Chapter 6
Inverse Synaptic Tagging by Arc

Hiroyuki Okuno, Anna Araki, and Keiichiro Minatohara

Abstract Long-term synaptic plasticity and memory formation require activity-dependent gene expression. However, it remains unknown how such activity-induced gene products are targeted to proper cellular compartments including synapses. Investigation of the targeting of the memory related-protein Arc from the soma to the synapses have elucidated a novel "inverse" synaptic tagging mechanism that enables Arc to specifically target the un-potentiated synapses. The findings provide new mechanistic insights into how the contrast between strong and weak synapses is maintained during long-term synaptic plasticity. Furthermore, they facilitate a better understanding of the molecular basis of biochemical memory at individual synapses and ultimately learning and memory.

Keywords Arc/Arg3.1 • CaMKII • Synaptic tagging and capture • Inverse synaptic tagging • Synaptic plasticity • Immediate-early genes

6.1 Introduction

The formation and sculpting neuronal circuits in the brain are not specific to the course of development but occur continuously throughout life. Synapses, connection sites between neurons, are added or removed from neuronal circuits daily (Bhatt et al. 2009; Holtmaat and Svoboda 2009). Synapses also undergo both positive and negative changes with respective to shape, size, and the efficiency of information transmission depending on the patterns of synaptic inputs (Bliss and Collingridge 2013; Kasai et al. 2003). These synaptic changes can be last for hours, days, months, or even throughout life (Abraham et al. 1985, 2002; Bliss and Lomo 1973; Dudek and Bear 1993; Hofer et al. 2009). These plastic properties of synapses are thought to be the fundamental cellular basis of our cognitive functions including learning and memory (Hebb 1949; Neves et al. 2008; Whitlock et al. 2006).

H. Okuno, Ph.D. (✉) • A. Araki, M.Sc. • K. Minatohara, Ph.D.
Medical Innovation Center, Graduate School of Medicine, Kyoto University,
53 Shogoin-Kawahara-cho, Sakyo-ku, Kyoto 606-8507, Japan
e-mail: okuno@sk.med.kyoto-u.ac.jp; araki.anna.28e@st.kyoto-u.ac.jp;
minatohara@sk.med.kyoto-u.ac.jp

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Experience-evoked gene expression, or more generally, neuronal activity-dependent gene expression in the brain is a prominent cellular event that occurs during various memory formation processes. Activity-dependent gene expression is indispensable for memory consolidation, reconsolidation, updates, and extinction (Kandel 2001; Nader and Hardt 2009; Okuno 2011; Silva et al. 1998) and is also critical for long-lasting synaptic modifications including long-term potentiation (LTP), long-term depression (LTD), and synaptic morphological changes (Bliss and Collingridge 2013; Govindarajan et al. 2006; Redondo and Morris 2011). This further corroborates the fundamental importance of these cellular processes in long-term memory formation and storage. In recent decades, a great deal of effort has been invested in identifying and charactering activity-dependent genes that critically regulate the synaptic and cellular events underlying memory formation and cognitive processing (Bourtchuladze et al. 1994; Brakeman et al. 1997; Flavell et al. 2008; Greer et al. 2010; Lanahan et al. 1997; Nedivi et al. 1993; Qian et al. 1993).

The neuronal immediate early gene *Arc* (also called *Arg*3.1) is among the most promising candidate memory regulatory genes (Bramham et al. 2010; Korb and Finkbeiner 2011; Shepherd and Bear 2011) because of its highly dynamic expression that is correlated with augmented neuronal activity required for cognitive processes such as spatial learning and memory consolidation (Guzowski et al. 1999; Kawashima et al. 2009; Ramirez-Amaya et al. 2005). This chapter provides an overview of the current knowledge of *Arc* function in synaptic plasticity. The inverse tagging model of Arc as a novel molecular mechanism for memory formation is also introduced. Finally, the *in vivo* relevance of inverse tagging mechanisms will be discussed.

6.2 The Plasticity-Related, Activity-Regulated Gene Arc

*Arc/Arg*3.1 was first isolated from rat seizure-induced hippocampal cDNA libraries (Link et al. 1995; Lyford et al. 1995). However, *Arc* has emerged as one of the most dynamically regulated and most sensitive genes in response to a wide variety of physiological stimuli including sensory inputs (Carpenter-Hyland et al. 2010; Tagawa et al. 2005) and cognitive burdens related to learning and memory (Fig. 6.1a) (Guzowski et al. 1999, 2000; Ramirez-Amaya et al. 2005). Because of its high responsiveness, *Arc* transcripts and Arc protein are now widely used as reliable activity markers for visualizing neuronal ensembles activated during specific behaviors or cognitive paradigms (Chawla et al. 2005; Mamiya et al. 2009; Ploski et al. 2008; Tse et al. 2011; Wintzer et al. 2014).

Arc is evolutionally conserved in vertebrates, and has no paralogue in genomes, suggesting that it has unique but critical roles. *Arc* encodes an approximately 400-amino acid protein that has no catalytic or other known functional motifs. Because Arc protein directly or indirectly interacts with many proteins, it is likely function as a scaffold/anchor protein (Fig. 6.1b). A large part of Arc's function is thought to occur postsynaptically. Biochemical and electron microscopy studies demonstrate

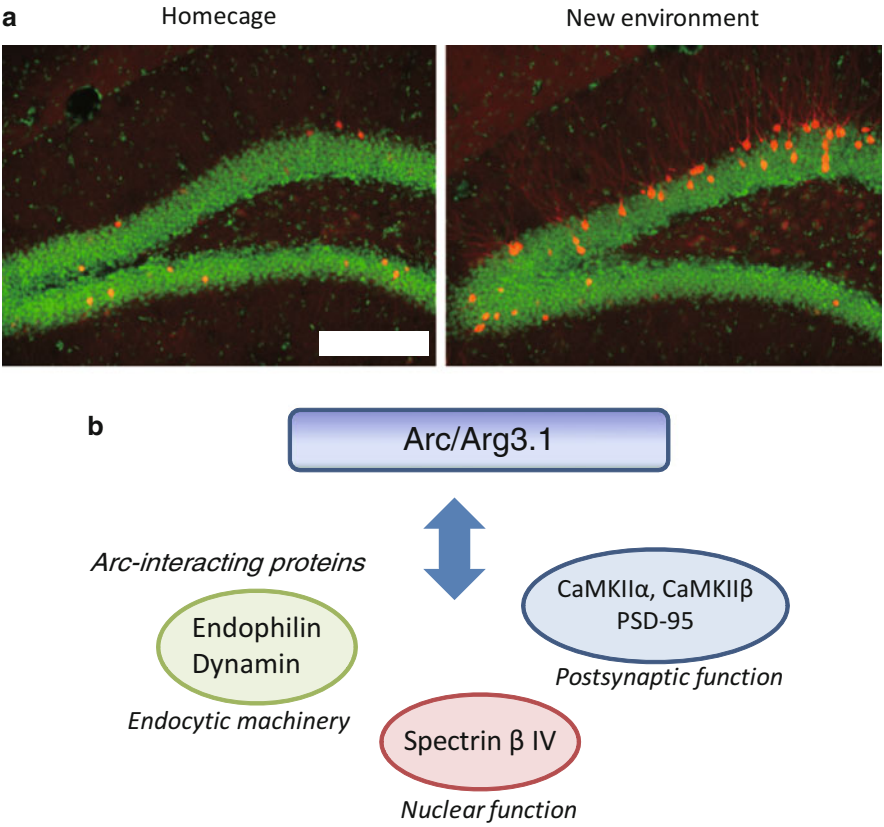

Fig. 6.1 Neuronal immediate-early gene Arc/Arg3.1. (**a**) Experience-induced Arc expression in the hippocampus. When mice are exposed to a new environment, Arc protein (*red*) is rapidly induced in the dentate gyrus of the hippocampus within a few hours (*right*). Much fewer neurons express Arc under the homecage condition (*left*). Nuclear staining is shown in *green*. Bar = 200 μm. (**b**) Arc protein and its binding partners. Arc protein is shown to interact with several proteins with different functions. Only some of known Arc-interacting proteins are shown (Color figure online)

that Arc protein is present in the postsynaptic density of activated neurons (Chowdhury et al. 2006; Moga et al. 2004; Rodriguez et al. 2008). At the postsynaptic site, Arc interacts with the endocytic proteins endophilin and dynamin to facilitate the removal of AMPA-type glutamate receptors (AMPARs) from the plasma membrane (Fig. 6.2a) (Chowdhury et al. 2006; Rial Verde et al. 2006; Shepherd et al. 2006). This biological function together with the activity-dependent expression of *Arc* accounts for the physiological roles of *Arc* in several forms of protein translation-dependent LTD (Park et al. 2008; Plath et al. 2006; Smith-Hicks et al. 2010; Waung et al. 2008) and homeostatic plasticity/synaptic scaling (Fig. 6.2b) (Beique et al. 2011; Chowdhury et al. 2006; Rial Verde et al. 2006; Shepherd

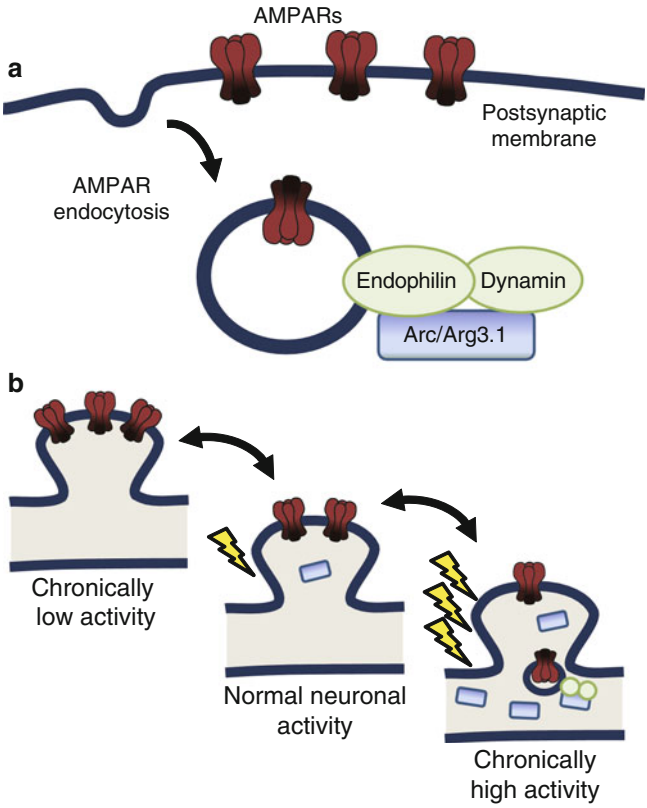

Fig. 6.2 Arc/Arg3.1 function at the postsynaptic site. (**a**) Role of Arc in AMPAR trafficking. Arc forms a complex with endophilin and dynamin. This endocytic machinery complex facilitates the removal of AMPARs from the postsynaptic membrane. (**b**) A model of Arc's role in homeostatic synaptic scaling. The activity-regulated dynamic expression of Arc together with Arc-dependent AMPAR endocytosis provides a favorable mechanism for homeostatic modulation of the surface AMPAR expression. (*Left*) Under conditions of chronically low neuronal activity, Arc expression is reduced and Arc has little effect on AMPA-receptor. (*Middle*) With normal neuronal activity, Arc molecules play a role to maintain AMPAR trafficking. (*Right*) Arc expression is augmented with persistent high neuronal activity, facilitating the Arc-dependent endocytosis of AMPARs

et al. 2006). However, these pivotal roles of *Arc* in the cell-wide weakening of glutamatergic synaptic strength are irreconcilable with a large body of evidence indicating that *Arc* is most strongly induced by stimuli that evoke LTP (Link et al. 1995; Rodriguez et al. 2008; Ying et al. 2002) and that both *Arc* mRNA and protein accumulate in the dendritic areas that receive high-frequency synaptic inputs (Moga et al. 2004; Steward et al. 1998; Steward and Worley 2001; Wallace et al. 1998). Arc protein is also enriched in the nuclei of neuronal cells, although its function there remains unclear at the moment (Bloomer et al. 2007, 2008; Korb et al. 2013).

6.3 Roles of Arc in Long-Term Synaptic Plasticity and Homeostatic Plasticity

Long-lasting synaptic enhancement (i.e., LTP) and suppression (i.e., LTD) are two major forms of synaptic plasticity; they function as the principal cellular mechanisms underlying memory formation and storage (Bliss and Collingridge 1993; Morris et al. 2003; Nabavi et al. 2014). *Arc* is induced effectively in neurons by various stimuli that evoke LTP and LTD (Link et al. 1995; Messaoudi et al. 2002; Waung et al. 2008). Importantly, the fact that LTP and LTD are impaired in *Arc*-deficient mice directly suggests the involvement of *Arc* in both forms of synaptic plasticity (Park et al. 2008; Plath et al. 2006). In particular, compelling evidence indicates that *Arc* plays crucial roles in various LTD processes. In the hippocampal CA1 region, *Arc* is upregulated in approximately 40 % of pyramidal cells after rodents are exposed to a novel environment (Guzowski et al. 1999; Ramirez-Amaya et al. 2005). Interestingly, LTD is preferentially induced in cells expressing *Arc* upon novelty exposure but not in *Arc*-negative neurons (Jakkamsetti et al. 2013). *Arc* mRNA is present in the dendritic regions, and its local translation to Arc protein is implicated in a site-specific LTD mechanism (Waung et al. 2008). Furthermore, rapid induction of Arc after LTD-inducing stimulation plays a role in cerebellar LTD in Purkinje cells (Smith-Hicks et al. 2010). Several studies show that *Arc* is also involved in LTP induction or maintenance, although the molecular mechanisms underlying synaptic enhancement remain obscure (Messaoudi et al. 2007; Plath et al. 2006).

Arc is also implicated in other types of synaptic adaptive changes, termed synaptic homeostasis. Synaptic scaling is a cell-wide homeostatic mechanism that changes the strength of all synapses in response to the perturbation of synaptic inputs (Turrigiano 2008, 2012). Through this mechanism, when the synaptic activity of neurons in the neuronal network is chronically suppressed, for example by the sodium channel blocker tetrodotoxin, the strength of neuronal synapses is globally augmented. Meanwhile, opposite situation such as chronic enhancement of synaptic activity with GABA receptor antagonists result in globally reduced synaptic efficiency. This bidirectional change at each synapse occurs in proportion to the initial strength (i.e., a multiplicative function), thus termed synaptic scaling. Synaptic scaling is generally thought to be advantageous for maintaining neuronal excitability within a certain dynamic range without affecting relative balance between strong and weak synapses (Turrigiano 2008). Activity-regulated Arc expression together with Arc's role in promoting AMPAR endocytosis constitutes a cell-autonomous mechanism that accounts for the homeostatic control of AMPAR surface expression levels (Shepherd and Huganir 2007). If all synaptic activity is chronically suppressed, neurons will shut down activity-dependent Arc expression. This reduction of Arc expression would favor the enhancement of synaptic strength, leading to the augmentation of cellular excitability. Conversely, if neurons continuously receive strong inputs to a majority of synapses, Arc will be robustly induced and accumulate throughout the neuronal somata and dendrites. In turn, this augmented Arc

expression would reduce overall synaptic strength within the activated neurons, decreasing responsiveness to excitatory inputs. In this way, cellular responsiveness or excitability is homeostatically controlled, at least in part, by activity-regulated Arc expression (Fig. 6.2b). Consistent with this model, synaptic scaling of AMPARs is lost in neurons lacking *Arc* (Beique et al. 2011; Shepherd et al. 2006).

6.4 Inverse Synaptic Tagging of Arc

The maintenance of long-term synaptic plasticity requires *de novo* synthesis of transcripts and proteins during a particular time window after synapses receive plasticity-inducing stimuli (Cooke and Bliss 2005; Kandel 2001; Morris et al. 2003; Okuno 2011). During this time window, newly synthesized plasticity-related proteins are thought to act at postsynaptic sites to facilitate the establishment and maintenance of long-term synaptic modifications (Redondo and Morris 2011; Rogerson et al. 2014). However, a fundamental question remains: how do the plasticity-related proteins, which are synthesized at the soma and dendrites, selectively target the synapses undergoing plastic changes? The synaptic tagging and capture hypothesis adopts a conceptual framework in which activity-triggered local changes at synaptic sites (i.e., synaptic tagging) permit the use of activity-induced plasticity-related proteins (i.e., capture) to stabilize and maintain changes in synaptic efficacy (Frey and Morris 1997; Martin et al. 2000; Morris 2006). The synaptic tagging and capture hypothesis succinctly explains how protein synthesis-dependent LTP reconciles input-specific synaptic modifications with the broad cellular distribution of newly synthesized proteins required for LTP maintenance (Govindarajan et al. 2006; Redondo and Morris 2011).

An opposite but non-mutually exclusive hypothesis is the *inverse* synaptic tagging model, which assumes the existence of synaptic tags that mark *non-potentiated* synapses and are involved in processes to prevent these synapses from being strengthened. A recent study indicates that Arc is involved in such an inverse synaptic tagging process (Okuno et al. 2012). The framework of the inverse synaptic tagging of Arc is described below.

6.4.1 Activity-Induced Arc Is Preferentially Accumulated in Inactive Synapses

As described above, *Arc* mRNA and protein expressions are tightly regulated by synaptic activity; LTP-inducing stimulation is the one of the most effective stimuli for inducing *Arc* in the hippocampus (Link et al. 1995; Moga et al. 2004; Steward et al. 1998). Furthermore, *Arc* mRNA and protein accumulate around the dendritic areas where strong inputs are delivered (Moga et al. 2004; Steward and Worley 2001; Wallace et al. 1998). Based on these observations, it is widely speculated that

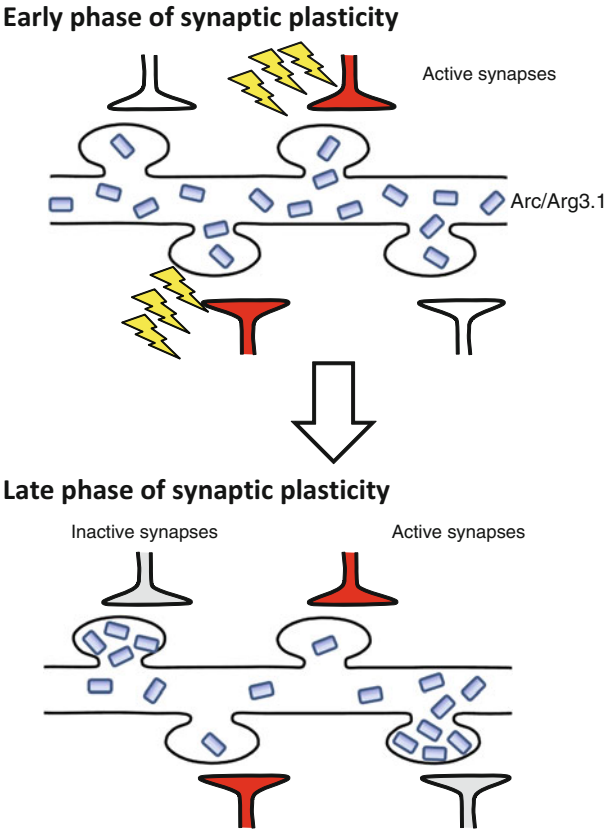

Fig. 6.3 Selective accumulation of activity-induced Arc/Arg3.1 in inactive synapses during the late phase of synaptic plasticity. Upon receiving plasticity-inducing synaptic inputs, newly synthesized Arc is delivered to the dendrites (*top*). Arc is then gradually lost from active synapses but accumulates in inactive synapses during a following period (*bottom*). This Arc accumulation in the inactive synapses relies upon selective interaction with the inactive form of CaMKIIβ

Arc protein directly regulates LTP induction and/or maintenance at LTP-expressing synapses (Bramham et al. 2010). However, recent experimental evidence suggests otherwise; Arc protein accumulates at the postsynapse when neuronal activity is pharmacologically suppressed both *in vitro* and *in vivo* (Kim et al. 2012; Okuno et al. 2012). Consistently, the synapse-specific presynaptic inhibition with tetanus toxin results in the site-specific accumulation of Arc protein at the postsynapses opposed to the inhibited presynapses. These experimental results suggest that Arc preferentially targets postsynapses under synaptically inactivated conditions (Fig. 6.3). If so, how does newly synthesized Arc behave in dendrites when synapses are activated, for example, by LTP-inducing stimulation? Administration of strong synaptic inputs leads to volume expansion in a subset of postsynapses, which reliably represents synaptic enhancement in individual synapses (Harvey and Svoboda 2007; Matsuzaki et al. 2004). Live imaging of Arc dynamics at dendrites shows that

newly synthesized Arc at the soma is less incorporated in expanded synapses, which are presumably active LTP-induced sites, compared to non-expanded inactive synapses (Okuno et al. 2012). These findings collectively indicate the preferential targeting of activity-induced Arc protein into inactive rather than active synapses (Fig. 6.3).

6.4.2 *Molecular Mechanisms of Arc Accumulation in Inactive Synapses: Dynamic Interaction between Arc and CaMKIIβ*

Arc protein possesses several domains involved in protein-protein interactions; biochemical screening has indeed unveiled several proteins that interact with Arc (Fig. 6.1b) (Bloomer et al. 2007; Chowdhury et al. 2006; Donai et al. 2003; Korb et al. 2013). Some Arc-interacting proteins are related to endocytic processes, while others are synaptic or nucleic proteins. Among those, so far reported, calcium/calmodulin dependent kinase type II (CaMKII) is the only protein whose interaction with Arc is dynamically regulated (Okuno et al. 2012).

CaMKII is one of the most abundant proteins associated with the postsynaptic density and acts as a key signaling mediator that may decode the spatiotemporal patterns of Ca^{2+} mobilization into kinase activity (Hudmon and Schulman 2002; Kennedy 2000; Lisman et al. 2002). CaMKII dynamically changes its conformation upon Ca^{2+} and calmodulin binding. Under Ca^{2+}/CaM-unbound conditions, the catalytic domain of CaMKII is masked by its regulatory domain (i.e., autoinhibitory domain), thus suppressing its kinase activity (Giese et al. 1998; Irvine et al. 2006). This state of CaMKII is referred to as its inactive form. Upon Ca^{2+}/CaM-binding, the autoinhibitory domain moves away from the catalytic domain; in this state, CaMKII exerts kinase activity on its substrates (i.e., active form). Two neuron-specific isoforms, CaMKIIα and CaMKIIβ, which are both expressed at synapses, have been suggested to have distinct biochemical properties and physiological roles in the regulation of synaptic functions (Fink et al. 2003; O'Leary et al. 2006; Okamoto et al. 2007; Thiagarajan et al. 2002). Interestingly, despite the overall high similarity between these isoforms, CaMKIIα and CaMKIIβ act differently on Arc protein. The inactive form of CaMKIIβ has a higher affinity for Arc than its active form, while the active form of CaMKIIα binds more readily to Arc than its inactive form (Okuno et al. 2012). Furthermore, CaMKIIβ has greater affinity for Arc than CaMKIIα. Therefore, CaMKIIβ rather than CaMKIIα likely plays a dominant role in Arc regulation at neuronal synapses. Because the activity state of CaMKII is mainly regulated by synaptic activity at the postsynaptic site (Fujii et al. 2013; Lee et al. 2009), Arc's synaptic localization at inactive synapses is possibly regulated through the strongest interaction between inactive CaMKIIβ and Arc, especially under synaptically suppressed conditions. Indeed, CaMKIIβ knockdown or knockout results in a dramatic decrease in Arc enrichment at synapses both *in vitro* and *in vivo* (Okuno et al. 2012).

CaMKIIβ is structurally distinct from CaMKIIα in that it has a unique amino acid sequence essential for specific binding to F-actin (O'Leary et al. 2006; Okamoto et al. 2007; Shen et al. 1998). Furthermore, Arc binds indirectly to F-actin (Lyford et al. 1995). Therefore, the inactive form of CaMKIIβ could serve as a molecular scaffold linking F-actin and Arc at the postsynaptic density. Interestingly, the F-actin/CaMKIIβ complex is disrupted in the presence of Ca^{2+}/CaM (Fink et al. 2003; O'Leary et al. 2006; Okamoto et al. 2007), similar to the destabilization of the Arc interaction with active CaMKIIβ. Therefore, sustained low Ca^{2+} concentration during synaptic inactivity would favor the stabilization of the F-actin/CaMKIIβ/Arc complex. However, it remains unclear whether the F-actin/CaMKIIβ/Arc complex accounts for Arc's effect on dendritic spine morphology (Peebles et al. 2010).

6.4.3 Arc in Inactive Synapses Reduces AMPAR Expression

At the postsynapse, Arc reduces the surface expression of AMPARs by facilitating endocytic processes (Fig. 6.2) (Chowdhury et al. 2006; Rial Verde et al. 2006). Thus, the preferential targeting of Arc to less active synapses via interaction with inactive CaMKIIβ would provide a mechanism for the synapse-specific control of AMPAR trafficking according to the history of local synaptic activity and inactivity. Indeed, the concentration of Arc at synapses during inactivity is negatively correlated with the surface expression levels of the GluA1 subunit of AMPARs at individual synapses (Fig. 6.4a) (Okuno et al. 2012). These findings indicate that the degree of maintenance of newly synthesized Arc in the synaptic pool quantitatively determines GluA1 turnover in an input-specific manner. Furthermore, the down-regulation of GluA1 surface expression in Arc-containing synapses but not Arc-lacking synapses is consistent with the notion that an inactivity-modulated concentration gradient of Arc plays a role in the clearance of initially upregulated GluA1 from less active synapses during the late phase of LTP (Kim et al. 2012). Because the number of glutamate receptors at the postsynaptic surface directly determines synaptic strength between neurons, Arc's role in AMPAR regulation critically contributes to maintaining weak synapses weak, while allowing strong, essential synapses to remain strong (Fig. 6.4b).

6.4.4 Inverse Synaptic Tagging

Although it is postulated and widely accepted that the tag-captured plasticity-related protein interaction provides the basis for the persistence of enhanced synaptic strength at stimulated inputs, the Arc dynamics described above suggest an alternative scenario (Fig. 6.5). In this scenario, some "inverse tags" may be specifically generated to sort newly synthesized plasticity-related proteins to inactive synapses via a molecular inactivity-sensing mechanism, thereby facilitating the shunting of

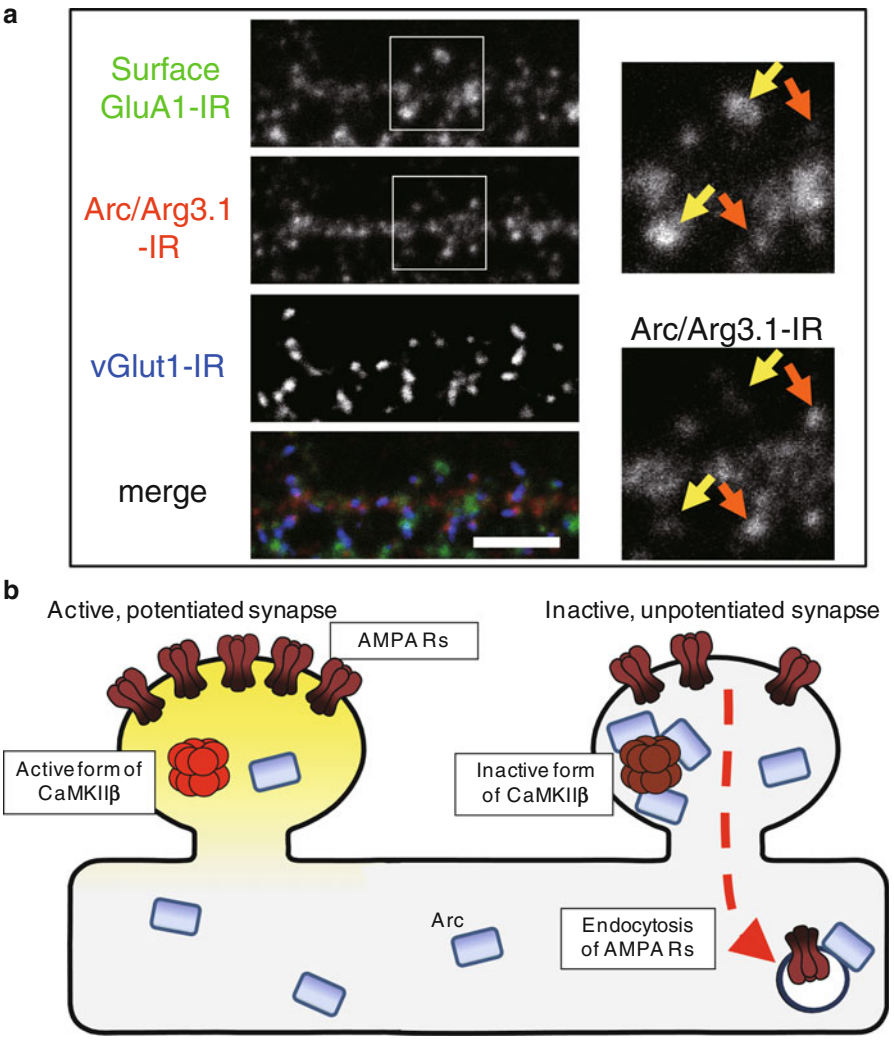

Fig. 6.4 Synapse-specific regulation of AMPARs by Arc/Arg3.1. (**a**) Synaptic Arc concentration determines surface expression levels of GluA1 in individual synapses. Representative triple immunostaining of a dendritic segment from hippocampal neurons in which Arc is induced and accumulates in synapses during synaptic inactivation. Framed areas are expanded on the *right*. Some spines contained high surface GluA1 signals but low Arc signals (*yellow arrows*), whereas others displayed the opposite pattern (*orange arrows*). Scale bar, 5 μm. Figures are reproduced from Okuno et al. (2012) with permission of Elsevier. (**b**) A model of Arc function on AMPAR clearance at active and inactive synapses. The surface expression of AMPARs is augmented at the synapses that receive strong inputs, which also trigger Arc induction. During the late phase of post stimulation, Arc is differently maintained in the synapses depending on the amount and history of synaptic activity. In the synapses that receive frequent inputs (active synapses), CaMKIIβ more likely to be activated, and thus its interaction with Arc is often weakened. As a result, Arc tends to flow out from the synapses. In contrast, synapses with low activity (inactive synapses) are more likely to contain the inactive form of CaMKIIβ, which provides a scaffold for Arc at the synapse. The CaMKIIβ-stabilized Arc has a greater chance to form a complex with the endocytic machinery, which subsequently promotes AMPA-R clearance from the synapse. Through such an activity-dependent control of synaptic localization, Arc may contribute to synaptic homeostasis while active, potentiated synapses remain unaffected (Color figure online)

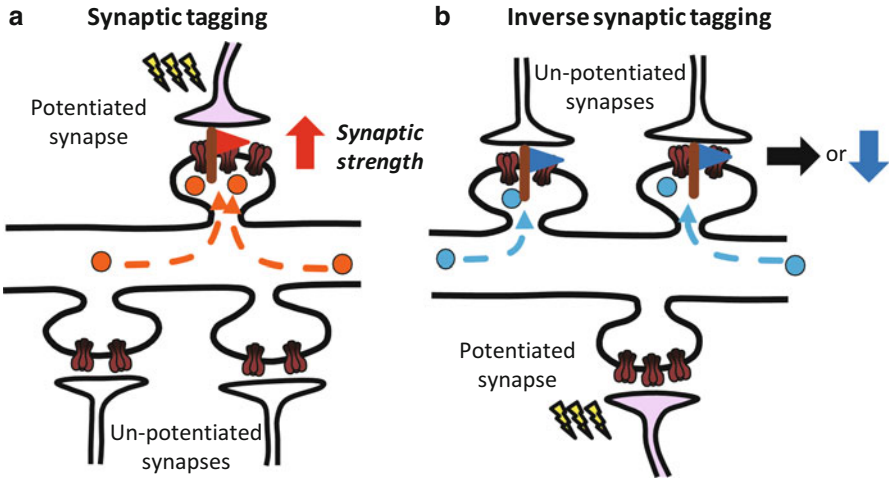

Fig. 6.5 Synaptic tagging and inverse synaptic tagging models. (**a**) Synaptic tagging. During the induction phase of LTP, plasticity-inducing stimuli develop a putative signature (tag) within the activated synapses (a *red flag*). This "synaptic tag" serves as a mark to distinguish the synapses to be potentiated from other non-stimulated synapses, and stimulus-induced plasticity-related proteins (*red circles*) are then captured based on the presence of the synaptic tags. The plasticity-related proteins are required to maintain the synaptic enhancement during the late phase of LTP. (**b**) Inverse synaptic tagging. In contrast to the synaptic tagging, the inverse synaptic tag (*blue flags*) is created in synapses other than the synapse to be potentiated. The stimulus-induced negative plasticity-related proteins (*blue circles*) are captured in the non-potentiated synapses, and play a role in preventing un-desired synaptic augmentation during the late phase of LTP (Color figure online)

weak inputs. In other words, some plasticity-related proteins might be excluded from active synapses that contain an active synaptic tag and would instead be captured by neighboring inactive synapses expressing an inverse tag such as inactive CaMKIIβ. The selective avoidance of actively tagged synapses by a negative plasticity factor such as Arc via a preferential interaction with an inverse tag may be considered the conceptual opposite of the classical notion of "synaptic tag and capture," and could thus be termed an "inverse synaptic tagging" process (Fig. 6.5). However, in principle, these two mechanisms could well function in parallel, thereby ensuring that the contrast between strong and weak inputs remains stable over time. This novel working model of the synapse-specific role of activity-induced Arc at less active synapses may well reconcile the requirement for Arc during the late phase of various forms of long-term synaptic plasticity as well as Arc's demonstrated role as a cell-wide mediator of AMPAR endocytosis during homeostatic plasticity and synaptic scaling (Shepherd and Bear 2011). Furthermore, the model provides new mechanistic insights on how the contrast between strong and weak synapses is maintained during long-term synaptic plasticity.

6.4.5 Synaptic Elimination

During postnatal development, neuronal circuits in the brain are initially formed through highly active synaptogenesis around birth. Subsets of synapses are subsequently selected and strengthened in a usage-dependent and activity-regulated manner, while many excess unnecessary synapses are weakened and eventually eliminated (Katz and Shatz 1996; Lichtman and Colman 2000). Many distinct molecular and cellular mechanisms appear to be involved in the synaptic elimination processes depending on the brain region and neuronal circuit. One of the most well-studied synaptic elimination occurs in the developing cerebellum, wherein Purkinje cells initially innervated by multiple climbing fibers are later dominated by a single climbing fiber during the course of postnatal development (Kano and Hashimoto 2009); *Arc* was recently reported to be critically involved in this process (Kawata et al. 2014; Mikuni et al. 2013). The studies show the Purkinje cell-specific knockdown of *Arc* both *in vitro* and *in vivo* significantly interfere with surplus climbing fiber elimination. Together with the evidence that Purkinje cell activation induces *Arc* mRNA and protein expression in the developing cerebellum (Mikuni et al. 2013; Smith-Hicks et al. 2010) and that weak climbing fiber synapses are preferentially subjected to synapse elimination (Hashimoto et al. 2009; Hashimoto and Kano 2003), these observations are concordant with the notion that Arc plays a role in suppressing synaptic strength at inactive, weak synapses through the inverse synaptic tagging mechanism.

In the mature brain, although the rate is substantially reduced, synaptogenesis and synaptic elimination still occur continuously (Bhatt et al. 2009; Holtmaat and Svoboda 2009). Recent advances in imaging technologies and molecular genetics clearly demonstrate that synaptic structural dynamics is correlated with cognitive functions including memory formation and storage (Fu and Zuo 2011; Kasai et al. 2003). A recent study shows that during fear memory formation, synapse elimination is selectively observed in active hippocampal neurons in contextual fear-conditioned mice (Sanders et al. 2012); such synaptic changes could represent a compensatory adaptation to enhanced synaptic strength in a subset of synapses during learning although whether or not these eliminated spines were functional remains unclear in the study. Provided that active neurons express Arc in the hippocampus, the synapse elimination observed in that study is also consistent with Arc's role in inverse synaptic tagging.

6.4.6 Role of Arc in Memory Formation

Several independent lines of Arc-null mice exhibit a wide range of cognitive deficits in tasks related to spatial memory, fear memory, taste aversion, and object recognition (Peebles et al. 2010; Plath et al. 2006). Consistently, Arc knockdown by antisense oligonucleotides in rats results in spatial and fear memory impairment

(Czerniawski et al. 2011; Guzowski et al. 2000; Ploski et al. 2008). In addition, cortical plasticity and neuronal representation are abnormal in *Arc*-knockout mice (Gao et al. 2010; McCurry et al. 2010; Wang et al. 2006). These lines of evidence strongly indicate *Arc* is indispensable for long-term memory formation and normal cortical responsiveness in the brain. Such Arc-dependent memory formation and cortical plasticity could be realized through inverse synaptic tagging of Arc, which functions to stabilize the contrast between strong and weak inputs over time by preventing undesired synaptic enhancement at weak synapses while sparing potentiated synapses.

Behavioral tagging is a phenomenon that could be interpreted as *in vivo* evidence of the synaptic tagging demonstrated in brain slices or cultured cells (Viola et al. 2014). In this paradigm, a weak training protocol that normally only produces short-term memory can be transformed to create long-term memories if the training is combined with a novel experience during a critical time window around the training (Ballarini et al. 2009; Moncada et al. 2011; Wang et al. 2010). *Arc* knockdown by antisense-oligonucleotides was recently reported to interfere behavioral tagging processes (Martínez et al. 2012). However, how *Arc*'s role in the inverse tagging process contributes to memory enhancement in the context of behavioral tagging remains to be investigated.

6.5 Conclusions

This chapter summarizes the function of the neuronal immediate early gene *Arc* and its possible roles in the inverse synaptic tagging process. The inverse synaptic tagging of Arc presents new mechanistic insights on how the contrast between strong and weak synapses may be maintained during long-term synaptic plasticity, and shed light on the fundamental role of the targeting of activity-induced gene products to synapses as a molecular basis of memory allocation at individual synapses. During the past decade, Arc has become recognized as a key regulator of synaptic plasticity and cognitive functions in the brain (Bramham et al. 2010; Okuno 2011; Shepherd and Bear 2011). As discussed above, the dysregulation of *Arc* caused abnormal neuronal circuit refinement, deficits in neuronal plasticity, and impaired memory function. Animal models implicate *Arc* in various neurodevelopmental disorders including fragile X syndrome (Park et al. 2008) and autism (Auerbach et al. 2011) as well as neurodegenerative diseases such as Alzheimer disease (Rudinskiy et al. 2012; Wu et al. 2011). Furthermore, recent large-scale human genetic studies suggest that mutations in patients with Schizophrenia are overrepresented in genes associated with the Arc signaling complex (Fromer et al. 2014; Kirov et al. 2012; Purcell et al. 2014). Therefore, further investigation of *Arc*'s role in the inverse synaptic tagging process is required to advance our understanding of how the brain manages memory and cognitive functions under normal and pathological conditions.

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