REVIEW

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c-Fos and neuronal plasticity: the aftermath of Kaczmarek's theory

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The development of molecular biology methods in the early 1980s led to a better understanding of the role of transcription factors in mammalian cells. The discovery that some transcription factors are critically important for cells to switch between different functional states was fundamental for modern molecular neurobiology. In the 1980s Leszek Kaczmarek proposed that, analogically to the cell cycle or to cell differentiation, long-term synaptic plasticity, learning, and memory should also require the activity of transcription factors. To test his hypothesis, he focused on c-Fos. His team showed that the c-Fos proto-oncogene is activated by synaptic plasticity and learning, and is required for these phenomena to occur. Subsequent studies showed that *timp-1* and *mmp-9* are c-Fos effector genes that are required for plasticity. The present review summarizes Kaczmarek's hypothesis and the major evidence that supports it. We also describe the ways in which knowledge of the molecular neurobiology of learning and memory advanced because of Kaczmarek's theory. Finally, we briefly discuss the degree to which his hypothesis holds true today after the discovery of non-coding RNAs, a novel class of regulatory molecules that were not taken into account by Leszek Kaczmarek in the 1980s.

Key words: neuronal plasticity, learning and memory, transcription factors, AP-1, MMP-9, c-Fos

INTRODUCTION

Gene expression and its master regulators, transcription factors, are indispensable for long-term neuronal plasticity, a phenomenon that underlies learning and memory. Although this view now sounds obvious and is experimentally proven, it was only hypothesized in the mid-1980s. The hypothesis was proposed independently by a few researchers, including Leszek Kaczmarek, a relative newcomer to the neuroscience field who in the mid-1980s joined the Nencki Institute of Experimental Biology. Over the years, he convinced dozens of researchers to focus their efforts on proving the hypothesis, and then searching for the detailed molecular mechanisms for the contribution of the transcription factor activator protein 1 (AP-1), to various forms of plasticity. The present review briefly describes our current understanding of the contribution of AP-1 to neuronal plasticity, with a particular focus on learning and memory. We also briefly discuss the participation of transcription factors other than AP-1 in these phenomena. Finally, we touch on the recent discovery of the contribution of non-coding RNAs (ncRNAs) to neuronal plasticity. This latter finding could not have been foreseen by Leszek Kaczmarek, or others who postulated the contribution of transcription factors to learning and memory, but ncRNAs are likely to extend the impact of transcription factors on plasticity beyond simply controlling the expression of individual genes.

KACZMAREK'S HYPOTHESIS

In the 1980s, Leszek Kaczmarek, Tom Curran, James Morgan, and Eric Kandel independently proposed a conceptual framework for the molecular basis of

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neuronal plasticity, learning, and memory (Curran and Morgan 1987, Goelet et al. 1986, Kaczmarek and Kamińska 1989). They relied on two important previous findings; first, establishing long-term memory in animals requires transcription and *de novo* protein synthesis; second, the characterization of the cellular functions of selected oncogenes. In the early 1980s, the development of new molecular biology tools allowed a better understanding of the cell cycle and cell differentiation. Especially instructive was the discovery of proto-oncogenes, the endogenous counterparts of viral oncogenes (e.g., v-Myc *vs.* c-Myc, v-fos *vs.* c-fos, etc.). Oncogenes that were found to be transcription factors were known to be involved in the induction of several undesirable cellular responses. Proto-oncogenes, similar to their viral equivalents, were transcription factors, but their activity was strictly regulated. Moreover, their activity was required to initiate long-term cellular responses. A primary function of transcription factors is the regulation of gene expression, and the overall conclusion was that long-term changes in cell biology require shifts of genetic programs. Leszek Kaczmarek was one of the first researchers who proposed that neurons are not exceptional in this regard, and alterations of neuronal gene expression that are driven by transcription factors should account for changes that underlie plasticity, learning, and memory. Thus, from the late 1980s to the mid-1990s, several researchers vigorously searched for proof that supported Kaczmarek's hypothesis, in which such transcription factors should be activated by neuronal activity in a protein synthesis-dependent manner. Kaczmarek's research on c-Fos, a component of the transcription factor AP-1, exemplifies research that sought to prove that genetic programs regulated by transcription factors, induce the structural and functional remodeling of neurons by adjusting the number of neuronal connections, synaptic strength, and the shape of dendritic spines. In turn, this leads to balanced neuronal plasticity and connectivity, both of which are needed for learning and memory to occur.

c-Fos expression as a marker of synaptic plasticity

The *c-fos* gene belongs to a group of early response genes (i.e., immediate early genes [IEGs]) that are activated upon stimulation without the involvement of newly synthesized proteins. c-Fos is a part of the AP-1 complex, a family of dimeric transcription factors that contain either Jun proteins (c-Jun, JunB, and JunD) or Jun and Fos proteins (c-Fos, FosB, Fra-1, and Fra-2) (Morgan and Curran 1991). In various types of cells, *c-fos* gene expression is rapidly induced (within minutes) by different types of stimuli in a protein synthesis-independent manner. In neurons, *c-fos* gene expression and subsequent c-Fos protein synthesis are rapidly induced by several types of neuronal stimulation, such as pentylenetetrazole-induced kindling, glutamate, kainate, electrical stimulation, and norepinephrine (Dragunow and Robertson 1987a, 1987b, Kaczmarek et al. 1988, Kaminska et al. 1994, Kuzniewska et al. 2016, Lukasiuk and Kaczmarek 1994, Morgan et al. 1987, Morgan and Curran 1988). Most importantly, c-Fos is induced under conditions of long-term neuronal plasticity, including learning and memory.

Pursuing his earlier observation that c-fos mRNA can accumulate in the brain after an injection of glutamate, norepinephrine, or even physiological saline (Kaczmarek et al. 1988), Kaczmarek discovered that mRNA and proteins that are encoded by two IEGs, *c-fos* and *zif268*, are expressed in different structures of the brain following various behavioral training regimens. In the early 1990s, he published the results of several experiments that clearly showed the expression of these genes in brain structures are functionally related to the behavioral tasks. The research showed that training a rat in a footshock-motivated brightness discrimination task, resulted in an early and transient increase in hippocampal c-fos expression (Tischmeyer et al. 1990). Similarly, the induction of long-term potentiation, a model of synaptic plasticity, in the entorhinal cortex-hippocampus pathway increased c-fos expression in both structures (Nikolaev et al. 1991). Specifically, long-lasting long-term potentiation, which likely underlies long-term memory, involves c-fos expression (Kaczmarek 1992). These results suggested that *c-fos* expression is involved in the formation of long-term memory traces. Later studies by Kaczmarek's group further pinpointed the expression of IEGs to particular brain structures that are involved in learned tasks. For example, after avoidance training, in which rats learned to avoid footshocks that were signaled by a tone or light stimulus by moving to another compartment of the experimental cage, they found that c-fos and zif268 mRNAs accumulated in the hippocampus and visual cortex; two regions of the brain that are involved in the acquisition of active avoidance responses (Nikolaev et al. 1992a). In a subsequent study, they found that the higher expression of c-fos coincided with an initial increase in performance at the beginning of training, whereas c-fos expression did not further increase after long training that resulted in a high level of performance (Nikolaev et al. 1992b). Importantly, they found that even after long-term training, c-fos expression could be induced by introducing a novel signaling stimulus, which elevated performance levels (Nikolaev et al. 1992b). The hypothesis that an increase in *c-fos* expression is associated with acquisition of the task, rather than behavioral

performance on the task, was supported by the results of Lukasiuk et al. (1999). In this study, an increase in c-Fos expression in the visual, sensory, and limbic cortices was observed after a single training session of two-way active avoidance, but not after the 10th session of such training, when animals already reached an asymptotic level of performance. These observations were paramount to understanding the close relationship between c-fos expression and learning, which is induced by novelty in the environment. These findings inspired a novel hypothesis proposed by Kaczmarek; transcription factors, particularly c-Fos as a part of the transcription factor AP-1, play a role in integrating information during learning (Kaczmarek 1993a). His experimental studies and review articles (Kaczmarek and Nikolajew 1990, Kaczmarek 1992, 1993a, 1993b, 1995) promoted the idea that transcription factors may play an important role in the integration of information during learning and memory processes. Kaczmarek was a driving force behind several important studies that tested this novel hypothesis, elegantly combining molecular biology with behavioral neuroscience. Kaczmarek and collaborators identified the necessary conditions for *c-fos* expression in the brain, and the molecular targets of c-Fos; thus providing a better understanding of c-Fos function in neurons.

Kaczmarek and colleagues described the constitutive levels of expression of c-Fos and Zinc finger-containing transcription factor 268 (Zif268) in the cortex and their modulation by visual deprivation and stimulation in rats and monkeys (for review, see Kaczmarek and Chaudhuri 1997). They demonstrated the precise regulation of *c-fos* and *zif268* by sensory stimulation during the postnatal development of ocular dominance columns in the monkey visual cortex (Kaczmarek et al. 1999). They also found that stimulation of the rat vibrissae resulted in c-Fos and Zif268 expression patterns in the somatosensory (barrel) cortex that closely corresponded to the stimulated vibrissae representation (Filipkowski et al. 2000, 2001). Moreover, they observed an increase in the DNA-binding activity of AP-1 and Zif268 in the rat visual cortex following light exposure (Kaminska et al. 1996). The precise sensory regulation of *c-fos* and *zif268* expression and the increase in DNA-binding activities, suggested that these two IEGs may couple information about external events with molecular cascades that affect cellular function. Further studies by Kaczmarek's group focused on the amygdala, a heterogeneous forebrain structure that consists of several functionally distinct nuclei. The amygdala is crucial for processing emotions, particularly learning fear and avoidance responses. They observed activation of the lateral, basal, medial, and cortical nuclei of the amygdala but not central nucleus of the amygdala following one session of two-way active avoidance training (Savonenko et al. 1999). Interestingly, housing conditions that affected the animals emotionality and learning also altered c-Fos expression in the amygdala following two-way avoidance training (Nikolaev et al. 2002). These findings suggested that factors which affect learning, also affect c-Fos expression. The blockade of basolateral amygdala activity with an infusion of an *N*-methyl-D-aspartate (NMDA) receptor antagonist, resulted in deficits in two-way avoidance learning and lower c-Fos activation in the central and medial nuclei of the amygdala, which are substantially innervated by the basolateral nucleus (Savonenko et al. 2003).

Immediate early genes, particularly *c-fos* mRNA and protein, soon became one of the most commonly used markers of neuronal activation (> 500 entries in PubMed to date). *c-fos*-based mapping provides single-cell resolution with low background expression. Neuroscientists eagerly began to utilize such expression to track brain activation patterns in response to learning particular behavioral tasks (for review, see Knapska et al. 2007). The major advantage of *c-fos*-based mapping over lesion studies, which were commonly used in behavioral neuroscience previously, was the resolution of *c-fos* and the possibility of simultaneously tracing brain activity in the entire brain. The advantage of the relatively high resolution of *c-fos* mapping is well illustrated by the results of Radwanska et al. (2002), who showed that the ventral, but not dorsal part of the lateral nucleus of the amygdala, is activated by aversive training. Numerous studies confirmed the intimate relationship between the pattern of *c-fos* expression and involvement of the activated structures in acquisition of the behavioral task (Knapska et al. 2007), which strengthened the role of *c-fos* and its protein as markers of neuronal activation. For example, when the remote memory of contextual fear conditioning was retrieved, c-Fos expression increased in the anterior cingulate cortex, which was shown to play a crucial role in this process. However, no increase was observed in the hippocampus, which appears to gradually disengage during memory consolidation (Frankland et al. 2004). c-Fos mapping also allowed the effects of pharmacological interventions on brain activation to be tested more easily. For example, Radwanska et al. (2010) showed noradrenergic modulation of the learning of two-way avoidance and associated changes in the neuronal activation of all nuclei of the amygdala.

c-fos-based mapping does not allow the manipulation of activity of the identified cells (i.e., to infer possible causal relationships between brain activation and behavior) or the temporal tracking of neuronal activity, unlike with lesions and electrophysiological recordings. Nonetheless, *c-fos*-based mapping opened new research avenues that were not possible with traditional techniques. *c-fos*-based mapping allowed the localization and

comparisons of neuronal circuits within specific brain structures at a resolution that was not previously possible. For example, it allowed the localization of neuronal circuits in the amygdala that are directly associated with learned and socially transferred fear (Knapska et al. 2006a) and appetitively and aversively motivated learning (Knapska et al. 2006b).

Technical advancements that have been made in recent years, particularly the development of *c-fos*-dependent genetic constructs for tracing neuronal circuit connectivity and the selective activation or inhibition of *c-fos*-expressing neurons, have enabled neuroscientists to make a quantum leap toward understanding their function. Such technical developments shifted the focus of functional studies from anatomically defined brain structures, toward neuronal circuits (i.e., groups of interconnected neurons) within these structures. Identifying and characterizing learning-related circuits were possible through the development of *c-fos*-dependent tools, which would not be conceivable without previous work on *c-fos* expression and localization. The study by Knapska and colleagues (2012) employed such a *c-fos*-dependent tool and is a good example of the advantages of the high resolution of such methods. The authors used *c-fos*-dependent reporter protein expression in behaviorally activated neurons to identify two groups of neurons within the lateral nucleus of the amygdala, that are functionally related to low and high levels of fear and their connectivity with other fear-related structures. Although the neurons that are the foundation of those circuits are spatially intermingled, they can be distinguished by their connectivity with the prefrontal cortex and ventral hippocampus (Knapska et al. 2012).

c-Fos is critical for synaptic plasticity

Many scientists have used c-Fos to reveal functional activation, but only a few researchers have sought to resolve the issue about the role of c-Fos in neurons. Why is c-Fos activated shortly after stimulation and deactivated soon afterward? Does it play a role in neuronal plasticity? Different functions, ranging from the short-term maintenance of cellular homeostasis to long-term changes that underlie neuronal plasticity, have been proposed in the literature, but none of them have been corroborated experimentally. Recent studies utilized *c-fos*-dependent tools and demonstrated that c-Fos-expressing neurons are involved in the formation of memory engrams (Gore et al. 2015, Tonegawa et al. 2015). These authors manipulated the activation of *c-fos*-expressing neurons, but they did not directly investigate the role of c-Fos protein in neuronal plasticity and memory formation. The first studies that attempted to directly assess the function of c-Fos in neurons used antisense oligodeoxynucleotides (Grimm et al. 1997), but such manipulations were shown to exert nonspecific effects in cells (Szklarczyk and Kaczmarek 1995, 1997). This technical difficulty was recently overcome by Kaczmarek's group using a novel approach based on RNA interference. They blocked c-Fos expression in the auditory cortex of mice, which resulted in a specific behavioral deficit in a sound discrimination task, accompanied by a decrease in cortical experience-dependent plasticity. Importantly, baseline excitability and basic auditory processing were unaffected, suggesting an important role for *c-fos* in experience-dependent plasticity and learning (de Hoz et al. 2018).

Downstream and upstream c-Fos

Synaptic activity rapidly activates c-Fos/AP-1, and its presence is critical for synaptic plasticity. Early studies showed that two constitutive transcription factors, cyclic adenosine monophosphate response element binding protein 1 (CREB) and serum response factor (SRF), are critical for *c-fos* promoter activation (Kalita et al. 2006, Kuzniewska et al. 2013, 2016, Ramanan et al. 2005, Robertson et al. 1995, Sheng et al. 1990, Sheng and Greenberg 1990, West et al. 2002). A recent analysis of regulatory elements in the c-*fos* gene promoter revealed the complexity in its activation. *c-fos* gene expression can be coordinated by enhancers that are located within the 50 kb region that is adjacent to the minimal promoter, together with activity-regulated transcription factors (Joo et al. 2016, Kim et al. 2010). Combinatorial regulation by enhancers enables the *c-fos* gene to be broadly responsive to various signaling pathways in different brain regions.

Knowledge of c-Fos effectors is in stark contrast to what is known about *c-fos* regulation. Despite many years of research that reported the activation of *c-fos* in various brain structures, its role in the regulation of specific gene expression is not well defined. Several attempts have been made to identify genes that are regulated by c-Fos in neurons using high-throughput techniques (Benito et al. 2011, Malik et al. 2014, Paletzki et al. 2008, Wu et al. 2004, Zhang et al. 2002). Numerous plasticity-related genes, including postsynaptic scaffolding proteins, ion channel constituents, receptors, and signaling molecules, were found to be dysregulated in models of high and low c-Fos expression. However, only the regulation of two c-Fos/AP-1-dependent plasticity-related genes was characterized in detail in neurons. The first example is tissue inhibitor of metalloproteinases 1 (*Timp-1*), a gene that was identified in a screen for plasticity candidates in the dentate gyrus (Nedivi et al. 1993). *Timp-1* was shown to be controlled by c-Fos/

AP-1 at the transcriptional level in response to seizures (Jaworski et al. 1999, Kaczmarek et al. 2002). Moreover, late long-term potentiation in the prefrontal cortex *in vivo* increased *Timp-1* expression, whereas constitutive TIMP-1 overexpression by means of adenoviral delivery disturbed late long-term potentiation (Okulski et al. 2007). Interestingly, the *mmp-9* gene that encodes an enzyme (matrix metalloproteinase-9 [MMP-9]) that is inhibited by TIMP-1 was confirmed to be a c-Fos/AP-1 target gene in neurons (Ganguly et al. 2013, Kuzniewska et al. 2013, Rylski et al. 2009). The role of AP-1 as a positive regulator of MMP-9 transcription in the brain following fear learning was reported by Ganguly et al. (2013). They found an increase in binding of the MMP-9 gene promoter by the AP-1 transcription factor proteins c-Fos and c-Jun in the amygdala, hippocampus, and prefrontal cortex, three brain structures that are involved in fear learning. The involvement of both c-Fos and MMP-9 in experience-dependent neuronal plasticity was also shown in the barrel cortex in adult mice (Kaliszewska et al. 2012). The activity of both proteins, TIMP-1 and MMP-9, is necessary for the structural and functional plasticity of neurons (Magnowska et al. 2016). MMP-9 is an extracellularly operating endopeptidase. Its enhanced transcription and enzymatic activity in neurons is observed in response to neuronal KCl-driven depolarization and seizure activity induced by kainate and pentylenetetrazole (Konopacki et al. 2007, Rylski et al. 2009, Szklarczyk et al. 2002, Wilczynski et al. 2008). MMP-9 mRNA is one of the transcripts that undergoes local synaptic translation to produce the protein that is rapidly released in response to stimulation (Dziembowska et al. 2012, Janusz et al. 2013, Konopacki et al. 2007, Michaluk et al. 2007). Moreover, MMP-9 is an essential regulator of dendritic spine dynamics (Jasinska et al. 2016, Kondratiuk et al. 2016, Michaluk et al. 2011, Szepesi et al. 2013, 2014). In addition to its role in brain physiology, MMP-9 was shown to be implicated in aberrant plasticity and contributes to various brain disorders, such as epilepsy, alcoholism, stress, and schizophrenia (Lepeta et al. 2017, Pijet et al. 2018, Samochowiec et al. 2010, Wilczynski et al. 2008, Zybura-Broda et al. 2016).

c-Fos is an epigenetic regulator of chromatin organization

The identification of AP-1-regulated effector proteins enabled a better understanding of the molecular basis of synaptic plasticity. However, despite multiple efforts, our knowledge about AP-1 targets in the brain is limited. This may reflect the unforeseen functions of c-Fos in the regulation of gene expression. The development of new genome-wide technologies, such as RNA sequencing (RNA-seq), chromatin immunoprecipitation (ChIP) assays with sequencing (Chip-seq), chromosome conformation capture with sequencing (Hi-C), and assay for transposase-accessible chromatin using sequencing (ATAC-seq), led to the discovery of new functions of the c-Fos/AP-1 complex. In addition to binding to proximal gene promoters, c-Fos was found to play a role as an epigenetic regulator of chromatin organization (Malik et al. 2014, Su et al. 2017). c-Fos binding was enriched at the enhancers, sequences located long distances from promoters, and effectively increased gene transcription in response to neuronal depolarization. Interestingly, activity-induced c-Fos binding was much more abundant at enhancer regions than at putative promoter sites (Malik et al. 2014). In the context of brain disorders, the identification of new functional AP-1 binding sites across the genome may help link single-nucleotide polymorphisms that might affect gene functions that are associated with enhancers.

Moreover, c-Fos can modify chromatin accessibility that is required for the initiation of chromatin opening and the expression of associated genes in response to electroconvulsive stimulation (Su et al. 2017). AP-1 was recently found to be a regulator of cell type-specific enhancer formation and cell identity during differentiation in non-neuronal cells (Phanstiel et al. 2017, Vierbuchen et al. 2017). The downregulation of AP-1 expression increased the reprogramming efficiency of induced pluripotent stem cells that were stimulated either with Yamanaka factors or chemicals (Chronis et al. 2017, Knaupp et al. 2017). These recent studies clearly show that the mechanisms of activity-dependent gene transcription that are regulated by c-Fos are much more complex than previously thought in the 1980s. As such, Kaczmarek's idea that c-Fos is an essential protein in learning and memory appears to be a brilliant hypothesis.

Involvement of other transcription factors in synaptic plasticity, learning, and memory

Is the involvement of c-Fos in neuronal plasticity exceptional? What about other IEGs? Zif268 was shown to be activated by various stimuli, including ongoing synaptic activity in the adult brain. Its activity is apparently closely related to neuronal plasticity (Knapska and Kaczmarek 2004), although no studies have directly linked its expression with neuronal plasticity. As suggested by Kaczmarek (1995), the expression of IEGs that are associated with neuronal activity may be functionally related to cell maintenance, the replenishment of synaptic release machinery and its contents, or directly to synaptic plasticity (e.g., by regulating the expression of proteins that are involved in long-term plastic changes).

Disentangling these possibilities can be achieved only by selectively blocking the expression of the gene under study and thorough scrutiny of the effects.

In addition to IEGs, the role of constitutive transcription factors, such as CREB and SRF, was studied in the context of neuronal plasticity. Numerous studies have manipulated the activity of CREB and demonstrated its role in memory formation (Balschun et al. 2003, Barco et al. 2003, Bourtchuladze et al. 1994, Bernabeu et al. 1997). However, interpretations of the role of CREB in plasticity are complicated because CREB deficiency also leads to cell death, a reduction of neuronal excitability, and a consequent deficit in synaptic plasticity (Benito and Barco 2014, Bieganska et al. 2012, Jancic et al. 2009, Jaworski et al. 2003). In contrast to CREB, SRF deletion does not influence the viability of neurons, but it produces deficiencies in hippocampal synaptic plasticity and learning (Etkin et al. 2006, Kuzniewska et al. 2016, Losing et al. 2017, Parkitna et al. 2010, Ramanan et al. 2005).

Beyond Kaczmarek's theory: non-coding RNAs

A fundamental obstacle in research on the molecular basis of learning and memory is the relatively slow identification of transcription factor target genes. Even in the case of c-Fos/AP-1, which is the most thoroughly studied example, very few target genes have been revealed, although methods for the high-throughput identification of transcription factor targets were already established some time ago. One explanation for this could be that the role of transcription factors goes beyond the control of selected mRNA expression. Above, we discussed c-Fos as a potential regulator of chromatin status. Recent developments in RNA biology have revealed additional ways that transcription factors can regulate gene expression in neurons.

Over the last decade, we learned that mRNAs, which encode proteins, represent only 3% of all transcribed RNAs. Several classes of ncRNAs, in addition to rRNA and tRNA, have been recently discovered and shown to be essential for mammalian cells, including neurons (Guennewig and Cooper 2014, Hu and Li 2017, Smalheiser 2014, Wang et al. 2017). ncRNAs are classified by their size into short ncRNAs (shorter than 200 bp) and long ncRNAs (as large as several kilobases). These two general classes can be further divided. For example, sncRNAs include tRNA, rRNA, siRNA piRNA, snoRNA and microRNA, with the latter ones being the most thoroughly studied sncRNAs in the nervous system (Guennewig and Cooper 2014, Hu and Li 2017, Smalheiser 2014, Wang et al. 2017). lncRNAs include intronic, antisense, and intragenic lncRNAs (Guennewig and Cooper 2014, Hu and Li 2017, Smalheiser 2014, Wang et al. 2017). Currently, the number of known lncRNAs in the human genome exceeds 100,000, and 40% of these are found in the brain. Moreover, the expression of several ncRNAs is regulated by neuronal activity. In fact, comparative genomics revealed that an increase in the number of expressed ncRNAs (mostly lncRNAs) corresponds to an increase in the cognitive ability of the investigated species (Guennewig and Cooper 2014). These observations support the hypothesis that lncRNAs are important for learning and memory.

ncRNAs regulate gene expression at many levels, from the control of epigenetic changes to transcription, translation, and protein function (Guennewig and Cooper 2014, Hu and Li 2017, Smalheiser 2014, Wang et al. 2017). Products of many genes, regulated by ncRNAs are proteins involved in synaptic plasticity, learning, and memory. A good example is microRNAs, which block the translation of several mRNAs that are important for synaptic and structural plasticity of the postsynaptic compartment. For example; mir-134 prevents the translation of LIM domain kinase 1, mir-181a prevents the translation of glutamate receptor 2 (GluA2), mir-125b prevents translation of the ionotropic glutamate receptor NMDA 2A (NR2A), and mir-223 inhibits the synthesis of ionotropic glutamate receptor NMDA 2B (NR2B) (Edbauer et al. 2010, Harraz et al. 2012, Saba et al. 2012, Schratt et al. 2006). However, each microRNA targets dozens of mRNAs; therefore, the contribution of microRNAs to the control of neuronal plasticity goes beyond the control of single target mRNA translation. This was nicely proven by a phenotype of mice with the brain-specific knockout of Dicer, an enzyme that is critical for microRNA biosynthesis. These mice exhibited the substantial enhancement of synaptic plasticity, learning, and memory (Konopka et al. 2010). Thus, microRNAs and some other ncRNAs (e.g. lncRNAs) seem to restrain synaptic plasticity in neurons. Several of these, however, are transcribed in a Pol II-dependent manner. Thus, their transcription is very likely to be controlled by the same transcription factors that are needed for synaptic plasticity to occur. In fact, CREB was shown to control mir-132 expression upon pilocarpine-induced seizures (Nudelman et al. 2010). These observations create an apparent paradox — the same transcription factor induces the expression of mRNAs that are important for plasticity (e.g., c-fos) whilst also inducing the expression of microRNAs that block the expression of synaptic proteins. A more detailed analysis of ncRNAs and the expression of their targets during synaptic plasticity will shed light on this discrepancy. Transcription factors affect the expression of hundreds of RNAs that do not necessarily contain their binding sites in promoter sequences (e.g., microRNA and lncRNA targets). There-

fore, knowledge of the impact of transcription factors on neuronal plasticity should be greatly expanded and spread throughout the cell by regulatory molecules that were not anticipated by researchers in the 1980s. Remaining to be established, however, is whether c-Fos/AP-1 in neurons regulates ncRNA expression.

CONCLUSIONS AND FUTURE PERSPECTIVES

Leszek Kaczmarek was one of the first researchers who proposed the hypothesis that the expression of genes and their regulators (i.e., transcription factors) is crucial for long-term neuronal plasticity that underlies learning and memory. He started to test this hypothesis experimentally and his efforts resulted in establishing a link between *c-fos* expression and neuronal plasticity, learning, and memory. He asked a key question about the role of c-Fos in neurons and inspired many researchers to search for the detailed molecular mechanisms of the contribution of AP-1 to various forms of plasticity. Studies of *c-fos* expression in learning and memory paved the way for using the *c-fos*-based mapping of neuronal activation, a technique with high resolution that has been commonly used by thousands of neuroscientists for the last 30 years. Gaining knowledge about *c-fos* also allowed the development of tools for tracing and manipulating the activity of behaviorally activated neurons. These techniques have revolutionized neuroscience in the last decade. Finally, the recent discovery of ncRNAs that contribute to neuronal plasticity suggests new ways by which transcription factors can impact neuronal plasticity, thus opening completely new avenues of research in the field.

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