*Nature Reviews Neuroscience* | AOP, published online 30 May 2012; doi:10.1038/nrn3272

Stockbyte

SYNAPTIC PLASTICITY

# ARC plays inverse tag at synapses

Activity-regulated transcription of the immediate early gene *Arc* is followed by targeting of ARC protein to the synapse, where (in addition to other effects) it is thought to weaken synaptic strength by promoting the endocytosis of AMPA receptors (AMPARs). However, the mechanisms by which ARC targets particular synapses are unknown. Okuno *et al.* now show that ARC localizes to synapses that exhibit reduced activity by interacting with an inactive form of $Ca^{2+}$/calmodulin-dependent protein kinase IIβ (CaMKIIβ).

The authors first examined how the synaptic localization of ARC is regulated by neuronal activity in cultured hippocampal neurons. They found that when previously active neurons were 'silenced' by the application of tetrodotoxin (TTX), newly synthesized ARC was enriched in the postsynaptic regions of the neurons. Suppressing the activity of individual synapses, by inducing the expression of tetanus toxin light chain in the presynaptic neuron, resulted in the postsynaptic accumulation of ARC in the 'silenced' synapses. This correlated with a reduction in the surface expression of the AMPAR subunit GluA1 at silenced synapses, suggesting that accumulation of ARC might contribute to resetting previously potentiated synapses. Furthermore, high-frequency electrical field stimulation, which induces expansion of active (or potentiated) dendritic spines, resulted in high levels of ARC in spines that did not exhibit expansion (that is, inactive spines).

To determine the *in vivo* relevance of their observations, the authors examined ARC accumulation in the visual cortex of mice in which neuronal activity was first activated by light exposure and then suppressed in one hemisphere by injection of TTX into one eye. As in their culture experiments, they found that ARC accumulated postsynaptically at higher levels in the inactive cortical regions.

These findings indicate that ARC is specifically targeted to inactive synapses. To determine the mechanisms involved, the authors looked for proteins whose binding to ARC might be regulated by activity. CaMKIIβ exists in an active, $Ca^{2+}$/calmodulin-bound form and an inactive, unbound form. The authors found that ARC binds preferentially to the inactive form of CaMKIIβ. Moreover, knockdown of CaMKIIβ using a small hairpin RNA suppressed the accumulation of ARC in inactive spines in cultured neurons, and CAMKIIβ-null mice showed no specific accumulation of ARC in the silenced hemisphere of the visual cortex.

This study provides a mechanism by which the contrast between strong and weak synapses can be maintained over time by activity (or inactivity). Proteins that 'tag' active synapses have been suggested to play a part in directing proteins involved in synaptic potentiation to those synapses. The authors thus suggest that CaMKIIβ acts as part of an 'inverse synaptic tag', marking inactive synapses for synaptic weakening.

*Katherine Whalley*

“Suppressing the activity of individual synapses … resulted in the postsynaptic accumulation of ARC in the 'silenced' synapses”

**ORIGINAL RESEARCH PAPER** Okuno, H. *et al.* Inverse synaptic tagging of inactive synapses via dynamic interaction of Arc/Arg3.1 with CaMKIIβ. *Cell* **149**, 886–898 (2012)



© 2012 Macmillan Publishers Limited. All rights reserved