MINISTRAP

# Message in the binding

File name: NRN_0306_DM1
Word count: 426
Accompanying picture: YES/no
File name of picture:

**URLs**

The translation of neurotransmission into appropriate postsynaptic signals is achieved through the clustering of neurotransmitter receptors and their associated signalling molecules in the postsynaptic density (PSD). This clustering is mediated by ligand-recruiting scaffold proteins such as PSD-95, but the mechanisms involved are unclear. Writing in the *Journal of Neuroscience*, Nonaka and colleagues report that it is the ligand-binding ability of PSD-95 that is important for its clustering and synaptic localization, as well as its association with the PSD.

The amino terminus of PSD-95 contains three tandem, ligand-binding PDZ domains, at least one of which is required for the clustering and synaptic targeting of PSD-95. What is the role of these tandem PDZ domains and their ligand interactions in the clustering and localization of PSD-95?

To address this question, Nonaka and co-workers constructed a series of full-length PSD-95 mutants lacking ligand-binding ability individually in each of PDZ1, PDZ2 and PDZ3, in both PDZ1 and PDZ2, or in all three. They showed that decreased ligand-binding affinity resulted in decreased clustering of PSD-95, and, furthermore, revealed an independent and approximately additive contribution of PDZ domains to this process. In addition, they found that ligand-binding deficiency caused the association of PSD-95 with the PSD to be destabilized, which suggests that ligand interactions have a role in anchoring PSD-95 to the PSD.

Surprisingly, the decreased ligand-binding affinity of mutant PSD-95 also resulted in aberrant spine morphology. Whereas mature PSD-95 clusters are normally localized in spines close to the dendritic shaft, a significant number of the surviving clusters formed by mutant PSD-95 were located away from this site, on the tips of elongated, seemingly immature spines. Moreover, there was an inverse correlation between the cluster–shaft distance and the amount of clustering. Combined with the finding that ligand-binding affinity contributes additively to clustering, this correlation implies that PDZ domains also make an additive contribution to spine maturation.

These findings suggest two separate functions for ligand-binding events at the PDZ domains of PSD-95: regulation of spine maturation, and recruitment of ligands into the PSD. The implication of multivalent PDZ binding ability is that the synaptic clustering of PSD-95, and its association with the PSD, can be dynamically modulated, potentially in response to local synaptic activity. Studies that disrupt the PDZ-binding ability of PSD-95 ligands should reveal the relative contribution of their interactions to synapse development and function.

*Daniel McGowan*

**ORIGINAL RESEARCH PAPER** Nonaka, M. *et al.* Essential contribution of the ligand-binding βB/βC loop of PDZ1 and PDZ2 in the regulation of postsynaptic clustering, scaffolding, and localization of post-synaptic density-95. *J. Neurosci.* **26**, 763–774 (2006)