Stanford

# Lu Chen

Professor of Neurosurgery and of Psychiatry and Behavioral Sciences

## CONTACT INFORMATION


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## Bio

### ACADEMIC APPOINTMENTS

- Professor, Neurosurgery
- Professor, Psychiatry and Behavioral Sciences - Center for Interdisciplinary Brain Sciences Research
- Member, Bio-X
- Member, Maternal & Child Health Research Institute (MCHRI)
- Member, Wu Tsai Neurosciences Institute

### ADMINISTRATIVE APPOINTMENTS

- Professor, Department of Psychiatry and Behavioral Science, (2016- present)
- Associate Professor, Department of Psychiatry and Behavioral Science, (2011- present)
- Professor, Department of Neurosurgery, (2016- present)
- Associate Professor, Stanford Institute of Neuro-Innovation and Translational Neuroscience, (2011- present)

### HONORS AND AWARDS

- NRSA Postdoc fellowship, NIH (2001)
- Beckman Young Investigator Award, Beckman foundation (2003)
- NARSAD Young Investigator Award, NARSAD (2005)
- Packard Fellow in Science and Engineering, David and Lucile Packard Foundation (2005)
- Keck Distinguished Young Scholar in Medical Research, W. M. Keck Foundation (2005)

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### PROFESSIONAL EDUCATION

- PhD, University of Southern California , Neurobiology (1998)

### LINKS

- Chen Lab website: http://neurosurgery.stanford.edu/research/chen/index.html

# Research & Scholarship

## CURRENT RESEARCH AND SCHOLARLY INTERESTS

The long-term goal of my research is to understand the cellular and molecular mechanisms that underlie synapse function during behavior in the developing and mature brain, and how synapse function is altered during mental retardation. In this broad research area, I am specifically interested in the homeostatic control of synaptic strength, the role of postsynaptic protein translation in this control, and the impairment of synapses in Fragile X syndrome that involves changes in postsynaptic protein translation and synaptic strength.

We recently discovered a role of all-trans retinoic acid (RA) in regulating synapse formation and synaptic strength, which we identified during studies of homeostatic synaptic plasticity. We found that RA is a potent activator of synaptic strength in mature neurons. Neuronal synthesis of RA is regulated by activity. When neuronal activity is blocked, RA synthesis is strongly stimulated. When applied directly, RA is sufficient to rapidly increase synaptic strength. Moreover, when we blocked RA synthesis in neurons, we abolished the increase in synaptic strength induced by activity blockade. Taken together, these results reveal a central role of RA in mediating activity blockade-induced increases in synaptic strength, and suggest that in adult brain, RA functions as a novel diffusible messenger that regulates synaptic transmission.

Subsequent experiments revealed that the synaptic effect of RA operates by stimulating the synthesis and insertion of new postsynaptic AMPA-receptors into existing synapses. What mediates the translational regulation function of RA? Combining electrophysiological, biochemical and ultrastructural approaches, we identified a novel role of the RA-receptor RARα in translational regulation. We found that RAR directly associates with specific RNA sequences in the 5'UTR of target mRNAs, and represses their translation. RA, by binding to RAR, releases this translational repression, probably by inducing a conformational change in RAR that leads to its dissociation from mRNA. To our knowledge, this is the first characterized translational regulatory mechanism that operates in a ligand-gated fashion.

How does the RA-dependent translational regulation intersect with other known mechanisms involved in dendritic protein synthesis and synaptic plasticity? We have recently found that the Fragile X Mental Retardation Protein (FMRP), an RNA-binding protein that regulates local protein translation in dendrites, is essential for increases in synaptic strength induced by RA or by neural activity blockade. Activity-dependent RA synthesis is maintained in Fmr1 knockout neurons, but RA-dependent activation of dendritic translation of AMPA-type glutamate receptors is impaired. Furthermore, we showed that the deficit in synaptic scaling in Fmr1 knockout neurons can be rescued by acute postsynaptic expression of FMRP, indicating that the role of FMRP is not developmental, but that it is part of the homeostatic synaptic machinery. Taken together, these findings identify an unexpected role for FMRP in regulating homeostatic synaptic plasticity downstream of RA. Our results raise the possibility that at least some of the symptoms of Fragile X syndrome, a form of mental retardation caused by loss of FMRP function, reflect impaired homeostatic plasticity and dysfunctional RA signaling, and suggest that modification of the RA-signaling pathway in homeostatic plasticity may be beneficial for treating this prevalent disorder.

# Teaching

## STANFORD ADVISEES

**Postdoctoral Faculty Sponsor**

Bing Cao, Jie Li, Omid Miry, Shruti Thapliyal

## GRADUATE AND FELLOWSHIP PROGRAM AFFILIATIONS

- Neurosciences (Phd Program)
- Psychiatry and Behavioral Science (Fellowship Program)

# Publications

## PUBLICATIONS

- **Synaptic retinoic acid receptor signaling mediates mTOR-dependent metaplasticity that controls hippocampal learning.** *Proceedings of the National Academy of Sciences of the United States of America*
  Hsu, Y., Li, J., Wu, D., Sudhof, T. C., Chen, L.
  2019

- **Disruption of Telomerase RNA Maturation Kinetics Precipitates Disease** *Molecular Cell*
  Roake, C. M., Chen, L., Chakravarthy, A., Raffa, G. D., Ferrell, Jr., J. E., Artandi, S. E.
  2019

- **Retinoic acid receptor RARalpha-dependent synaptic signaling mediates homeostatic synaptic plasticity at the inhibitory synapses of mouse visual cortex.** *The Journal of neuroscience : the official journal of the Society for Neuroscience*
  Zhong, L., Chen, X., Park, E., Sudhof, T. C., Chen, L.
  2018

- **Homeostatic synaptic plasticity as a metaplasticity mechanism-a molecular and cellular perspective.** *Current opinion in neurobiology*
  Li, J., Park, E., Zhong, L. R., Chen, L.
  2018; 54: 44–53

- **The fragile X mutation impairs homeostatic plasticity in human neurons by blocking synaptic retinoic acid signaling.** *Science translational medicine*
  Zhang, Z., Marro, S. G., Zhang, Y., Arendt, K. L., Patzke, C., Zhou, B., Fair, T., Yang, N., Sudhof, T. C., Wernig, M., Chen, L.
  2018; 10 (452)

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