Molecular Organization of Mammalian Inhibitory Synapses

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Appropriate brain function demands effective synaptic transmission of information between various brain regions. Correct synapse formation, synaptic signaling, and a balance of excitation and inhibition (E/I) are crucial in this regard. Undoubtedly, E/I imbalance may explain the development of several neurological disorders. Emerging information about inhibitory synapse organizers has provided a molecular framework for understanding E/I balance at the synapse, circuit and systems levels. In this talk, I will present two exemplary studies that aim to enhance our understanding on molecular organization of mammalian inhibitory synapses.

In the first part, I will introduce our recent studies that aim to identify new molecular mechanisms underlying synapse development. We discovered a novel synaptogenic adhesion molecule calsyntenin-3 that specifically induces presynaptic differentiation at inhibitory synapses. Furthermore, β-neurexins were affinity-purified through mass spectroscopy as complexed with calsyntenin-3, and functionally involved in calsyntenin-3-mediated presynaptic differentiation. I will also present a series of unpublished data to highlight a subset of conflicting issues.

In the second part, I will present data on a novel inhibitory synapse regulator named as IQ Motif and SEC7 Domain-containing Protein 3 (IQSEC3). IQSEC3 interacts with gephyrin, a key synapse scaffold molecule to organize various aspects of inhibitory synapse development. Our studies suggest that IQSEC3 is an important regulator of activity-dependent inhibitory synapse development in coordination with gephyrin and Npas4, suggesting that Npas4 directs broad transcription programs for circuit inhibition.