Protein Processing and Plasticity

The Cold Spring Harbor Laboratory Learning & Memory meeting (April 9–13, 2003), organized by Jack Byrne, Joseph LeDoux, and Erin Schuman, spotlighted the molecular mechanisms underlying plasticity, with a majority of the sessions focusing on molecular level analysis of learning and memory systems. Representatives from leading laboratories around the world presented insightful data in all of the sessions, covering material that included local synaptic control, genetics and behavior, proteomics and protein regulation, consolidation/reconsolidation, extinction and the hippocampus, and other cortical systems. This report will focus on specific themes that emerged from several of the molecular sessions.

Protein Translation at the Dendrite

A particular emphasis was on molecules that control translation initiation, such as the mammalian target of rapamycin (mTOR), a protein kinase that regulates cap-dependent translation as well as the translation of a specific class of mRNAs containing oligopyrimidine tracts in their 5′UTRs (5′TOP mRNAs), and eIF2, which mediates the binding of the initiator Met-tRNA to the ribosome, thereby regulating most mRNA translation.

A presentation from the labs of Emmanuel Landau and Robert Blitzer, at Mt. Sinai School of Medicine, investigated regulation of mTOR in the hippocampus by high-frequency stimulation (HFS) sufficient to induce protein synthesis-dependent LTP. They showed that HFS induced phosphorylation of the mTOR protein and its substrate protein 6K, and that HFS increased the expression of the 5′TOP-encoded protein eEF1A. Confocal microscopy revealed increased protein phosphorylation and expression throughout the dendrites of the stratum radiatum. Importantly, these increases were blocked by the NMDA receptor-blocking agent D-APV, and were not induced by stimulation that induced decremental LTP. These data suggest that HFS-dependent LTP induces rapid phosphorylation of proteins that are key components of the mTOR pathway, and that this regulation provides a mechanism for rapid activation of translation at the dendrite.

Individuals from the lab of Eric Klann (Baylor College of Medicine) presented work on the regulation of both mTOR and eIF2, focusing on the regulation of these molecules during protein synthesis-dependent LTD that is induced by activation of group 1 metabotropic glutamate receptors (mGluRs) by the mGluR agonist DHPG. LTD, induced by applying DHPG to hippocampal slices, induced phosphorylation of eIF2α, which would decrease the availability of the initiator Met-tRNA to bind to the ribosome, and subsequently, decrease the translation of most mRNAs. In addition, DHPG application activated the mTOR pathway, resulting in an increase in the phosphorylation of ribosomal protein S6 and the translation of at least two 5′TOP mRNAs, elongation factor 2, and S6 itself. These data indicate that mGluR-dependent LTD induces bidirectional regulation of protein translation by inhibiting overall mRNA translation via the phosphorylation of eIF2α, while at the same time, stimulating the mTOR pathway and the subsequent translation of 5′TOP mRNAs.

Protein Degradation and Trafficking at the Dendrite

Taken together, the above reports provided insight into the mechanisms that may regulate protein synthesis-dependent plasticity in the hippocampus. However, the picture is not complete without considering regulated protein degradation at the dendrite, as well as protein translation.

Presentations from the labs of Kelsey Martin (UCLA) and Erin Schuman (CalTech), addressed this issue by concentrating on regulation of the ubiquitin/proteasome pathway. This pathway targets proteins for degradation by first tagging the protein by the covalent attachment of a ubiquitin molecule. The tagged protein is subsequently degraded by the proteolytic action of the proteasome, a large multimeric protease complex. A presentation by Kelsey Martin reported that application of membrane permeant inhibitors of the proteasome to isolated Aplysia sensory-motor cocultured neurons resulted in a long-lasting increase in synaptic strength and enhanced 5-HT-induced synaptic facilitation. In addition, data suggested that both pre- and postsynaptic substrates of the proteasome could regulate this phenomenon, as application of the inhibitor to isolated sensory neurons increased neurite outgrowth, and application to the isolated motor neuron increased the glutamate-evoked PSP. A presentation from Erin Schuman’s lab reported that, in cultured hippocampal neurons, ubiquitin was present in the soma, dendrites, and occasionally spines. In addition, application of a proteasome inhibitor inhibited GluR1/2 receptor internalization that is normally induced by application of AMPA or NMDA. Ongoing research in this laboratory is aimed at elucidating the degraded proteins involved in GluR trafficking.

Summary

Local regulation of protein translation and trafficking and its role in mediating long-term forms of potentiation and depression was the clear hot topic at this year’s Cold Spring Harbor Laboratory Learning & Memory meeting. Researchers are attacking this issue from both sides of the problem (protein translation and degradation) using several different model systems. This combination of efforts is beginning to reveal the intriguing interplay between initial second-messenger cascades engaged by activity and the regulation of translation and protein degradation. Although great progress has been made, the field needs to understand better the relationship between transcriptional and translational control, and the ways in which the newly synthesized proteins act coordinately to induce a persistent change in strength of the synapse. We eagerly await the next Learning & Memory meeting at Cold Spring Harbor to hear the next chapter.

Susan Cushman, Ph.D.
Assistant Editor
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Susan Cushman

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