Postsynaptic mechanisms during synaptic plasticity at the Drosophila neuromuscular junction

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Abstract

The ability of established synaptic connections to strengthen and weaken (synapse plasticity) underlies higher order behavior such as learning and memory. Several gaps remain in our understanding of the cellular and molecular changes in pre- and postsynaptic cells associated with synapse plasticity. Using the *Drosophila* larval neuromuscular junction as a convenient model system throughout my dissertation work, I have concentrated on understanding various molecular mechanisms that underlie this phenomenon. ^ Specifically, I have addressed fundamental issues governing the postsynaptic cell in these processes, such as: (i) what are the crucial proteins required to scaffold the postsynaptic apparatus during plasticity? (ii) what are the molecules that are brought together at this scaffold and how are their levels regulated during plasticity? and finally (iii) what are the signals that initiate the formation of these scaffolds during plasticity? More specifically, I have uncovered a mechanism by which a novel synaptic protein, Guk-holder (Gukh), coordinates the formation of a tripartite complex at the synapse with two proteins containing multiple protein-protein interaction domains: Discs Large (DLG) and Scribble (Scrib) (Mathew et al., 2002). By bringing DLG and Scrib together at the synapse, Gukh likely coordinates the function of these two complexes. ^ As stated above Fasciclin II (FasII) is one of several molecules that is localized to the synapse by Dig (Thomas et al., 1997a), and its levels and symmetric distribution at the synapse have been found to be important for regulating synapse plasticity (Ashley et al., 2005; Schuster et al., 1996b). I showed that FasII also undergoes fast recycling at the synaptic membrane and that this recycling is regulated by the *Drosophila* homolog of Amphiphysin (Amph)-(Mathew et al., 2003). Such a mechanism would be compatible with a potential activity dependent regulation of FasII levels during plasticity. ^ To understand the initial signaling mechanisms by which synaptic scaffolds are organized during synapse formation, I further investigated the role of the Wingless receptor Dfrizzled2 (DFz2) in this process. Wg signaling has been previously implicated in synapse development and proper localization of postsynaptic proteins (Packard et al., 2002). In these studies I uncovered an unconventional mechanism involved in transducing the Wg signal in the muscle cell. I show that DFz2 is cleaved at the synaptic plasma membrane, and the c-terminus of the molecule traffics to the nucleus. This nuclear import of DFz2 is dependent upon Wg signaling and is important to transduce the downstream effects of Wg signaling at synapses (Mathew et al., 2005 in press). (Abstract shortened by UMI.) ^

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Molecular biology|Neurosciences|Cellular biology

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