SYNAPTIC PLASTICITY

Assertive authorities

Epigenetic and microRNA (miRNA)-dependent regulation of brain function are two processes that have received considerable attention in recent years. The NAD-dependent histone deacetylase sirtuin 1 (SIRT1) has previously been implicated in neurological disorders but its physiological role in normal brain function was unknown. Gao *et al.* now show that one mechanism by which SIRT1 modulates synaptic plasticity is through miRNA-dependent regulation of the transcription factor cyclic AMP-responsive element-binding (CREB) protein.

SIRT1 has been shown to have a number of functions that are linked to cell metabolism and cellular stress responses. To test the physiological role of SIRT1 in the CNS, the authors generated transgenic mice that lack SIRT1 deacetylase activity in the CNS (SIRT1Δ). These mice exhibited impaired memory performance in fear-conditioning paradigms, a novel object recognition task and a spatial memory task (the Morris water maze). As the hippocampus is important for these forms of memory, the authors performed electrophysiological studies on acute hippocampal slices from SIRT1Δ mice. Theta-burst stimulation of Schaffer collaterals induced long-term potentiation (LTP) in CA1 neurons of control mice but not of SIRT1Δ mice without affecting basal neurotransmission. These results indicate that lack of SIRT1 activity affects LTP induction in the hippocampus.

Next, the authors investigated the protein levels of brain-derived neurotrophic factor (BDNF) and CREB, two factors with established roles in LTP induction. They found that in the hippocampus of SIRT1Δ mice the protein levels of both factors were significantly reduced compared with those in wild-type mice. Furthermore, BDNF mRNA levels were decreased in the hippocampus of SIRT1Δ mice compared with controls but those of CREB were normal, pointing to a post-transcriptional mechanism for the downregulation of CREB protein levels.

miRNAs repress gene expression by inhibiting mRNA translation and have key roles in numerous aspects of brain function. Therefore, the authors investigated whether CREB protein levels were under the regulation of miRNAs. Microarray analysis showed that the expression levels of multiple miRNAs differed between control and SIRT1Δ mice. miR-134 was of particular interest, as it had previously been shown to be a brain-specific miRNA and to regulate dendritic spine formation *in vitro*. The authors identified miR-134 binding sites in the 3′ untranslated region of *CREB* (also known as *CREB1*) and showed, using *in vitro* assays, that this miRNA regulates CREB expression through a post-translational process.

Next, the authors showed that SIRT1 binds to regulatory DNA sequences upstream of the miR-134 locus and inhibits miR-134 expression upon binding. Furthermore, they showed that loss-of-function mutants of SIRT1 inhibited CREB activity *in vitro* and that this could be restored by adding miR-134-inhibiting oligonucleotides. This indicates that SIRT1 loss-of-function impairs CREB activity through a miR-134-mediated post-translational mechanism.

To examine the role of miR-134 in synaptic plasticity and memory formation, miR-134 was overexpressed in CA1 neurons. This was found to impair hippocampus-dependent memory formation in wild-type mice and LTP induction in hippocampal slice cultures. Therefore, miR-134 overexpression in CA1 neurons mimics the effects of SIRT1 loss-of-function. Conversely, miR-134 knockdown in CA1 neurons of SIRT1Δ mice rescued hippocampus-dependent memory formation, restored LTP in acute hippocampal slices and restored normal protein levels of CREB and BDNF in the hippocampus.

These results indicate that SIRT1 has a key role in synaptic plasticity and memory formation by regulating the protein levels of CREB through miR-134-mediated repression. This mechanism is distinct from the previously described signalling pathway of SIRT1 in neuroprotection. Therefore, the miR-134-dependent SIRT1 signalling pathway might be a therapeutic target for the treatment of cognitive impairments caused by alterations in synaptic plasticity and memory that accompany neurodegeneration, as well as other disorders, such as addiction.

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ORIGINAL RESEARCH PAPERS Gao, J. *et al.* A novel pathway regulates memory and plasticity via SIRT1 and miR-134. 11 Jul 2010 *Nature* (doi:10.1038/nature09271)