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Review

Towards a better understanding of cognitive behaviors regulated by gene expression downstream of activity-dependent transcription factors

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ABSTRACT

In the field of molecular and cellular neuroscience, it is not a trivial task to see the forest for the trees, where numerous, and seemingly independent, molecules often work in concert to control critical steps of synaptic plasticity and signalling. Here, we will first summarize our current knowledge on essential activity-dependent transcription factors (TFs) such as CREB, MEF2, Npas4 and SRF, then examine how various transcription cofactors (TcoFs) also contribute to defining the transcriptional outputs during learning and memory. This review finally attempts a provisory synthesis that sheds new light on some of the emerging principles of neuronal circuit dynamics driven by activity-regulated gene transcription to help better understand the intricate relationship between activity-dependent gene expression and cognitive behavior.

1. Introduction

Over the last 25 years or so, it has become evident that activity-dependent gene expression plays essential roles in not only globally controlling memory persistence, but most importantly also to define and determine the genesis and decay of local memory traces. Significant cognitive deficits were associated with aberrant functions of activity-dependent transcription factors (TFs) both in mice and in humans (West & Greenberg, 2011). Consistent with this notion, many of their target genes that are strongly induced by neuronal activity (often referred to as immediate early genes (IEGs)) show high utility as biomarkers of activated neurons (Okuno, 2011). Conversely, disturbed IEG expression correlates with cognitive disorders under many pathophysiological states (Cohen & Greenberg, 2008). Recent evidence has further revealed that activity-regulated TFs may not just function as molecular switches that activate IEG promoters to control expression of downstream genes. The state of activity-regulated TFs might dynamically allocate memory within a functional neuronal circuit (Liu et al., 2012; Mayford, 2014; Yiu et al., 2014), and this may be a mechanism to assign the active neuronal ensemble that defines a memory engram within a given brain area (Silva, Zhou, Rogerson, Shobe, & Balaji, 2009). A number of recent IEG promoter-based labeling and cell manipulation studies support this idea (Kawashima, Okuno, & Bito, 2014). However, key conceptual advances sometimes fail to draw public attention, especially when early critical findings are fragmented and presented in many different and controversial pieces.

Here we will aim to first summarize recent advances in the research of individual activity-dependent TFs (Table 1), then will present an outlook of the technical advances that recently provide a new framework for understanding activity-dependent gene expression in the context of cognitive behavioral neuroscience.

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Table 1
Brief summary of basic properties and recent findings on transcription factors/cofactors related to cognitive functions described in the Sections 1–5 of the text.

Activity-dependent transcription factor	Target sequence	Cofactor	Localization and activation	Downstream genes (e.g., Cognitive effects)		References
CREB	CRE	CRTC1, CBP	Constitutively bound to target Ca^{2+}-dependent phosphorylation	*c-fos, Arc, BDNF, Egr-1*	Memory enhancer	Josselyn et al. (2001) Han et al. (2007)
MEF2	MRE	CBP	Constitutively nucleus	*c-fos, Arc*	Memory repressor	Flavell et al. (2008) Rashid et al. (2014)
Npas4	Not determined		Ca^{2+}-dependent Npas4 induction and DNA binding	*BDNF*	Regulation of inhibitory/ excitatory circuits	Lin et al. (2008) Spiegel et al. (2014)
SRF	SRE	TCL, MKL1	Constitutively bound to the target	*c-fos, Arc, Egr-1*	LTP induction and maintenance/LTD maintenance	Ramanan et al. (2005) Posern and Treisman (2006)
DREAM / KChIP3	DRE (Shared with CREB/ CREM binding sites)		Ca^{2+} binding dependent release form the promoter	*c-fos, Npas4, Mef2c*	DG-enriched LTP enhancer	Carrion et al. (1999) Mellstrom et al. (2014)
MeCP2	Methyl CpG		Ca^{2+}-triggered phosphorylation dependent release from the promoter	*CREB, BDNF, Sst, Mef2c*	causative gene for *Rett* syndrome (a type of autism)	Guy et al. (2011) Chahrour et al. (2008)

2. Molecular biology of a leading neuronal activity-dependent transcription factor that facilitates memory formation: CREB

Ca^{2+}/cyclic AMP response element-binding protein (CREB) is widely expressed in the brain and other organs, throughout development, and is critical in many forms of cognitive behavior, including memory formation and allocation (Bourtchuladze et al., 1994; Gruart, Benito, Delgado-Garcia, & Barco, 2012; Han et al., 2007; Kida et al., 2002; Silva, Kogan, Frankland, & Kida, 1998; Silva et al., 2009; Suzuki et al., 2011; Yin et al., 1994; Zhou et al., 2009). CREB is further implicated in many brain functions such as neuronal survival, proliferation, ischemia, circadian clock, plasticity, and feeding behavior (Gau et al., 2002; Mantamadiotis et al., 2002; Martin & Kandel, 1996; Nonaka, 2009). Despite its overwhelming importance, the pursuit of what defines its regional and downstream specificity has remained rather elusive.

Essentially, CREB localizes in the nucleus, binds to a cAMP-responsive element (CRE) sequence, -TGACGTCA-, and is activated downstream of various kinase cascades stimulated by cAMP, Ras, and/or Ca^{2+} signaling, all of which converge on the phosphorylation of Ser^{133} residue (Arthur et al., 2004; Bito et al., 1996; Finkbeiner et al., 1997; Ginty et al., 1994; Gonzalez & Montminy, 1989; Hardingham et al., 1997; Impey et al., 1996; Naqvi et al., 2014; Sheng et al., 1991). CREB associates with well-known co-factors, CREB binding protein (CBP) and its homologue p300 (Goodman & Mandel, 1998). These bind to p-Ser^{133} of CREB in response to external stimuli and then recruit the RNA polymerase II-containing transcription initiation complex, while they also acetylate histone to loosen the nearby chromatin structure. CBP chromatin immunoprecipitation (ChIP)-seq data revealed that upon stimulation CBP-binding sites on the whole genome increased from 1000 to ~28,000 (Kim et al., 2010). CBP/p300 were shown to have possible crosstalk with TFs other than CREB (Ramos et al., 2010). These lines of evidence suggest that CBP may not be a CREB-specific cofactor, but rather a common scaffold for RNA polymerase II at enhancers and promoters. This study further indicated that CBP and p300, seemingly redundant transcriptional cofactors (TcoFs), displayed some extent of specificity (Ramos et al., 2010).

Recent evidence indicated that CREB phosphorylation at Ser^{133} may not be the sole CREB activation mechanism in all CREB-regulated genes. Comparative CREB ChIP-chip analysis in different cell types revealed that out of ~4000 gene promoters occupied by CREB, transcription of only ~100 genes was actually up-regulated in response to forskolin, a cAMP production stimulant. Furthermore, distinct cell types showed differential induction of alternate sets of ~100 genes although there was no specificity at the level of either CREB expression or p-CREB status (Zhang et al., 2005). Thus, novel mechanisms that determine cellular specificity of CREB activation await to be identified.

Coincidently, CREB-regulated transcriptional co-activator (CRTC) or transducer of regulated CREB activity (TORC) was identified as a co-factor that binds the bZIP domain of CREB, and activate CREB in a manner that acts in parallel to CREB phosphorylation (Altarejos & Montminy, 2011; Conkright et al., 2003). Of three known isoforms, CRTC1-3, CRTC1 is the dominant TcoF isoform expressed in the nervous system (Watts, Sanchez-Watts, Liu, & Aguilera, 2011). CRTC1 translocates from cytosol to nucleus in response to synaptic activity (Ch'ng et al., 2012) and its overexpression in the hippocampus results in enhanced contextual memory (Nonaka et al., 2014; Sekeres et al., 2012). Furthermore, CRTC1 regulates dendritic morphology (Li, Zhang, Takemori, Zhou, & Xiong, 2009). *In vivo* studies suggested that CRTC1 promotes transcription of CRE-dependent genes such as *c-fos*, *BDNF*, *Arc* (also termed as *Arc/Arg3.1*) and *Egr-1*(also termed as *zif-268*), and revealed interesting brain region-specificity in regulation of task-dependent CRTC1 nuclear shuttling (Nonaka et al., 2014). Therefore, CRTC1 might play a role in determining CREB specificity at both the circuit and the chromosomal levels in the brain.

3. An activity-dependent transcription factor that represses memory: MEF2

Myocyte enhancer factor-2 (MEF2) is a TF that has originally been characterized for its role during muscle development. It is now evident, however, that MEF2 regulates neuronal development and survival. MEF2 has four isoforms, MEF2A-D, which are expressed in a brain-region specific manner (Rashid, Cole, & Josselyn, 2014). It constitutively localizes in the nucleus and binds to MRE. The consensus motif of MRE appears more tolerant in brain (underlined sequence of TGTTACT(A/t)(a/t)AAATAGA(A/t)) than as found in the muscle, which might account for how MEF2 induces distinct sets of genes in those tissues (Andres, Cervera, & Mahdavi, 1995). Transcriptome analyses using MEF2-deficient cells identified many downstream genes including *c-fos* and *Arc* (Flavell et al., 2008).

An emerging view for the role of MEF2 in cognition in the mature brain is that MEF2 may act as a repressor for memory (Rashid et al., 2014). MEF2 may gate memory formation as it undergoes task-dependent phosphorylation and degradation. MEF2 also negatively regulates spine density (Cole et al., 2012;

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