Editorial: Exciting Dendritic Spines

Chi W. Pak and James R. Bamburg*

Department of Biochemistry and Molecular Biology, Molecular, Cellular and Integrative Neuroscience Program and Cell and Molecular Biology Program, Colorado State University, Fort Collins, CO 80523, USA

This special issue of The Open Neuroscience Journal features articles about dendritic spine architecture, dynamics and function in health and disease. This introductory article provides an overview and perspective for the various contributions.

The ability of a synapse to alter its strength based on use (synaptic plasticity) reigns as the basis of most cellular models of learning and memory [1]. However, if synaptic plasticity is king, then the dendritic spine is its kingdom. The dendritic spine, which houses the majority of excitatory synapses in the mammalian central nervous system, also undergoes dynamic changes to its shape (structural plasticity) in an activity-dependent manner. Indeed, strengthening of the synapse, or long-term potentiation (LTP), is often associated with spine head enlargement, whereas weakening of the synapse, or long-term depression (LTD), is often associated with spine head shrinkage. Underlying structural plasticity is the cytoskeleton protein, actin, whose dynamics and organization ultimately shape spine morphology, and which can also influence synaptic plasticity through modulation of membrane receptor insertion, removal and function. Thus, actin is both governed by and governs the king and kingdom. This special issue of The Open Neuroscience Journal explores many different aspects of dendritic spine morphology, regulation and function in health and disease.

The birth, maturation, and death of a dendritic spine are ultimately regulated by actin-binding proteins, which, as a group, can influence the dynamics and organization of actin (see **Pontrello and Ethell** and **Lin and Webb in this Issue**). However, because their activities sometimes overlap and/or complement each other, the effects of individual actin-binding proteins on spine geometry (size, shape, and density) are sometimes contradictory or difficult to interpret mechanistically. Surprising modes of actin dynamics have already emerged from biochemical studies in which actin-binding proteins are used in combination. For instance, a recent study on single actin filament dynamics in the presence of cofilin, actin interacting protein 1 (Aip1) and coronin1a, demonstrated a burst of disassembly not previously observed [2]. More studies using combinations of spine-localized proteins need to be performed to fully understand the molecular basis for spine morphological changes in response to activity.

In addition, the effects of some actin-binding proteins on spine geometry may be indirectly related to actin-binding, since some actin-binding proteins are required for the correct localization of other spine-associated proteins (see **Lin and Webb**). More importantly, the effects of actin-binding pro teins in dendritic spines have been difficult to predict because the architecture of actin filaments within dendritic spines has remained elusive. Whereas retrograde flow analysis of actin within dendritic spines suggests polymerization occurs only at the crown of the spine head, immunostaining of newly incorporated actin subunits suggests actin polymerization occurs both at the crown of the spine head as well as at the base of the neck [3]. The architecture of actin within dendritic spines of various shapes needs to be determined.

Within dendritic spines, both neurotransmitter receptors and adhesion complexes can stimulate signaling pathways that regulate multiple downstream actin-binding proteins. The Rho GTPases and their downstream kinases, p12 activated kinases (PAKs), Rho kinase (ROCK), and LIM kinases (LIMKs), have emerged as central figures in regulating both structural and functional (also called synaptic) plasticity through actin-binding proteins (see **Asrar and Jia**; **Okada and Soderling**; **Vicente-Manzanares and Horwitz**). However, adhesion complexes and Rho GTPase signaling may also be involved in a positive feedback loop that signals for either spine maturation or retraction, suggesting a more active role for actin polymerization and dynamics in linking functional and structural plasticity (see **Vicente-Manzanares and Horwitz**). In addition, at least some actin-binding proteins bridge functional and structural plasticity concomitantly by regulating the surface-expression of glutamate receptors (α-amino-3-hydroxy-5-methyl-4isoxazole-propionic acid (AMPA) and N-methyl-D-aspartate (NMDA)) and the actin cytoskeleton (see **Okada and Soderling**). However, functional and structural plasticity can, in principle, be mechanistically dissociated [4]. In this study, functional plasticity required synaptic insertion of a functional AMPA receptor (AMPAR), whereas structural plasticity required the presence of the C-terminal tail of AMPAR alone, which could facilitate actin polymerization through unknown mechanisms.

Surprisingly, signaling molecules can also be carried from the dendritic shaft to spines by microtubules, which may stimulate actin polymerization and structural plasticity (see **Gu and Zheng**). The extent to which actin is regulated by microtubule-dependent interactions is most likely underappreciated, since drebrin and myosinVa are also known to associate with microtubule plus-end tracking proteins [5, 6]. In addition, microtubule invasion into spines may require interactions with the actin cytoskeleton and mechanisms which regulate invasiveness may depend on the activities of multiple actin-binding proteins.

*Address correspondence to the Guest Editor at the Department of Biochemistry and Molecular Biology, Colorado State University, Fort Collins, CO 80523, USA; Tel: 970-491-6096; Fax: 970-491-0494;
E-mail: jbamburg@lamar.colostate.edu

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The importance of Rho GTPase signaling, actin-binding proteins, and structural plasticity to cognitive development is highlighted by several autistic spectrum disorders, which include X-linked mental retardations, Fragile X and Rett syndrome (see **Arikkath**). The loss of Fragile X related protein 2 (Fxr2), an autosomal homologue of Fragile X mental retardation protein (FMRP), leads to a developmental delay in spine shape maturation, similar to what is observed in FMRP knockouts (see **Deng and Dunaevsky**). However, the effects of knocking out FMRP and Fxr2 are not entirely identical, indicating only partially overlapping functions.

In general, a strong correlation between cognitive dysfunction and abnormal spine morphologies observed in developmental disorders suggests the importance of spine geometry in synaptic signaling. In fact, abnormal spine shapes have been observed in neurodegenerative diseases, such as Alzheimer disease [7]. Early computational studies also suggests that by geometry alone the dendritic spine could compartmentalize synaptic signals. However, spine geometry *per se* likely has little influence on compartmentalization (see **Lee and Yasuda**). Rather, the extent of compartmentalization is determined by the potential for interactions with other proteins within spines. Thus, proteins with multiple interaction partners are more likely to remain sequestered within its parent spine.

The compartmentalization of synaptic signals is also likely to be relevant to homeostatic synaptic plasticity (or metaplasticity). Homeostatic synaptic plasticity is the ability of the neuron to maintain its overall excitability within a dynamic range to protect it from uncontrolled LTP that can cause a breakdown in synapse specificity. If plasticity within single synapses is king, homeostatic plasticity, which regulates the strength of multiple synapses, is the pope. Proteins that bind to actin may also potentially regulate homeostatic plasticity; for instance, the ratio of CAMKII α to β is changed in homeostatic plasticity. CAMKII β can bind directly to actin, whereas CAMKII α cannot. In addition, drebrin, an actin-binding protein that regulates actin stability in dendritic spines downstream of AMPA receptors [8], can regulate homeostatic plasticity after NMDA receptor blockade [9]. Future studies in homeostatic plasticity may ultimately provide insights into differences observed between the acute inhibition of actin-binding proteins as opposed to their longer term loss, which have thus far confounded interpretations about the relevant effects of actin-binding proteins in disease.

The articles contained within this special issue of The Open Neuroscience Journal should provide both the novice and the expert with a current understanding of dendritic spine architecture and signaling. They should also show many of the areas where our understanding is incomplete. Because of their small size and ability to rapidly change morphology, dendritic spines present major challenges for microscopic imaging that require new technology. Although we have made great strides in understanding spine components and some aspects of their organization and function, we are left with many of the same fundamental questions we have sought to answer. How does the density and shape of spines affect its signaling capacity? What relevance do these parameters have on cognitive dysfunction? How can dysfunctions be corrected? As the central cellular compartment involved in the molecular signaling for learning and memory, dendritic spine research does, indeed, have an exciting future.

Finally, we want to express our appreciation to the scientists from 7 countries who reviewed the articles in this special issue. Their comments and suggestions have helped improve the quality of the content and the delivery of the information in a way that we hope will be more understandable to everyone. These individuals are (alphabetically): Janet Alder, Deanna Benson, Ora Bernard, Thomas Blanpied, Wenbiao Gan, Yasunori Hayashi, David Kovar, Frederic Laumonnier, Yu-chih Lin, Sutherland Maciver, Richard Mains, Ania Majewska, Keith Murai, Margareta Nikolic, Menahem Segal, Linda VanAelst, and Alissa Weaver.

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