Seminars in Cell & Developmental Biology 77 (2018) 63–72

Contents lists available at ScienceDirect

Seminars in Cell & Developmental Biology

journal homepage: www.elsevier.com/locate/semcdb

Review

The Arc of cognition: Signaling cascades regulating Arc and implications for cognitive function and disease

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ARTICLE INFO

Article history:
Received 16 June 2017
Received in revised form
13 September 2017
Accepted 14 September 2017

Keywords:
Arg3.1
Immediate early gene
Transcriptional regulation
Promoter
Homeostatic plasticity
Hyperexcitability

ABSTRACT

The activity-regulated cytoskeletal (Arc) gene is implicated in numerous synaptic plasticity paradigms, including long-term potentiation and depression and homeostatic plasticity, and is critical for consolidating memory. How Arc facilitates these forms of plasticity is not fully understood. Unlike other neuronal immediate-early genes, Arc encodes a protein that shuttles between the somatodendritic and nuclear compartments to regulate synaptic plasticity. Little attention has been paid to Arc's role in the nucleus. Here, we highlight the regulatory elements and signaling cascades required to induce Arc transcription and discuss the significance of Arc nuclear localization for synaptic plasticity and scaling. We integrate these findings into the context of cognitive function and disease and propose a model in which Arc mediates an effect on memory as a "chaser" of synaptic activity through homeostatic scaling.

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1. Introduction

Cognitive functions, such as learning and memory, require tight regulation of neuronal gene expression, a prerequisite for long-term synaptic plasticity. The activity-regulated cytoskeletal (*Arc*, also known as *Arg3.1*) immediate-early gene (IEG) was discovered as a gene induced by seizures in the hippocampus [1,2] and is implicated in numerous neuronal functions such as synaptic plasticity, including long-term potentiation (LTP, synaptic strengthening), and long-term depression (LTD, synaptic weakening), and homeostatic plasticity [3–9]. Arc is activated during synaptic activity and learning [1,2,10,11] and is essential for memory consolidation [6,12]: *Arc* knock out (KO) mice fail to form long-lasting memories, whereas short-term memory remains intact [6].

Arc is a single-copy gene, conserved in vertebrates, and predominantly expressed in cortical and hippocampal glutamatergic neurons. Unlike many IEGs, *Arc* does not encode a classical transcription factor, although it regulates transcription [13]. Arc is involved in numerous neuronal signaling pathways [7,9,14,15] and

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https://doi.org/10.1016/j.semcdb.2017.09.023
1084-9521/

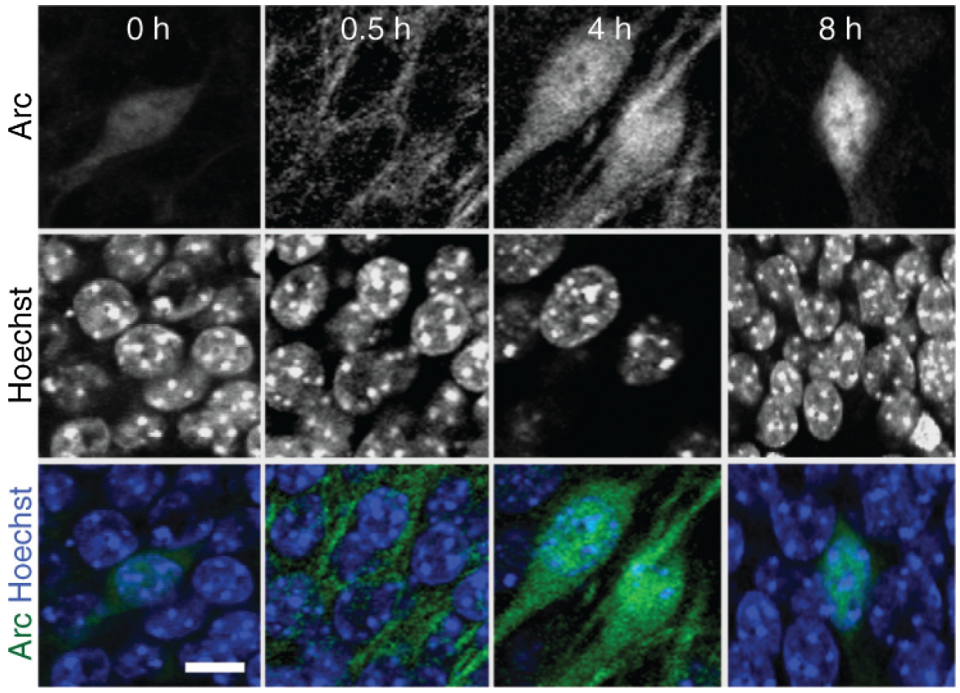

Fig. 1. Arc becomes enriched in neuronal nuclei after stimulation.
Immunohistochemical staining of Arc and Hoechst nuclear staining in mouse hippocampal sections after exposure to a novel environment for 0–8 h. Scale bar, 10 μm. Reprinted with permission from Macmillan Publishers Ltd: [*Nature Neuroscience*] [13], copyright (2013).

regulates network stability *in vivo* [16]. Expression, localization and stability of Arc are tightly regulated [11,17]. Unusual among IEGs, Arc mRNA is quickly transported or stabilized at active synapses upon synaptic activity, suggesting translation of Arc protein near sites of local synaptic activity [11]. At synapses, Arc regulates synaptic strength by promoting AMPA receptor internalization [7] and modulates spine morphology [16]. Half an hour after induction, Arc shuttles to the nucleus where most of it is localized 8 h after stimulation (Fig. 1) [13], implying that Arc might function as a cytosolic and nuclear protein [13,18].

Thus, studying Arc offers an exceptional opportunity to explore links among gene expression, synaptic activity and cognitive function. While many studies explored Arc's role in the somatodendritic compartment (reviewed in this issue), our understanding of *Arc* induction and its role in the nucleus is incomplete. Here, we will discuss the signaling and regulatory elements that induce *Arc* transcription, highlight the significance of Arc nuclear localization, and disentangle its roles for cognitive function and disease.

2. Functional response elements required for *Arc* induction

Activating gene expression in neurons is essential for learning-related long-term changes [19]. Upon neuronal activation, calcium ions rapidly enter the cell via synaptic N-methyl-D-aspartic acid (NMDA) receptors and voltage-gated calcium channels (VGCCs). This activates calcium-dependent signaling cascades that turn on transcription factors to induce transcription of target genes [19,20]. Neuronal activity-regulated gene induction occurs in two waves, based on the latency of their expression after stimulation. First, IEGs, including *Arc* and transcription factors, are activated rapidly and transiently within minutes of stimulation [21,22]. While induction of IEGs is the result of activation of pre-existing signaling pathways, *de novo* transcription of IEGs is essential for subsequent induction of the late-response genes (LRGs) [23].

What mechanisms govern rapid expression of the early-response genes? The transcriptional machinery is poised just downstream of the transcription start site (TSS) of IEGs, allowing fast transcriptional activation upon neuronal activity [24]. Further, regulatory genomic sequences, such as promoter and enhancer regions, have been extensively studied to map patterns of neuronal activation in response to distinct stimuli or animal behavior at the cellular level [25–29]. Discovery of these key regulatory elements in the *c-fos* and other IEGs facilitated the identification of transcription factors that bind these structures, and defined the upstream signaling cascades that lead to activity-dependent modifications of the factors [30–32]. Consequently, monitoring IEG transcription or the activity of a reporter gene constructed from regulatory regions of an IEG can report on the activity of signaling cascades.

To elucidate the transcriptional control of a gene, one must understand how much of the gene locus to evaluate. While many genes have regulatory elements within several kB of the TSS, long-range actions of enhancers are known [33,34]. Presumably, these actions reflect high-order chromatin structures that bring distal DNA elements in physical proximity to the gene in question. A common approach is to search for consensus DNA binding sites for well-known transcription factors in regions adjacent to the studied gene. While this approach can certainly discover regulatory DNA elements, it is inherently biased and bears the caveat that not all cognate sites are active. Thus, it is crucial to directly test function.

Previous Arc reporter gene studies by Kuhl and colleagues identified two serum response elements (SREs) positioned at ~0.9 and ~1.5 kb upstream of the transcription initiation site of the *Arc* gene. However, their requirement to induce transcription was inconclusive [35]. More recent work by the Bito and Finkbeiner laboratories uncovered regulatory elements in the *Arc* promoter region that are essential for activity-dependent transcriptional regulation [27,28] (Fig. 2). Using a DNaseI hypersensitivity assay, Pintchovski and colleagues applied an unbiased approach to look for open chromatin regions, structures assumed requisite for active transcription [28]. This approach is beneficial as it overcomes the haunting concern associated with reporter gene assays where the DNA may not be fully chromatinized and, thus, may not reflect the physiolog-