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Molecular Mechanisms Underlying Neuronal Differentiation and Synaptic Plasticity

Keywords: gene regulation, RNA, alternative splicing, neuron, synapse, autism

Background and Motivation

Brain is highly organized hard-wired system composed of >100 billion of neurons diversified morphologically and functionally. It is still very questionable and mysterious how diversity of neuronal cell types and the resulting complexity of the neural circuit are organized by a quite limited number of genes (<30000 genes in human). To the end we have studied the RNA-based regulations by which neural differentiation and plasticity are organized temporally and spatially. Recently we are specially focusing on alternative splicing – a powerful tool for generating several gene products from a single gene. Molecular diversity has been suggested to contribute to the complexity and diversity of organisms. Our research goal is to uncover mechanisms of alternative splicing in neurons and then to explore the physiological relevance of huge molecular diversity by alternative splicing in central nervous system.

Originality

Whereas many scientists have well studied how cells are diversified from a single fertilized egg precisely and how specific cell types are induced efficiently on stem cell biology with ES or iPS cells, it is still not well understood how differentiated cells are recognized each other to organize the specific network and well synergized as a organic system. We are now focusing on alternative splicing as a critical mechanism underlying diversity and specificity of cell-to-cell recognition. Brain, a hard-wired system composed of huge number of diversified neurons, is much more complicated than any other organs. Therefore, given that most of neuronal genes Is highly subjected to alternative splicing, we think that alternative splicing programs in central nervous system would be the most representative model for studying the physiological relevance of molecular diversity to diversity and specificity in vertebrate.

Impact and Perspective

Significant amount of pre-mRNAs are known to be highly subjected to alternative splicing in not only brain but also other tissues. It is speculated that alternative splicing could be also controlled in similar fashions by several kinds of external stimuli (temperature, chemical or physical stimuli, food intake, hypoxia, exercise etc.) in non-neuronal tissues. Therefore, the outcome from my project may propose a fundamental model for adaptation, acquired properties, complexity and diversity of mammalian cells by dynamic regulation of alternative splicing.

It has been revealed that de-regulation of alternative splicing in central nervous system causes several mental diseases (e.g. autism, schizophrenia, bipolar disease), suggesting that the molecular diversity derived from alternative splicing is implicated in our mental activity as emotion and cognition. Therefore, insight into neuronal circuit deficits in these mice may provide pathological insights into these human disorders and some hints for the clinical therapy.

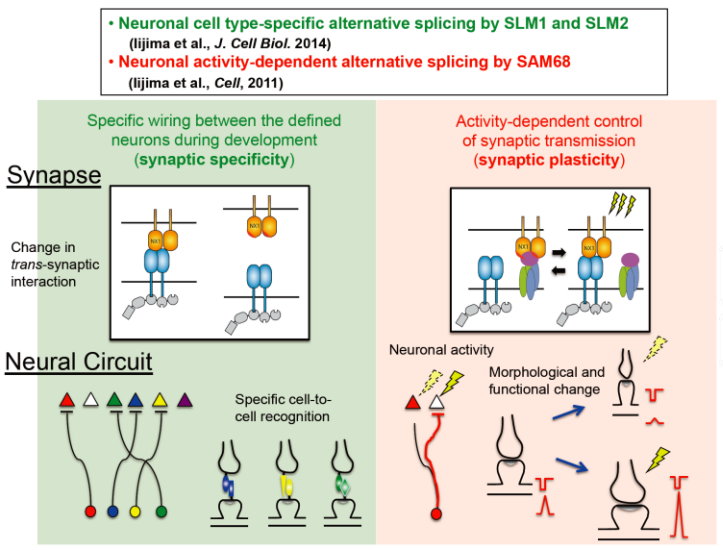

Fig.1 Model of dynamic regulation of synapse formation and functions by neuronal alternative splicing

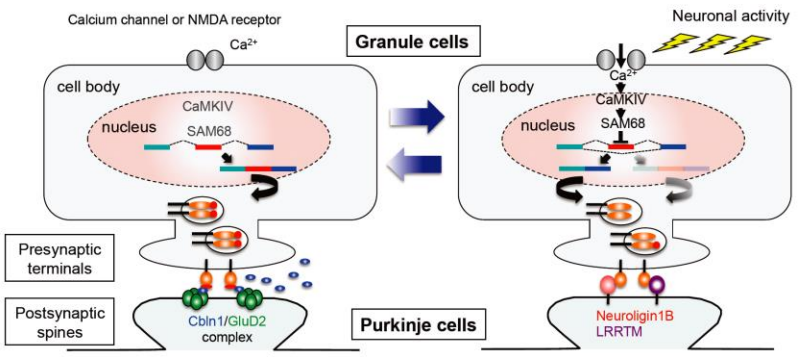

Fig.2 Activity-dependent alternative splicing decision of synapse organising molecules Neurexin-1 by RNA-binding protein SAM68 and dynamic change in *trans*-synaptic interaction of postsynaptic partner's proteins.

■ For more information:

www.u-tokai.ac.jp/tuiist/english/tt/announcement_iijima.html

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