Plenary Session Speech (I)

How to build synapses: New mechanisms by extracellular scaffolding proteins

Speaker : Michisuke Yuzaki 柚崎通介

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Location:生物醫學科學研究所 B1B會議室
Institute of Biomedical Sciences (IBMS) B1B

Time: Sept. 11 15:45-16:30

Abstract

The human brain contains ~10^{14} connections, known as synapses, within a vast network of neurons. Abnormal synaptic connections likely contribute to various neuropsychiatric, neurodevelopmental and neurological disorders, such as schizophrenia, autism spectrum disorders and Alzheimer's diseases. Thus, it is crucial to clarify the mechanisms by which vast numbers of connections are precisely established, maintained, and modified throughout life. Synaptic organizers, which mediate formation, elimination and maintenance of synaptic connections, are classified into secreted factors, such as Wnt and FGF, and cell adhesion molecules, such as neurexins and neuroligins. Recently, a new class of synaptic organizers, secreted extracellular scaffolding proteins (ESPs), such as C1q family proteins, LGI1, neuronal pentraxins and glial thrombospondins, have been discovered[1]. They serve as a scaffold for pre- and postsynaptic membrane proteins at the synaptic extracellular matrix. For example, Cbln1, a prototype of the C1q family synaptic organizers, is unique in that it is secreted from presynaptic neurons in an activity-dependent manner[2], and rapidly induces synapse formation in adult brain[3,4]. Epileptic seizures repress Cbln1 mRNA in the ventral tegmental area, leading to impaired sociability in mice (Krishnan et al., Nature 543:507-12, 2017). In contrast, Cbln4 regulates inhibitory synapses between somatostatin-positive interneurons and pyramidal neurons in the cortex (Favuzzi et al., Science 363:413-7, 2019; Fossati et al., Neuron 104:1081-94, 2019). In this lecture, I would like to summarize what is known so far about synaptic organizers focusing on the C1q family of ESPs. I would also like to discuss how we could develop new therapeutic reagents against neuropsychiatric and neurological disorders based on the known structures of known ESPs[5].

Selected 5 recent publications:

Ibata K, Kono M, Narumi S, Motohashi J, Kakegawa W, Kohda K, Yuzaki M. Activity-dependent secretion of synaptic organizer Cbln1 from lysosomes in granule cell axons. **Neuron** 102:1184-1198, 2019

Kakegawa W, Kato A, Narumi S, Miura E, Motohashi J, Takahashi A, Kohda K, Fukazawa Y, Yuzaki M*, Matsuda S. Optogenetic control of synaptic AMPA receptor endocytosis reveals roles of LTD in motor learning. **Neuron** 99:985-998, 2018. (*Lead corresponding author)

Wakayama S, Kiyonaka S, Arai I, Kakegawa W, Matsuda S, Ibata K, Nemoto YL, Kusumi A, Yuzaki M, Hamachi I. Chemical labelling for visualizing native AMPA receptors in live neurons. **Nature Commun**. 8:14850, 2017.

Elegheert J, Kakegawa W, Clay JE, Shanks N, Behiels E, Matsuda K, Kohda K, Miura E, Rossmann M, Mitakidis N, Motohashi J, Chang VT, Siebold C, Greger IH, Nakagawa T, Yuzaki M*****, Aricescu AR*. Structural basis for integration of GluD receptors within synaptic organizer complexes. **Science** 353: 295-299, 2016. (*****co-corresponding author).

Kiyonaka S, Kubota R, Michibata Y, Sakakura M, Takahashi H, Numata T, Inoue R, Yuzaki M, Hamachi I. Allosteric activation of membrane-bound glutamate receptors using coordination chemistry within living cells. **Nature Chem** 8 :958-967, 2016.

Plenary Session Speech (I)

Brain age gap: Technical considerations and clinical implications

Speaker: Wen-Yih Tseng 曾文毅

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AcroViz Inc. Taiwan
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Time: Sept. 11 15:45-16:30

Abstract

MRI-derived brain-age prediction provides a promising approach to assess an individual's brain age relative to healthy populations. Brain-age prediction can be derived by extracting age-related changes in gray matter and white matter from T1-weighted and diffusion MRI, respectively, using machine learning algorithms. The brain age gap (BAG), defined as the difference between estimated brain age and chronological age, is significantly increased in patients with neurological, psychiatric or even metabolic disorders. However, the role of BAG in mediating brain structures and cognitive variables is still unclear. Previously, we have used 478 cognitively healthy subjects' brain MRI scans to develop brain age prediction models for predicting white matter or gray matter brain age with the mean absolute error of about 4.4 years. We transferred the in-house models to an open databank, the Cam-CAN dataset, in which complete records of dementia risk factors, brain MRI scans, and cognitive assessments are available. Structural equation models were applied to investigate the mediation effect of BAG between dementia risk factors and intellectual abilities. We discovered that a higher burden of modifiable dementia risk factors was causally associated with more decline in intellectual abilities, and it was significantly mediated ($p = 0.017$) by a larger BAG, denoting an older brain. Moreover, a greater slope ($p = 0.02$) of association between intellectual decline and BAG was observed when subjects were exposed to higher dementia risks. In this cross sectional study, we have demonstrated how BAG relates to the degree of dementia risk factors and to intellectual changes and clarified their causal relationship via BAG.

Selected 5 recent publications:

1.Chen CL, Hsu YC, Yang LY, Tung YH, Luo WB, Liu CM, Hwang TJ, Hwu HG, Tseng WYI* (2020) Generalization of diffusion magnetic resonance imaging–based brain age prediction model through transfer learning. NeuroImage (accepted).

2.Chen PY, Chen CL, Hsu YC, Cam-CAN, Tseng WYI* (2020) Fluid intelligence is associated with cortical volume and white matter tract integrity within multiple-demand system across adult lifespan. NeuroImage 212:116576

3.Chen CL, Shih YC, Liou HH, Hsu YC, Lin FH, Tseng WYI* (2019) Premature white matter aging in patients with right mesial temporal lobe epilepsy: A machine learning approach based on diffusion MRI data. Neuroimage Clin 24:102033.

4.Tseng CH, Chien YH, Lee NC, Hsu YC, Peng SF, Tseng WYI*, Hwu WL* (2019) Gene therapy improves brain white matter in aromatic L-amino acid decarboxylase deficiency. Ann Neurol 85:644-652.

5.Tsai TH, Su HT, Hsu YC, Shih YC, Chen CC, Hu FR*, Tseng WYI* (2019) White matter microstructural alterations in amblyopic adults revealed by diffusion spectrum imaging with systematic tract-based automatic analysis. British Journal of Ophthalmology 103:511-516

Plenary Session Speech (I)

Axon connection: From refinement during development to integration in mature brain

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Time: Sept. 11 15:45-16:30

Abstract

During embryonic development neurons make connections with each other to build neural network required for a functional brain. However, these initial axon connections are continued to be refined throughout the entire lifetime. In this talk, I will use my research on C. elegans motor axons and mouse hippocampal adult-born neurons as examples to describe 1) how axons are guided by axon guidance receptor and disease-related genes to find their target area during embryonic development and 2) how adult-born neurons extend axons in an entire mature environment to properly integrate into the existing functional circuitry.

Selected 5 recent publications:

Murray KD, Liu X-B., King AN, Luu J, **Cheng H.-J*** (2020) Age-related changes in synaptic plasticity associated with mossy fiber terminal integration during adult neurogenesis. *eNeuro* (in press).

Chen S-Y, Ho C-T, Liu W-W, Lucanic M, Shih H-M, Huang P-H, **Cheng H.-J*** (2018) Regulation of axon repulsion by MAX-1 SUMOylation and AP-3. *Proc Natl Acad Sci USA* 115: E8236-E8245.

Failor S, Chapman B, **Cheng H.-J*** (2015). Retinal waves regulate afferent terminal targeting in the early visual pathway. *Proc Natl Acad Sci USA* 112: E2957-E2966.

Chen, S-Y, Huang P-H*, **Cheng H.-J*** (2011) Disrupted-in-Schizophrenia 1-mediated axon guidance involves TRIO-RAC-PAK small GTPase pathway signaling. *Proc Natl Acad Sci USA* 108: 5861-5866.

Faulkner RL, Jang M-H, Liu X-B, Duan X, Sailor, KA, Kim J Y, Ge S, Jones EG, Ming G-L, Song H, **Cheng H.-J*** (2008). Development of hippocampal mossy fiber synaptic outputs by new neurons in the adult brain. *Proc Natl Acad Sci USA* 105:14157- 14162.

Plenary Session Speech (I)

Novel treatments and biomarkers of mental disorders: based upon DAOA/DAO/NMDA pathway

Speaker: Hsien-Yuan Lane 藍先元

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Time: Sept. 11 15:45-16:30

Abstract

While second-generation antipsychotics are increasingly used, treatment for schizophrenia remains a great challenge. NMDAR dysfunction plays vital roles in pathogenesis of schizophrenia. However, there have been lack of suitable biomarkers and enhancers for schizophrenia. Previously, we have found that glycine transporter-1 (GlyT-1) antagonist, N-methylglycine (sarcosine), can improve symptoms of schizophrenia. Sarcosine can also improve depression-like behaviors in rodent models and in human depression, even better and faster than citalopram, a commonly used selective serotonin reuptake inhibitor (SSRI) antidepressant. This presentation will update the current status of the development of novel glutamate-related biomarkers and modulators, based upon DAOA/DAAO/NMDAR pathway, for early diagnosis and treatment of schizophrenia.

I will present data from clinical trials with benzoate, the pivotal D-amino acid oxidase (DAAO) inhibitor, in chronic- and treatment-resistant forms of schizophrenia. Results suggest that adjuvant benzoate therapy can improve cognitive function of patients, irrespective of clinical improvement, supporting cognition as an independent, primary outcome measure. Lately, we also found that adjuvant benzoate therapy improved symptomatology of patients with ultra-resistant (clozapine-resistant) schizophrenia. In addition, it can also benefit the treatment of early-phase Alzheimer disease. Further, we will show findings suggesting that peripheral makers including DAAO activator (DAOA; or named G72) and cystine/glutamate antiporter system xc- may identify a unique subgroup of patients of schizophrenia who will be responsive to novel NMDAR enhancers.

To sum up, this presentation, composed of several works on novel NMDAR-related biomarkers and modulators for early diagnosis and novel treatment, may help the development of pharmacotherapy and diagnosis for schizophrenia.

Selected 5 recent publications:

1.Lane HY et al. (2013). Add-on treatment of benzoate for schizophrenia: a randomized, double-blind, placebo-controlled trial of D-amino acid oxidase inhibitor. JAMA Psychiatry 70:1267-1275

2.Huang CC, Wei IH, Huang CL, Chen KT, Tsai MH, Tsai P, Tun R, Huang KH, Chang YC, Lane HY*, Tsai GE (2013) Inhibition of glycine transporter-I as a novel mechanism for the treatment of depression. Biol Psychiatry 74:734-741

3.Lin CH, Chen PK, Chou LJ, Chang YC, Chen YS, Tsai GE, Lane HY* (2014) Benzoate, a D-amino acid oxidase inhibitor, for the treatment of early-phase Alzheimer disease: a randomized, double-blind, placebo-controlled trial. Biol Psychiatry 75:678-685

4.Lin CH, Chang HT, Chen YJ, Lin CH, Huang CH, Tun R, Tsai, G, Lane HY* (2014) Distinctively higher plasma G72 protein levels in patients with schizophrenia than in healthy individuals. Mol Psychiatry 19:636

5.Lin CH, Lin CH, Chang YC, Huang YJ, Chen PW, Yang HT, Lane HY* (2018) Sodium benzoate, a D-amino acid oxidase inhibitor, added to clozapine for the treatment of schizophrenia: a randomized, double-blind, placebo-controlled trial. Biol Psychiatry 84:422-432