LEARNING AND MEMORY

RICTOR in acti(o)n

Little is known about the molecular mechanisms that mediate the consolidation of short-term memory into long-term memory. Costa-Mattioli and colleagues now show a crucial role for mammalian target of rapamycin complex 2 (mTORC2) in this process, specifically through its control of actin polymerization.

mTORC2 is a multiprotein complex of which one defining component is RICTOR, a protein involved in actin cytoskeleton regulation. As actin polymerization is required for memory consolidation, the authors assessed the potential contribution of mTORC2 to long-term memory formation.

They first showed that various triggers of synaptic plasticity — including glutamate and NMDA — induced mTORC2 activity, as measured by phosphorylation of AKT at Ser473, in CA1 in mouse hippocampal slices. mTORC2 was also activated by repeated tetanic stimulation, which is known to induce long-lasting, late-phase long-term potentiation (L-LTP), but not by a single train of tetanic stimulation, which induces only short-lasting, early-phase LTP (E-LTP). Repeated tetanic stimulation did not induce L-LTP in mice in which *Rictor* was conditionally deleted in the forebrain (*Rictor* fb-knockout (KO) mice). As a single train of tetanic stimulation induced E-LTP similarly in wild-type and *Rictor* fb-KO mice, these findings indicate that mTORC2 is required for the transition from E-LTP to L-LTP.

Accordingly, behavioural experiments showed a role for mTORC2 in long-term memory. In a contextual fear-conditioning task — which assesses hippocampus-dependent fear-learning — *Rictor* fb-KO mice had similar short-term memory (measured 2 h after training) as wild-type mice, but their long-term memory (measured 24 h after training) was impaired. They also performed worse than wild-type mice in the Morris water maze, which measures hippocampus-dependent spatial long-term memory.

TORC2 is a highly conserved protein complex, and is also present in *Drosophila*. The authors showed that *rictor* mutant flies had impaired long-term olfactory memory compared with wild-type flies, whereas there was no difference in a short-lasting form of memory.

What is the mechanism through which mTORC2 promotes long-term memory formation? Compared with wild-type mice, *Rictor* fb-KO mice had both a lower F-actin/G-actin ratio (indicating reduced actin polymerization) and reduced activity of RAC1 GTPase — a regulator of actin dynamics — in CA1. To test whether altered actin dynamics underlie the impaired L-LTP in *Rictor* fb-KO mice, the authors pharmacologically stimulated actin polymerization using a low dose of jasplakinolide. This rescued L-LTP induced by repeated tetanic stimulation in hippocampal *Rictor* fb-KO slices. Furthermore, a post-training intra-CA1 infusion of jasplakinolide promoted long-term contextual fear memory in *Rictor* fb-KO mice. Conversely, blocking actin polymerization prevented L-LTP in wild-type slices. Interestingly, jasplakinolide was able to promote L-LTP in wild-type slices after a single train of tetanic stimulation (which normally only induces E-LTP) and also enhanced contextual fear memory in wild-type mice. Together, these data indicate that reduced actin polymerization underlies the impaired L-LTP and long-term memory in *Rictor* fb-KO mice and that stimulating actin polymerization can enhance L-LTP and long-term memory under conditions that normally elicit only short-lasting changes in synaptic strength.

If mTORC2 stimulates actin polymerization, and actin polymerization promotes L-LTP and long-term memory, then directly boosting mTORC2 activity should also improve L-LTP and long-term memory. Indeed, increasing mTORC2 activity using the small molecule A-443654 increased actin polymerization and facilitated L-LTP in wild-type hippocampal slices, and an intraperitoneal injection of this molecule after training in a Pavlovian fear-conditioning task improved contextual long-term memory in wild-type mice but not in *Rictor* fb-KO mice.

> “stimulating actin polymerization can enhance L-LTP and long-term memory”

The currently known ‘molecular switches’ that promote the transition of short-term to long-term memories are all factors that regulate gene expression, which is in keeping with the idea that long-term memory requires new protein synthesis. The new study has identified mTORC2 as another molecular switch — one that regulates structural aspects of long-term memory formation.

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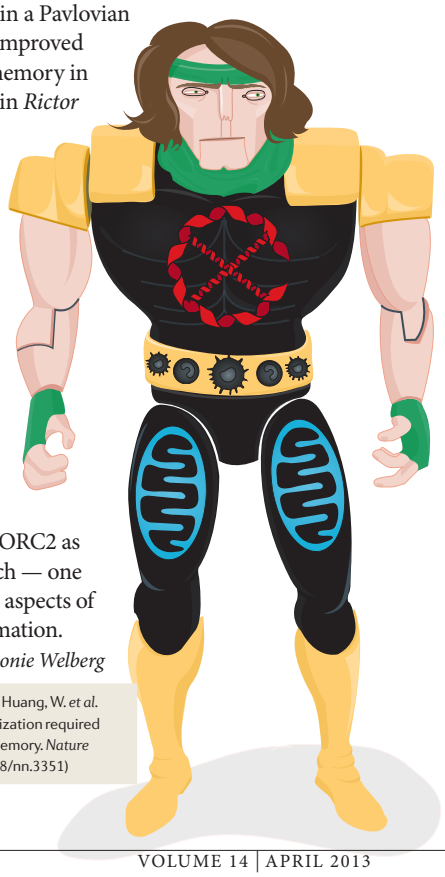

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