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 – An endogenous neuronal retrovirus?

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ARTICLE INFO

Article history:
Received 11 August 2017
Received in revised form
18 September 2017
Accepted 19 September 2017
Available online xxx

Keywords:
Arc
Synaptic plasticity
Retrovirus
Retrotransposon
Evolution
Gag
HIV

ABSTRACT

The neuronal gene *Arc* is essential for long-lasting information storage in the mammalian brain and has been implicated in various neurological disorders. However, little is known about Arc's evolutionary origins. Recent studies suggest that mammalian Arc originated from a vertebrate lineage of Ty3/*gypsy* retrotransposons, which are also ancestral to retroviruses. In particular, Arc contains homology to the Gag polyprotein that forms the viral capsid and is essential for viral infectivity. This surprising connection raises the intriguing possibility that Arc may share molecular characteristics of retroviruses.

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1. Introduction

Brains have evolved to process and store information from the outside world and do so through synaptic connections between interconnected networks of neurons. The age-old question of Nature vs. Nurture has been replaced with questions of how experience modifies and shapes the genetic hard wiring of the brain. Despite the fundamental importance of information storage in the brain, we still lack a detailed molecular and cellular understanding of the processes involved. Moreover, the evolutionary origins of these processes remain unclear. Studies over the last decade have shown that "junk" sequences in animal genomes have viral or retrotransposon origins that can comprise as much 50 percent of the genome [1]. In some cases, these random sequence insertions or transposable elements have resulted in the generation of new genes with important functions in higher vertebrates [2–4]. The role of these retroviral elements is not limited to germline insertions, as recent studies have shown that somatic mosaicism caused by LINE-1 retroelements in neurons of the brain is common and could cause alterations in brain development, ultimately resulting in disease [5]. Interestingly, many of these transposon-derived genes are expressed in the brain, but their molecular functions remain to be elucidated. Recent studies have made a surprising connection between the immediate early gene *Arc* and the retroviral Group-specific antigen (Gag) polyproteins [6–8]. In this review, I discuss the potential implications for the evolutionary history of this important mediator of synaptic plasticity and highlight how Gag biology may provide insight into the molecular functions of Arc protein.

2. Arc – a master regulator of synaptic plasticity

Memory encoding and storage involves a number of unique cell biological processes that ultimately result in long-term changes in

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http://dx.doi.org/10.1016/j.semcdb.2017.09.029
1084-9521/

synaptic strength, such as long-term potentiation (LTP) and depression (LTD) [9]. These include: 1. Rapid transcription (within min) of key genes in response to neuronal activity [10]. 2. Signaling pathways that are rapidly transmitted from synapses to the nucleus [11]. 3. Transport of select mRNAs in RNA granules to dendrites, where local translation can occur [12]. 4. Synaptic remodeling that involves membrane trafficking of neurotransmitter receptors, such as the ionotropic AMPA-type glutamate neurotransmitter receptors (AMPARs) from postsynaptic membranes [13]. 5. Actin-dependent structural rearrangement and synapse remodeling [14]. Arc has been implicated in all of these processes in the vertebrate brain [15–17]. Arc's expression in the brain is highly dynamic; its transcription is tightly coupled to encoding of information in neuronal circuits *in vivo*. *Arc* mRNA is transported to dendrites and becomes enriched at sites of local synaptic activity, where *Arc* mRNA is locally translated into protein [18]. This exquisite regulation of mRNA and protein localization/expression suggests that Arc plays an important role in synaptic function and cognition. Indeed, mice that lack Arc exhibit profound deficits in memory consolidation, despite intact short-term memory and learning acquisition [19]. Arc plays a critical role in AMPAR trafficking via its interaction with the endocytic machinery [20,21], which is required for protein synthesis-dependent forms of LTD [22,23]. This endocytic pathway also maintains levels of surface AMPARs in response to chronic changes in neuronal activity through synaptic scaling, thus contributing to homeostasis of neuronal strength [24]. This may prevent saturation of synaptic strength, allowing a single neuron to encode multiple memories. Arc has also been implicated in actin polymerization at synapses, which may mediate the maintenance of LTP [25]. In addition, Arc is critical for experience-dependent plasticity in visual cortex (VC) *in vivo* [26], as Arc-deficient synapses in VC are rendered insensitive to the effects of both experience and deprivation. This is a striking phenotype, reminiscent of mice that lack important signaling kinases such as calcium/calmodulin-dependent protein kinase II (CaMKII) [27] or neurotransmitter receptors such as the NMDA-type glutamate receptor [28], which are thought to have pleiotropic roles in plasticity and memory. This implies that Arc, which is regulated downstream of these signaling pathways, is one of the main effector proteins at the synapse required for transducing experience into long-lasting synaptic changes in the brain. In addition, Arc has been implicated in various neurological disorders that include Alzheimer's disease [29,30], monogenic forms of intellectual disability such as Angelman [31,32] and Fragile-X Syndromes [22], and schizophrenia [33–35]. Thus, understanding Arc's function provides a platform for determining how brains store information and mediate cognition. While much progress has been made in understanding the role of Arc in synaptic plasticity, the underlying molecular mechanisms of Arc's biochemical function remain unclear.

3. Possible viral and transposon influences on the evolution of synaptic plasticity

Evolution is rife with examples of arms races and it is becoming increasingly clear that viruses have influenced the evolution of animal genes [36]. Viruses take advantage of cellular processes in cells for replication purposes, hosts evolve defense mechanisms, and a positive feedback loop ensues. This is particularly evident in the case of retrotransposons and retroviruses, which randomly insert genetic material into the host's genome [37]. Arc contains structural elements that may have originated from the Ty3/*gypsy* retrotransposon family [7] (Fig. 1), although the role these Gag elements play in Arc function has not been explored. The Ty3/*gypsy* retrotransposons are ancient forms of RNA-based self-replicating elements that are present in animal, plant, and fungal kingdoms and are considered ancestral to modern retroviruses. In particular, genes that originate from these transposon insertions often contain conserved domains similar to the Gag polyprotein, which is required for the formation of retrovirus capsids [38]. However, the functional relevance of these domains in animal genes remains unclear. There is evidence that coding sequences derived from Ty3/*gypsy* and other retroviral-like elements have been repurposed for cellular functions repeatedly during evolution [37,39]. For example, multiple envelope genes of retroviral origins have been co-opted during mammalian evolution to promote cell–cell fusion and syncytiotrophoblast formation in the developing placenta [40,41]. There are more than one hundred Gag-derived genes in the human genome alone [8,39], and genetic knockouts of their murine orthologs have revealed that some, like *Arc*, are essential for embryonic development and/or cognition [19,42–45]. For example, a mouse knock-out of the Sushi-ichi-related retrotransposon homologue 11/Zinc finger CCHC domain-containing 16 (Sirh11/Zcchc16) exhibits defects in attention, impulsivity and working memory that may be related to a role in regulating the noradrenergic system [42]. However, the molecular function of these Gag-derived proteins has been poorly characterized, and whether they have been co-opted to serve similar cellular processes remains an open question.

4. Is Arc a neuronal gag?

Formation of mature retroviral virions is a multistep process that requires the uncleaved Gag polyprotein [46] (Fig. 2). HIV Gag contains four major protein domains that perform specific functions during virus replication within the host cell: matrix (MA), capsid (CA), nucleocapsid (NC), and p6 [38]. The Gag polyprotein is ultimately proteolytically cleaved into its constituent parts to allow for formation of the mature viral particle, after it is released from the host cell. The mature virus particle also includes a membrane coat that contains the viral envelope protein (Env). Following cleavage, the CA protein self-assembles into structures that allow for formation of the mature virion [47]. During assembly in the host cell, the polyprotein precursor associates with the inner face of the cell membrane via the MA domain, where it participates in the initial packaging of viral RNA. The NC domain has two zinc knuckle motifs that interact with the viral RNA and confer some specificity for which RNA is packaged, although if viral RNA is not present, cellular RNA is also packaged into capsids [48,49]. Mutations in NC that interfere with RNA binding lead to formation of non-infectious viruses. The p6 domain of HIV Gag recruits the endosomal sorting complex required for transport (ESCRT) machinery, which catalyzes the membrane fission step to release the HIV virions from the cell [38]. Immature retroviral capsids are formed by the uncleaved Gag polyprotein, and the major stabilizing interactions are made by the C-terminal domain (CTD) of the CA region [50]. Arc has both primary sequence [8] and structural similarity to CA of HIV and Foamy Virus Gag polyproteins [7,51] (Fig. 1), suggesting that Arc may share functional similarities to Gag proteins. The assembled structure of the CA protein has been extensively studied and has been resolved both by X-ray crystallography and cryo-EM as an arrangement of hexamers that are connected dimerically through N- to C-terminal interactions [52]. Despite low sequence conservation across viruses and retrotransposons, Gag structure and function are maintained with four main functional roles (Fig. 2): 1. Membrane/lipid binding. 2. Self-assembly into capsids. 3. RNA binding. 4. Release from cells in viral particles.

While these essential functions of Gag are conserved across the retroviruses, there is heterogeneity on how these functions are performed. For example, Foamy Virus Gags have evolved different RNA-binding motifs to HIV Gag and bind RNA through

Please cite this article in press as: J.D. Shepherd, Arc – An endogenous neuronal retrovirus? Semin Cell Dev Biol (2017), http://dx.doi.org/10.1016/j.semcdb.2017.09.029