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Review

The role of epigenetic regulation in learning and memory

Ji-Song Guan *, Hong Xie, XinLu Ding

Tsinghua-Peking Center for Life Sciences, MOE Key Laboratory of Protein Sciences, Center for Epigenetics and Chromatin Biology, School of Life Sciences, Tsinghua University, Beijing 100084, China

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ABSTRACT

The formation of long-term memory involves a series of molecular and cellular changes, including gene transcription, protein synthesis and synaptic plasticity dynamics. Some of these changes arise during learning and are subsequently retained throughout life. 'Epigenetic' regulation, which involves DNA methylation and histone modifications, plays a critical role in retaining long-term changes in post-mitotic cells. Accumulating evidence suggests that the epigenetic machinery might regulate the formation and stabilization of long-term memory in two ways: a 'gating' role of the chromatin state to regulate activity-triggered gene expression; and a 'stabilizing' role of the chromatin state to maintain molecular and cellular changes induced by the memory-related event. The neuronal activation regulates the dynamics of the chromatin status under precise timing, with subsequent alterations in the gene expression profile. This review summarizes the existing literature, focusing on the involvement of epigenetic regulation in learning and memory. We propose that the identification of different epigenetic regulators and signaling pathways involved in memory-related epigenetic regulations will provide mechanistic insights into the formation of long-term memory.

Contents

Introduction

Learning and the formation of new memories require the structural and functional remodeling of synapses (Martin et al., 2000; Lamprecht and LeDoux, 2004) through tightly regulated cellular and molecular regulation machines. In response to a specific pattern of neuronal activity, synaptic strength undergoes long-lasting reduction or enhancement, known as long-term depression (LTD) and long-term potentiation (LTP), underlying the cellular mechanism of memory formation (Martin et al., 2000; Cooper, 2005; Bliss and Collingridge, 1993). At the molecular level, the neuronal activation triggers modification, trafficking and new protein synthesis of memory-related molecules through intracellular signaling cascades (Dash et al., 2007), gene transcription and protein synthesis (Davis and Squire, 1984; Barondes and Jarvik, 1964). However, it is still unclear how these changes in memory-related molecules are maintained in the long term in supporting various cellular events during memory formation, consolidation and retrieval.

What is the molecular mechanism involved in regulating memory formation and maintenance? In this review, we discuss the role of epigenetic modifications in regulating the cellular processes involved in neuronal memories. Epigenetic regulation has been widely recognized as a mechanism for making stable changes in the cellular status during development and for some heritable phenomena that require cellular memory (Ringrose and Paro, 2004; Levenson and Sweatt, 2005; Lipsky, 2013). Recent studies revealed the critical role of epigenetic

* Corresponding author at: Medical School Building D206, School of Life Sciences, Tsinghua University, Beijing 100084, China.
E-mail address: jsguan@mail.tsinghua.edu.cn (J.-S. Guan).

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regulation in synaptic plasticity and memory (Kaas et al., 2013; Liu et al., 2009; Lubin et al., 2008; Rudenko et al., 2013; Stefanko et al., 2009; Sui et al., 2012; Yu et al., 2011; Guan et al., 2009). The types of epigenetic modifiers and their metabolic dynamics are specifically regulated in particular brain regions (Baker-Andresen et al., 2013; Gupta-Agarwal et al., 2012; Levenson et al., 2004, 2006; Mori et al., 2013; Miller et al., 2008; Bousiges et al., 2013; Chwang et al., 2006). During learning, different epigenetic regulators work in concert to converge the upstream cascade signaling and manipulate downstream gene transcription with precise timing. We propose that epigenetic regulation has two functions in learning and memory formation: as a 'gating' mechanism that enables gene expression changes that are important for learning, and a 'stabilizing' mechanism, which enables the maintenance of gene expression changes that is important for memory consolidation. We hypothesize that such dual roles of epigenetic regulation allow cellular memory to form the basis of circuitry memory, where information regarding different properties is stored in discrete neuronal cells (Xie et al., 2014).

Epigenetic modifications in memory formation

Nucleosomes, the basic units used by eukaryotic chromatin to pack huge genomes into the cell nucleus, contain an octamer of histone proteins, which are two pairs of the core histones H2A, H2B, H3 and H4 surrounded by 147 bp of DNA. The protruding N-terminal tails of the histone proteins, which are known to interact with nucleosomal DNA, undergo post-translational modifications (Jiang et al., 2008). As summarized in Fig. 1, various epigenetic modifications change the status of chromatin, thereby affecting gene transcription. Histone acetylation usually enhances transcription, because the acetyl group on lysine releases compacted DNA to be accessible to the transcription machinery, facilitating transcriptional initiation and elongation (Shahbazian and Grunstein, 2007). The addition of the acetyl group is catalyzed by histone acetyltransferases (HATs). The removal of the acetyl group is mediated by histone deacetylases (HDACs). Histone phosphorylation, which is tightly associated with histone acetylation, affects transcription in a histone microenvironment-dependent manner (Chwang et al., 2006; Banerjee and Chakravarti, 2011). The histone tail is usually phosphorylated by nuclear kinase and dephosphorylated by protein phosphatase (Brami-Cherrier et al., 2009; Koshibu et al., 2009). Another important histone modification is histone methylation, which is related to either transcription activation or repression (Kouzarides, 2007). The histone methylation is catalyzed by the SET domain of histone methyltransferases (HMTs) and removed by histone demethylases (HDMs), such as LSD1 and JMJD2 (Fuke et al., 2004; Shin and Janknecht, 2007). In addition to post-translational modifications on histones, other epigenetic processes include DNA methylation, non-coding RNAs, prions and prion-like phenomena, chromosomal position effects and Polycomb mechanisms. DNA methylation preferentially occurs on cytosine nucleotides adjacent to guanine nucleotides by adding a methyl group to the five prime positions of the cytosine base via DNA methyltransferases (DNMTs) (Turker, 1999; Bird, 2002; Goll and Bestor, 2005), including DNMT3a and DNMT3b for de novo synthesis, and DNMT1 for maintenance. Although the mechanism of DNA demethylation is still unclear, the recent discovery of ten-eleven translocation (TET) family enzymes suggests the existence of a demethylation pathway through oxidizing 5-methylcytosine to 5-hydroxymethylcytosine, followed by thymine DNA glycosylase (TDG)-mediated base excision repair or passive excision by DNA repair (Kohli and Zhang, 2013). These epigenetic modifications are critical for transcriptional regulation, as well as long-lasting cellular status changes in development and heritable phenomena.

Compelling evidence from pharmacological and genetic studies has revealed that various epigenetic regulators may be involved in learning and memory (Table 1). One of the most well-demonstrated epigenetic modifications is histone acetylation. The administration of trichostatin A and sodium butyrate as global HDAC inhibitors (HDACi) enhanced long-term memory but not short-term memory, whereas genetic disruption of HATs impaired the formation of long-term memory

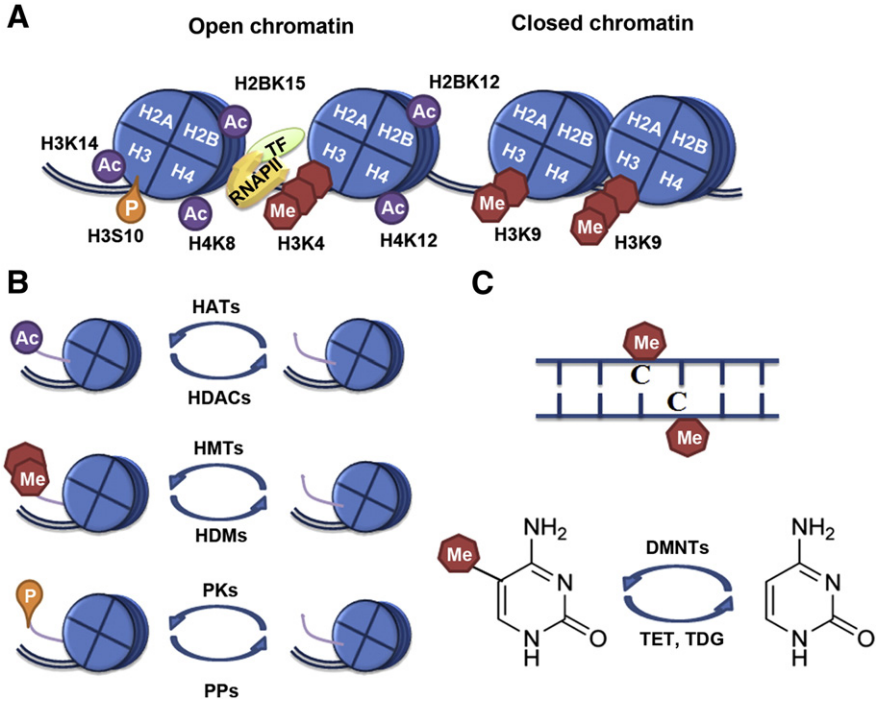

Fig. 1. Illustration of epigenetic modification involved in learning and memory. (A) 146 bp of DNA coiled around histone octamers forms chromatin, which can be turned in to open state or closed state by different combinations of histone modifications. In an open state, transcriptional machinery is accessible to the chromatin, while in a closed state, the machinery is prevented from binding to the gene region. (B) (C) Epigenetic modification enzymes catalyze the addition and removal of modification groups. HATs catalyze the addition of acetyl group and HDACs remove it. HMTs and HDMs are responsible for the addition and removal of methyl group, respectively. The histone tail is phosphorylated by PPs and dephosphorylated by PKs. Finally, the DNMTs add a methyl group to the cytosine base while the active DNA demethylation is conducted by TETs or through TDG-mediated base excision repair. CH3, methyl group; Ac, acetyl group; P, phosphoryl group; RNAPII, RNA polymerase II; TF, transcription factor.