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Review

Epigenetic regulation of *Fgf1* transcription by CRTC1 and memory enhancement

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ABSTRACT

Recent evidence demonstrates that epigenetic regulation of gene transcription is critically involved in learning and memory. Here, we discuss the role of histone acetylation and DNA methylation, which are two best understood epigenetic processes in memory processes. More specifically, we focus on learning-strength-dependent changes in chromatin on the *fibroblast growth factor 1* (*Fgf1*) gene and on the molecular events that modulate regulation of *Fgf1* transcription, required for memory enhancement, with the specific focus on CREB-regulated transcription coactivator 1 (CRTC1).

1. Introduction

Activity-dependent changes in gene transcription and de novo protein synthesis are required for memory processes (Alberini, 2009; Klann and Dever, 2004; Mayford et al., 2012). On the other hand, a deficiency in activity-dependent gene transcription is involved in cognitive decline prominent in many neuropsychiatric disorders, such as Alzheimer's disease and depression, as well as in memory loss during healthy ageing (Greer and Greenberg, 2008; West and Greenberg, 2011). Epigenetic modifications have recently emerged as one of the central mechanisms regulating gene transcription in the brain (Day and Sweatt, 2010; Graff and Tsai, 2013; Peixoto and Abel, 2013).

The cAMP-responsive element-binding protein (CREB)-dependent gene expression is essential for synaptic plasticity, learning and memory (Barco et al., 2002; Barco et al., 2005; Bito et al., 1996; Bourtchuladze et al., 1994; Deisseroth et al., 1996; Impey et al., 1998; Josselyn et al., 2004; Kida et al., 2002; Kida and Serita, 2014; Mayford et al., 2012; Silva et al., 1998; Suzuki et al., 2011). The CREB- regulated transcriptional coactivators or cAMP-responsive transcriptional coactivators (CRTCs, also referred to as TORCs) may potentiate the interaction of CREB with CBP/p300 (Xu et al., 2007) and significantly increase CREB transcriptional activity independently of Ser133 phosphorylation (Conkright et al., 2003; Iourgenko et al., 2003) (Fig. 1). CRTC1 is translocated from the synapses/dendrites to the nucleus in response to neural activity and learning (Ch'ng et al., 2012; Kovacs et al., 2007; Li et al., 2009; Nonaka et al., 2014; Parra-Damas et al., 2017; Uchida et al., 2017a). Some reports have shown recently that CRTC1 plays a key role in synaptic plasticity and memory formation in rodents (Nonaka et al., 2014; Sekeres et al., 2012; Uchida et al., 2017a; Zhou et al., 2006a). Moreover, CRTC1 is associated with memory enhancement and memory maintenance via epigenetic regulation of gene transcription (Hirano et al., 2016; Uchida and Shumyatsky, 2017; Uchida et al., 2017a).

In this review, we will begin by describing previous studies and recent progress demonstrating that histone acetylation and DNA methylation are importnat for memory. We will then describe the role of CRTC1-mediated epigenetic regulation of the *fibroblast growth factor 1 (Fgf1)* gene transcription in memory enhancement. We will also address how CRTC1 and FGF1 pathways may contribute to the development of memory-related disorders.

2. Epigenetic mechanisms in memory formation

An increasing evidence has indicated that epigenetic modifications of histones in neuronal cells constitute a powerful mechanism of memory processing (Day and Sweatt, 2010; Graff and Tsai, 2013; Peixoto and Abel, 2013).

2.1. Histone acetylation

Among the various types of histone modifications (acetylation, phosphorylation, methylation, ubiquitylation, sumoylation, ADP-ribosylation, deamination, proline isomerization), histone acetylation is one of the most well studied. In histone acetylation, a negatively charged

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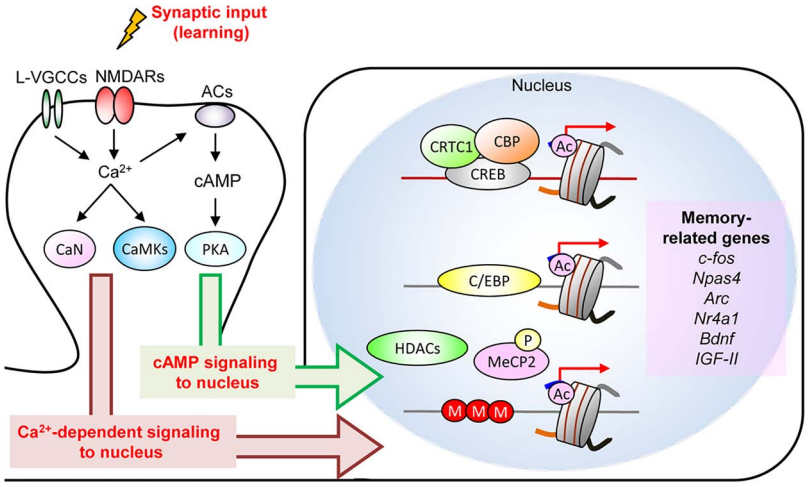

Fig. 1. Learning-dependent gene expression program required for memory formation.
Activation of L-type voltage-sensitive calcium channel (L-VGCCs) and NMDA receptors (NMDARs) triggers calcium influx and induce calcium-dependent signaling molecules such as calcineurin (CaN) and Ca^{2+}/calmodulin-dependent protein kinases (CaMKs). Calcium influx also activates cAMP signaling pathway such as protein kinase (PKA) via Ca^{2+}-sensitive adenylate cyclase (ACs). These molecules regulate the activity of transcription modulators (CREB, CBP, HDACs, CRTC1, and MeCP2) via phosphorylation and dephosphorylation. These transcriptional modulators contribute to the control of activity-dependent gene transcription which is required for synaptic plasticity and memory formation. Ac: acetylation; P: phosphorylation; M: DNA methylation.

Table 1
Brief summary of the role of HDACs/DNMTs/TET1 in memory formation.

Molecules		Findings	References
HDACs	HDAC1	Hippocampal HDAC1 is required for extinction learning via H3K9 deacetylation.	Bahari-Javan et al. (2012)
	HDAC2	HDAC2 deficiency causes increased synapse number and memory facilitation.	Guan et al. (2009)
		HDAC2 overexpression decreases dendritic spine density, synaptic plasticity, and memory formation.	
		S-nitrosylation of HDAC2 is involved in recent memory updating.	Graff et al. (2014)
	HDAC3	Focal deletion of HDAC3 in hippocampal CA1 region of adult mice enhances long-term memory.	McQuown et al. (2011)
		A prolonged HDAC3 depletion in forebrain reduces memory.	Nott et al. (2016)
		HDAC3 knockdown in hippocampal CA region of adult mice enhances long-term memory.	Uchida et al., (2017a)
		Enzymatic activity of HDAC3 is required for long-term memory formation	
	HDAC4	HDAC4 regulates synaptic transmission and memory without deacetylating histones.	Sando et al. (2012)
		Selective loss of HDAC4 in brain results in impairments in hippocampal-dependent memory and long-term synaptic plasticity.	Kim et al. (2012)
	HDAC5	Loss of HDAC5 does not impact learning and memory.	Kim et al. (2012)
		HDAC5 deficiency leads to spatial memory impairment.	Agis-Balboa et al. (2013)
	HDAC7	HDAC7 in the hippocampus is involved selectively in the consolidation of contextual fear memory.	Jing et al. (2017)
HATs	CBP/p300	CBP +/− mice show impairments of chromatin acetylation, synaptic plasticity, and memory.	Alarcon et al. (2004)
		HAT activity of CBP is required for memory consolidation.	Korzus et al. (2004)
		CREB-binding domain of CBP is required for memory formation.	Wood et al. (2006)
		p300 is required for the formation of long-term memory.	Oliveira et al. (2011)
		HAT activity of p300 is required for memory formation.	Oliveira et al. (2007)
	PCAF	PCAF KO animals show memory deficits.	Maurice et al. (2008)
		PCAF activator treatment enhances memory for fear extinction and prevents fear renewal.	Wei et al. (2012)
	KAT5 (Tip60)	KAT5 is required for H4K12 acetylation, synaptic plasticity, and memory enhancement.	Uchida et al. (2017a)
		KAT5 is required for long-term memory maintenance via H4K16 acetylation.	Hirano et al. (2016)
DNMTs	DNMT1	DNMT1 knockout mice show normal memory.	Morris et al. (2014)
	DNMT1/3a	Double knockout mice show abnormal long-term plasticity in the hippocampal CA1 region together with deficits in learning and memory.	Feng et al. (2010)
	DNMT3a	DNMT3a knockout mice show reduced memory and abnormal synaptic plasticity.	Morris et al. (2014)
	DNMT3a2	Reducing hippocampal Dnmt3a2 levels in young adult mice impairs memory formation.	Oliveira et al. (2012)
		Restoring hippocampal Dnmt3a2 levels in aged mice rescues cognitive ability.	
TETs	TET1	TET1 deficiency leads to abnormal hippocampal long-term depression and impaired memory extinction	Rudenko et al. (2013)
		Hippocampal TET1 overexpression leads to impairment of contextual fear memory.	Kaas et al. (2013)

We apologize to the authors whose articles were not cited here due to space limitation.

acetyl group is added to lysin (K) residues of histone proteins (Graff and Tsai, 2013). Histone deacetylase (HDAC) inhibitors including trichostatin A, suberoylanilide, valproic acid, and sodium butyrate ameliorate cognitive deficits and improve learning and memory (Alarcon et al., 2004; Bredy et al., 2007; Guan et al., 2009; Korzus et al., 2004; Levenson et al., 2004; McQuown et al., 2011; Peleg et al., 2010; Wood et al., 2005). The enzymes primarily responsible for reversible histone acetylation that control memory are histone acetyltransferase (HAT) CBP/p300 and histone deacetylase HDAC2 (Table 1). These two molecules have opposite effects on memory. CBP loss-of-function mutation in mice shows decreased fear memory (Alarcon et al., 2004; Korzus et al., 2004; Wood et al., 2006). Also, p300 is required for long-term recognition memory and fear memory (Oliveira et al., 2007). Conversely, HDAC2 knockout mice show increased fear memory, whereas HDAC2 overexpression reduces memory (Guan et al., 2009). In addition, there is considerable evidence indicating the role of class 1 HDAC family (HDAC1, HDAC2, HDAC3, and HDAC8) in memory formation (Table 1). Viral-mediated overexpression of HDAC1 in the mouse hippocampus increases fear extinction, whereas pharmacological blockade of HDAC1 leads to impaired extinction (Bahari-Javan et al., 2012). The same paper also reported that HDAC1 regulates an activity-dependent gene (*c-fos*), suggesting a key role of HDAC1 in transcriptional regulation of memory-related genes. Both the focal deletion of HDAC3 in the CA subregion of hippocampus as well as HDAC3 inhibition via RGFP136 significantly enhances long-term memory (McQuown et al., 2011). Similarly, viral-mediated acute knockdown of