BIOAPHICAL SKETCH

NAME: **Sheng, Zu-Hang, PhD**

POSITION TITLE: **Senior Investigator and Chief of Synaptic Function Section**

EDUCATION/TRAINING

| INSTITUTION AND LOCATION | DEGREE  (if applicable) | Completion Date  MM/YYYY | FIELD OF STUDY |
| --- | --- | --- | --- |
| Shanghai Jiao-Tong University, China | MS | 01/1987 | Microbiology |
| University of Pennsylvania, Philadelphia | PhD | 09/1992 | Biochemistry |
| University of Washington, Seattle | Postdoctoral | 11/1996 | Neuroscience |
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**Personal Statement**

Neurons are highly polarized cells consisting of complex dendritic arbors and a single long axon with extensive branches and terminals, thus facing exceptional challenges in maintaining cellular and energy homeostasis in distal axons and synapses. I have a broad background in neurobiology and cell biology, with specific expertise in axonal transport of mitochondria and lysosomes in the maintenance of local energy metabolism, degradation capacity, and synaptic efficacy. As a senior investigator, I lead a multidisciplinary team to study fundamental processes affecting neurological disorders and brain repair after injury. Using genetic mouse models and human iPSC-derived neuronal systems combined with live and super-resolution imaging and genetic editing, we are investigating (1) how axonal mitochondrial transport and energy maintenance are regulated to sense changes in synaptic activity, mitochondrial energetics, axon injury, and pathological stress; (2) how neurons coordinate late endocytic transport and autophagy-lysosomal function to maintain axon degradation capacity; (3) how presynaptic cargo transport maintains the formation of new synapses and remodeling of mature synapses; and (4) how impaired axonal transport and energy deficits contribute to neurodevelopmental disorders, aging-associated neurodegeneration, and CNS regeneration failure after brain injury. To tackle these broad problems, we have developed adult/aging neuron systems from mouse models at disease stages, as well as live-imaging assays to study axonal transport and energy metabolism. These studies have led to the identification of three motor adaptor and anchoring proteins (syntaphilin, snapin, and syntabulin) that regulate axonal transport of mitochondria, endolysosomes, and presynaptic cargos. Our studies elucidated mechanisms (1) maintaining synaptic efficacy through presynaptic energy sensing and mitochondrial anchoring; (2) facilitating CNS regeneration by reprogramming mitochondrial transport and repairing local energetics in response to brain injury; (3)maintaining axonal degradation capacity or “axonostasis” by coordinating bi-directional transport of endo-lysosomes; and (4)enhancing axonal energy metabolism through transcellular signaling from oligodendrocytes to axons. Pursuing these investigations conceptually advances our knowledge of axonal mitochondrial pathology, energy deficits, lysosomal dysfunction, and synaptic modulation in injury and neurodegeneration.

1. Kang J-S, Tian J-H, Zald P, Pan P-Y, Li C, Deng C, and Sheng Z-H. (2008). Docking of axonal mitochondria by syntaphilin controls their mobility and affects short-term facilitation. ***Cell*** 132, 137-148.
2. Xie\* Y, Zhou\* B et al., and Sheng Z.-H. (2015). Endo-lysosome deficits augment mitochondria pathology in spinal motor neurons of asymptomatic fALS-linked mice. ***Neuron*** 87, 355-370.
3. Li S, Xiong G-J, Huang N, and Sheng Z-H. (2020). Crosstalk of energy sensing and mitochondrial anchoring sustains synaptic efficacy by maintaining presynaptic metabolism. ***Nature Metabolism*** 2, 1077.
4. Chamberlain KA\*, Huang N\*, Xie Y, LiCausi F, Li S, Li Y, and Sheng Z-H. (2021). Oligodendrocytes enhance axonal energy metabolism by deacetylation of mitochondrial proteins through transcellular delivery of SIRT2. ***Neuron*** 109, 3456-3472.

**Positions and Employment**

1997-2007 Investigator, Head of Synaptic Function Unit, NINDS, NIH

2007-present Senior Investigator, Chief of Synaptic Function Section, NINDS, NIH

**Other Experience and Program contributions**

## 1997-2001 Co-chair, NIH Nerve-Muscle Special Interest Group

2000, 2001, 2020 Member, NINDS Tenure-track Search Committee

2002-2004 Member, NIH Institutional Biosafety Committee

2002-2006 Member, NIH Neuroscience Seminar Committee

2008-2012 Member, HHMI-NIH Research Program Advisory Committee

2008-2012 Member, NINDS/NIDCD Animal Care and Use Committee

2010, 2013-2020 Member, NIH Earl Stadtman Search Committee: Neuroscience, Cell Biology

2015-2016 Co-chair, NIH Earl Stadtman Search Committee: Cellular Neuroscience

2020- Member, NINDS Light Imaging and EM Core Facility Steering Committee

2022- Member, the NINDS Tenure Review Committee

**Honors**

* Elected as an AAAS Fellow (2016) and ASCB Fellow (2017) for distinguished contributions to the field of axonal transport of mitochondria and endo-lysosomes in the maintenance of axonal energy and cellular homeostasis and synaptic function in health and diseases.
* Awarded Dr. Francisco S. Sy Award for Excellence in Mentorship at U.S. Department of Health & Human Services (2021) and NINDS Director’s Award for Mentoring (2002, 2021).
* Awarded NIH Director Award (2023) for seminal contributions to the understanding of axonal mitochondrial and lysosomal transport and maintenance of bioenergetics and cellular homeostasis*.*

**Editorial Boards**

2006-2018 Editorial Board, *The Journal of Biological Chemistry (JBC)*

2016-2018 Associate Editor, *Autophagy*

2015- Editorial Board (Monitoring Editor), *Journal of Cell Biology (JCB)*

**Grant Reviews**

NIH Study Section (SYN) / NSF / NICHD Intramural Grant Review / The Wellcome Trust / MRC Research Foundation, UK / Alzheimer's Society Research Foundation / European Commission Grant

**Selected Journal Reviews** **(from over 30 journals)**

Cell Reports **/** Current Biology **/** Developmental Cell / Developmental Neurobiology / eLife / EMBO Journal **/** Human Molecular Genetics / Journal of Cell Biology **/** Journal of Cell Science **/** Journal of Neurochemistry **/** Journal of Neuroscience **/** Molecular Cell Biology / Neuron / Nature Cell Biology **/** Nature Neuroscience **/** Nature Reviews Neuroscience / Neurobiology of Diseases / PLOs Biology **/** PNAS

**Mentoring Experience**

Served as a mentor for 10 graduate students (NIH joint PhD Programs), 6 HHMI-NIH research scholars, and over 20 postdoctoral and 10 postbac fellows since 1997.

Awarded an NINDS Director’s Award for Mentoring (2002, 2021) and Dr. Francisco Sy Award for Excellence in Mentorship at HHS (2021).

* 12 trainees were appointed to academic faculty positions
* 2 trainees were appointed as Program Director in the NIH Extramural Program
* 1 trainee was awarded an NIH K99/R00; 2 trainees were awarded an NIH K08 Award
* 6 trainees were awarded an NINDS Competitive Fellowship Award

**Meeting Organization**

2008 Symposium chair at the Biennial Meeting of European Neuroscience at Geneva

2009 Symposium chair of International Conference on Channels and Synapses

2012 Symposium co-chair of Mitochondrial Trafficking and Function in Neuronal Health and Diseases

2014 Organizer and session chair at 4th International Symposium on Membrane Biology

2016 Organizer and session chair at 6th International Symposium on Membrane Biology

2017 Symposium chair at the 5th Annual Molecular Psychiatry Meeting, San Francisco

2022 Symposium co-chair at ISN-APSN 2022 Biennial Meeting in Honolulu, Hawaii

**Selected Invited Talks (43 from over 100 talks):** **Invited talks at conferences**: 4 talks at GRC; 3 talks at ACBS and SfN annual meetings; 3 talks at EMBO Workshops; 2 talks at European Neuroscience Forum; Keynote at 11th Physiology and Disease Symposium; Japanese Neuroscience Conference; International Society for Neurochemistry. **Invited seminars** at Harvard, George Washington, University of Alabama, University of Toronto, University of Michigan, Cornell, Case Western, Cleveland Clinic, University of Tokyo, Mount Sinai, University College London, University of Pittsburgh, University of Wisconsin-Madison, Scripps Research Institute, UCSF and the Gladstone, Weizmann Institute of Science Israel, University of Oxford, Ohio State, University of Florida, Rutgers, Washington University in St. Louis, University of Maryland, University of Virginia, Indiana University, Saarland University, Germany, Riken Brain Science Institute, Japan, University of Pennsylvania, University of Cambridge

**Research Support**

My laboratory has been funded by the Division of Intramural Research (DIR) of NINDS, NIH since 1997, and the current funding is assigned into two DIR ZIA awards that support 12-14 positions in my lab.

**ZIA NS002946** Sheng (PI) 09/01/1997-present. Axonal transport of endo-lysosomes and presynaptic cargos for the maintenance of axon cellular homeostasis and presynaptic function

**ZIA NS003029** Sheng (PI) 09/01/2006-present. Mitochondrial transport and energy metabolism in synaptic transmission and neuronal degeneration and regeneration

**Contributions to Science**

1. **Mitochondrial transport and presynaptic energy metabolism in the maintenance of synaptic efficacy.** Synaptic activity imposes large energy demands that are met by local ATP synthesis through glycolysis and mitochondrial oxidative phosphorylation. ATP drives action potentials, supports synapse assembly and remodeling, fuels synaptic vesicle filling and recycling, thus sustaining synaptic transmission. Neurons face exceptional challenges in maintaining presynaptic energy homeostasis, particularly during intensive synaptic activity. Recent studies have started to uncover the mechanisms underlying activity-dependent and energy-sensitive regulation of presynaptic energetics, or ‘synaptoenergetics’. We identified syntaphilin (SNPH) as a static anchor for axonal mitochondria and revealed that motile axonal mitochondria passing through synapses contribute to the variability of synaptic strength. We recently revealed a mechanistic crosstalk between presynaptic energy sensing and mitochondrial anchoring. Sustained synaptic activity induces presynaptic energy deficits that could be rescued by recruiting mitochondria through an interplay between AMPK-PAK energy signaling and SNPH-mediated mitochondrial anchoring on presynaptic F-actin, thus maintaining prolonged synaptic efficacy. Energy-sensitive regulation of synaptic mitochondrial maintenance is an important mechanism sustaining synaptic plasticity, conceptually advancing our understanding of neurological disorders that are associated with bioenergetic failure and synaptic dysfunction.
2. Kang J-S, Tian J-H, et al, and Sheng Z-H. (2008). Docking of axonal mitochondria by syntaphilin controls their mobility and affects short-term facilitation. ***Cell*** 132, 137-148.
3. Sun\* T, Qiao\* H, Pan P-Y, Chen Y, and Sheng Z-H. (2013). Mobile axonal mitochondria contribute to the variability of presynaptic strength. ***Cell Reports*** 4, 413-419.

**NIH News Press** | “NIH researchers discover how brain cells change their tune”.

1. Li S, Xiong G-J, Huang N, and Sheng Z-H. (2020). Crosstalk of energy sensing and mitochondrial anchoring sustains synaptic efficacy by maintaining presynaptic metabolism. ***Nature Metabolism*** 2, 1077. **NIH Press** “NIH scientists reveal how the brain may fuel intense neural communication”.

**Science** | Research Highlight “Mitochondrial anchoring in synapses”.

1. Li S and Sheng Z-H. (2022). Energy matters: presynaptic metabolism and the maintenance of synaptic transmission. ***Nature Reviews Neuroscience*** 23, 4-22.
2. **Removing chronically stressed mitochondria from axons under pathological states.** Axonal mitochondrial dysfunction is a central problem associated with neurodegenerative diseases, where various chronic pathological stresses induce progressive mitochondrial dysfunction, leading to chronic energy deficits in distal axons. Thus, distal mitochondria need to be removed and replaced when they age or are damaged, thus constituting a critical step in maintaining or restoring axonal bioenergetics. Axonal mitochondrial trafficking and anchoring depend on the balance of motors and anchoring proteins, so that stressed mitochondria can be remobilized for replacement by healthy ones. Our study in mature neurons revealed two unique features for mitophagy: **(1)** Parkin-mediated mitophagy is much slower compared with non-neuronal cells, and **(2)** chronic mitochondrial stress induces mitophagy mainly in the soma and proximal regions. We further investigated the response of axonal mitochondria to mild stress in WT neurons and ALS- and AD-modeled neurons, which exhibit chronic mitochondrial defects. Those stressed mitochondria are selectively remobilized towards the soma by the bulk release of the mitochondrial anchoring protein SNPH via mitochondria-derived cargos. SNPH release from axonal mitochondria is robustly activated in the early stages of ALS- and AD-related neurons. We also elucidated a Mul1-mediated mechanism recovering stressed mitochondria by enhancing ER-Mito contacts.Therefore, our studies demonstrate first-line surveillance of axonal mitochondria, and thus mildly stressed mitochondria can be transported to the soma for recovery before activation of mitophagy, therein preserving axonal energy supply in the early stages of disease.
3. Lin\* M-Y, Cheng\* X-T et al., Sheng Z.-H. (2017).Releasing syntaphilin removes stressed mitochondria from axons independent of mitophagy under pathophysiological conditions. ***Neuron*** 94, 595-610.
4. Puri R, Cheng X-T, Lin M-Y, Huang N, andSheng Z-H. (2019). Mul1 restrains Parkin-mediated mitophagy in mature neurons by maintaining ER-mitochondrial contacts. ***Nature Communi*** 10, 3645.
5. Cheng X-T, Huang N, Sheng Z-H. (2022). Programming axonal mitochondrial maintenance and bioenergetics in neurodegeneration and regeneration. ***Neuron*** 110, 1899-1923.

**(3) Promoting CNS regeneration by reprogramming mitochondrial anchor SNPH**. While young neurons possess robust growth capacity, mature CNS neurons typically fail to regenerate after injury. To survive an injury, neurons require high energy supply to power repair events. One fundamental question is whether declined mitochondrial transport seen in mature neurons contributes to regeneration failure? *Snph* KO mice provide an ideal model to investigate whether enhanced mitochondrial transport facilitates axonal regrowth by removing damaged mitochondria and replenishing healthy ones in injured nerves. This is particularly problematic in spinal cord injury (SCI). We revealed that injury induces local mitochondrial damage; elevated SNPH expression in adult mice results in damaged mitochondria remaining stationary, leading to local energy crisis that accounts for regeneration failure in the CNS. Enhancing mitochondrial transport removes damaged mitochondria and replenishes axons with healthy ones to power regeneration. By collaborating with Xiao-Ming Xu’s lab (Indiana University), we demonstrated that *snph-/-*mice subjected to SCI display enhanced regeneration of cortico-spinal tract (CST) axons passing through the lesion and accelerated delivery of healthy mitochondria into the regenerating CST axons. *Snph-/-* mice displayed forelimb dexterous improvement after C5 SCI. Thus, repairing energy supply is a promising strategy to promote axonal regeneration and functional recovery after CNS injuries. We further elucidated an intrinsic energetic repair pathway that boosts axonal energy supply by reprogramming mitochondrial anchoring in response to injury-ischemia in mature neurons. PAK5 is a brain mitochondria-targeted kinase with declined expression in mature axons, where PAK5 synthesis and signaling is spatiotemporally activated in response to injury-ischemia. PAK5 signaling remobilizes and replaces damaged mitochondria via a phosphorylation switch that turns off the SNPH anchor. Thus, reprogramming for enhanced PAK signaling can reverse energy crisis and facilitate CNS regeneration. Our recent study also revealed a new transcellular signaling pathway through which oligodendrocyte (OL)-derived NAD-dependent SIRT2 boosts axonal energy metabolism by deacetylation of mitochondrial proteins ANT1/ANT2. SIRT2 is undetectable in neuronsbut highly enriched in mature OLs and released within exosomes. OL-to-axon delivery of SIRT2is an efficient mechanism for boosting axonal mitochondrial energetics, thus providing a therapeutic target for restoring axonal energy deficits in neurological disorders.

1. Zhou B, Yu P, Lin M‑Y, Sun T, Chen Y, and Sheng Z-H. (2016). Facilitation of axon regeneration by enhancing mitochondrial transport and rescuing energy deficits. ***Journal of Cell Biology*** 214, 203-119. **The New England Journal of Medicine** | “Mitochondrial mobility and neuronal recovery”.

**Nature** | News Research Highlights: “Mitochondria make nerves grow”.

1. Han et al., (2020). Recovering energy deficits promotes CNS axonal regeneration and functional restoration after spinal cord injury. ***Cell Metabolism*** 31, 623-641.

**NIH News Press** | “Boosting energy levels within damaged nerves may help them heal”.

1. Huang N, Li S, Xie Y, Han Q, Xu X-M, and Sheng Z-H. (2021). Reprogramming an energetic AKTPAK5 axis boosts axon energy supply and facilitates neuron survival and regeneration after injury and ischemia. ***Current Biology*** 31, 3098-3114.

**Current Biology** | Dispatch by Twiss: “Resetting the axon’s batteries”.

1. Chamberlain KA\*, Huang N\*, Xie Y, LiCausi F, Li S, Li Y, and Sheng Z-H. (2021). Oligodendrocytes enhance axonal energy metabolism by deacetylation of mitochondrial proteins through transcellular delivery of SIRT2. ***Neuron*** 109, 3456-3472.

**NIH News Press** | “Signaling from neighboring cells provides power boost within axons”.

**Neuron** | Preview by Kramer-Albers “Glial exosomes boost axonal energetics”.

**(4) Axonal transport of autophagic-endo-lysosomal organelles for the maintenance of distal degradation capacity or “axonostasis”.** Lysosomes serve as degradation hubs for autophagic and endocytic organelles that are generated in distal axons and transported to the cell body where mature lysosomes are enriched. Lysosomes are also recruited to distal axons to achieve local degradation capacity. Therefore, bidirectional transport plays a critical role in the maintenance of axonal and synaptic homeostasis. We revealed that snapin acts as an adaptor attaching dynein motors to late endosomes (LEs) and drives LE transport from distal axons to the soma. We also revealed a motor-adaptor sharing mechanism by which LE-loaded dynein-snapin complexes mediate the retrograde transport of autophagosomes upon their fusion with LEs in distal axons, thus maintaining effective autophagic clearance. We also showed that axonal degradation capacity is maintained by the delivery of “fresh” degradative lysosomes from the soma, and that the endo-lysosomal pathway modulates synaptic vesicle (SV) pool size by shuttling SV components for degradation.

1. Cai Q, Lu L, Tian J-H, Zhu Y-B, Qiao H, and Sheng Z-H. (2010). Snapin-regulated late endosomal transport is critical for efficient autophagy-lysosomal function in neurons. ***Neuron*** 68, 73-86.
2. Cheng X-T, Zhou B, Lin M-Y, and Sheng Z-H. (2015). Axonal autophagosomes acquire dynein motors for retrograde transport through fusion with late endosomes. ***Journal of Cell Biology*** 209, 377-386.
3. Di Giovanni J and Sheng Z-H. (2015). Regulation of synaptic activity by snapin-mediated endo-lysosomal transport and sorting. ***EMBO J*** 34, 2059-2077.
4. Farfel-Becker T, Roney JC, Cheng X-T, Li S, Cuddy SR, and Sheng Z-H. (2019). Neuronal soma-derived degradative lysosomes are continuously delivered to distal axons to maintain local degradation capacity. ***Cell Reports*** 28, 51-64.

**(5) Autophagy-lysosomal dysfunction contributes to the pathogenesis of major neurodegenerative diseases and lysosomal storage disorders.** Our central hypothesis is that neurons coordinate bidirectional transport of endo-autophagic-lysosomal organelles for the maintenance of distal degradation capacity; transport defects lead to autophagic stress, axonal dystrophy, and degeneration. We provided *in vitro* and *in vivo* evidence that impaired lysosomal transport and autophagic clearance are early fALS-linked pathological events in distal axons of spinal motor neurons, thus causing them to be more vulnerable to dying-back degeneration. We also provided guidelines for labeling degradative lysosomes in*in vitro* and *in vivo* nervous systems to characterize how lysosomal distribution, trafficking, and functionality contribute to neuronal health and disease progression. We recently revealed that lipid-mediated motor-adaptor sequestration impairs axonal lysosome delivery leading to autophagic stress and dystrophy inNiemann-Pick disease type C. Elucidation of these mechanisms is broadly relevant given that axonal lysosomal deficits associate with major neurodegenerative diseases.

1. Xie\* Y, Zhou\* B et al., and Sheng Z.-H. (2015). Endo-lysosome deficits augment mitochondria pathology in spinal motor neurons of asymptomatic fALS-linked mice. ***Neuron*** 87, 355-370.

**NIH News Press |**“NIH scientists identify a transport defect in a model of familial ALS”.

1. Cheng X-T et al & Sheng Z-H. (2018). Characterization of LAMP1-labeled non-degradative lysosomal compartments in nervous systems. ***Journal of Cell Biology*** 217, 3127-3139.

**JCB** | Spotlight Article “Neuronal endosomes to lysosomes: A journey to the soma”.

1. Roney JC, Li S, Farfel-Becker T, Huang N, Sun T, Xie Y, Cheng X-T, Lin M-Y, Platt FM, and Sheng Z-H. (2021). Lipid-mediated motor-adaptor sequestration impairs axonal lysosome delivery leading to autophagic stress and dystrophy in Niemann-Pick type C. ***Developmental Cell*** 56, 1452-1468.

**Developmental Cell** | Preview by Yap and Winckler “Lysosomes to the rescue”.

**Nature Reviews Molecular Cell Biology** | HIGHLIGHT “Lysosome transport interrupted”.

1. Roney JC. Cheng X-T, and Sheng Z-H. (2022). Neuronal endo-lysosomal transport and lysosomal functionality in maintaining axonostasis. ***Journal Cell Biology*** 221,

**Complete List of Published Work in My Bibliography:**

[**https://www.ncbi.nlm.nih.gov/myncbi/1zS8q6nFSJhQT/bibliography/public/**](https://www.ncbi.nlm.nih.gov/myncbi/1zS8q6nFSJhQT/bibliography/public/)

**Sheng Lab webpage:**

[**https://research.ninds.nih.gov/sheng-lab**](https://research.ninds.nih.gov/sheng-lab)