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Emerging themes in neuronal activity-dependent gene expression

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ABSTRACT

In this review, we attempt to discuss emerging themes in the regulation of neuronal activity-regulated genes, focusing primarily on an important subset of immediate-early genes. We first discuss earlier studies that have illuminated the role of *cis*-acting elements within the promoters of immediate-early genes, the corresponding transcription factors that bind these elements, and the roles of major activity-regulated signaling pathways. However, our emphasis is on new studies that have revealed an important role for epigenetic and topological mechanisms, including enhancer-promoter interactions, enhancer RNAs (eRNAs), and activity-induced DNA breaks, that have emerged as important factors that govern the temporal dynamics of activity-induced gene transcription.

A fundamental question in neurobiology concerns understanding how adaptive behaviors are developed in response to cues from the environment. While this question has been investigated from numerous perspectives, early studies conducted more than fifty years ago demonstrated that the formation of lasting behavioral adaptations, including long-term memories, requires new protein synthesis to occur during a brief window immediately following the exposure to a stimulus (Flexner et al., 1963). For instance, transcriptional inhibitors were found to be effective in blocking the late phase of long-term potentiation (L-LTP) only when they were administered either prior to or immediately after the application of a stimulus (Frey et al., 1996; Messaoudi et al., 2002; Nguyen et al., 1994). These observations suggested that by identifying the proteins that are synthesized during this short window and characterizing their functions, one could obtain significant insights into how experience exerts its profound influence on behavior.

It was in the backdrop of these developments that Greenberg and Ziff, 1984 reported that stimulation of quiescent fibroblasts with serum triggers a very rapid induction of the proto-oncogene, c-*fos*. This finding was significant for at least two reasons: first, it demonstrated that rapid changes to gene expression are, in fact, an important component of the cellular response to stimuli from the external environment. Second, it paved the way for subsequent studies, which identified that c-*fos* and other so-called immediate-early genes are also rapidly induced in the brain in response to various paradigms of neuronal stimulation (Lanahan and Worley, 1998; Morgan et al., 1987). With advances made in next-generation sequencing technologies, it is now known that neuronal stimuli trigger the induction of hundreds of activity-regulated genes, many of which facilitate changes to neural circuits by modulating dendritic growth, synaptic remodeling, and excitatory/inhibitory balance (West and Greenberg, 2011). For example, one of the activity-induced genes, *Arc* (activity-regulated cytoskeletal), plays a key tole in various forms of synaptic plasticity and behavior (Korb and Finkbeiner, 2011). ARC levels are rapidly elevated in response to neuronal activity evoked by sensory stimulation or experience, and regulates both Hebbian and non-Hebbian forms of synaptic plasticity by promoting the endocytosis of AMPA receptors. *Arc* knock-out mice exhibit a specific deficit in the late phase of LTP and LTD (long-term depression), which is strongly dependent on activity-dependent gene expression. Likewise, although *Arc* knock-out mice can learn new behavioral tasks as efficiently as wild-type mice, they show defects in memory consolidation (Guzowski et al., 2000; Plath et al., 2006; Ploski et al., 2008). Furthermore, mutations in neuronal activity-regulated genes and disruptions in activity-dependent gene transcription networks manifest in various neurological disorders (Ebert and Greenberg, 2013). A proper understanding of the signaling pathways and molecular features that regulate neuronal activity-dependent transcription is therefore likely to be enormously significant.

1. Promoter regulatory elements and transcription factors in neuronal activity-dependent gene expression

The observations that external stimuli could rapidly induce gene expression changes led to investigations into identifying the *cis*-acting regulatory elements that are important for stimulus-coupled transcription. In an elegant study involving deletion analysis of upstream

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sequences of a cloned human *c-fos* gene, Treisman first identified an element called the serum response element (SRE) that was essential for serum stimulation of *c-fos* induction (Treisman, 1985). From HeLa cell nuclear extracts, he then identified the protein, the serum response factor (SRF), that binds to the SRE of the *c-fos* gene (Treisman, 1986). Separate DNA affinity purification experiments resulted in the isolation of a ternary complex consisting of SRE, SRF, and another protein, called Elk-1, that confers serum inducibility of *c-fos* (Hipskind et al., 1991; Shaw et al., 1989). Subsequent to these studies, it was shown that the SRE and SRF also contribute to *c-fos* induction in neuronal cells (Misra et al., 1994).

Meanwhile, it was discovered that calcium influx through voltage-gated calcium channels is the key initiating event that drives *c-fos* expression in neuronal cells (Morgan and Curran, 1986). Furthermore, the ability of calmodulin inhibitors to block stimulus-dependent *c-fos* induction led to the hypothesis that calcium influx could activate a calmodulin-kinase-dependent cascade that ultimately modifies the activity of a transcriptional activator of the *c-fos* gene and drives its expression (Morgan and Curran, 1986). By again resorting to promoter deletion analysis, a distinct *cis*-acting element that was necessary for calcium-dependent activation of *c-fos* transcription was identified (Sheng et al., 1988). This element proved to be identical to the cyclic AMP response element (CRE) that had been described by within the rat *somatostatin* gene promoter (Montminy et al., 1986). In fact, using DNA affinity chromatography, the transcription factor that binds to the CRE element was identified and named CREB (for cAMP-responsive element binding protein), and it was further described that phosphorylation of CREB at serine-133 was crucial for CREB-dependent gene activation (Gonzalez and Montminy, 1989). These features were subsequently shown to be important for calcium-dependent induction of *c-fos* transcription in neuronal cells (Sheng et al., 1990, 1991).

While these and other studies in cultured cells seemed to suggest that individual *cis*-acting elements could act independently to regulate the expression of *c-fos* and other immediate-early genes in a stimulus-specific manner, analysis of *Fos-LacZ* reporter constructs demonstrated that mutation of either the SRE or the CRE element was sufficient to prevent *c-fos* induction in response to stimulation of neuronal activity in the mouse brain (Robertson et al., 1995). These observations indicate that the regulation of immediate-early genes in response to physiological stimuli requires the collaborative actions of multiple *cis*-acting elements (Misra et al., 1994; Robertson et al., 1995).

The identification of *cis*-acting promoter elements and transcription factors that bind these elements cleared the path for elaborating the signaling cascades that transduce extracellular signals to the nucleus and activate gene transcription. Following early studies, it became clear that calcium influx specifically through *N*-methyl-D-aspartate receptors (NMDARs) and L-type voltage-sensitive calcium channels (LVSCCs) initiates multiple signal transduction pathways that transmit information regarding an external stimulus to the nucleus and affect activity-dependent gene transcription in neurons (Deisseroth et al., 2003). For instance, calcium influx through NMDARs and LVSCCs allows for the recruitment of the calcium-binding protein, calmodulin (CaM), which translocates to the nucleus and activates the calcium/CaM-dependent protein kinases, CaMKII and CaMKIV. In response to stronger stimulation, calcium/calmodulin also causes the activation of the Ras-mitogen-activated protein kinase (MAPK) pathway. Both these pathways ultimately converge on the transcription factors, CREB, SRF, and Elk-1. Phosphorylation of CREB at serines-133, −142, and −143, SRF at serine-103, and Elk-1 at serine-383 have been shown to stimulate transcription in numerous ways, such as by stabilizing protein-protein interactions, recruiting transcriptional activators, and altering the chromatin environment within the promoters of immediate-early genes (Deisseroth et al., 2003; Esnault et al., 2017; Misra et al., 1994; Rivera et al., 1993; Wang et al., 2005; Xia et al., 1996).

In addition to protein kinases, calcium/calmodulin signaling also activates the phosphatase calcineurin, which targets a distinct set of transcription factors in response to neuronal activity. For instance, calcineurin-mediated dephosphorylation activates the myocyte enhancer factor 2 (MEF2) family transcription factors that control synapse development by regulating the expression of important neuronal activity-regulated genes, including *Nr4a1*, *Arc*, *Homer1a*, and *Bdnf* (Flavell et al., 2006, 2008). Calcineurin also dephosphorylates a member of the nuclear factor of activated T cells (NFAT) family of transcription factors, NFATc4, in response to neuronal activity. Under basal conditions, NFATc4 is predominantly cytosolic in hippocampal neurons, however, calcineurin-mediated dephosphorylation causes NFATc4 to translocate to the nucleus, where it targets genes essential for neuronal plasticity (Crabtree and Olson, 2002). Taken together, these and other studies elaborated a model in which exposure to an external stimulus activates dedicated signaling cascades that modulate either the binding or the activity of sequence-specific transcription factors within the promoters of neuronal immediate early genes, and drives gene induction.

2. Epigenetic mechanisms in neuronal activity-dependent gene expression

In an effort to understand how activity-dependent phosphorylation of CREB leads to transcription activation, Goodman and colleagues screened a human thyroid cDNA library with radiolabeled CREB and isolated a 265 kDa protein that specifically bound to serine-133 phosphorylated CREB, which they named CREB-binding protein (CBP) (Chrivia et al., 1993). In subsequent studies, CBP was shown to be a crucial co-activator of CREB-dependent transcription (Arias et al., 1994; Kwok et al., 1994; Parker et al., 1996). The prevailing model during this time was that DNA-binding transcription factors work primarily by recruiting and stabilizing the basal transcription machinery at promoters, and initial studies involving CBP interaction with RNA polymerase II (RNAPII) suggested that CBP could function as a transcriptional adaptor protein for CREB and other transcription factors (Kee et al., 1996; Kwok et al., 1994). However, it was soon discovered that CBP and its closely related protein, p300, have potent histone acetyltransferase (HAT) activity (Ogryzko et al., 1996).

The idea of histone acetylation as a potential mechanism of transcriptional activation originated as early as the discovery of histone acetylation itself (Allfrey et al., 1964); however, it was the purification of histone acetyltransferases and their similarity to previously identified transcriptional co-activators/adapters that provided the first direct evidence linking histone acetylation to gene activation (Brownell et al., 1996; Brownell and Allis, 1996; Ogryzko et al., 1996; Yang et al., 1996). Together with the demonstration that CBP/p300 was able to cooperatively stimulate transcription only on chromatin templates (Kraus and Kadonaga, 1998), these studies suggested that the important functions of CBP/p300 in transcriptional activation could arise from their ability to acetylate histones and render chromatin more permissive to transcription.

These observations coincided with major advancements in the understanding of epigenetic mechanisms, including DNA methylation, histone post-translational modifications, and ATP-dependent chromatin remodelers, in transcriptional regulation. These developments triggered a shift in emphasis from sequence-specific factors to delineating chromatin regulatory mechanisms of neuronal activity-dependent transcription (Qiu and Ghosh, 2008a). In this regard, initial observations that neuronal stimulation causes CBP phosphorylation and activation in a calcium and CaMKIV-dependent manner, and that CBP phosphorylation is necessary for transcriptional activation first linked neuronal activity-dependent signaling pathways with chromatin-modifying activities (Chawla et al., 1998; Hu et al., 1999; Impey et al., 2002). Meanwhile, a screen for activators of calcium-dependent gene expression in neurons led to the identification of a novel transactivator named CREST that is expressed in the developing brain and associates with CBP (Aizawa et al., 2004). Interestingly, CREST is also present in a

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