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

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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.

Keywords

Arg3.1; immediate early gene; transcriptional regulation; promoter; homeostatic plasticity; hyperexcitability

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

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Conflicts of interest: none.

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 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 hours 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 translation [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 physiological conditions of the gene [28]. This study identified two novel enhancer elements located ~6.5 and ~1.4 kb upstream of the *Arc* TSS and multiple highly conserved regions containing putative binding sites for factors associated with plasticity [28], such as the nuclear factor of activated T cells [36], nuclear factor kB [37] and myocyte-specific enhancement factor 2 (MEF2) [38]. The proximal enhancer region harbors two conserved “Zeste-like” elements that respond to synaptic activity and BDNF and convey transcriptional responses in an NMDAR-, PKA- and ERK-dependent fashion [28]. The distal enhancer bears a functional and highly conserved SRE that binds serum response factor (SRF) to allow regulation of *Arc* upon stimulation, including synaptic activity, BDNF and forskolin, an activator of adenylyl cyclase that generates cAMP [28] (Fig. 2).

That SRF/SRE regulates *Arc* transcription implies a signaling pathway that connects gene expression, synaptic activity and ultimately behavior. Mice deficient in SRF had significant defects in learning and memory [39] and gene expression changes [40]. SRE-dependent transcription can be induced by stimulation with BDNF or synaptic activity via the Ras/ERK pathway (see Section 4). Besides, the *Arc* promoter contains a partial CRE site near the SRE [28] and an unidentified protein kinase A (PKA)-responsive region [27,28]. Likewise, *Arc* induction by calcium and cAMP in rat pheochromocytoma (PC12) cells (though not in neuronal cells) depends on signaling through PKA and MAPK-ERK [35], suggesting induction of Arc transcription in neurons is activated through other pathways. Using comparative genome mapping and luciferase reporter assays, Kawashima and colleagues identified a synaptic activity-responsive element (SARE) in the *Arc* promoter region that enables synapse-to-nucleus signaling in activated neurons [27]. This activity-sensor is a ~100-bp element ~7 kb upstream of the *Arc* TSS in the mouse genome and holds a cluster of neuronal activity-dependent cis-elements, including binding sites for CREB, SRF and MEF2 [27,41] (Fig. 2). While CREB, SRE, SRF, and MEF2 have been implicated in activity-dependent gene expression [38,40,42–45], the SARE element provides evidence of a clustering and requirement of these *cis*-elements in such proximity, necessary and sufficient

to convey rapid, activity-induced *Arc* transcription in cultured neurons [27]. These studies identified elements within the *Arc* promoter region that recapitulate important features of the induction of Arc mRNA [2,27,28,46]. Further studies demonstrated the applicability of the Arc promoter for live imaging of cortical activity [47–50]. Bito and colleagues engineered an activity-dependent promoter, enhanced SARE (E-SARE) that allows activity-dependent, long-distance axonal tracing *in vivo*, expanding the repertoire of genetic approaches to dissect brain circuits [48].

3. Three-dimensional spatial and epigenetic regulation of *Arc* transcription

How are regulatory genomic sequences, such as promoter and enhancer regions, spatially regulated in 3D and how might this affect normal and aberrant cognitive function? At low transcriptional activity, the *Arc* promoter is occupied by the negative elongation factor (NELF) complex, stalling transcriptional machinery. A distal enhancer region of *Arc* produces regulatory RNA sequences that bind to the NELF complex when the enhancer region moves into proximity of the *Arc* promoter via distinct loop formations, thus liberating the *Arc* promoter from the negative regulator and promoting transcription [51,52]. Another intriguing model for enhancer-dependent regulation of transcription was described for other IEGs, including *fos* and neuronal PAS domain protein 4 (*Npas4*). Their promoter activities are low at baseline when the genomic sequence is in linear form. Transcription is activated upon topoisomerase IIβ-induced DNA double-strand breaks (DSBs) that mobilize promoter sequences into proximity with enhancer elements via short-range promoter-enhancer DNA loopings [52,53]. Such a model may be applicable to *Arc* by yet-unknown interactions (see Section 5). What effects do activity-regulated changes in the 3D genome and epigenetic modifications have on transcriptional mechanisms underlying learning, plasticity and cognition? Interestingly, mutations in genes encoding scaffolding proteins for the 3D genome and regulatory non-coding DNA were associated with disease-affecting cognitive functions, such as intellectual disability and autism [52,54,55]. DNA methylation and demethylation are epigenetic processes that underlie long-term changes, including maintenance and persistence of memory by regulating gene transcription [56], and dysregulated DNA methylation may contribute to human cognitive disorders [57]. *Arc* contains so-called CpG sites in its promoter and intragenic locus that recruit methyl-DNA binding proteins to methylate cytosines [58] (Fig. 2). Penner and colleagues [58] reported changes in the methylation status of *Arc* in the hippocampus: Aged rats had more methylation than adult rats under resting conditions [58]. Changes in DNA methylation after exploratory behavior suggested a regulatory effect on the transcriptional expression of *Arc* in response to certain behaviors [58] and an additional epigenetic component regulating Arc.

4. Signaling cascades regulating Arc transcription

Arc expression increases after seizures in the hippocampus and cortex [1,2]. However, additional stimuli induce *Arc*, including neuronal activity in response to learning [11,59–61]. What downstream signaling cascades relay the changes in neuronal activity to alterations in *Arc* transcription?

NMDA receptor activation seems to be necessary to induce *Arc* transcription and important for localizing Arc mRNA [1,2,62]. Although the action of both NMDA and AMPA receptors is required to mediate changes in synaptic efficacy, the potential regulatory role of AMPA receptors underlying Arc function initially remained unexplored. Rao and colleagues demonstrated, low levels of *Arc* transcription at baseline conditions can be further decreased by selectively activating AMPA receptors [63]. Conversely, inhibiting AMPA receptors strongly potentiated Arc induction, suggesting that AMPA receptors are negative regulators of *Arc* transcription [63] (Fig. 2). This function is conveyed via a mechanism coupling AMPA receptor function to a pertussis toxin-sensitive G protein, leaving translation and stability of Arc mRNA unaffected [63]. Selectively blocking AMPA or NMDA receptors upon stimulation of *Arc* transcription via BDNF highlighted a bidirectional regulation of Arc by NMDA and AMPA receptors, whereby the ratio of NMDA-to-AMPA receptor activation may determine Arc expression [63]. This finding is relevant: it uncovered a novel aspect of AMPA receptor function in regulating gene expression and pointed at how Arc may function in LTP and LTD to produce opposing changes in synaptic strength [63,64].

Arc transcription is accelerated by activating muscarinic acetylcholine receptors [65] and BDNF via its receptor TrkB [28,46,63] (Fig 2.). BDNF and synaptic activity are linked: BDNF induces synaptic activity, and synaptic activity stimulates BDNF release [66]. Endogenous BDNF is not required for synaptic activity-induced *Arc* transcription, but synaptic activity is required for BDNF-induced *Arc* expression [63]. *Arc* induction by BDNF depends on mitogen-activated protein kinases (MAPK) [46]. The extracellular signal-regulated protein kinase (ERK) links signaling pathways downstream of the plasma-membrane receptors to *Arc* expression. This signaling also includes Arc transcriptional activation via group 1 metabotropic glutamate receptors (mGluRs) [8,67,68]. Upon activation, ERK phosphorylates coactivators of the SRF, such as Elk-1, a ternary complex factor (TCF), which binds SREs in the *Arc* promoter to activate transcription [69]. However, ERK regulates many transcription factors besides TCF and SRF [70]. Induction of BDNF-LTP is coupled to ERK-dependent phosphorylation of calcium-and cAMP-response element binding protein (CREB)[46], a transcription factor that is required for the transcription of CRE-driven genes [71–73]. ERK also signals through a Zeste-like factor that interacts with a Zeste-like response element in the Arc promoter [28] (Fig. 2). Zeste was discovered as an invertebrate transcription factor without a mammalian ortholog [74] nor a role in plasticity-related neuronal gene expression [75]. Pintchovski and colleagues showed the Zeste-like site responded transcriptionally to synaptic activity, depending on NMDA receptor, PKA and ERK [28].

The *Arc* promoter has a partial MEF site near the SRE [28] that may be regulated by signaling pathways other than those that activate CREB (Fig. 2). MEF-dependent transcription is activated, for instance, by calcium influx that causes calcium-dependent dephosphorylation of MEF2 proteins [38]. Reducing MEF2 expression in hippocampal neurons promotes formation of excitatory synapses [38], suggesting MEF2 target genes affect synaptic scaling. Consistently, *Arc* induction by MEF2 could prompt AMPA receptor internalization [19,64].

5. The role of Arc in the nucleus

Although Arc was previously detected in the nucleus [76,77], studies addressing its nuclear function have lagged behind. Bloomer and colleagues found substantial expression of Arc in the nuclei of hippocampal neurons and HEK 293T cells where it is associated with promyelocytic leukemia (PML) nuclear bodies [77]. These sites are found in most mammalian cell nuclei and associated with transcriptional regulation [78–80]. Importantly, Arc co-localized with βSpIVΣ5, an isoform of spectrin that associates with PML nuclear bodies and the nuclear matrix [81]. Co-expression of Arc and βSpIVΣ5 increased PML bodies in HEK 293T cells, implying that Arc plays a role in PML nuclear body formation [77]. However, the mechanisms governing Arc nuclear localization were enigmatic. Work by Korb and colleagues [13] suggested Arc nuclear localization affects synaptic plasticity by regulating PML nuclear bodies that are important for neuronal development and associated with neurodegenerative disorders [13,82–84]. After exposure of mice to a novel environment and pharmacological induction of prolonged increased activity, Arc becomes enriched in neuronal nuclei *in vivo* and *in vitro* [13] (Fig 1.). Yet, what drives Arc nuclear localization? Korb and coworkers identified multiple *cis*-acting elements that direct it to nuclei, including a Pat7 nuclear localization signal, a nuclear export signal, and a nuclear retention domain. While short periods of activity decrease Arc nuclear localization, long periods increase it [13]. Moreover, using pharmacology, Korb and colleagues were able to deduce the signaling pathways that regulate Arc nuclear localization upon activity: Inhibition of the MEK-ERK pathway hampered the import of Arc into the nucleus in response to a long BDNF treatment, suggesting this signaling is critical [13]. Nikolaienko and co-workers recently extended these findings by showing that ERK directly phosphorylates Arc and promotes the early cytosolic localization of Arc in stimulated hippocampal neuronal cultures while it does not alter its slow nuclear accumulation [85].

Strikingly, upon activity-dependent translocation to the nucleus, Arc regulates homeostatic plasticity by increasing expression levels of PML, which hampers *GluA1* (also called *Gria1*) transcription and leads to downscaling of synaptic strength [13] (Fig. 2). PML nuclear bodies presumably regulate GluA1 by sequestering and degrading CREB-binding protein (CBP), a well-characterized interaction partner of PML which facilitates transcription of CRE-dependent activity-regulated genes, including GluA1 [13,86]. While Arc modulates synaptic strength by decreasing surface AMPA receptor expression, this effect was primarily associated with its function at the synapse [7,9,16]. However, Arc also reduces total GluA1 levels [7], suggesting an effect additional to regulating endocytosis. Indeed, by expressing Arc that is excluded from the nucleus hampered its ability to decrease surface GluA1 levels [13], implying Arc contributes to the scaling effect in the nucleus.

Others have reported that Arc interacts with other factors that might provide additional mechanisms by which it could regulate gene expression. Nuclear Arc interacts with the histone acetyltransferase and subunit of a chromatin-remodeling complex, Tip60 [87]. Increased synaptic activity promotes recruitment of this complex to the Arc promoter where it favors transcriptional activation by regulating the histone mark H3K9me2 [88]. Additionally, acute cocaine treatment in mice induces accumulation of Arc in striatal

medium spiny neurons where it acts as a brake on chromatin remodeling and gene regulation [89].

Remarkably, exploration of a novel environment and increased neuronal activity by sensory or optogenetic stimulation leads to DNA DSBs in neurons of adult wild-type mice, which is augmented in a transgenic mouse model of Alzheimer's disease [90]. Neuronal activity induces topoisomerase IIβ (Topo IIβ)-mediated DSBs in the promoters of IEGs, such as *Fos, Npas4* and *Egr1* [53]. Knockdown of Topo IIβ mitigated DSB formation and decreased early-response gene expression upon neuronal stimulation [53], suggesting a novel mechanism for regulating transcriptional induction of IEGs. Although *Arc* is a relatively short gene and Topo IIβ may preferentially modulate transcription of long genes [91,92], Arc translocation to the nucleus might enable interactions with Topo IIβ, activating transcriptional processes relevant to homeostatic plasticity and cognition. Recurrent DSBs have been allocated to long genes associated with neural circuit formation and accurate cognitive function in neural progenitor cells [93,94], suggesting DSBs are a physiologically relevant and beneficial mechanism of activity-dependent gene regulation in the brain.

6. Dissecting Arc's role in cognitive function

Proper cognitive function enables animals to respond to environmental stimuli in an appropriate way. Learning and memory are important substrates of cognition and are regulated by experience-driven alterations in neuronal connectivity.

Arc-deficient animals have deficits in memory task performance that require long-term recall [6,10,12,95] which is not evident when animals are tested over shorter times. Conventionally, this has been tightly linked to deficits in memory consolidation. If true, this would point to a critical function of Arc in learning and memory at a late phase in the process.

Furthermore, *Arc* is induced during sleep [96]. Sleep is perceived to help consolidate memories formed during the day [97,98]. Sleep deprivation leads to a brain-region specific increase of Arc mRNA [99,100], without affecting Arc protein expression [96]. Thus, in addition to Arc's role during the actual experience, it may act later to convert short-term to long-term memories, raising the question as to how Arc mediates long-term memory formation.

A prevailing view is that activity induces *Arc* transcription to stabilize specific synapses [5,15,62]. But how would this work? Transcription is rapid [101], however, is it rapid enough to generate Arc mRNA, transport it to specific, particularly distally localized synapses, and translate it in time to strengthen the synapse that initially triggered synaptic potentiation? If this is not true, what is the model? Does activity induce local Arc translation and nuclear *Arc* transcription in parallel, thus enabling *Arc* transcription to refill sites where Arc mRNA was depleted after local protein synthesis? Presumably, some neuronal dendrites receive input from different synaptic circuits. Different synapses on the same dendrite could simultaneously be undergoing LTP and LTD, two forms of activity-dependent synaptic plasticity that presumably act in concert to form lasting memories. While synapse-specific

changes in efficacy are critical for memory formation, those changes appear to be relative to other synapses within the same neuron, targeted by other circuits and must occur under conditions that keep the overall excitability of the neuron within a certain range [102]. This may be the only way to functionally distinguish a synaptic circuit that represents a memory without spuriously strengthening synapses that are part of other circuits, which would reduce the specificity and resolution of the memory. If the requirement for Arc in memory consolidation was solely due to a critical role in promoting synaptic strength [5,15], Arc KO mice might be hypoexcitable because they lack the critical factor to strengthen synapses in response to excitation. In contrast, Arc may primarily regulate learning and memory through synaptic scaling [13,16]. Rather than being targeted to distinct active synapses to strengthen them, Arc might enable long-term memory formation by scaling synaptic strength after stimulation (Fig. 3). In this case, one would predict the opposite effect. The brains of Arc-deficient mice should be hyperexcitable from lack of negative feedback. This way, Arc might preserve any relative differences in synaptic efficacy that were introduced, while keeping the overall level of synaptic strengths in a range where new learning can occur. Indeed, Peebles and colleagues demonstrated the latter model is true: Behavioral analysis and electroencephalogram (EEG) data showed that Arc KO and mutant mice have increased seizure susceptibility and network hyperexcitability [16]. The capacity of hyperexcitable circuits to store enduring memories is diminished, implying that hyperexcitability or deficits in synaptic homeostasis *per se* are sufficient for a memory consolidation effect, presumably due to a reduced dynamic range. A model where Arc mediates memory through scaling fits well with the aspect of timing. Instead of producing Arc in time to strengthen the synapse that triggered the memory, Arc could act as a “chaser”, induced by synaptic activity but acting after synaptic strengthening occurred to bring global activity back within an acceptable range, while preserving relative differences in synaptic strength induced by the memory-forming experience (Fig. 3). Thus, if Arc-deficient mice have a fundamental defect in synaptic scaling, the spatial maps they form may lack the resolution or the stability of maps that are formed under normal conditions.

Activity regulates Arc at almost every conceivable level from the production and trafficking of Arc transcripts, the extent of Arc mRNA translation, the localization, translocation and post-translational modification of Arc protein and the decay of Arc mRNA and protein. The emerging picture underscores the centrality of Arc to the biological mechanisms that convert transient experience into long term adaptive changes in the brain. Unsurprisingly, while the above model explains many of the observations in the field, some studies suggest that Arc contributes to learning and memory via additional mechanisms. For instance, work by Bramham and colleagues [15,103] indicates a direct role for Arc in LTP, suggesting other mechanisms in addition to Arc’s role in scaling.

7. Implications of Arc in homeostatic plasticity and disease

Consistent with the idea of imbalanced excitation and inhibition, work on neurological disorders, including epilepsy, Alzheimer’s disease (AD) and autism spectrum disorder (ASD), linked hyperexcitable circuits with deficits in long-term memory formation [104–106]. Palop and colleagues observed attenuated Arc expression in transgenic mice with neuronal production of human amyloid precursor protein (hAPP) and hAPP-derived

amyloid-β (Aβ) peptides, a hallmark of AD [106]. Similar to the Arc KO and mutant mice studied by Peebles and colleagues [16] (see Section 6), the hippocampi of these animals were hyperexcitable, and periodic seizures induced very high expression of Arc in some cells [106]. Consistent with a role for Arc in regulating synaptic homeostasis, insufficient levels of Arc may prevent the network from scaling the excitability of synapses back into a normal range after stimulation. This would lead to hyperexcitability at baseline and a reduced network capacity to store new memories due to a greatly reduced dynamic range. Evidence supporting abnormal Arc levels in AD patient brain autopsies and mouse models of AD is compelling [107], yet controversial [108]. Given that Arc was discovered in a search for genes expressed after seizures [1,2], one explanation may be related to whether an individual had an epileptic event recently. Sparsity of *Arc* induction in hippocampal neurons is associated with a mouse model of Down syndrome (DS) [109], the leading chromosomal deficit causing intellectual disability. DS yields an extra copy of APP, and the brains of DS patients contain amyloid plaques and other pathology reminiscent of AD [110], suggesting some related mechanisms. Thus, Aβ may alter synaptic plasticity by mitigating Arc levels that lead to dysregulated homeostatic scaling and ultimately, to a hyperexcitable brain that is poorly suited to form memories.

These studies suggest Arc contributes to the pathophysiology of neurological conditions that affect cognitive function. The atomic structure of the Arc N-terminal lobe is inhibited by small chemicals, implying that Arc's action may be targeted by drugs [18,111] and may open up new avenues to cures.

8. Conclusion

In light of the implications of its regulation of synaptic plasticity and memory consolidation, Arc has been studied from various perspectives (reviewed in this issue). Here, we used a bottom-up approach to describe the regulation of Arc transcription from regulatory elements in the Arc promoter via signal transduction pathways. The multifaceted array of regulatory elements and their interplay with key transcription factors and other effector molecules that govern *Arc* transcription is complex and not yet fully understood. Although we can now link certain response elements that are necessary for *Arc* induction to specific stimuli, most of the investigated conditions are fairly non-physiological, often involving tonic application of an agonist. *In vivo*, however, synapses activate several pathways simultaneously (rather than in isolation), and the temporal pattern of activation is crucial, raising the question as to how distinct signaling pathways work in combination and via different patterns to regulate *Arc in vivo*. It is intriguing to picture the Arc promoter as a unique combination lock that integrates and processes combinations of different types and patterns of stimuli to activate different factors bound to distinct response elements to induce transcription in a way no factor can by itself.

Once Arc is induced, it further mediates its effects through a variety of mechanisms in a temporally and spatially regulated manner [3,5]. Shortly after stimulation, Arc is localized predominantly to the cytoplasm where it is involved in AMPA receptor endocytosis [7,9]. Within hours of stimulation, however, Arc is almost exclusively localized to the nucleus where it modulates homeostatic scaling through interaction with PML nuclear bodies [13]

and other yet unknown mechanisms. A role of Arc in regulating memory at a later time point through homeostatic scaling fits well with data from mouse models of cognitive disorders including AD and epilepsy where hyperexcitability is a prevalent theme [104,106]. Insufficient levels of Arc may hamper the network from scaling the excitability of synapses back to a baseline range following stimulation, leading to hyperexcitability and a diminished network capacity to store new memories.

Ultimately, further research will help to better understand the relationship between the signaling that induces Arc and the complex physiological response that it produces.

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Highlights

- Arc induction is regulated by AMPA- and NMDA-receptor signaling
- Upstream functional response elements critically regulate *Arc* transcription
- Nuclear Arc regulates homeostatic plasticity through GluA1 transcription
- Arc-deficiency may prevent circuits from scaling and lead to hyperexcitability

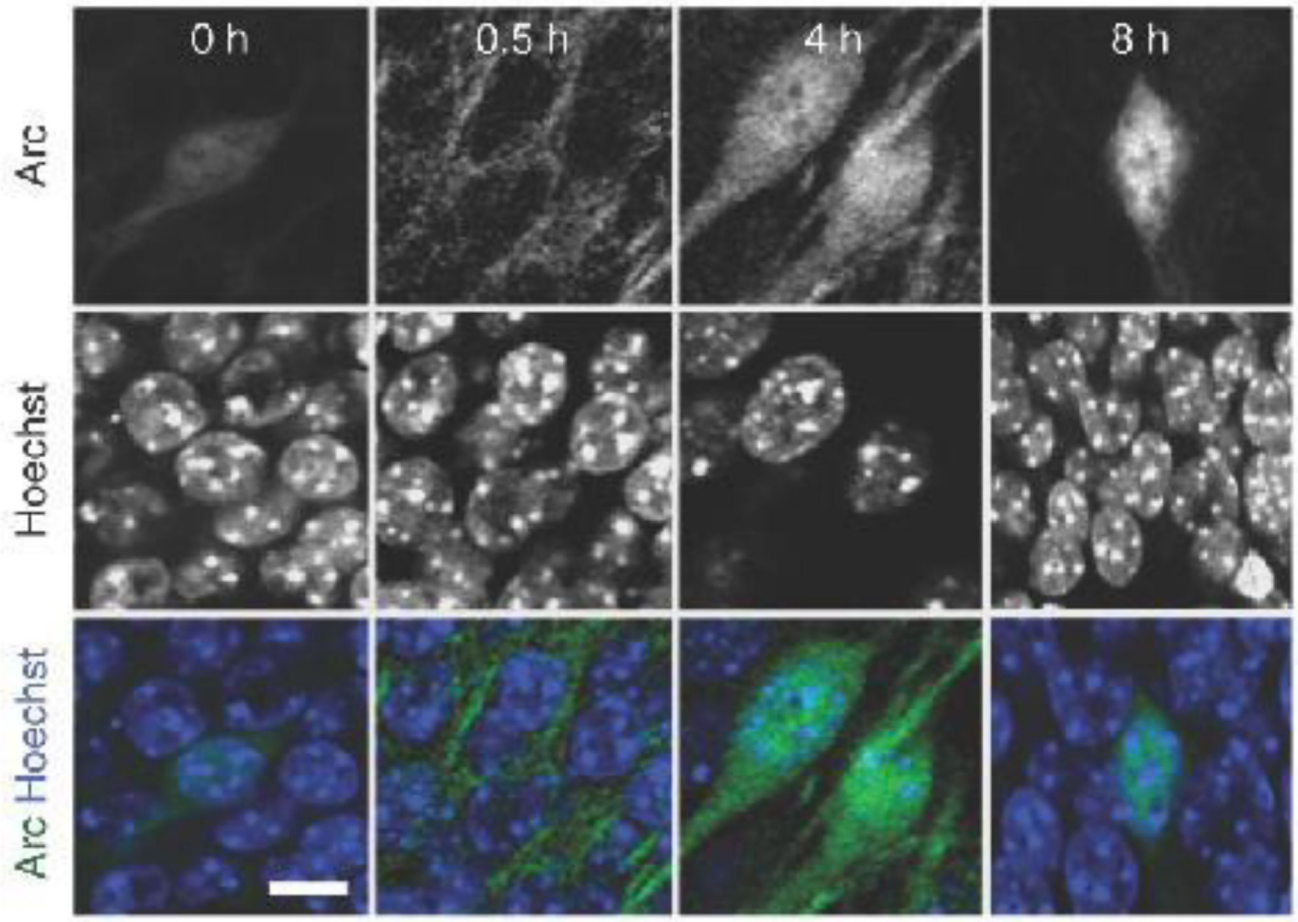

Fig. 1. Arc becomes enriched in neuronal nuclei after stimulation

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

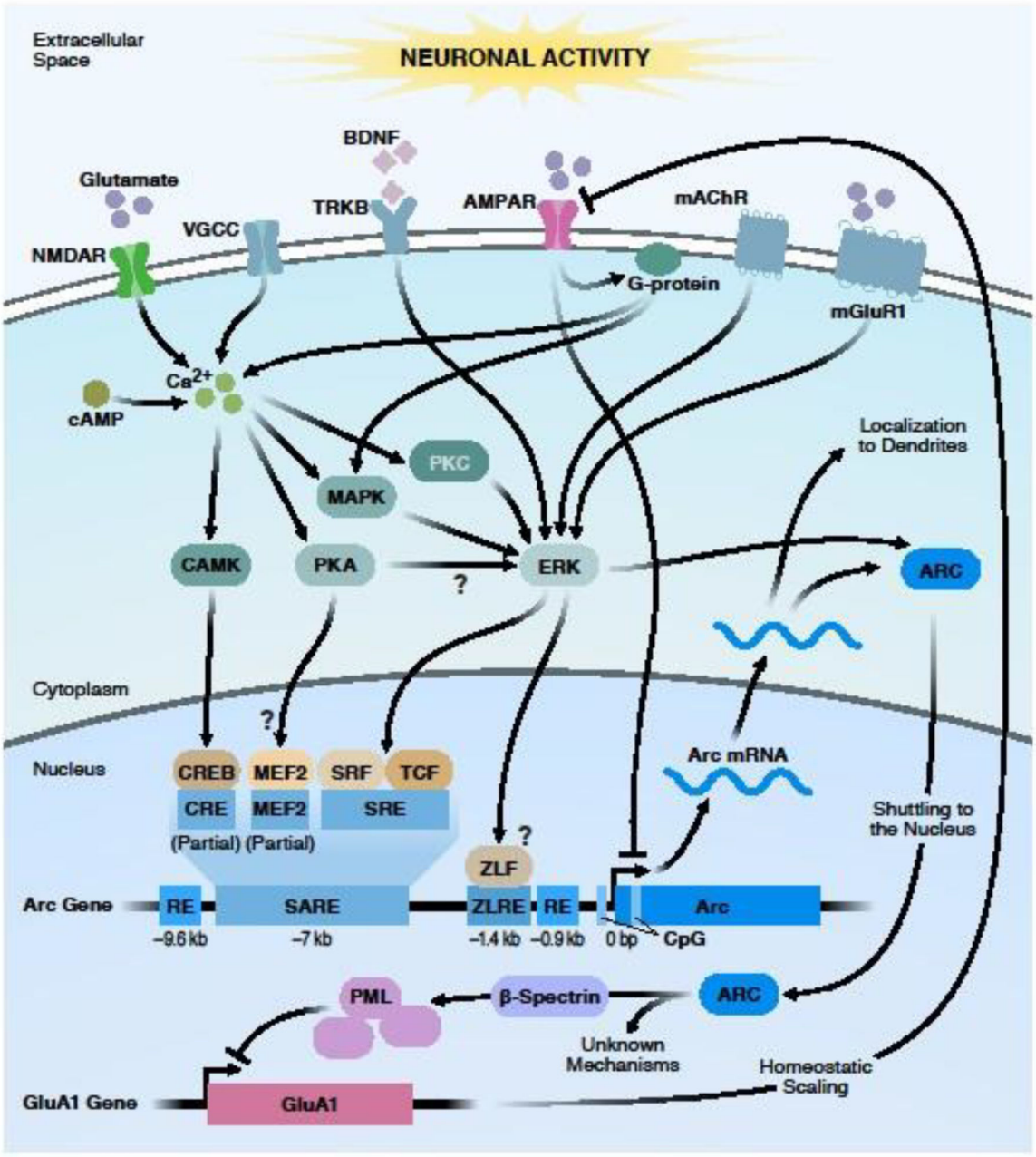

Fig. 2. Signaling cascades regulating Arc expression and its nuclear role

Neuronal activity promotes intracellular calcium influx via NMDA and voltage gated calcium channels (VGCC). *Arc* transcription is induced through various signaling cascades. Signaling via NMDA receptors, TrkB and mGluR receptors, induces Arc transcription through one or multiple downstream effector molecules (kinases), such as calcium/calmodulin-dependent kinase (CAMK), protein kinase A (PKA), and protein kinase C (PKC). Several pathways converge upstream of extracellular-signal-regulated kinase (ERK). Signaling is further relayed on nuclear transcription factors and co-activators, including cAMP responsive element binding protein (CREB), myocyte enhancer factor 2 (MEF2),

serum-response-factor (SRF), ternary complex factor (TCF), and a putative Zeste-like factor (ZLF) that bind distinct regulatory elements (blue boxes) in the *Arc* promoter, downstream of the transcription start site (see Sections 2 and 4 for details). Signaling through activation of AMPA receptors impedes *Arc* transcription by mechanisms involving G-protein signaling. After transcription, *Arc* mRNA is exported to the cytoplasm. Response elements (REs) in the Arc promoter also negatively regulate *Arc* transcription. *Arc* mRNA is localized to dendrites to serve local translation and synaptic function. Arc translocates to the nucleus where it increases the formation of PML nuclear bodies through β-spectrin, leading to reduced transcription of GluA1, indicative of a nuclear role in regulating homeostatic scaling. Nuclear Arc also interacts with the histone acetyltransferase and subunit of a chromatin-remodeling complex, Tip60 (not shown, see Section 5). Abbreviations: AMPAR, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; bp, base pair; BDNF, brain-derived neurotrophic factor; cAMP, cyclic adenosine monophosphate; GluA1, AMPA-selective glutamate receptor 1; kb, kilobase; mAChR, muscarinic acetylcholine receptor; MAPK, mitogen-activated protein kinase; mGluR1, group 1 metabotropic glutamate receptors; NMDAR, N-methyl-D-aspartic acid receptor; PML, promyelocytic leukemia; TrkB, tropomyosin-receptor kinase B; SARE, synaptic activity-responsive element; SRE, serum response element; ZLRE; zeste-like response element; VGCC, voltage-gated calcium channel.

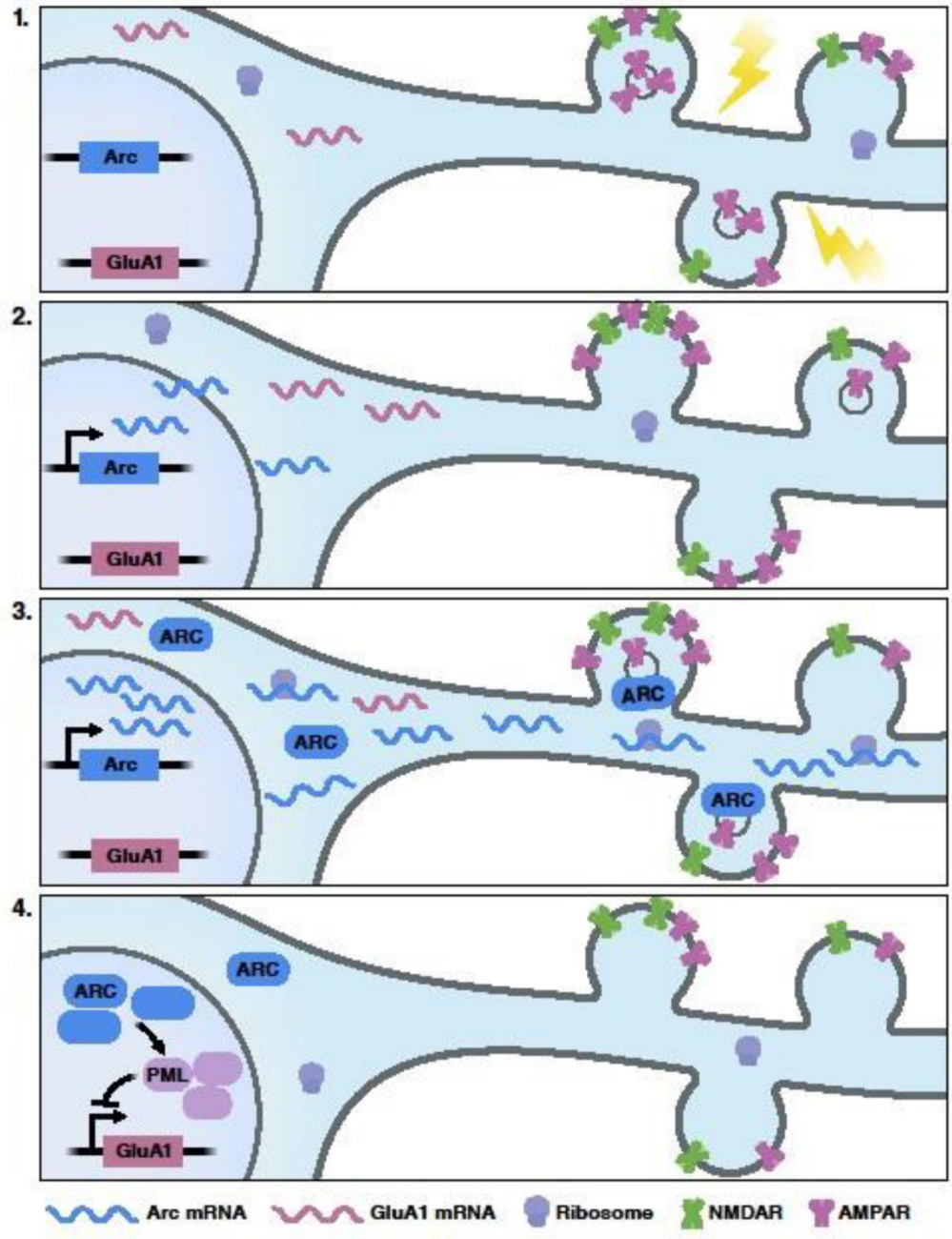

Fig. 3. A dual role for Arc in regulating homeostatic scaling

The schematic shows a scenario in which a dendritic region receives input from different synaptic circuits (panel 1). Distinct spines on the same dendrite simultaneously undergo synaptic strengthening (LTP, two spines) and synaptic weakening (LTD, one spine), illustrated via insertion or internalization of AMPA receptors to/from the plasma membrane, respectively. In the nucleus, neuronal activity induces *Arc* transcription approximately within minutes to half an hour after stimulation (panel 2). Subsequently, Arc mRNA is exported to the cytoplasm and transported to dendrites, where it may serve as a template for local protein synthesis (panel 3). Locally available Arc protein decreases synaptic strength

by promoting surface AMPA receptor endocytosis (panel 3). Hours after stimulation, Arc is almost exclusively localized to the nucleus where it further regulates homeostatic scaling by downregulating GluA1, the gene encoding the AMPA-selective glutamate receptor 1 (panel 4). After strengthening has occurred, Arc may act to bring the overall excitability of the neuron (depicted by the number of AMPA receptors throughout the panels) back to a baseline range, while preserving relative differences in synaptic efficacy, critical for memory formation (see Section 6). Abbreviations, see Fig. 2.