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Review

Abnormal kalirin signaling in neuropsychiatric disorders

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ABSTRACT

Changes in dendritic spines structure and function play a critical role in a number of physiological processes, including synaptic transmission and plasticity, and are intimately linked to cognitive function. Alterations in dendritic spine morphogenesis occur in a number of neuropsychiatric disorders and likely underlie the cognitive and behavioral changes associated with these disorders. The neuronal guanine nucleotide exchange factor (GEF) kalirin is emerging as a key regulator of structural and functional plasticity at dendritic spines. Moreover, a series of recent studies have genetically and functionally linked kalirin signaling to several disorders, including schizophrenia and Alzheimer's disease. Kalirin signaling may thus represent a disease mechanism and provide a novel therapeutic target.

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Contents

Introduction

Most excitatory synapses in the mammalian forebrain are located on small protrusions from dendrites called dendritic spines. Actin dynamics can rapidly induce changes in spine morphology, which modulates synaptic properties and the potential for plasticity (Carlisle and Kennedy, 2005; Alvarez and Sabatini, 2007). Spine dynamics are tightly regulated throughout life. During development, spine dynamics play a critical role in neural circuit formation. In mature neurons, synaptic activity drives spine dynamics, contributing to remodeling of neural circuits and experience-dependent plasticity (Carlisle and Kennedy, 2005; Alvarez and Sabatini, 2007). Several decades of research have documented changes in spine size and number associated with a number of physiological, behavioral, and pathological conditions. Importantly, circuit-level analysis indicates that relatively small changes in synapse strength or number may have a much greater effect on the overall function of circuits (Chklovskii et al., 2004; Chen and Nedivi, 2010).

Postmortem neuropathological studies have revealed that dendritic spine morphology and number are altered in a number of disorders of the central nervous system (Penzes et al., 2011). These alterations have been well characterized in intellectual disability, Down's syndrome (Kaufmann and Moser, 2000), Rett syndrome (Zhou et al., 2006), Fragile X syndrome (Bagni and Greenough,

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2005), autism spectrum disorders (ASD) (Hutsler and Zhang, 2010), schizophrenia (Glantz and Lewis, 2000; Sweet et al., 2009) and addiction (Robinson and Kolb, 1997, 2004; Zhou et al., 2007). Furthermore, synaptic pathology has been associated with neurodegenerative disorders including Alzheimer's (Knobloch and Mansuy, 2008), Parkinson's (Day et al., 2006), and Huntington's disease (Spires et al., 2004).

Spine morphogenesis is driven by actin remodeling and membrane trafficking events, which are regulated by small GTPase signaling (Tolias et al., 2011). When they are in the active, GTP-bound state small GTPases promote actin remodeling and trafficking; they become inactive by hydrolyzing GTP to GDP. Abnormal small GTPase signaling has been associated with several human pathologies. Signaling pathways involving Rac and Ras are particularly important since a large proportion of genes causing intellectual disability encode proteins in the small GTPase pathway (Ramakers, 2002; Newey et al., 2005). GTPases are modulated by guanine nucleotide exchange factors (GEFs) and GTPase activating proteins (GAPs). GEFs and GAPs are complex, multidomain signaling proteins that may serve as signaling hubs by integrating multiple signals and have cell- and tissue-specific functions (Carlisle and Kennedy, 2005). Among these, the Rac/Rho-GEF kalirin has been associated with a range of psychiatric and neurodegenerative disorders.

Kalirin expression is highly enriched in the forebrain. The most abundant isoform of the *KALRN* gene, kalirin-7, is localized to dendritic spines on cortical pyramidal neurons (Fig. 1a and b) where it plays a key role in structural and functional plasticity at excitatory synapses (Penzes and Jones, 2008). Kalirin facilitates remodeling of the actin cytoskeleton, leading to changes in spine size and density by activating Rac1 and its downstream effector, p21-activate kinase (PAK) (Penzes et al., 2001, 2003). Kalirin-7 has also been shown to mediate activity-dependent plasticity in dendritic spines. Xie et al. (2007) found that NMDAR activation-induced spine enlargement and increases in synaptic expression of AMPARs were kalirin-7-dependent. Given these well-characterized effects of kalirin on synaptic plasticity at dendritic spines, it seems likely that changes in expression of kalirin, mutations, or alterations of its upstream or downstream signaling partners that occur in human disorders would lead to aberrant dendritic spine number and morphology. Consistent with this, kalirin has been functionally and genetically implicated in the pathogenesis of several human disorders, most of which are associated with changes in cognitive function and present with dendritic spine pathology (Table 1). Here we will discuss recent studies linking aberrant regulation of dendritic spine plasticity by altered kalirin signaling with several psychiatric and neurological disorders.

Kalirin and schizophrenia

Schizophrenia is a psychiatric disorder that affects cognition and perception of reality that impacts 0.5%–1% of the population. Symptoms emerge during late adolescence or early adulthood. The cause of this disease is unknown and there are no effective treatments for the negative and cognitive symptoms. One of the most consistent neuropathological findings in postmortem studies of schizophrenia patients is reduced spine density in forebrain regions. Spine loss in the dorsolateral prefrontal cortex (DLPFC) (Glantz and Lewis, 2000) and auditory cortex has been observed in postmortem studies in schizophrenic patients (Sweet et al., 2009). Loss of dendritic spines has also been reported in the subiculum and CA3 (Kolomeets et al., 2005; Steen et al., 2006). A number of classical regulators of spine plasticity have been genetically and functionally linked to schizophrenia; conversely, the protein products of a number of schizophrenia risk genes have been shown to modulate spine morphology (Penzes et al., 2011). Further investigation of these proteins might shed light on the molecular mechanisms underlying spine pathology in schizophrenia. Interestingly, several lines of evidence link altered kalirin signaling with schizophrenia.

In a postmortem study, kalirin mRNA was found to be reduced in the DLPFC of schizophrenia patients, irrespective of antipsychotic treatment (Hill et al., 2006). Interestingly, kalirin loss correlated with spine loss on layer 3 PFC neurons (Hill et al., 2006). Another postmortem study reported changes in protein levels of kalirin-7 (duo), and other proteins in the kalirin signaling pathway, in the DLPFC and ACC in schizophrenia patients (Rubio et al., 2012). Regional differences are also becoming apparent in kalirin expression in schizophrenia. In a recent study, Deo and colleagues demonstrated that kalirin-9 is upregulated, while other kalirin forms are not altered, in auditory cortex in schizophrenia (Deo et al., 2012). This upregulated kalirin-9 might contribute to reduced dendritic branching in the auditory cortex in schizophrenia, as overexpression of the kalirin-9 isoform in cultured neurons reduced dendritic arborization (Deo et al., 2012).

The above studies implicate kalirin in the pathophysiology of schizophrenia. But what about etiology, does kalirin play a role? A recent genome-wide association study (GWAS) in a Japanese population (Ikeda et al., 2011) detected association signals with schizophrenia at the region of the *KALRN* gene. Although single locus analysis did not reach genome-wide significance, the study confirmed a shared polygenic risk of schizophrenia between the Japanese and the Caucasian samples. An independent study also supported this association (St. Jean, 2008). Following up on these findings, Kushima et al. (2010) re-sequenced all exons of the *KALRN* gene and identified several rare missense mutations enriched in patients with schizophrenia as compared to non-psychiatric controls. A number of these sequence alterations are predicted to have functional and damaging consequences. The authors detected a significant association of the P2255T mutation (OR = 2.09) as well as combined association of all mutations (OR = 2.07) with schizophrenia. One of these mutaions, T1207M, occurs in the spectrin repeat region, proximal to the RacGEF domain that is present in all isoforms of kalirin. Interestingly, several of these mutations are in exons encoding protein domains present in kalirin-9 or -12 but not kalirin-7, including the R2049K mutation in the RhoGEF domain and the P2255T, P2265S and G2296C mutations that are just downstream of the RhoGEF domain. Thus, multiple rare missense mutations in *KALRN* may contribute to genetic risk in schizophrenia.

Kalirin-interacting proteins and schizophrenia

Recent studies also demonstrate that kalirin-7 physically and functionally interacts with several proteins previously implicated in schizophrenia. Kalirin-7 directly interacts with DISC1 (disrupted in schizophrenia) (Millar et al., 2003), the protein product of a leading schizophrenia susceptibility gene. DISC1 functions as a scaffold for kalirin-7, and modulates the access of kalirin-7 to Rac1, controlling the duration and intensity of Rac1 activation in response to NMDAR activation (Hayashi-Takagi et al., 2010). In this context, DISC1 functions as a scaffold that enhances the kalirin-7/PSD-95 interaction. Kalirin's release from DISC1 enhances its GEF activity, thus leading to changes in spine structure. Knockdown of DISC1 in cultured neurons for extended periods of time causes a reduction in spine area (Hayashi-Takagi et al., 2010). If schizophrenia-associated mutations disrupt DISC1's scaffolding function, they would be expected to have deleterious consequences on spine morphogenesis through altered kalirin signaling (Fig. 2).

Kalirin also interacts with and is modulated by the 5-HT_{2A} serotonin receptor (Fig. 2), a target of atypical antipsychotics which has also been genetically linked to schizophrenia (Golimbet