Shimada T, and Yamagata K. (2018) "Pentylenetetrazole-Induced Kindling Mouse Model." ***JoVE*** (136).

Shimada T, Yoshida T, and Yamagata K. (2016) "Neuritin Mediates Activity-Dependent Axonal Branch Formation in Part via FGF Signaling." ***J. Neurosci.*** 36(16):4534-4548.

Sugiura H, Yasuda S, Katsurabayashi S, Kawano H, Endo K, Takasaki K, Iwasaki K, Ichikawa M, Kobayashi T, Hino O, and Yamagata K. (2015) "Rheb activation disrupts spine synapse formation through accumulation of syntenin in tuberous sclerosis complex." ***Nat. Commun.*** 6:6842.

Masui K, Tanaka K, Ikegami S, Villa GR, Yang H, Yong WH, Cloughesy TF, Yamagata K, Arai N, Cavenee WK, and Mischel PS. (2015) "Glucose-dependent acetylation of Rictor promotes targeted cancer therapy resistance." ***Proc. Natl. Acad. Sci. USA*** 112(30):9406-9411.

Shimada T, Takemiya T, Sugiura H, and Yamagata K. (2014) "Role of Inflammatory mediators in the pathogenesis of epilepsy." ***Mediators Inflamm.*** 2014:901902.

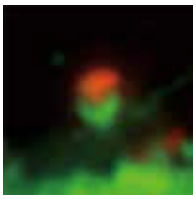
Yasuda S, Sugiura H, Katsurabayashi S, Shimada T, Tanaka H, Takasaki K, Iwasaki K, Kobayashi T, Hino O, and Yamagata K. (2014) "Activation of Rheb, but not of mTORC1, impairs spine synapse morphogenesis in tuberous sclerosis complex." ***Sci. Rep.*** 4:5155.

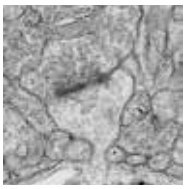
Kim SY, Yasuda S, Tanaka H, Yamagata K, and Kim H. (2011) "Non-clustered protocadherin." ***Cell Adh. Migr.*** 5(2):97-105.

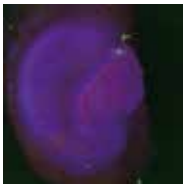
Project Leader **Kanato Yamagata** Synaptic Plasticity Project

Synaptic Plasticity and Brain Diseases: Elucidating the mechanism for developmental epilepsy, intellectual disability and autism

Our project examines the molecular basis of activity-dependent synaptic plasticity. In particular, we have cloned a set of immediate early genes (IEGs) that are rapidly transcribed in neurons involved in information processing, and that are essential for long term memory. IEG proteins can directly modify synapses and provide insight into cellular mechanisms that support synaptic plasticity. Furthermore, these IEG products have been shown to be involved in developmental brain disorders, including refractory epilepsy, intellectual disability and/or autism.

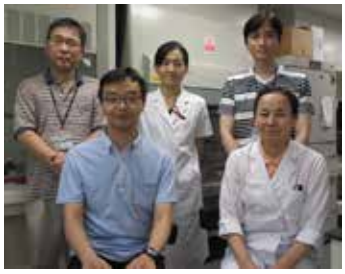






"We have clarified mechanisms of refractory epilepsy, intellectual disability and/or autism caused by impaired synaptic plasticity. Based on the novel mechanisms we found, we are trying to find new treatments for developmental brain disorders"

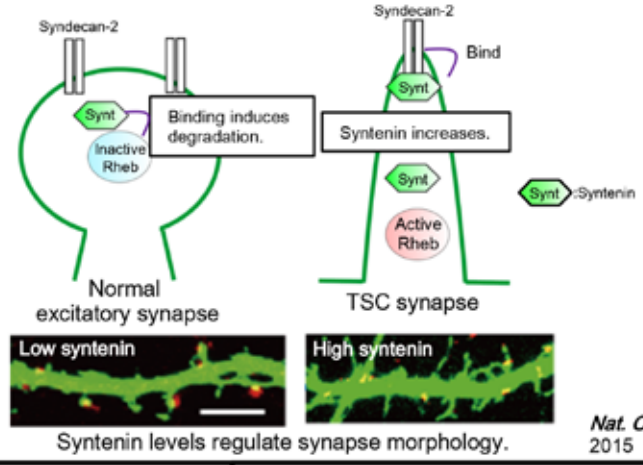
For example, COX-2 and mPGES-1 are prostaglandin synthases and exacerbate neuronal cell death after seizures, leading to intractable epilepsy. Arcadlin is a protocadherin and induces spine shrinkages after seizures, resulting in developmental delay or amnesia. Rheb regulates excitatory synapse formation via syntenin.
Its constitutive activation causes TSC (tuberous sclerosis complex), which is accompanied by epilepsy, mental retardation and autism.
Finally, neuritin is a secreted or membrane-anchored protein and induces neurite branching. It may be involved in temporal lobe epilepsy.
Thus, rapid de *novo* transcription provides novel insights into the cellular and neural network basis of behavioral plasticity.
We will also explore the possibility that these IEG products could be therapeutic targets for developmental disorders. We are making genetic mouse models of developmental disorders and are testing several drug inhibitors against IEGs for such diseases.



Synaptic Plasticity

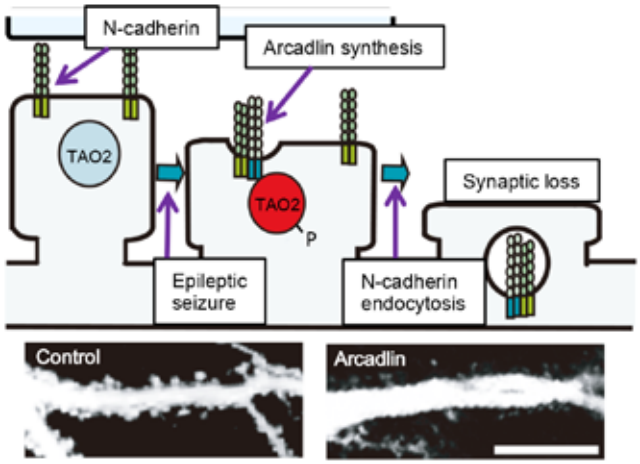
Our Recent Topics

Mechanism of abnormal synapse formation in tuberous sclerosis model animals:



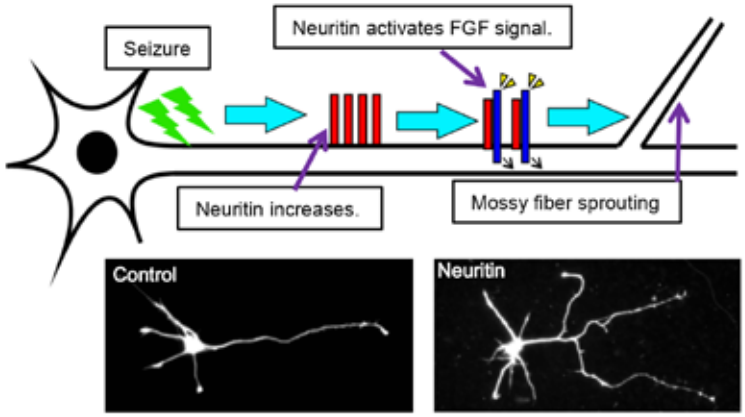
Syntenin levels regulate synapse morphology. *Nat. Commun.* 2015

Mechanism of spine retraction after the epileptic seizure:



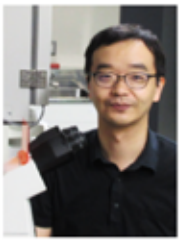
Overexpression of Arcadlin reduces spine number. *Neuron* 2007

Mechanism of mossy fiber sprouting in epilepsy model animals:



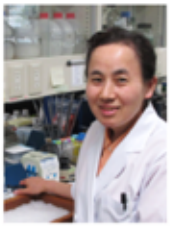
Overexpression of Neuritin promotes axonal branch formation. *J. Neurosci.* 2016

Members



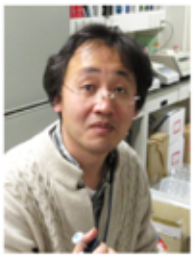
Tadayuki Shimada

Chihiro Hisatsune



Hiroko Sugiura

Keiko Moriya



Shin Yasuda

Synaptic Plasticity