Regulation of Dendritic Spine Morphogenesis by PSD-95

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Background:

Many brain functions rely on the precise assembly of neuronal synapses and activity-dependent molecular changes in their composition. Our understanding of the proteins involved in the organization of excitatory neuronal synapses has rapidly increased in recent years. Indeed, the molecular nature and function of the postsynaptic density (PSD), macromolecular protein complexes underneath the postsynaptic membrane, has been extensively explored (Kim and Sheng, 2004). However, little is known about how major PSD components including PSD-95 regulate the formation and plasticity of dendritic spines and glutamatergic synapses.

Molecular mechanisms of spine morphogenesis

The Shank/ProSAP family of multidomain proteins is known to play an important role in organizing synaptic multiprotein complexes (Sheng and Kim, 2000). We found that Shank interacts with beta-PIX, a guanine nucleotide exchange factor for the Rac1 and Cdc42 small GTPases, and various bPIX-associated signaling molecules including p21-associated kinase (PAK), an effector kinase of Rac1/Cdc42 (Park et al., 2003). Notably, Shank promotes synaptic accumulation of bPIX and PAK. Considering the involvement of Rac1 and PAK in spine dynamics, these results suggest that Shank recruits bPIX and PAK to spines for the regulation of postsynaptic structure.

The small GTPases Rac1 and Cdc42 are key regulators of the morphogenesis of actin-rich dendritic spines in neurons. However, little is known about how activated Rac1/Cdc42 regulates dendritic spines. Insulin receptor substrate 53 (IRSp53), which is highly expressed in the postsynaptic density (PSD), is known to link activated Rac1/Cdc42 to downstream effectors for actin regulation in non-neural cells. We discovered that PSD-95 interacts with and promotes synaptic localization of IRSp53 (Choi et al., 2005). Overexpression of IRSp53 increases the density of dendritic spines but does not affect their length or width. Conversely, short-interfering RNA-mediated knock-down of IRSp53 reduces the density, length, and width of spines. In addition, the

density and size of spines are decreased by a dominant-negative IRSp53 with a point mutation in the Src homology 3 (SH3) domain and a dominant-negative proline-rich region of WAVE2 (Wiskott-Aldrich syndrome protein family Verprolin-homologous protein), a downstream effector of IRSp53 that binds to the SH3 domain of IRSp53. These results suggest that PSD-95 interaction is an important determinant of synaptic IRSp53 localization and that the SH3 domain of IRSp53 links activated Rac1/Cdc42 to downstream effectors for the regulation of spine morphogenesis.

References:

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