Plenary session speech

Dendrite Arborization and Pruning

Cheng-Ting Chien(簡正鼎)
Distinguished Fellow, Institute of Molecular Biology, Academia Sinica

Date: 9/4 (Sun) 13:10~13:55
Ph.D.Biochemistry and Molecular Biology, Stony Brook University, New York, USA

Abstract

One way to characterize different types of neurons isby their distinct morphology, mainly the dendritic trees. One fascinating research direction is how neurons grow such exuberant and distinct patterns of dendrites after their birth. We have been using Drosophila dendritic arborization (da) neurons as the model system to study dendrite growth and pruning during development. There are four types of da neurons (classes I-IV) with class IV da (C4da) neurons being the most complex in morphology. We study cellular machineries underlying endocytosis and exocytosis that are highly active during dendrite elaboration. Golgi outposts are dynamic in dendrites and are regulated in their transport during growth and pruning. Dendrites of C4da neurons innervate epithelial cells that support growth and prevent fasciculation. Protein glycosylation that modifies cell surface receptors that phagocytoses fragmentated dendrites during pruning.

Selected recent publications:

1. 1. Yang, W.-K., Peng, Y.-H., Li, H., Lin, H.-C., Lin, Y.-J., Lai, T.-T., Suo, H., Wang, C.-H. Lin, W.-H., Ou, C.-Y., Zhou, X., Pi, H., Chang, H. C, Chien, C.-T.* (2011) Nak regulates localization of clathrin sites in higher-order dendrites to promote local dendrite growth. Neuron, 72(2) 285-299.
2. 2. Lin, C.-H., Li, H., Lee, Y.-N., Cheng, Y.-J., Wu, R.-M., and Chien, C.-T.* (2015) Lrrk regulates the dynamic profile of dendritic Golgi outposts through the golgin Lava lamp.J. Cell Biol., 210(3) 471-483. (The first two contribute equally).
3. 3. Nithianandam, V. and Chien, C.-T.*, (2018) Actin blobs prefigure dendrite branching sites. J. Cell Biol., 217(10) 3731-3746.
4. 4. Yang, W.-K., Chueh, Y.-R., Cheng, Y.-J., Siegenthaler, D., Pielage, J. and Chien, C. -T.* (2019) Epidermis-derived L1CAM homolog Neuroglianmediates dendrite enclosure and blocksheteroneuronaldendrite bundling. Curr. Biol., 29(9), 1445-1459.
5. 5. Hsun, H., Sung,H.-H., Cheng, Y.-J., Yeh, H.-F., Pi, H., Giniger, E., Chien,C.-T.*Fringe-positive Golgi outposts converge temporal Furin 2 convertase activity and spatial Delta signal to promote dendrite pruning(in revision).

Plenary session speech

From Biomarkers to Clinical Trials: Lessons of Translational Brain Cancer Stem Cell Biology

John S. Kuo(郭樹勳)
Vice President
Chair Professor, Graduate Institute of Biomedical Sciences
Director, Neuroscience and Brain Disease Center
China Medical University
Yu Shan Scholar, Ministry of Education, Taiwan
Professor, The University of Texas at Austin.

Date: 9/4 (Sun) 13:10~13:55

Ph.D.,MIT (Whitehead Institute for Biomedical Research)
M.D.,Harvard Medical School (Harvard-MIT Division of Health Sciences and Technology)

Abstract

Patients diagnosed with malignant brain tumors such as brain metastases or the primary brain cancer, glioblastoma (GBM), carry a poor prognosis for long term survival and suffer a significantly diminished quality of life. The challenges of tumor heterogeneity, rapid recurrence and therapeutic resistance will be discussed in the context of translational biology studies using patient-derived cancer stem cells and xenograft models. Discovery of new clinically relevant biomarkers from developmental neurobiology approaches, ion channel studies and immuno-screening discovery strategies lead to new perspectives on GBM molecular diagnosis and therapeutics. Preclinical and clinical trial studies of novel cancer alkylphosphocholine analogs for diagnostic detection, fluorescence visualization and therapeutic strategies will also be presented as the foundation of new theranostic strategy for many different cancers.

Selected recent publications:

1. Grudzinski JJ, Hall LT, Cho S, Liu G, Traynor A, Lee MH, Longino M, Pinchuk A, Jaskowiak C, Bednarz B, Weichert J, **Kuo JS**(2022) "Clinical imaging and dosimetry of a pan-cancer targeting alkylphosphocholine analog, ^{124}I-NM404." *Radiation* 2: 215-227.

2. Kukreja L, Li C, Ezhilan S, Iyer V, **Kuo JS**(2022)"Emerging epigenetic therapies for brain tumors." *NeuroMolecular Medicine* 24 (1): 41-49.

3. Umlauf BJ, Clark PA, Lajoie JM, Georgieva JV, Bremner S, Herrin BR, **Kuo JS*,** Shusta EV* (2019) "Identification of variable lymphocyte receptor antibodies that can target therapeutics to pathologically exposed brain extracellular matrix." *Science Advances* 5 (5): eaau4245.

4. Pointer KB, Clark PA, Eliceiri KW, Robertson G*, **Kuo JS***(2017) "Administration of non-torsadogenic human Ether-à-go-go Related Gene (hERG) inhibitors is associated with better survival for high hERG-expressing glioblastoma patients." *Clinical Cancer Research* 23 (1): 73-80.

5. Zhang RR, Schroeder AB, Grudzinski JJ, Rosenthal EL, Warram JM, Pinchuk AN, Eliceiri KW, **Kuo JS***, Weichert JP* (2017) "Beyond the margins: Real time detection of cancer using targeted fluorophores." *Nature Reviews Clinical Oncology* 14 (6): 347-364.

Plenary session speech

Lysophosphatidic acid (LPA): Chemical signature of neuropathic pain and fibromyalgia

Hiroshi Ueda(植田弘師)
Chair Professor, Department of Pharmacology, National Defense Medical Center, Taipei, Taiwan, and Academic Advisor/Principal Investigator, Laboratory for the Study of Pain, Research Institute for Production Development, Kyoto, Japan

Date: 9/4 (Sun) 13:10~13:55
Ph.D.Kyoto University, Japan

Abstract

Since the first discovery that the bioactive lipid, lysophosphatidic acid (LPA) receptor type 1 ($LPAR_1$) signaling plays a role in the initiation of neuropathic pain (NeuP), accumulated reports have supported the original findings and extended the study toward possible therapeutic applications in various chronic pain models. In the representative neuropathic pain model using partial sciatic nerve injury, the initial non-selective and intense pain signals cause a production of LPA, which in turn amplifies the LPA production through an $LPAR_3$-mediated microglia activation and cytokine production. $LPAR_3$-mediated microglia activation also produces BDNF, which in turn decreases KCC2 and converts the $GABA_A$ receptor function to excitatory one. $LPAR_1$-mechanisms also upregulate Cavα2δ1 channel subunit in DRG and cause a demyelination and Aβ-fiber sprouting, which may form abnormal pain synapses. All these mechanisms underlie the pharmacotherapy and pathophysiology of neuropathic hyperalgesia and allodynia. $LPAR_1$ and $LPAR_3$-mediated mechanisms were also evidenced in paclitaxel-induced, diabetic NeuP and central post stroke pain. Close relationship between NeuP and LPA levels in CSF was also supported by several clinical observations. Compared with NeuP, on the other hand, the establishment of diagnosis and treatments for fibromyalgia (FM) are largely delayed. We have developed empathic psychological stress- or intermittent cold stress-induced animal models, which mimic the clinical features in terms of pathophysiology (female predominant, wide spread, long lasting pain) and pharmacotherapy (sensitive to pregabalin or duloxetine, but not to morphine or NSAIDs). The generalized pain in FM models was also abolished by $LPAR_{1/3}$ antagonists or $LPAR_1$or $LPAR_3$-gene deficiency. All these findings suggest that $LPAR_{1/3}$ signaling could be a promising therapeutic target for most of chronic pain. In the meeting I will also discuss the systems in pathophysiology for chronic pain in terms of pain memory in the brain and peripheral immune system.

Selected recent publications:

1. Inoue M, Rashid MH, Fujita R, Contos JJA, Chun J, Ueda H, Initiation of neuropathic pain requires lysophosphatidic acid receptor signaling. Nature Med 10:712-718, 2004
2. Ueda H, Neyama H, LPA1 receptor involvement in fibromyalgia-like pain induced by intermittent psychological stress, empathy. Neurobiol Pain 1: 16-25, 2017
3. Ueda Het al.,Involvement of lysophosphatidic acid-induced astrocyte activation underlying the maintenance of partial sciatic nerve injury-induced neuropathic pain. Pain, 159:2170-2178, 2018
4. Ueda Het al., Allodynia by splenocytes from mice with acid-induced fibromyalgia-like generalized pain and its sexual dimorphic regulation by brain microglia. Front Neurosci. 14: 600166, 2020
5. Ueda H, Pathogenic mechanisms of lipid mediator lysophosphatidic acid in chronic pain. Progress in lipid research. 81: 101079, 2021 (Review)

Plenary session speech

On the neural language of the cerebellum

Reza Shadmehr
Professor of Biomedical Engineering and Neuroscience
Johns Hopkins School of Medicine

Date: 9/4 (Sun) 13:10~13:55
Ph.D., University of Southern California

Abstract

A slow sensory system presents major problems for movement control. Yet, despite this shortcoming the healthy brain composes exquisite movements. Textbooks posit that this remarkable ability is due to the cerebellum, a structure that learns to predict sensory consequences, thus overcoming time delays. However, cerebellar neurons fire in patterns that do not correspond well with movements. For example, neuronal activity is modulated long after the movement has ended. Thus, the language with which the cerebellum expresses its predictions has remained a mystery.

The idea that we have explored is that in the cerebellum, the fundamental unit of computation may not be a single neuron, but a group of neurons that share the same teacher. In this analogy, the teacher is the inferior olive, organizing the students (Purkinje cells) into groups. To test this idea, we have measured activity of neurons in macaques and marmosets and found that while activity of individual neurons is difficult to decipher, activity of a group of neurons that shares the same teacher is a rather precise predictor of the ongoing movement, particularly during deceleration and stopping.

Selected recent publications:

1. Herzfeld DJ, Vaswani PA, Marko MK, and Shadmehr R (2014) A memory of errors in sensorimotor learning. Science 345:1349-135.

2. Herzfeld DJ, Kojima Y, Soetedjo R, and Shadmehr R (2015) Encoding of action by the Purkinje cells of the cerebellum. Nature 526:439-442.

3. Herzfeld DJ, Kojima Y, Soetedjo R, and Shadmehr R (2018) Encoding of error and learning to correct for that error by the Purkinje cells of the cerebellum. Nature Neuroscience 21:736-743.

4. Sedaghat-Nejad E, Pi JS, Hage P, Fakharian MA, Shadmehr R (2022) Synchronous spiking of cerebellar Purkinje cells during control of movements. Proc. National Academy of Sciences (USA)119:e2118954119.

5. Shadmehr R (2020) Population coding in the cerebellum: a machine learning perspective. Journal of Neurophysiology 124:2022-2051.