Study reveals reciprocal activity of brain proteins necessary for learning and memory

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A UCLA team reports that a protein called IDOL targets and prevents overproduction of the synaptic protein ApoER2, an adjustment that allows connections between neurons to change during the learning process for humans and animals. The researchers conclude that reciprocal IDOL/ApoER2 activity in the brain allows synapses to undergo formation and disassembly as learning occurs.

Humans (and mice) learn by trial and error, a process that neuroscientists can explain on a cellular level. As learning proceeds, contact points called "synapses" between neurons in a circuit strengthen during successful "trials," while non-productive circuits gradually weaken and fade away. The ability to reorganize pathways like this in the brain depends in part on cell shape. Stable synapses form when a neuron extends parts called "dendrites," which often have spines that serve as landing platforms for incoming nerve fibers. By contrast, synapses weaken as dendrites shrink or spines decrease in number or size. Strong synaptic connections also display a membrane protein called ApoER2; investigators reasoned that elimination of useless synapses might require removal of ApoER2. Working in animal models of Alzheimer's disease, this research group previously reported that IDOL triggered degradation of the LDL receptor, a protein that is highly similar to ApoER2.

The team confirmed that IDOL, whose normal job is to trigger destruction of unnecessary proteins, resides at synapses in normal mouse brains. The researchers then upset the normal balance between IDOL and ApoER2 in a number of experimental contexts, including cultured neurons, mouse brain tissue slices, and living mice. Overall, they found that an abundance of ApoER2 in neurons was inversely related to IDOL activity. Experimental boosting of IDOL protein levels triggered ApoER2 loss in cortical neurons, as predicted, and impaired the formation of spines on dendrites. By contrast, experimental IDOL depletion in neurons cultured from the hippocampus, a primary site of memory storage in the brain, provoked unusually high ApoER2 expression, shrank dendritic spines, and blocked increases in synapse strength typically seen after intense electrical stimulation, a phenomenon called LTP (or long-term potentiation). Finally, mice engineered to lack the IDOL protein performed poorly in behavioral tests of spatial memory and fear-based conditioning. This work shows that IDOL protects neurons from producing too much ApoER2 protein and "locking in" to a cellular size, shape and structure incompatible with learning.

The paper reveals the IDOL/ApoER2 pair as key players governing cellular changes necessary for learning and memory, a highly researched topic in biology. Concurrently, the lab, which has up to now focused on lipid metabolism, has studied a different role played by IDOL in regulating levels of LDL, or "bad," cholesterol. The convergence of two different fields on IDOL raises the possibility that abnormal lipid metabolism is linked to cognitive disorders, such as Alzheimer's disease, for which high cholesterol is a risk factor.

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More information: Jie Gao et al. The E3 ubiquitin ligase IDOL regulates synaptic ApoER2 levels and is important for plasticity and learning, *eLife* (2017). DOI: 10.7554/eLife.29178

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