Project Leader **Nobuaki Maeda** Neural Network Project

Mechanisms of Neural Network Formation: Neuronal migration and synapse formation

In the developing nervous system, diverse types of neurons are generated from neural progenitors, and migrate to specific destinations. Then, neurons extend axons toward specific target cells and form synapses on them. These developmental processes require complex cell-cell and cell-extracellular matrix interactions. The extracellular matrix is an intricate network of molecules composed of proteoglycans, hyaluronan, and fibrous glycoproteins, which fill up the extracellular space. In the meshwork of extracellular matrix, various signal molecules such as growth factors and chemokines are stored.

"We are interested in the roles of the extracellular matrix in neuronal network formation. In the developing nervous system, the extracellular matrix plays a dynamic role in regulating the behaviors of diverse types of neurons."

To explore the functions of extracellular matrix in the developing neural networks, we adopted two animal models: mouse cerebrum and *Drosophila* neuromuscular junction (NMJ). Using in *utero* eletroporation and live cell imaging techniques, we are investigating the migration of excitatory neurons in the mouse neocortex. *Drosophila* NMJ is a readily accessible model of excitatory synapses, which resemble the glutamatergic synapses of vertebrate central nervous system. By using the sophisticated genetic tools of *Drosophila*, it is possible to unravel the complicated roles of extracellular matrix in the synapse formation.

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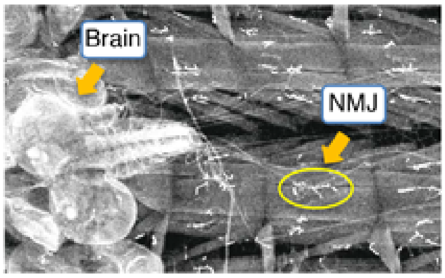
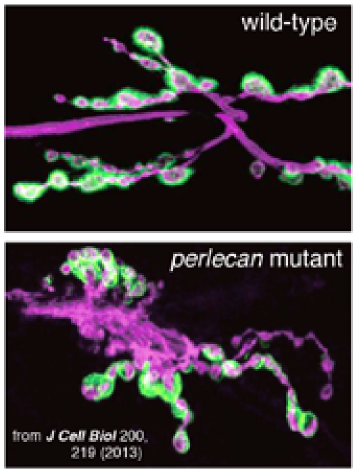
Neural Network

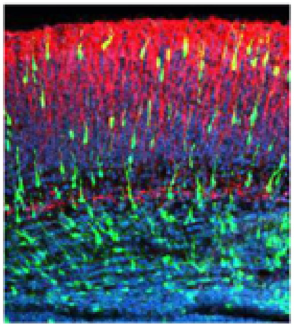


Brain and NMJ
of *Drosophila larva*

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

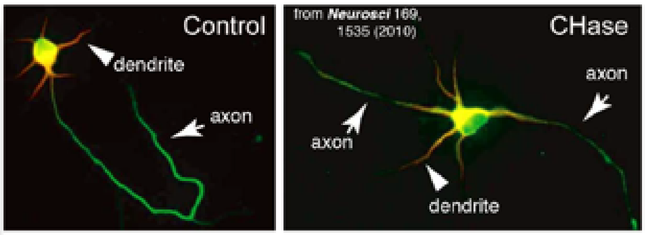
We demonstrated that Perlecan bidirectionally regulates pre- and post-synaptic Wnt signaling by precisely distributing Wnt at NMJ.





Migrating neurons in
the mouse neocortex

In the developing cerebral cortex, newborn neurons first extend several short processes, one of which differentiates into an axon during their migration to the pial surface (neuronal polarization).

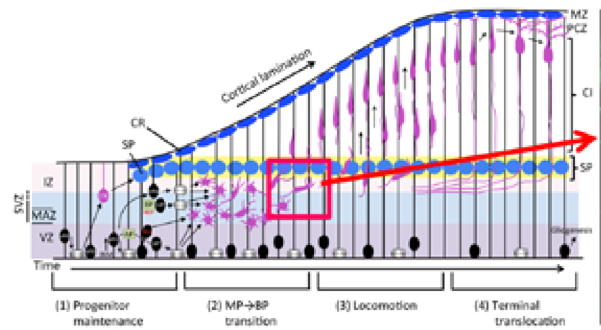


We revealed that chondroitin sulfate proteoglycans
play critical roles in neuronal polarization.

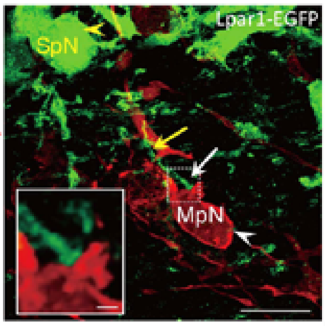
Senior Research Scientist Chiaki Ohtaka-Maruyama

Subplate layer in development and evolution of neocortex

How does mammalian neocortex acquire a unique six-layered structure that is a structural basis for the complex neural circuits, the remarkable product of evolution? To approach this question, we are focusing on the subplate (SP) neurons in the developing neocortex: one of the first born and matured cortical neurons that disappear postnatally. Recently, we found that SP neurons play critical roles in radial neuronal migration by forming transient glutamatergic synapses on migrating young neurons. Moreover, SP layer is rich in extracellular matrix, which may play important regulatory roles in the neuronal polarization. Functional elucidation of SP layer should lead to the better understanding of brain development and evolution.



from *Front Neurosci.* 9, 447(2015)



from *Science* 360, 313 (2018)

Differentiation and radial migration of neocortical neurons

Subplate neurons (SpN) extend axons (yellow arrow), and form transient synapses (white arrow) on multipolar migrating neurons (MpN).

The synaptic transmission induces multipolar-to-bipolar transition of MpNs.

Neural Network