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Commentary

Dendritic spine plasticity as an underlying mechanism of neuropathic pain: Commentary on Tan et al.

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The dendritic spine as a fundamental player in CNS plasticity and its potential role in pain plasticity

Since the time of Ramon y Cajal, the dendritic spine, or "espina" as Cajal first named it, has been an enigmatic figure in the area of neuroscience. At first a prime character in Cajal's neuron doctrine (Ramon y Cajal, 1899), the last two decades have led to remarkable advances in our understanding of the role of dendritic spines in the form and function of the nervous system. Many, but not all, principle neurons in the brain have spines decorating their dendrites and these spines are almost always the postsynaptic site for an excitatory synapse (Arellano et al., 2007). We now know that spines demonstrate remarkable plasticity in response to increases in presynaptic activity and that this plasticity is orchestrated by a complex symphony of signaling localized to the spine (Yuste, 2010; Yuste and Bonhoeffer, 2001). In terms of function, recent studies have shown clear changes in spine morphology in several important neurological developmental disorders and changes in spine shape are linked to major functions of the brain like learning and memory. This latter function appears to be linked to the establishment of long-term potentiation (LTP) suggesting that changes in spine morphology, in particular toward a mushroom-shaped morphology, are a critical component of amplification of synaptic signaling in the CNS (De Roo et al., 2008).

Despite this explosion of interest and understanding in the dendritic spine biology, the role of spine plasticity in chronic pain and/or pain amplification has been largely ignored until relatively recently. Three papers by Andrew Tan, Bryan Hains, Stephen Waxman and colleagues (Tan et al., 2008b, 2009, 2011), the most recent of which was published in this issue of Experimental Neurology (Tan et al., 2011), shed considerable light on the role of spine plasticity in the development and maintenance of neuropathic pain. These papers also open up exciting new areas for pain researchers, affording opportunities to gain more extensive insight into mechanisms underlying chronic pain conditions. To understand these opportunities fully, we should first consider some of the fundamentals of spine plasticity in the brain and then relate these findings to our current understanding of pain amplification mechanisms in the spinal dorsal horn.

Molecular mechanisms of spine plasticity

The revelation that the same conditions that induce LTP also induce morphological changes in dendritic spines mediated by actin polymerization was one of the earliest observations that links structural and functional plasticity (Fifkova, 1985). Many of these changes appear to be linked to brain derived neurotrophic factor (BDNF), which is critical both for the development of dendritic spines and expression of LTP (An et al., 2008; Shimada et al., 1998; Tanaka et al., 2008). BDNF signals, among some other pathways (Yoshii and Constantine-Paton, 2010), through tyrosine receptor kinase B (TrkB) to activate the Phosphatidylinositol-3-kinases (PI3K) pathway (Huang and Reichardt, 2003). PI3K mediates the conversion of PI(4,5)P2 to PI(3,4,5)P3. In cultured hippocampal neurons, PI3K and PI(3,4,5)P3 concentrates at the tip of protrusions that will eventually differentiate into an axon. Moreover, the activation of the PI3K pathway is important for polarization during axonal development and its inhibition mislocalizes the polarity proteins PAR3 and PAR6, indicating the importance of the PAR complex as downstream effectors of PI3K induced neuronal polarization (Shi et al., 2003). A conserved

Abbreviations: AMPA, 2-amino-3-(5-methyl-3-oxo-1,2-oxazol-4-yl)propanoic acid; aPKC, atypical protein kinase C; BDNF, brain derived neurotrophic factor; CCI, chronic constriction injury; DHPG, dihydroxyphenylglycine; FMRP, fragile X mental retardation protein; IL-6, interleukin 6; KO, knockout; LIMK, LIM Kinase; LTD, long-term depression; LTP, long-term potentiation; mGluR1/5, metabotropic glutamate receptor 1/5; NK1, neurokinin receptor type 1; PAK, p21-associated kinase; PDK1, phosphoinositide-dependent kinase 1; PI3K, phosphatidylinositol-3-kinases; PAR, polarity complex proteins; PGE_2, prostaglandin E_2; PKCζ, protein kinase Cζ; PKMζ, protein kinase Mζ; PP, protein phosphatase; Rac1, ras-related C3 botulinum toxin substrate 1; Tiam1, T-cell lymphoma invasion and metastasis 1; TrkB, tyrosine receptor kinase B; WDR, wide dynamic range.

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signaling pathway comprised of the Rho GTPase ras-related C3 botulinum toxin substrate 1 (Rac1), PAR3, PAR6 and atypical protein kinase C (aPKC) mediates cellular polarity in various biological contexts (Macara, 2004). PAR3 spatially restricts the Rac1 guanine exchange factor T-cell lymphoma invasion and metastasis 1 (Tiam1) to dendritic spines which allows for localized activation of Rac1 and actin-dependent dendritic spine morphogenesis (Zhang and Macara, 2006). Moreover, evidence suggests the activation of atypical protein kinase C (aPKC) may be dependent on the activity of PI3K and Rac1 (Ghosh et al., 2008). Ectopic expression of constitutively active aPKC results in increased density of dendritic spines while the expression of the kinase dead mutant fails to produce mature spines (Zhang and Macara, 2008). Collectively, current evidence suggests that Rac1-PARs-aPKCs may act as complex that mediates the genesis and maturation of dendritic spines (Fig. 1A).

Substantial evidence demonstrates that Rac1 activity is essential for the maturation of dendritic spines (Zhang and Macara, 2006). Rac1 activates p21-associated kinase (PAK), which activates LIM kinase. This cascade results in the phosphorylation of ADF/cofilin, a key regulator of actin polymerization (Yang et al., 1998). ADF/cofilin is dephosphorylated by protein phosphatase (PP)2Ac (Castets et al., 2005) and Slingshot (Van Troys et al., 2008). ADF/cofilin phosphorylation (inactivation) and dephosphorylation (activation) correlate with spine growth and shrinkage during LTP and long-term depression (LTD) respectively (Chen et al., 2007; Fedulov et al., 2007; Rex et al., 2009; Zhou et al., 2004). Interestingly, this process may be

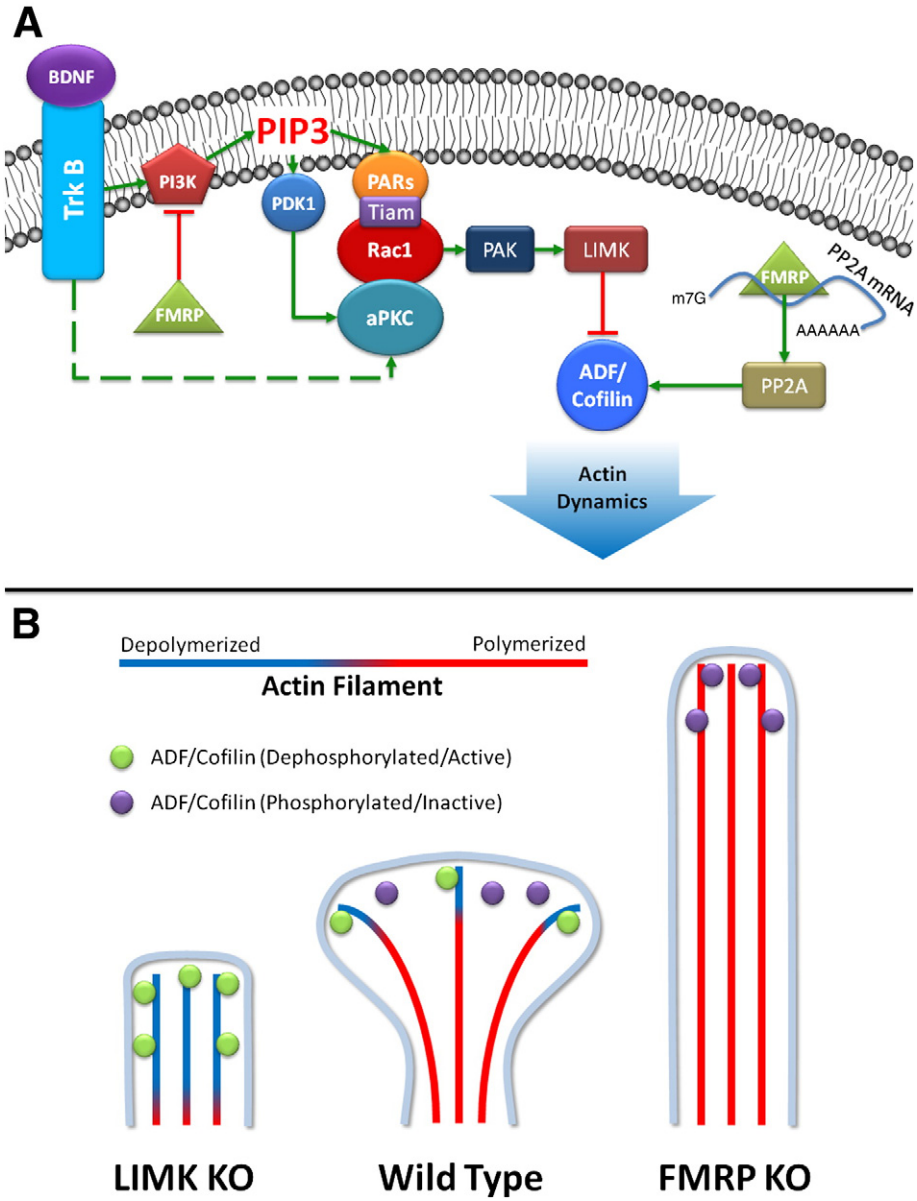

Fig. 1. A) BDNF signals through the TrkB receptor to activate PI3K. PI3K in turn mediates the conversion of PIP2 to PIP3, both PI3K and PDK1 accumulate at the leading tip of growing protrusions that would differentiate into a dendritic spine. PIP3 recruits the polarity protein PARs which can activate Tiam, leading to the activation of Rac1. This allows for a localized activation of Rac1 and prevents its inappropriate activation. aPKCs function in a complex which include PARs and Rac1. The activity of aPKCs is dependent on Rac1 and PI3K-PDK1. Rac1 activates PAK which in turn activates LIMK. ADF/cofilin, a key regulator of actin polymerization, is phosphorylated by LIMK and dephosphorylated by PP2A. FMRP represses the function of PI3K and recruits PP2A mRNA. B) Systematic spatially and temporally regulated activation of various pathway leads to the sculpting of mushroom-shaped dendritic spines. ADF/cofilin activation and inactivation at the tip of a growing spine depolymerizes actin, which in concert with other pathways allows for the formation of mushroom shaped spine *(wild type)*. Genetic loss of LIMK, which causes Williams Syndrome, leads to excessive ADF/cofilin activation due to dephosphorylation leading to increased depolymerization of actin and production of "stubby" spines *(LIMK KO)*. Loss of FMRP function causes Fragile X Syndrome which leads to increased PI3K activity and ADF/cofilin inactivation, causes increased polymerization of actin and long dendritic spines. Loss of FMRP may also prevent the localized expression of PP2A leading to dysregulation in local ADF/cofilin activation and actin depolymerization *(FMRP KO)*.