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Signaling networks in focus

Arg kinase signaling in dendrite and synapse stabilization pathways: Memory, cocaine sensitivity, and stress

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ABSTRACT

The Abl2/Arg nonreceptor tyrosine kinase is enriched in dendritic spines where it is essential for maintaining dendrite and synapse stability in the postnatal mouse brain. Arg is activated downstream of integrin α3β1 receptors and it regulates the neuronal actin cytoskeleton by directly binding F-actin and via phosphorylation of substrates including p190RhoGAP and cortactin. Neurons in mice lacking Arg or integrin α3β1 develop normally through postnatal day 21 (P21), however by P42 mice exhibit major reductions in dendrite arbor size and complexity, and lose dendritic spines and synapses. As a result, mice with loss of Arg and Arg-dependent signaling pathways have impairments in memory tasks, heightened sensitivity to cocaine, and vulnerability to corticosteroid-induced neuronal remodeling. Therefore, understanding the molecular mechanisms of Arg regulation may lead to therapeutic approaches to treat human psychiatric and neurodegenerative diseases in which neuronal structure is destabilized.

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Signaling network facts

- Abl2/Arg is unique among nonreceptor tyrosine kinases because of its ability to directly bind the actin cytoskeleton and microtubules.
- Neurons in mice that lack Arg develop normally, but by late adolescence *arg*−/− mice have significantly smaller dendrite arbors, reduced numbers of dendritic spines and synapses, altered synapse morphology, and impairments in behavior.
- Arg differentially regulates dendrite maintenance and synapse stability via distinct biochemical mechanisms.
- Mutations in Arg signaling networks have been implicated in a variety of human disorders, including autism spectrum disorders, drug addiction, and schizophrenia.

1. Introduction

Neurons in the developing brain dynamically reorganize their dendritic branches and spines in order to acquire elaborate morphologies and integrate into active signaling networks. Once formed, however, neuronal structure must be maintained for extended periods of time to ensure proper connectivity. In fact, the destabilization of neuronal structure is commonly observed in many psychiatric and neurodegenerative diseases, where it is a contributing factor that compromises brain function. Research over the past decade has elucidated distinct signaling cascades that regulate long-term dendrite and dendritic spine stability (Lin and Koleske, 2010). This review will focus on Arg, a central regulator of neuronal stability. Arg (Abl-related gene, or Abl2) and its paralog Abl are the vertebrate members of the Abl nonreceptor

Abbreviations: Arg, Abl-related gene; F-actin, filamentous actin; SH2, SH3, Src homology domain 1,2; P21, P42, postnatal day 21, 42; *argKD*, *arg* knockdown; p190, p190RhoGAP, 190 kDa GTPase activating protein for Rho; p120, p120RasGAP, 120 kDa GTPase activating protein for Ras; PH, pleckstrin homology domain; CaLB, Ca^{2+}-dependent phospholipid binding domain; NMDA, *N*-methyl-D-aspartate receptor; mEPSC, miniature evoked postsynaptic current; NTA, N-terminal acidic domain; ECM, extracellular matrix.

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tyrosine kinase family that also includes *Caenorhabditis elegans* Abl, and *Drosophila* (D-) Abl. These kinases play fundamental roles in translating extracellular signals from adhesion and growth factor receptors into cytoskeletal rearrangements that power changes in cell shape and movement (Bradley and Koleske, 2009).

Arg is most highly expressed in the brain, where it is enriched in dendritic spines, reaching a concentration of 400–600 nM (Koleske et al., 1998). The Arg N-terminal half has tandem SH3, SH2, and kinase domains. The SH3–SH2 domains form an inhibitory scaffold that engages the back of the kinase domain and holds it in an inactivate state (Nagar et al., 2003). Engagement of the SH3, SH2, or kinase domains with cell-surface receptors, kinase substrates, or adaptor proteins is believed to release this inhibitory conformation and allow kinase activation. Additionally, following this release, kinase activation can be reinforced by phosphorylation of key tyrosine residues in the activation loop and the linker region between the SH2 and kinase domain (Bradley and Koleske, 2009; Tanis et al., 2003). Abl family kinases also contain unique C-terminal extensions that interact with cytoskeletal regulators and directly with the actin and microtubule cytoskeletons. In particular, Arg, has at least three tandem SH3 domain binding motifs (P-XX-P), two distinct F-actin binding domains, and a microtubule binding domain (Bradley and Koleske, 2009; MacGrath and Koleske, 2012; Miller et al., 2004; Wang et al., 2001).

2. Functions

Arg signaling is essential for diverse physiological roles beyond the scope of this review, including breast cancer invasion and metastasis, viral, bacterial, and parasite infection, T cell development, and neurotransmitter release (Bradley and Koleske, 2009). This review will focus on Arg function in the regulation of neuronal structural stability.

2.1. Memory

Dendrites and synapses develop normally in the hippocampus and cortex of mice lacking *arg* and are indistinguishable from wild type littermates in size and morphology by weaning at postnatal day 21 (P21). However, these structures are destabilized by early adulthood (P42), leading to significantly smaller dendrite arbors and a 30% loss of synapses, Fig. 1 (Gourley et al., 2012; Moresco et al., 2005; Sfakianos et al., 2007). Knockdown of *arg* (*argKD*) in neuronal cultures recapitulates the dendrite morphology and dendritic spine reductions found in vivo, indicating that Arg functions cell-autonomously to control morphological stability (Lin et al., 2013). In mice, the loss of dendrites and synapses correlates temporally with the onset of impairment in novel object recognition, a behavior that is dependent on proper hippocampal and cortical connectivity. For example, *arg*−/− mice can identify an object as novel at P21, but lose this ability as they age to adulthood.

2.2. Cocaine sensitivity

Arg has also been implicated in structural changes produced in response to cocaine administration. Chronic exposure to drugs of abuse causes dendritic spine rearrangements, behavioral inflexibility, drug sensitization, and ultimately addiction. For example, repeated cocaine administration reduces dendritic spine density and increases the head size of spines that remain within the prefrontal cortex (Gourley et al., 2012). The dendrites in *arg*−/− mice already contain fewer spines and the remaining spines do not enlarge in response to cocaine. As a result, Arg-deficient mice have an increased psychomotor response and behavioral sensitivity to cocaine administration (Gourley et al., 2009, 2012). Alterations in other key components of the Arg signaling cascade may also contribute to cocaine-induced pathology. For example, integrin β1 receptor, a major Arg regulator in the brain, shows increased expression following cocaine exposure (Wiggins et al., 2009) and its loss results in exaggerated psychomotor sensitivity to cocaine (Warren et al., 2012).

2.3. Stress

The stress hormone corticosterone contributes to structural remodeling of dendrites and dendritic spines in multiple brain regions including the hippocampus, prefrontal cortex, and amygdala. Repeated stressor exposure induces immediate structural rearrangements (Vyas et al., 2002), as well as persistent loss of dendritic arbors and spines in distinct brain regions (Gourley et al., 2013). Interestingly, mice with a reduced gene dosage of the Arg substrate *p190RhoGAP* are vulnerable to behavioral and structural impairments at sub-threshold corticosterone exposure (Gourley et al., 2013), suggesting that Arg-mediated signaling events may contribute to neuronal response to stressor exposure. Future studies should identify the specific biochemical mechanism(s) responsible for this vulnerability.

3. Cascades

3.1. p190RhoGAP-RhoA control of dendrite stability

The Rho GTPase inhibitor p190RhoGAP (p190) is a major substrate of Arg. In neurons, active p190 inhibits RhoA GTPase to regulate dendrite arbor size (Hernandez et al., 2004; Sfakianos et al., 2007). Arg phosphorylates p190 on Y1105, which, along with a second phosphorylation site Y1087, promotes p190 binding to two SH2 domains in p120RasGAP (p120). p120 uses its PH and CaLB domains to recruit the p190:p120 complex to the plasma membrane of cells where it attenuates RhoA GTPase activity at the cell edge (Bradley et al., 2006). Elevated RhoA activity in neurons destabilizes dendrites via downstream effectors including ROCKII (Sfakianos et al., 2007; Threadgill et al., 1997). Thus, Arg signaling through p190:p120 complex in neurons acts as a brake on RhoA activation to preserve dendrite stability. Reducing RhoA or ROCKII signaling in *arg*−/− mice and *argKD* cultures blocks hippocampal dendrite loss. However, this reduction in RhoA activity does not rescue synapse loss, resulting in fully elaborated dendritic arbors that have significantly fewer spines (Lin et al., 2013; Sfakianos et al., 2007). These data suggest Arg acts via additional mechanisms to regulate dendritic spine and synapse stability.

3.2. NMDA receptor control of dendritic spine and synapse stability

Our lab has recently found that the reduction of dendritic spine density in *argKD* cultures can be rescued by blocking NMDA receptor activity via inhibition of the NR2B subunit with ifenprodil (Lin et al., 2013). This treatment does not rescue dendrite destabilization resulting in neurons with diminished dendrite arborization, but normal dendritic spine densities along the remaining branches. Furthermore, *argKD* neurons have altered synaptic transmission with a lower frequency and higher amplitude of mEPSCs consistent with the reduced number of synapses and larger spine head size (Lin et al., 2013). NMDA receptor expression and function is regulated by tyrosine phosphorylation of the intracellular tail of NR2B (Gladding and Raymond, 2011), however, mechanistic details of an interaction between Arg and the NMDA receptor are unknown. Future experiments should elucidate whether and how Arg interacts with the NR2B subunit to control synapse and spine stability.

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