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Arc – An endogenous neuronal retrovirus?

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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.

Keywords

Arc; synaptic plasticity; retrovirus; retrotransposon; evolution; Gag; HIV

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

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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 synaptic strength, such as long-term potentiation (LTP) and depression (LTD) [9]. These include: 1. Rapid transcription (within minutes) 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] (Figure 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] (Figure 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] (Figure 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 (Figure 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 C-terminal glycine-arginine-rich patches (referred to as GR boxes) [53]. What aspects of Gag function are conserved in Arc? Worley and colleagues showed that a fragment of Arc that contains the CA N-terminal Gag homology domain (NTD; aa207–278) bound to CaMKII and the AMPAR chaperone Tarpγ2/stargazin [7]. These interactions may be important for Arc's role in regulating AMPAR trafficking at inactive synapses [54], although it remains unclear how this domain regulates protein-protein interactions in its native conformation in cells. It is intriguing that Arc retains as much conservation with the retrovirus Gags as other viral families, such as the Foamy Viruses [51]. Ty3 retrotransposons can form oligomeric particles that resemble retroviral capsids [55], and Arc also has a propensity to oligomerize [56]. Can Arc form viral-like capsids in cells and what are the functional implications of oligomerization or self-assembly? Arc is also predicted to have an MA-like domain (Figure 1), with a high density of basic amino acids in its N-terminus [8]. The MA domain of HIV Gag determines lipid interactions through charge interactions and a myristoylation moiety, which targets Gag to the plasma membrane during capsid formation and RNA encapsulation [49, 57]. Does Arc's putative MA domain target Arc to membranes important for its intracellular trafficking role?

Retroviral Gag uses host cellular trafficking machinery during virion formation and release from the cell, although the precise route of release and entry depends on cell and virus type [47, 58]. While ESCRT binding to the p6 domain is essential for HIV virion release [59], in some cells, such as macrophages, virions will bud into multivesicular bodies (MVBs) and released through an exosome route rather than direct budding at the plasma membrane [60]. One study showed that HIV Gag binds the adaptor protein complex AP-3 and that this interaction was essential for capsid assembly, budding into MVBs and virion release [61]. Another study found that Gag binds to AP-2, a clathrin adaptor protein, preventing virion release [62]. Interestingly, both adaptor complexes were shown to directly bind purified Gag *in vitro*. Arc also binds AP-2 directly [21], another potentially conserved protein-protein interaction. Similar to virion release, entry of mature retrovirus virions also requires host cellular machinery. The HIV Env protein allow virus entry into cells by binding cell surface receptors and allowing membrane fusion. The precise route of particle entry into the

cytoplasm remains unclear [58], however, with some studies showing direct fusion and entry through the plasma membrane, while others show that full fusion and entry occurs via endosomes [63, 64]. Dynamin may play an important role in allowing full fusion to occur [64], although it is not clear if this occurs through a direct interaction with Gag or through modulation of membranes/the actin cytoskeleton. It is tempting to speculate that Arc's role in intracellular trafficking of receptors evolved from these kinds of retroviral Gag/host cell interactions.

Intriguingly, aspects of *Arc* mRNA regulation also resemble some viral RNAs, as *Arc* contains an internal ribosomal entry site (IRES) that allows cap-independent translation [65, 66]. In addition, the RNA binding protein Staufen interacts with HIV Gag and is a critical host cellular cofactor for viral RNA encapsulation [67]. Staufen is also a critical regulator of dendritic mRNA trafficking in neurons, including *Arc* mRNA, that is important for synaptic plasticity [68]. *Arc* mRNA regulation, such as dendritic transport and degradation, is primarily regulated by its 3'UTR [69, 70], although precisely how this occurs is unknown. It will be of interest to determine whether the UTR similarly evolved from viral or transposon origins. The parallels between dendritic mRNA regulation and virus-RNA interactions are striking and further suggest that complex neuronal cell biology may have viral origins.

5. Conclusion

Arc evolved from a random retrotransposon insertion event, most likely from Ty3/*gypsy*. This may have occurred in a tetrapod ancestor in between fish and amphibians, as fish contain gypsy elements that resemble Arc but exhibit more recent transposon activity and do not seem to be bona fide genes. Interestingly, the *Drosophila* homologues of *Arc*, *dArc1* and *dArc2*, also exhibit high homology to the Ty3/*gypsy* family of retrotransposons [7]. However, other insect lineages seem to lack true Arc genes: as they also contain retrotransposon elements that indicate recent transposition and are not true orthologues. This suggests that the fly Arc homologue may have been derived from an independent retrotransposon event from the same Ty3/*gypsy* retrotransposon family (Dr. Cédric Feschotte, personal communication). Once *Arc* became a functional gene, it became highly conserved in the vertebrate lineage and its role in synaptic plasticity seems conserved from birds to humans [33, 34, 71]. Future studies should determine the functional implications of Arc's resemblance to Gag.

A major paradox that remains to be solved is the dichotomy of a protein that is highly dynamic and short-lived within neurons, yet is required for long-term synaptic plasticity and consolidation of memory. Does this occur strictly through acute AMPAR regulation or through manipulation of the actin cytoskeleton at synapses? Alternatively, does Arc regulate gene expression or state-dependent changes through RNA processing in the nucleus or dendrites that lead to long-lasting information storage? New directions include: investigating whether Arc can self-assemble into viral-like capsids or form structures that can regulate RNA transport in dendrites, or even whether Arc is secreted from cells and able to transport genetic material similar in manner to retroviruses. It is fascinating to think that some of the most complex processes performed by neurons may have originated from ancient forms of life!

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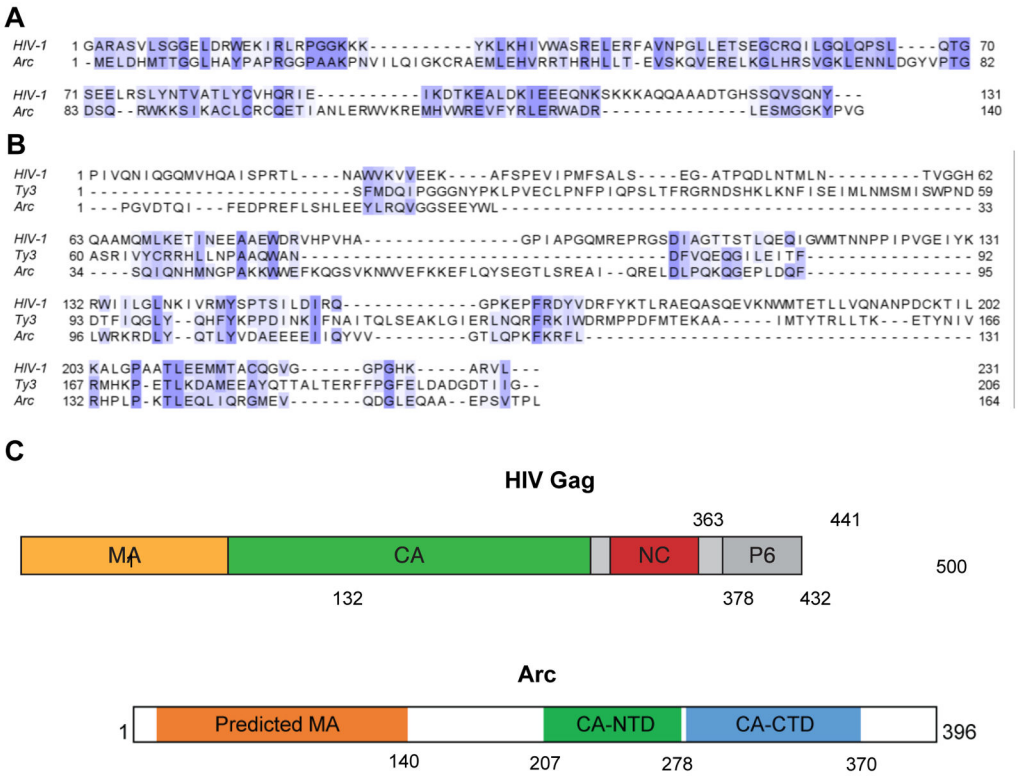

Figure 1. Conservation of Gag homology domains in Arc

A. Alignment of HIV-1 MA and Arc's putative MA domain, taken from Campillos *et al*, 2006 [8], using BLAST alignment of human HIV-1 (Uniprot #P03367) and rat Arc (Q63053). Sequence similarity = 18%. **B.** Alignment of HIV-1, Ty3/Gypsy (Q12173) and the rat Arc CA domain taken from Campillos *et al*, 2006 [8]. Degree of conservation is color coded, with white indicating no conservation and dark blue indicating high or perfect conservation. CA sequence similarity (HIV and Arc) = 9%. **C.** Domain organization of HIV-1 Gag and Arc. Arc's putative MA domain is predicted by computational modeling [8], but not experimentally. The Arc CA domains are based on crystal structures of these fragments [7].

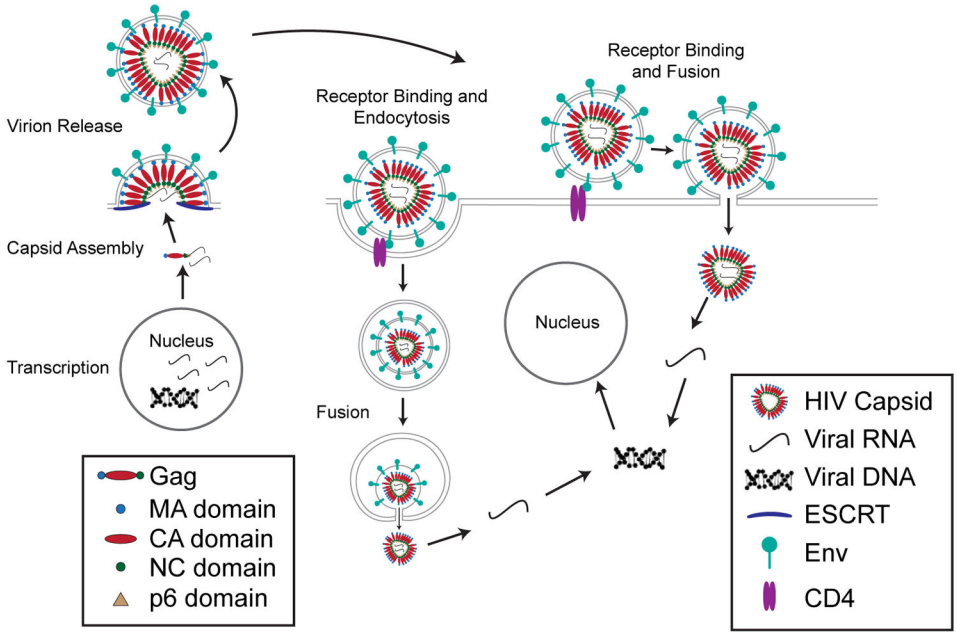

Figure 2. Role of the Gag polyprotein in the HIV life-cycle

HIV Gag protein self-assembles (determined by the CA domain) in the cytosol and at the plasma membrane (determined by the MA domain), while the capsid encapsulates viral RNA (via the NC domain) that is transcribed by the host cell. The immature HIV capsid is secreted in an ESCRT-dependent manner (via the p6 domain) with membrane that contains the viral envelope protein (Env). The mature HIV capsid is formed by cleavage of Gag, which results in conformational changes in the structure of the capsid. The mature virus particles bind host cells through surface receptors (such as CD4) and membrane fusion occurs. Alternatively, virus particles are first endocytosed prior to fusion and particles released into the cell after full fusion occurs in the endosome. Ultimately, viral RNA is released from the particles and is reversed transcribed into viral DNA that is integrated into the host genome via other viral proteins.