Laboratory of Neuronal Cell Biology

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Our laboratory was started in March 2009. Our main interest is to understand the mechanisms and roles of mRNA transport and local translation in neuronal dendrites using mice.

The transport of specific mRNAs and local control of translation represent an important gene expression system that provides localized protein synthesis in dendrites at just the right time and place. It is believed that this system controls the location at which neurites will connect to each other, thereby forming neural networks. Our laboratory is researching factors regulating mRNA transport and local translation, their target mRNAs, and the mechanisms of localized protein synthesis in order to better understand its relation to the formation of synapses and neural networks, memory, learning, and behavior.

I. Identification and characterization of components of local translational machinery

Specific mRNAs are recruited into "RNA granules" in neuronal dendrites. RNA granules are macromolecular complexes composed mainly of mRNAs and ribosomes, and mediate the transport and local translation of their mRNA cargoes in response to synaptic stimulation (Figure 1).

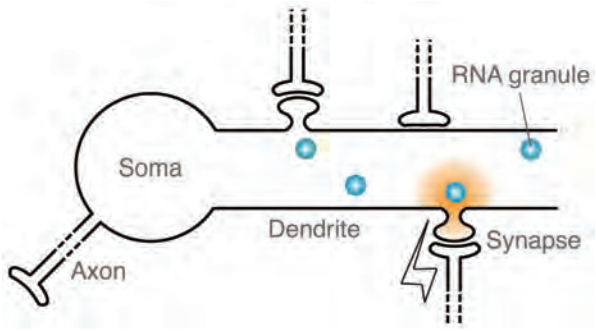

Figure 1. A model for local translation in neuronal dendrites. Specific mRNAs are recruited into RNA granules and transported to dendrites. Translation of the mRNAs is induced locally upon synaptic stimulation, which modifies local postsynapses to regulate synaptic connection and network formation.

We have identified RNG105, an RNA-binding protein, as a component of RNA granules. RNG105 dissociates from RNA granules after synaptic stimulation, which is accompanied by the induction of mRNA translation near the granules, suggesting its involvement in local translation. Furthermore, we have generated RNG105 knockout mice and shown that RNG105 deficiency affects the formation and maintenance of synapses and neuronal networks (Figure 2). We are further studying the molecular mechanism underlying the RNG105 knockout phenotype by identifying and characterizing RNG105-associated mRNAs and proteins.

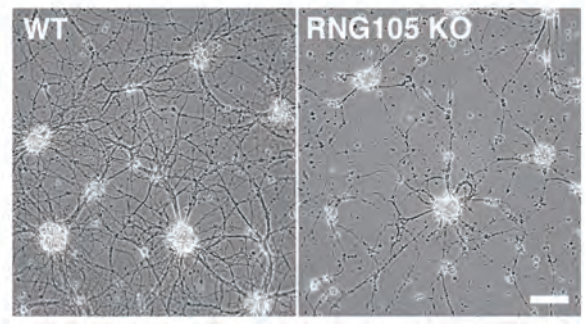

Figure 2. Phase contrast images of primary cultured neurons from wild-type (WT) and RNG105 knockout (KO) fetal brains. RNG105 knockout neurons formed poor networks compared to wild-type neurons. Scale bar, 100 μm.

We have also identified an RNG105 paralog, RNG140. RNG105 and RNG140 were localized to distinct RNA granules and showed different expression pattern and subcellular localization. Particularly, RNG105 was highly expressed in the brain of embryos, whereas RNG140 was highly expressed in the brain of adults. These results suggest that different kinds of RNA granules function in distinct neuronal cell types at distinct developmental stages.

II. Mechanisms regulating local translation in dendrites

RNA granules are densely packed structures and translationally dormant during transport, but they become less compact during conversion into translating polysomes after synaptic stimulation. We will study the mechanisms regulating the stimulation-dependent local translation by analyzing translational regulation of RNG105-associated mRNAs in neuronal dendrites.

III. Roles of local translation in higher order brain functions

RNG105 knockout neonates were born normally but died soon after birth because of respiratory failure, suggesting defects in the brainstem functions of RNG105 knockout mice. Because of the neonatal lethality, analyses of RNG105 roles have been limited to embryonic brains and neurons. In order to examine the roles of RNG105 in memory, learning, and behavior in adult mice, we are generating conditional RNG105 knockout mice. We will further generate knockout mice for RNG140 and RNG105- and RNG140-associated mRNAs and proteins to analyze their roles in higher order brain functions.