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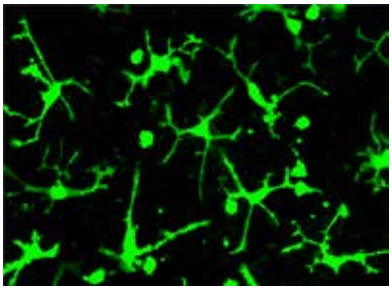
Project Leader **Hiroshi Sakuma** Developmental Neuroimmunology Project

Towards a Better Understanding of Neuro-immune Interactions in the Developing Brain

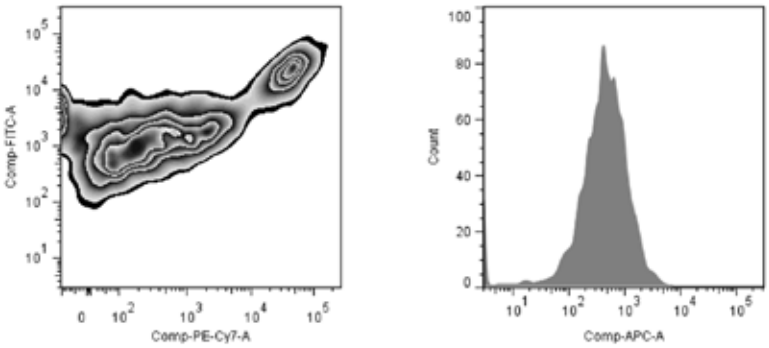


Our research focuses on the role of the immune system in the developing brain. Immune and inflammatory responses not only combat pathogens but also play a variety of physiological roles in the central nervous system. Microglia are brain-resident immune cells and play multiple roles in protection from pathogens and clearance of debris. In addition, recent studies have shed light on unexpected functions of microglia in regulating physiology. For example, microglia actively participate in the brain development by modulating synapses.

"We are investigating the mechanisms by which microglia maintain homeostasis in the developing brain."

Our main research areas include:

1) Development and differentiation of microglia
2) Neuron-microglia interaction
3) In-vitro differentiated myeloid cells for cell therapy
4) Autoantibodies associated with neurological diseases
5) New biomarkers for pediatric immune-mediated neurological diseases



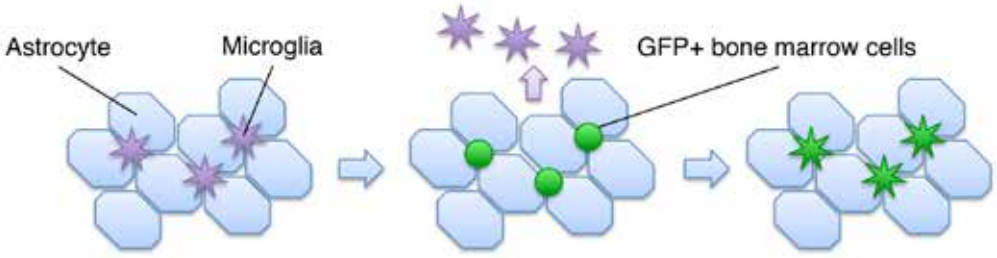
Flow cytometric analysis of microglia

Developmental Neuroimmunology

Research topics

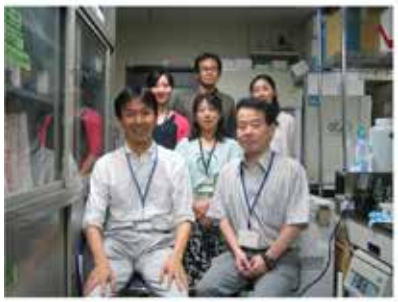
Do astrocytes nurture microglia?

Microglial progenitors originate from the yolk sac and develop into mature microglia in the fetal brain. This observation suggests that non-microglial brain cells support microglial development. We speculated that astrocyte-microglia interaction, both contact-dependent and -independent, is critical for development of microglia. Based on this hypothesis, we have tried to induce microglia from hematopoietic stem-cells by co-culture with astrocytes. When bone-marrow lineage negative cells were co-cultured on an astrocyte monolayer for one week, they developed into microglia-like cells characterized by process-bearing morphology and the expression of microglial markers including CX3CR1 and TREM-2. Differentiation of microglia-like cells was further facilitated by interleukin-34 and TGF-β. These findings provide a theoretical basis for optimizing treatment of neurological diseases by hematopoietic cell transplantation.



Members

Hiroshi Sakuma	Tomonori Suzuki	Yasuo Hachiya
Takako Matsuoka	Taiki Shima	Hiroko Tada
Kuniko Kohyama	Hiroya Nishida	Masaharu Hayashi
Setsuko Hasegawa	Ayuko Igarashi	



Developmental Neuroimmunology

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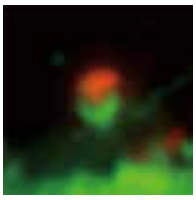
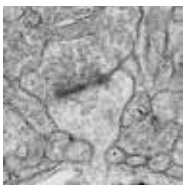
Project Leader **Kanato Yamagata** Synaptic Plasticity Project

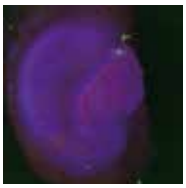
Synaptic Plasticity and Brain Diseases:

Elucidating mechanisms causing developmental epilepsy, intellectual disability, and autism

We study 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.



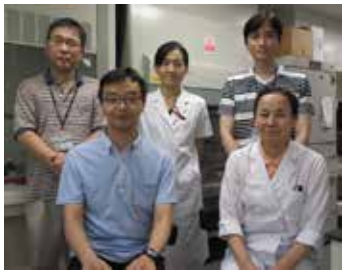




"We have clarified mechanisms of refractory epilepsy, intellectual disability and/or autism caused by impaired synaptic plasticity. Based on the novel mechanisms we found, we are trying to find new treatments for developmental brain disorders"

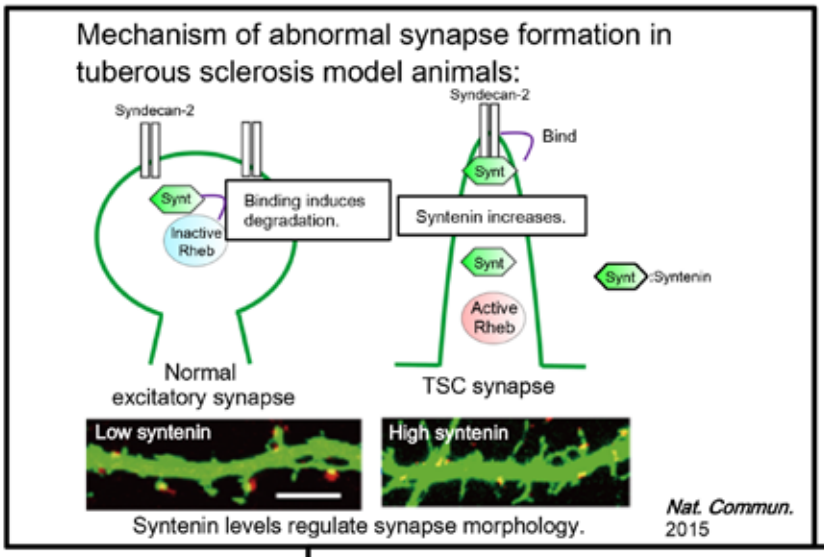
For example, COX-2 and mPGES-1 are prostaglandin synthases that exacerbate neuronal cell death after seizures, leading to intractable epilepsy. Arcadlin is a protocadherin that induces spine shrinkages after seizures, resulting in developmental delay or amnesia. Rheb regulates excitatory synapse formation via syntenin. Constitutive activation of Rheb 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, analysis of rapid de *novo* transcription provides novel insights into the cellular and neural network basis of behavioral plasticity.

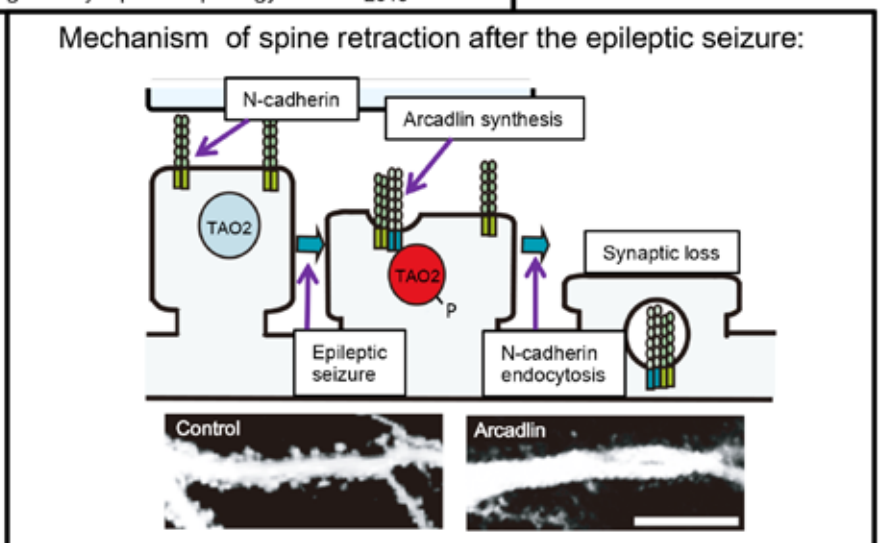
We are also exploring the possibility that these IEG products could be therapeutic targets for developmental disorders. We are making genetic mouse models of developmental disorders and are testing the effects of several drug inhibitors against IEGs.

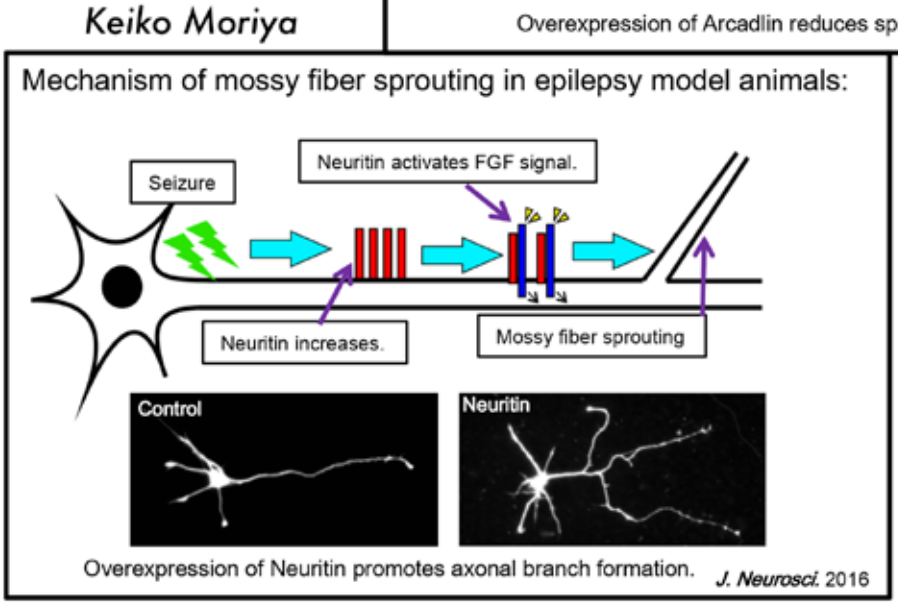


Synaptic Plasticity

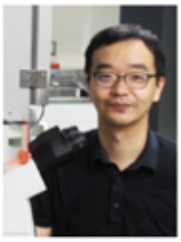
Recent Research Topics





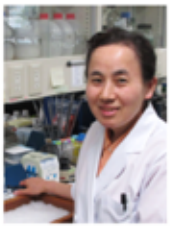


Members



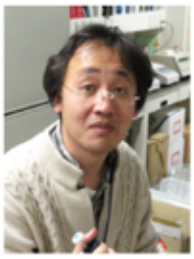
Tadayuki Shimada

Chihiro Hisatsune



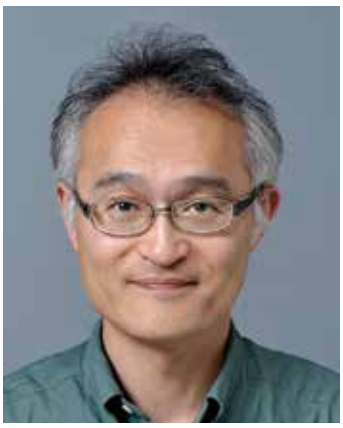
Hiroko Sugiura

Keiko Moriya



Shin Yasuda

Synaptic Plasticity



Project Leader **Haruo Okado** Neural Development Project

Brain Development and Maintenance

Various factors control differentiation of neural stem cells and survival of the resulting neurons, and aberrancy in these processes are associated with intellectual disability, age-related brain disorders, and brain tumors. We aim to elucidate the mechanisms of development and maintenance of brain functions, ultimately to develop methods for the prevention and treatment of intractable cranial nerve diseases.

Various gene-targeted mice

in utero electroporation

"We are studying the effects of various genetic and environmental factors on the molecular mechanisms of brain development and maintenance, with the ultimate goal of developing new treatments for mental diseases."

Laboratory Members

Hirai S, Hotta K, and Okado H. (2018) "Developmental Roles and Evolutionary Significance of AMPA-Type Glutamate Receptors." ***Bioessays.*** 2018 2018 Sep;40(9):e1800028.

Hirai S, Hotta K, Kubo Y, Nishino A, Okabe S, Okamura Y, and Okado H. (2017) "AMPA glutamate receptors are required for sensory-organ formation and morphogenesis in the basal chordate." ***Proc. Natl. Acad. Sci. USA.*** 114: 3939-3944.

Nakajima K, Hirai S, Morio T, and Okado H. (2015) "Benzodiazepines induce sequelae in immature mice with inflammation-induced status epilepticus." ***Epilepsy & Behavior*** 52: 180-186.

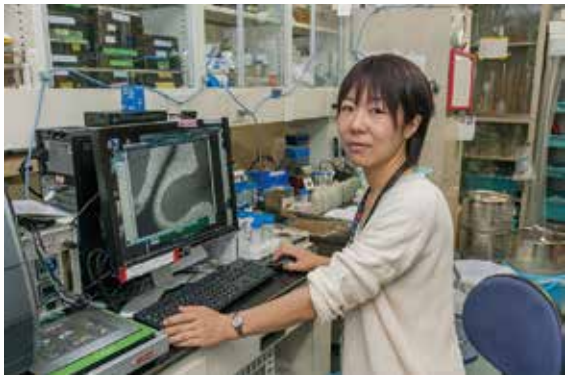
Ohtaka-Maruyama C, Hirai S, Miwa A, Heng JI, Shitara H, Ishii R, Taya C, Kawano H, Kasai M, Nakajima K, and Okado H. (2013) "RP58 regulates the multipolar-bipolar transition of newborn neurons in the developing cerebral cortex." ***Cell Rep.*** 3: 458-471.

Hirai S, Miwa A, Ohtaka-Maruyama C, Kasai M, Okabe S, Hata Y, and Okado H. (2012) "RP58 controls neuron and astrocyte differentiation by downregulating the expression of Id1-4 genes in the developing cortex." ***EMBO J.*** 31: 1190-1202.

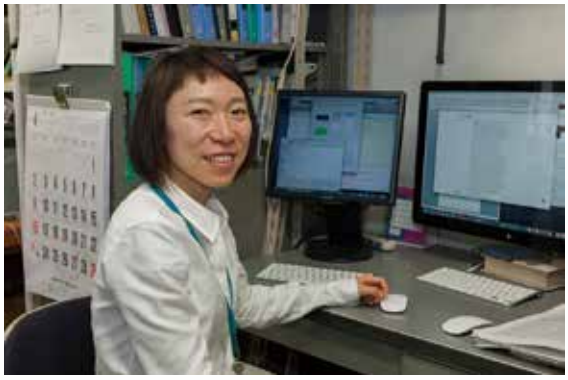
Ohtaka-Maruyama C, Hirai S, Miwa A, Takahashi A, and Okado H. (2012) "The 5'-flanking region of the RP58 coding sequence shows prominent promoter activity in multipolar cells in the sub- ventricular zone during corticogenesis." ***Neuroscience*** 201: 67-84.

Okado H, Ohtaka-Maruyama C, Sugitani Y, Fukuda Y, Ishida R, Hirai S, Miwa A, Takahashi A, Aoki K, Mochida K, Suzuki O, Honda T, Nakajima K, Ogawa M, Terashima T, Matsuda J, Kawano H, and Kasai M. (2009) "Transcriptional repressor RP58 is crucial for cell-division patterning and neuronal survival in the developing cortex." ***Dev. Biol.*** 331: 140-151.

Neural Development



Shinobu Hirai

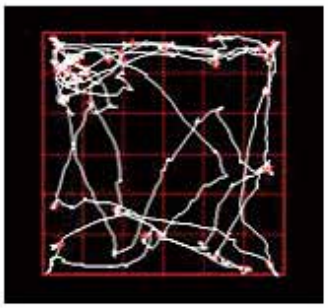


Tomoko Tanaka

Our major projects include

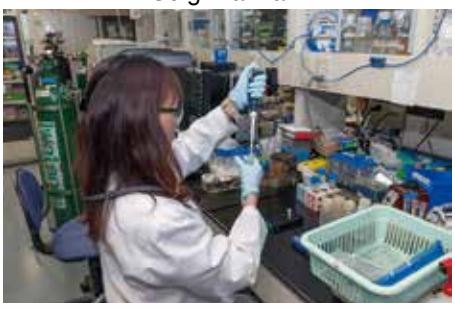
1) **Understanding how the transcriptional repressor, RP58, regulates brain development and maintenance.**
2) **Altering the nutritional environmental factors to manipulate brain development and functions.**
3) **Understanding the roles of environmental factors in development and aging of brain functions.**

Yoshie Matsumoto

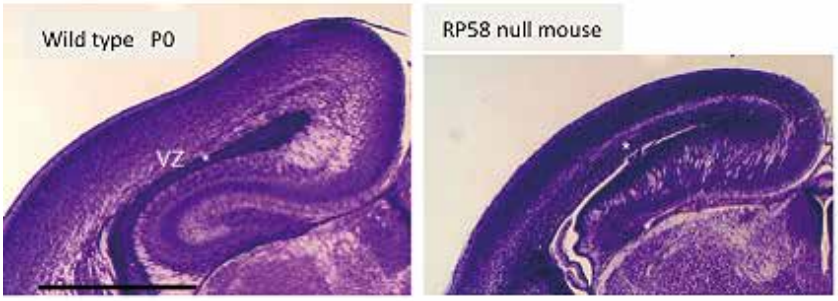


Locomotion, anxiety, memory, and sociality of mice are evaluated using a tracking system. Neuronal activity can be analyzed using an *in vivo* system.

Seigi Kanzaki



Tomoko Fukuoka



RP58 is required for development of the cerebral cortex. The cell-cycle exit of progenitor cells, neuronal radial migration and maturation of cortical neurons are impaired in RP58-deficient mice.

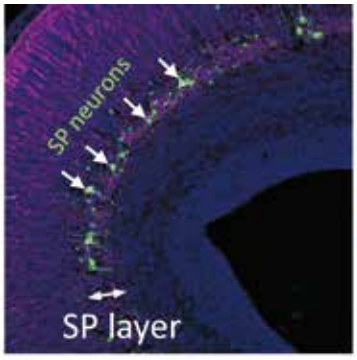
Neural Development

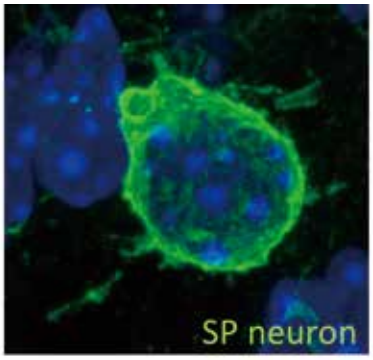
Senior Research Scientist **Chiaki Ohtaka-Maruyama**

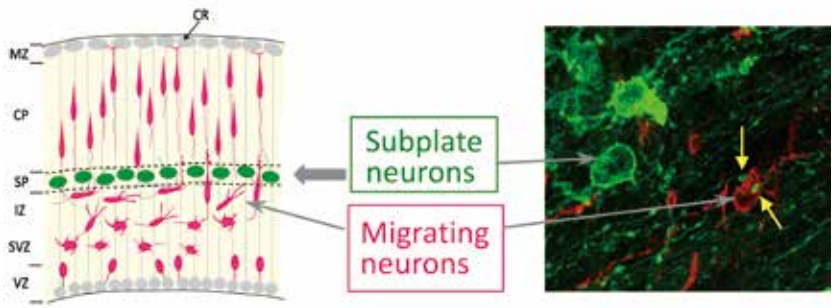
Mechanisms of Neural Network Formation: Neocortical development and synapse formation

How does the mammalian neocortex acquire the unique six-layered structure that is considered to be the structural basis for the remarkable evolution of complex neural circuits? To approach this question, we are focusing on subplate (SP) neurons which develop and mature extremely early during cortical development but disappear postnatally. Recently, we found that SP neurons play an important role in radial neuronal migration via direct interaction with young migrating neurons. Moreover, the SP layer is surrounded by a rich extracellular matrix (ECM), suggesting that it may be an important signaling center for mammalian corticogenesis. Functional elucidation of SP layer should lead to the better understanding of brain development during evolution.

"We are interested in the roles of the subplate later in the development of the cerebral cortex. It is suggested that this transient cell population plays a crucial role as a metaphorical "control tower" during neocortical formation."







Ohtaka-Maruyama C, Okamoto M, Endo K, Oshima M, Kaneko N, Yura K, Okado H, Miyata T, Maeda N ., Synaptic transmission from subplate neurons controls radial migration of neocortical neurons. ***Science 360***,313-317 (2018)

Nomura T, Ohtaka-Maruyama C, Yamashita Y, Wakamatsu Y, Murakami Y, Calegari F, Suzuki K, Gotoh H, Ono K. Evolution of basal progenitors in the developing non-mammalian brains. ***Development 143***: 66-74. (2016)

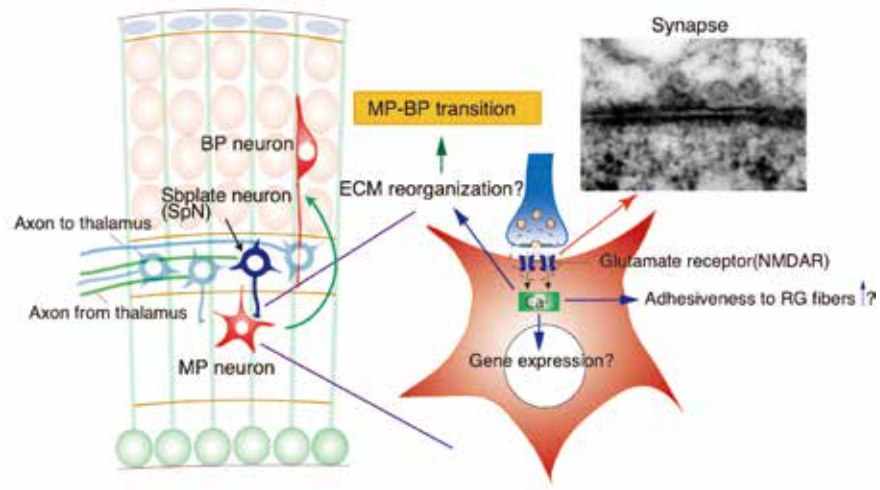
Ohtaka-Maruyama C and Okado H. Molecular pathways underlying projection neuron production and migration during cerebral cortical development. ***Front Neurosci.*** 9:447. (2015)

Ohtaka-Maruyama C, Hirai S, Miwa A, Heng JI, Shitara H, Ishii R, Taya C, Kawano H, Kasai M, Nakajima K, Okado H., RP58 regulates the multipolar-bipolar transition of newborn neurons in the developing cerebral cortex. ***Cell Reports.,*** 3, 458-471(2013)

Kamimura, K., Ueno, K., Nakagawa, J., Hamada, R., Saitoe, M. and Maeda, N. (2013) "Perlecan regulates bidirectional Wnt signaling at the Drosophila neuromuscular junction." ***J Cell Biol*** 200, 219-233.

Kamimura, K., Maeda, N. and Nakato H. (2011) "In vivo manipulation of heparan sulfate structure and its effect on Drosophila development." ***Glycobiology*** 21, 607-618.

Neural Network

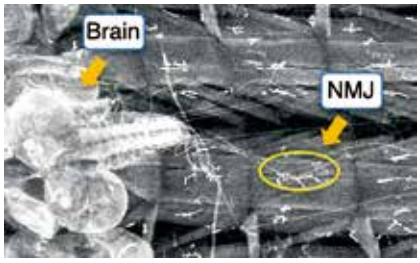


Newly born neurons initially exhibit slow multipolar migration.
Later, the migration mode switches to faster locomotion.

Our study revealed that subplate neurons send signals via synapses to multipolar migrating neurons, leading to conversion of their migration mode to faster locomotion.

Functions of proteoglycans in synapse formation

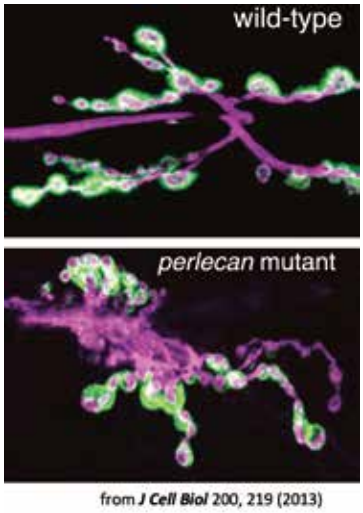
The SP layer has a rich extracellular matrix (ECM). To explore the functions of the extracellular matrix in developing neural networks, we use the Drosophila neuromuscular junction (NMJ) as a model system. The Drosophila NMJ is a readily accessible system of excitatory synapses, which resembles the glutamatergic synapses of vertebrate central nervous systems.



Brain and NMJ
of *Drosophila larva*

Perlecan is a secreted heparan sulfate proteoglycan, and its gene deletion leads to diverse defects at the Drosophila NMJ.

We demonstrated that Perlecan bidirectionally regulates pre- and post-synaptic Wnt signaling by precisely distributing Wnt at the NMJ.



from ***J Cell Biol*** 200, 219 (2013)

Members

Keisuke Kamimura
Kumiko Hirai
Aiko Odajima
Noe Kaneko
Ai Fujii
Kaori Miura

Neural Network