Cell Research (2009) 19:920-921.

www.nature.com/cr

RESEARCH HIGHLIGHT

Histone modifier, the gatekeeper of good memory

Zilong Qiu[1, 2]

[1]*Neurobiology Section, Division of Biology, University of California, San Diego, La Jolla, CA 92093, USA;* [2]*Institute of Neuroscience, Chinese Academy of Sciences, Shanghai 20031, China*
Cell Research (2009) **19**:920-921. doi: 10.1038/cr.2009.93; published online 3 August 2009

How do we learn and how do we remember? Learning and memory has long been one of the most fascinating questions in biology. In the 1970s, Squire LR *et al*. provided evidence that gene expression processes are critical for memory by showing that memory consolidation is disrupted when gene transcription or translation is blocked during the learning process [1]. In the following decades, much knowledge has been obtained about how transcription factors can turn on gene expression in response to neural activity and thus contribute to memory formation [2]. Thanks to the progress of molecular biology in the last decade, it appears more and more clear that gene expression should be investigated in the context of intact chromatin, which is formed by DNA and histones. Indeed, besides classic transcription factors, DNA modification and histone modification complexes are found to play crucial roles in regulating gene expression. Do these histone modification complexes also play roles in learning and memory?

Histone deacetylase complexes (HDACs) can remove negative charged acetyl groups from histones. Less acetylated histone will form tighter chromatin structure with DNA making it harder to be transcribed. Thus HDACs normally work as transcription repressors. The HDAC family contains about several classes of members and the detailed physiological functions of most of them are not well understood. During the last few years, pharmacological evidence has implicated the role of HDACs in learning, memory and synaptic plasticity [3]. In the May 7th issue of Nature, a research article by Guan *et al*. provides compelling genetic evidence and finally narrows down these effects to one molecule, histone deacetylase complex 2 (HDAC2) [4].

In a previous study, Fischer *et al*. showed that HDAC blockers could ameliorate neurodegenerative and cognitive phenotypes in an Alzheimer disease mouse model [5]. More importantly, they found that HDAC blockers enhance learning and memory tasks even in wild type mice. To find out the molecular targets of these effects, Guan *et al*. first use the specific HDAC inhibitor SAHA (suberoylanilide hydroxamic acid) to focus on two candidates, HDAC1 and HDAC2. The authors next used an elegant knock-in strategy to overexpress HDAC1 or HDAC2 specifically in neurons. The overexpression of HDAC2, but not HDAC1, showed impaired performance in fear conditioning, open field tests, and spatial learning tasks. This is an interesting discovery, and suggests that very close family members of HDACs perform different physiological functions.

To address the function of endogenous HDAC2, Guan *et al*. generated neuronal specific HDAC2 knockout mice by crossing HDAC2 floxed mice with a nestin-Cre line. Consistent with gain-of-function experiments, they found that fear conditioning is enhanced in HDAC2 knockout mice. It is of great importance to examine whether spatial learning, short and long term memory, or memory retrieval are also altered. Notably, they found that only a few specific lysine residues of histone protein C-terminal tail show increased acetylation. This suggested that HDAC2 may specifically act on a certain group of lysine residues of histone protein, which may play critical roles in regulating target gene expression.

What are molecular and cellular mechanisms underlying the negative effect of HDAC2 for memory formation? Authors used Golgi staining to show that the number of spines, representation of excitatory synapses, on hippocampal CA1 pyramidal neurons dramatically increased in HDAC2 knockout mice compared to wild type mice, whereas, HDAC2 overexpressing mice have fewer spines than wild type. They also showed that the presynaptic marker, synaptophysin, increases in HDAC2 knockout and decreases in HDAC2 overexpressing mice. These results suggest that HDAC2 may play a critical role in controlling excitatory synapse formation *in vivo*. However, more work is needed to confirm whether HDAC2 functions in a cell autonomous manner, whether spine numbers are altered using more physiological imaging methods and whether inhibitory synapses also

Correspondence: Zilong Qiu
E-mail: zqiu@ucsd.edu; zqiu@ion.ac.cn

are altered. In terms of synapse function, the authors measured LTP in hippocampal CA1 region. Consistent with behavior phenotypes, they found that LTP is compromised in HDAC2 overexpressing mice and facilitated in HDAC2 knockout mice. It is of interest to ask whether facilitated LTP observed in HDAC2 knockout mice is simply due to the fact that they have more excitatory synapses and whether the electrophysiological property of single synapse is altered after deleting HDAC2 genetically.

Since HDAC2 is a transcriptional repressor, it is logical to deduce that HDAC2 regulates a variety of learning and memory related genes expression. Indeed, the authors found that HDAC2 binds to several important activity-regulated genes, such as *BDNF*, *Egr1* and *Fos*, as well as synapse formation related genes and glutamate receptor genes. The fact that HDAC2 binds to *CREB* and *CBP* gene promoters leads the authors to suggest that HDAC2 may contribute to a well-established CREB-CBP pathway to regulate activity-dependent gene expression and learning and memory. Again, whether HDAC2 indeed plays a negative role in regulating CREB-CBP-dependent genes expression needs further gain- and loss-of-function data to support. After identifying these putative HDAC2 target genes, it will be important to examine the expression levels of these genes in HDAC2 overexpression and knockout mice, which will finally close the logical loop that genes controlled by HDAC2 contribute to learning and memory.

How does HDAC2 bind to chromatin? Mandel and colleagues found that HDAC1 and HDAC2 could bind to coREST, a corepressor of REST and form a corepressor complex to bind DNA [6]. In this study, Guan *et al*. confirmed this previous finding. They found that HDAC2 associates with coREST in neurons. Then they suggest that coREST contributes to the recruitment of HDAC2 onto gene promoters. How this corepressor complex regulates gene expression upon neural activity will be a very interesting question to be addressed in the future.

Finally, the authors showed that HDAC2 is indeed the target of HDAC inhibitor-SAHA, which could improve learning and memory in wild type mice. They showed that SAHA treatment almost photocopied HDAC2 knockout phenotypes, such as increased freezing rate and spine number. SAHA has no effect in HDAC2 knockout mice but rather stronger effect in HDAC2 overexpressing mice. This finding suggests that SAHA, which is already clinical available, could function as a potential memory enhancing drug.

The observation that HDAC2 plays such a specific role in controlling learning and memory greatly increases our understanding of molecular basis of memory. Although the detailed molecular mechanisms of HDAC2 regulating memory largely remain unclear, it is important to realize that the potential of memory is profound. It seems that HDAC2 is an interesting potential-keeping molecule. Under normal conditions, HDAC2 leaves memory quite some room and keeps our brains away from being saturated with input. When it is blocked either pharmacologically or genetically, the memory capability of brain vastly increases.

In the next stage of molecular basis of learning and memory, histone modifiers will no doubt take the center stage. Besides histone acetylase and deacetylase complexes, there are histone methyltransferase and demethylase complexes, which have only recently been cloned and characterized [7, 8]. How do these histone modifiers regulate neuronal gene expression? Are they responsive to neural activity? Are they critical for learning and memory? It is not hard to imagine that studies of this kind will soon become available and further deepen our understanding of how gene expression machinery contributes to the high cognitive function of the brain.

Referenes

1 Squire LR, Barondes SH. Actinomycin-D: effects on memory at different times after training. *Nature* 1970; **225**:649-650.
2 Silva AJ, Kogan JH, Frankland PW, Kida S. CREB and memory. *Annu Rev Neurosci* 1998; **21**:127-148.
3 Vecsey CG, Hawk JD, Lattal KM, *et al*. Histone deacetylase inhibitors enhance memory and synaptic plasticity via CREB:CBP-dependent transcriptional activation. *J Neurosci* 2007; **27**:6128-6140.
4 Guan JS, Haggarty SJ, Giacometti E, *et al*. HDAC2 negatively regulates memory formation and synaptic plasticity. *Nature* 2009; **459**:55-60.
5 Fischer A, Sananbenesi F, Wang X, Dobbin M, Tsai LH. Recovery of learning and memory is associated with chromatin remodelling. *Nature* 2007; **447**:178-182.
6 Ballas N, Battaglioli E, Atouf F, *et al*. Regulation of neuronal traits by a novel transcriptional complex. *Neuron* 2001; **31**:353-365.
7 Kubicek S, Jenuwein T. A crack in histone lysine methylation. *Cell* 2004; **119**:903-906.
8 Lan F, Nottke AC, Shi Y. Mechanisms involved in the regulation of histone lysine demethylases. *Curr Opin Cell Biol* 2008; **20**:316-325.