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Mechanisms of Neuroligin Function in Inhibitory Postsynaptic Differentiation

The establishment of accurate synaptic transmission underlies neural network processing and nervous system function. The organized deployment of specialized synaptic machinery is a key cellular process that shapes the synapse and its transmission properties, yet the molecular mechanisms involved in assembling the synaptic apparatus are largely unknown. This work has focused on the role of Neuroligins, a family of postsynaptic adhesion molecules, in mediating differentiation of inhibitory, GABAergic and glycinergic, postsynapses.

Evidence is provided indicating that the central role of Neuroligin 2 in the assembly of the inhibitory postsynapse is mediated through a molecular interaction with the inhibitory scaffolding protein Gephyrin, and a specific activation of the signaling protein Collybistin. Neuroligin 2 is shown to be critical for proper inhibitory postsynaptic scaffold recruitment in neurons and, together with Gephyrin and Collybistin, sufficient to mediate the recruitment of GABAA receptors.

A novel Gephyrin-binding motif characteristic of the Neuroligin protein family was identified. As all Neuroligins were shown to have the capacity to bind Gephyrin, it is possible that several Neuroligin paralogues have auxiliary functions at the inhibitory postsynapse. In accordance with this notion, the stoichiometry and composition of Neuroligin oligomers was determined in neurons to be dimeric and both homo- and heteromeric. Additionally, cellular mechanisms were identified which regulate the assembly and trafficking of Neuroligin oligomers, and evidence was provided indicating their potential involvement in Autism pathology.