Seminars in Cell & Developmental Biology xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Seminars in Cell & Developmental Biology

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

Review

Arc protein: a flexible hub for synaptic plasticity and cognition

Oleksii Nikolaienko, Sudarshan Patil, Maria Steene Eriksen, Clive R. Bramham*

Department of Biomedicine and KG Jebsen Center for Neuropsychiatric Disorders, University of Bergen, Jonas Lies vei 91, N-5009, Bergen, Norway

ARTICLE INFO

Article history:
Received 13 June 2017
Received in revised form 6 September 2017
Accepted 6 September 2017
Available online xxx

Keywords:
Synaptic plasticity
Immediate early gene
Memory
Protein-protein interactions
Protein structure
Post-translational modifications

ABSTRACT

Mammalian excitatory synapses express diverse types of synaptic plasticity. A major challenge in neuroscience is to understand how a neuron utilizes different types of plasticity to sculpt brain development, function, and behavior. Neuronal activity-induced expression of the immediate early protein, Arc, is critical for long-term potentiation and depression of synaptic transmission, homeostatic synaptic scaling, and adaptive functions such as long-term memory formation. However, the molecular basis of Arc protein function as a regulator of synaptic plasticity and cognition remains a puzzle. Recent work on the biophysical and structural properties of Arc, its protein-protein interactions and post-translational modifications have shed light on the issue. Here, we present Arc protein as a flexible, multifunctional and interactive hub. Arc interacts with specific effector proteins in neuronal compartments (dendritic spines, nuclear domains) to bidirectionally regulate synaptic strength by distinct molecular mechanisms. Arc stability, subcellular localization, and interactions are dictated by synaptic activity and post-translational modification of Arc. This functional versatility and context-dependent signaling supports a view of Arc as a highly specialized master organizer of long-term synaptic plasticity, critical for information storage and cognition.

Contents

Abbreviations: Aβ, amyloid beta; AMPAR, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; AD, Alzheimer's disease; APP, amyloid precursor protein; Arc, activity-regulated cytoskeleton-associated protein; BDNF, brain-derived neurotrophic factor; AFM, atomic force microscopy; CaMK, calcium/calmodulin-dependent protein kinase; Dnm2, dynamin 2; DLS, dynamic light scattering; Endo, endophilin; ERK, extracellular signal-regulated kinase; FMRP, fragile-X mental retardation protein; GluA1, glutamate receptor subunit A1; GKAP, guanylate kinase-associated protein; GSK3, glycogen synthase kinase 3; GWAS, genome-wide association study; LTD, long-term depression; LTP, long-term potentiation; NMDAR, N-methyl-D-aspartate glutamate receptor; PML-NB, promyelocytic leukemia nuclear body; PSD, postsynaptic density PS1 presenilin-1; PTM, post-translational modification; SUMO, small ubiquitin-like modifier; SCZ, schizophrenia; TARP, Transmembrane AMPAR regulatory protein; TrkB, tropomyosin-related receptor tyrosine kinase B; WAVE1, Wiskott-Aldrich syndrome verprolin homology protein-1.

* Corresponding author at: Department of Biomedicine, University of Bergen, Jonas Lies vei 91, N-5009, Bergen, Norway.
E-mail address: Clive.Bramham@biomed.uib.no (C.R. Bramham).

http://dx.doi.org/10.1016/j.semcdb.2017.09.006
1084-9521/

1. Introduction

The adaptive capacity of the brain depends on synaptic plasticity – the ability of a synapse to change in strength in response to use or disuse. Plasticity in neural circuits shapes emotional responses, cognitive flexibility, and underlies memory formation. Clinically, aberrant synaptic plasticity is thought to contribute to disorders of cognition, including autism, schizophrenia, and Alzheimer's disease. The cell biological mechanisms of synaptic activity-dependent Hebbian plasticity have been widely studied in long-term potentiation (LTP) and long-term depression (LTD), whereas homeostatic plasticity, or synaptic scaling, refers to bidirectional compensatory changes in synaptic strength in response to altered patterns of neuronal firing activity. Modifications in glutamatergic synaptic strength lasting more than 2–3 h after induction commonly require *de novo* transcription, protein synthesis and degradation [1]. Several lines of evidence implicate the immediate early gene protein, Arc, as an indispensable component in the formation of stable LTP, LTD, and synaptic scaling, leading to the notion of Arc as a master regulator of long-term synaptic plasticity [2–4].

The spatial-temporal control of *Arc* gene expression, from transcription to dendritic mRNA localization and translation, were discussed in earlier reviews [2,3,5,6]. Here, we focus on recent insights on the Arc protein itself under four main themes: 1) Arc protein interaction networks and the role of specific binding partners as mediators of Arc signaling in synaptic and nuclear compartments, 2) Arc structure and biophysical properties. Arc is flexible and capable of reversible self-oligomerization, and crystallization of the C-terminal domain reveals a peptide binding pocket, 3) Post-translational modifications, including recent work on Arc SUMOylation and phosphorylation, and 4) Arc and human cognition, with a focus on genetic variation in Arc complexes. Taken together, the evidence supports a role for Arc as an activity-induced hub protein, specialized for mediating and coordinating synaptic plasticity in mammalian glutamatergic neurons. Finally, we propose a working model of Arc function and discuss outstanding issues and future directions in coupling the diverse functionality of Arc to cognition and a systems level understanding of long-term synaptic plasticity.

2. Arc protein interaction networks

Table 1 lists the Arc binding partners identified so far, the methods used to identify the interaction, and the protein regions required for interaction if known. Fig. 1 presents the Arc interaction network visualized using STRING database, version 10.5 [7], along with a simplified model of Arc signaling effector pathways.

2.1. Synaptic actions of Arc

2.1.1. Arc interaction with endocytic machinery and regulation of AMPAR endocytosis

Arc interacts with components of the clathrin-mediated endocytosis machinery, endophilin-3 (Endo3) and dynamin 2 (Dnm2), to promote postsynaptic internalization of AMPA-type glutamate receptors and recruitment to recycling endosomes [8,9]. Both metabotropic glutamate receptor-dependent LTD and homeostatic downscaling require Arc-facilitated endocytosis of GluA1-containing AMPARs. Overexpression of wild-type Arc, but not Arc lacking the endophilin binding domain, causes synaptic downscaling, GluA1 endocytosis and shrinkage of dendritic spines [9–11]. Recently, direct interaction of Arc with the clathrin adapter protein 2 (AP-2) was shown to be responsible for Dnm2 recruitment and GluA1 endocytosis upon Arc overexpression [12].

2.1.2. Arc interaction with presenilin 1: processing of APP and Notch1

Arc endosomes containing Endo3 and Dnm2 are also implicated in the activity-dependent trafficking of amyloid precursor protein (APP) and generation of β-amyloid (Aβ) peptides. Arc directly binds presenilin 1 (PS1) [13,14], a core component of the γ-secretase complex which cleaves APP to generate Aβ peptides. Ultrastructural and subcellular fractionation experiments further indicate the presence of Arc-PS1-APP recycling endosomes in dendritic spines [13]. Similarly, Arc is required for activity-dependent endocytosis and γ-secretase-mediated cleavage of Notch1 [15]. Proteolytic cleavage of Notch1 liberates the active intracellular domain, NICD1, which enters the nucleus where it acts as a co-transactivator with transcription factors. The γ-secretase-mediated activation of Notch1 is decreased in the absence of Arc and requires association of Arc with endophilin. In mice with conditional deletion of *Notch1* in the hippocampal CA1 region, the magnitudes of LTP and LTD are clearly reduced while early maintenance is not affected [15]. However, whether Arc-dependent Notch1 signaling regulates LTP and LTD is currently unknown.

The determinants of cargo specificity in Arc endosomes is a major issue. Selective trafficking of AMPARs may be explained by Arc's interaction with AP-2 and TARPγ2 (stargazin), a transmembrane AMPAR regulatory protein with functions in AMPAR trafficking and localization in the PSD [12,16]. Arc binding to PS1 mediates recruitment of γ-secretase, yet it is unclear how recruitment of APP and Notch1 occurs.

2.1.3. Arc interaction with PSD-95 and GKAP

Arc coimmunoprecipitates with the NMDAR GluN1 subunit and interacts with scaffold proteins of the postsynaptic density (PSD), including PSD-95 (DLG4, SAP90) and guanylate kinase-associated protein (GKAP) [16–18]. Arc interaction with PSD-95 is implicated in the regulation of signaling via the BDNF receptor, TrkB. Under normal conditions, recruitment of PSD-95 to TrkB promotes TrkB-coupled phospholipase C signaling and facilitates LTP. However, when Arc levels are excessively high, as occurs when proteasomal degradation is impaired, PSD-95 is sequestered by Arc and signaling via TrkB is impaired [19]. During homeostatic plasticity, ubiquitination and degradation of GKAP results in remodeling of the PSD, including changes in its PSD-95 and Shank composition [20]. When GKAP degradation is selectively inhibited, synaptic scaling is blocked, suggesting that GKAP removal at synapses is a prerequisite for Arc action in homeostatic scaling [20].

Please cite this article in press as: O. Nikolaienko, et al., Arc protein: a flexible hub for synaptic plasticity and cognition, Semin Cell Dev Biol (2017), http://dx.doi.org/10.1016/j.semcdb.2017.09.006