_v1.7$WT channel open-probability ninefold. Using a kinetic model of $Na_v1.8$, we showed that a reduction of $Na_v1.8$ current by even 25–50% increases rheobase and reduces firing probability in small DRG neurons expressing $Na_v1.7$L848H. $Na_v1.8$ subtraction also reduces the amplitudes of subthreshold membrane potential oscillations in these cells. Our results show that within DRG neurons that express peripheral sodium channel $Na_v1.7$, the $Na_v1.8$ channel amplifies excitability at a broad range of membrane voltages with a predominant effect close to the AP voltage threshold, while $Na_v1.7$ plays a major role at voltages closer to resting membrane potential.

Our data show that dynamic-clamp reduction of $Na_v1.8$ conductance by 25–50% can reverse hyperexcitability of DRG neurons expressing a gain-of-function $Na_v1.7$ mutation that causes pain in humans and suggests, more generally, that full inhibition of $Na_v1.8$ may not be required for relief of pain due to DRG neuron hyperexcitability.

**ORIGINAL PAPER**
Vasylyev, D.V., P. Zhao, B.R. Schulman, and S.G. Waxman. 2024. Interplay of $Na_v1.8$ and $Na_v1.7$ channels drives neuronal hyperexcitability in neuropathic pain. *J. Gen. Physiol.* 156 (11): e202413596. https://doi.org/10.1085/jgp.202413596

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# Sephin1 prevents TDP-43 toxicity

A pathological hallmark of ALS is the abnormal accumulation of misfolded proteins (e.g., TDP-43) and enlarged endoplasmic reticulum (ER), indicating ER stress. To resolve this stress, cells initiate the Unfolded Protein Response (UPR). However, unresolved stress leads to apoptosis. In ALS, UPR activation fails to resolve proteostasis impairment. UPR activation modulators, among them Sephin1, reduce protein aggregates and improve motor neuron survival in ALS models.

We demonstrate that following glutamate intoxication, Sephin1 increases motor neuron survival by reducing mitochondria ROS production and extranuclear TDP-43. Sephin1 reduces abnormal splicing because of TDP-43 nuclear loss of function following oxidative stress. In $SOD1^{G93A}$ mice, Sephin1 treatment decreases TDP-43 in triton-insoluble fraction, improving motor neuron survival in spinal cord. Sephin1 improves motor neuron survival, motor function, and survival of mutated TDP-43 transgenic zebrafish. Sephin1 improves motor neuron survival in ALS models by reducing TDP-43 cytoplasmic mislocalization and its toxicity.

These findings open new therapeutic opportunities for Sephin1 in neurodegenerative pathologies with TDP-43 proteinopathy, including ALS.

## ORIGINAL PAPER

Abgueguen, E., M. Tortarolo, L. Rouviere, S. Marcuzzo, L. Camporeale, A. Henriques, L. Pasetto, G.R. Culley, V. Bonetto, A. Marian, B.L. Lejeune, A. Visbecq, G. Lauria, E. Kabashi, N. Callizot, C. Bendotti, and P.Y. Minio. 2025. Sephin1 reduces TDP-43 cytoplasmic mislocalization and improves motor neuron survival in ALS models. *Life Science Alliance* 8 (9): e202403195. https://doi.org/10.26508/lsa.202403195

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# Loss of parvalbumin neuron cilia in LRRK2 Parkinson's disease

Parkinson's disease–associated, activating mutations in the LRRK2 kinase block primary cilium formation in cell culture and in specific cell types in the brain. In the striatum that is important for movement control, about half of astrocytes and cholinergic interneurons, but not the predominant medium spiny neurons, lose their primary cilia.

Here, we show that mouse and human striatal parvalbumin interneurons that are inhibitory regulators of movement also lose primary cilia. Without cilia, these neurons are not able to respond to Sonic hedgehog signals that normally induce the expression of Patched RNA, and their numbers decrease. In addition, in mouse, glial cell line–derived neurotrophic factor–related Neurturin RNA is significantly decreased.

These experiments highlight the importance of parvalbumin neurons in cilium-dependent, neuroprotective signaling pathways and show that LRRK2 activation correlates with decreased Neurturin production, resulting in less neuroprotection for dopamine neurons.

## ORIGINAL PAPER

Lin, Y.-E., E. Jaimon, F. Tonelli, and S.R. Pfeffer. 2024. Pathogenic *LRRK2* mutations cause loss of primary cilia and Neurturin in striatal parvalbumin interneurons. *Life Science Alliance* 8 (1): e202402922. https://doi.org/10.26508/lsa.202402922

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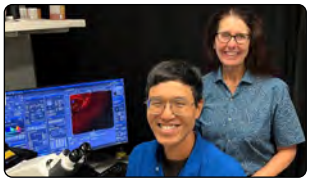

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# Metabolic resistance of Aβ3pE-42, an epitope of donanemab

The amyloid β peptide (Aβ), starting with pyroglutamate (pE) at position 3 and ending at position 42 (Aβ3pE-42), predominantly accumulates in the brains of Alzheimer's disease. Consistently, donanemab, a therapeutic antibody raised against Aβ3pE-42, has been shown to be effective in recent clinical trials. Although the primary Aβ produced physiologically is Aβ1-40/42, an explanation for how and why this physiological Aβ is converted to the pathological form remains elusive.

Here, we present experimental evidence that accounts for the aging-associated Aβ3pE-42 deposition: Aβ3pE-42 was metabolically more stable than other Aβx-42 variants; deficiency of neprilysin, the major Aβ-degrading enzyme, induced a relatively selective deposition of Aβ3pE-42 in both APP transgenic and *App* knock-in mouse brains; Aβ3pE-42 deposition always colocalized with Pittsburgh compound B–positive cored plaques in APP transgenic mouse brains; and under aberrant conditions, such as a significant reduction in neprilysin activity, aminopeptidases, dipeptidyl peptidases, and glutaminyl-peptide cyclotransferase-like were up-regulated in the progression of aging, and a proportion of Aβ1-42 may be processed to Aβ3pE-42.

Our findings suggest that anti-Aβ therapies are more effective if given before Aβ3pE-42 deposition.

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**ORIGINAL PAPER**
Iwata, N., S. Tsubuki, M. Sekiguchi, K. Watanabe-Iwata, Y. Matsuba, N. Kamano, R. Fujioka, R. Takamura, N. Watamura, N. Kakiya, N. Mihira, T. Morito, K. Shirotani, D.M.A. Mann, A.C. Robinson, S. Hashimoto, H. Sasaguri, T. Saito, M. Higuchi, and T.C. Saido. 2024. Metabolic resistance of Aβ3pE-42, a target epitope of the anti-Alzheimer therapeutic antibody, donanemab. *Life Science Alliance* 7 (12): e202402650. https://doi.org/10.26508/lsa.202402650

# Regulation of proteostasis by sleep in Alzheimer's disease

Sleep and circadian rhythm dysfunctions are common clinical features of Alzheimer's disease (AD). Increasing evidence suggests that in addition to being a symptom, sleep disturbances can also drive the progression of neurodegeneration. Protein aggregation is a pathological hallmark of AD; however, the molecular pathways behind how sleep affects protein homeostasis remain elusive.

Here, we demonstrate that sleep modulation influences proteostasis and the progression of neurodegeneration in *Drosophila* models of tauopathy. We show that sleep deprivation enhanced Tau aggregational toxicity resulting in exacerbated synaptic degeneration. In contrast, sleep induction using gaboxadol led to reduced toxic Tau accumulation in neurons as a result of modulated autophagic flux and enhanced clearance of ubiquitinated Tau, suggesting altered protein processing and clearance that resulted in improved synaptic integrity and function.

These findings highlight the complex relationship between sleep and regulation of protein homeostasis and the neuroprotective potential of sleep-enhancing therapeutics to slow the progression or delay the onset of neurodegeneration.

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**ORIGINAL PAPER**
Ortiz-Vega, N., A.G. Lobato, T. Canic, Y. Zhu, S. Lazopulo, S. Syed, and R.G. Zhai. 2024. Regulation of proteostasis by sleep through autophagy in *Drosophila* models of Alzheimer's disease. *Life Science Alliance* 7 (11): e202402681. https://doi.org/10.26508/lsa.202402681

# Enhanced spinal cord injury recovery in GlcNAc6ST1/4 DKO mice

Spinal cord injury (SCI) damages neural circuits and triggers pro-inflammatory responses, resulting in locomotor impairment. The carbohydrate sulfotransferases GlcNAc6ST1 and GlcNAc6ST4 modulate the function of blood monocytes and microglia. However, their specific roles and enzymatic relationships in neuroinflammation and functional recovery after SCI remain unclear.

In this study, we demonstrate that mice deficient in both GlcNAc6ST1 and GlcNAc6ST4 (DKO) exhibit improved locomotor recovery compared with mice with a single deficiency. DKO mice exhibit reduced levels of monocytes and activated macrophages/microglia at the injury site alongside increased serotonergic neural fibers, indicating enhanced neural plasticity. RNA sequencing reveals down-regulation of collagen I genes and up-regulation of genes encoding synaptic membrane components in the injured DKO spinal cord. In addition, GALAXY glycomic analysis shows an absence of GlcNAc-6-sulfated *N*-glycans in the DKO spinal cord.

These results suggest that GlcNAc6ST1 and GlcNAc6ST4 play complementary roles in promoting detrimental inflammatory responses post-SCI. Targeting these sulfotransferases could offer a novel therapeutic strategy to improve locomotor recovery after SCI.

## ORIGINAL PAPER

Morozumi, M., T. Ozaki, K. Nishitsuji, Y. Takeda-Uchimura, A. Matsumoto, S. Ito, S. Imagama, N. Ishiguro, H. Yagi, K. Kato, T.O. Akama, T. Kosugi, S. Maruyama, K. Kadomatsu, S.D. Rosen, L.J. Noble-Haeusslein, and K. Uchimura. 2025. Enhanced locomotor recovery in mice lacking GlcNAc6ST1 and GlcNAc6ST4 following spinal cord injury. *Life Science Alliance* 8 (11): e202503469. https://doi.org/10.26508/lsa.202503469

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