[S1-1] *[4/21/2000 (Fri) 09:10~09:50/Byulkwan Auditorium, Bldg 26]*

Molecular organization of glutamatergic synapses

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Glutamate (NMDA, AMPA/Kainate and metabotropic) play a major role in excitatory synaptic transmissions in brain. For proper synaptic transmission at glutamatergic synapses, glutamate receptors should be immobilized at synaptic membrane and coupled to down stream effector molecules as well as cytoskeletal proteins. Recently a set synaptic anchoring/scaffold proteins has been shown to interact with glutamate receptor subunits as well as other molecules including signaling proteins and cytoskeletal proteins. Examples of relatively well known anchoring/scaffold proteins for glutamate receptors include PSD-95, GKAP, S-SCAM, Shank, GRIP, PICK1 and Homer.

Specifically, the C-terminus of NMDA receptor subunits interacts with the PDZ domains of PSD-95 or S-SCAM through the well known tSXV-PDZ interaction. Similarly the C-terminus of AMPA receptor subunits interacts with the PDZ domains of GRIP or PICK1. The proline-rich C-terminus of metabotropic glutamate receptor subunits interacts with the EVH1 domain of Homer.

In addition to interacting with glutamate receptor tails, these anchoring/scaffold proteins interact with various signaling proteins, indicating that these scaffold proteins may bring relevant signaling molecules to the close proximity of glutamate receptors. For instance, PSD-95 interacts with a number of signaling molecules including neuroanl nitric oxide synthase, synGAP, spanGAP (Pak, Kim and Sheng, unpublished observation) and AKAP79 (Colledge and Scott, 29th Society for Neuroscience). GRIP interacts with liprin that is linked to receptor tyrosine phosphatases (Wyszynski, Kim and Sheng, unpublished observation). PICK1 interacts with PKC alpha. Homer interacts with IP3 receptor.

An emerging theme in the field of synaptic scaffold proteins is the presence of mother scaffold proteins that may link various primary scaffold proteins. For instance, GKAP interacts with both PSD-95 and S-SCAM. A novel synaptic protein Shank interacts with all glutamate receptor-interacting proteins including GKAP, GRIP and Homer, suggesting Shank

may bring all glutamate receptor complexes together for their intimate physical and functional coupling. In addition, Shank interacts with cortactin that is linked to actin, a cytoskeletal protein enriched at synaptic spine. The domain organization of Shank appears to be regulated by extensive alternative splicing observed in Shank isoforms.

More interestingly, recent evidence indicates that some anchoring/scaffold proteins are involved in the trafficking of glutamate receptor subunits. Accordingly, assembly and disassembly of these anchoring/scaffold proteins appear to be regulated by synaptic activity.

In conclusion, the identification and characterization of anchoring/scaffold proteins at glutamatergic synapses will eventually help us to understand the molecular mechanisms underlying the formation, maintenance, and more interestingly the activity-dependent changes of excitatory glutamatergic synapses.