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Review

Role of actin cytoskeleton in dendritic spine morphogenesis

Yuko Sekino [a,b,c], Nobuhiko Kojima [a], Tomoaki Shirao [a,*]

[a] *Department of Neurobiology and Behavior, Gunma University Graduate School of Medicine, 3-39-22 Showa-machi, Maebashi, Gunma 371-8511, Japan*
[b] *Division of Neuronal Network, Institute of Medical Science, University of Tokyo, Tokyo, Japan*
[c] *Core Research for Evolution Science and Technology, Japan Science and Technology Corporation, Kawaguchi, Japan*

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Abstract

Dendritic spines are the postsynaptic receptive regions of most excitatory synapses, and their morphological plasticity play a pivotal role in higher brain functions, such as learning and memory. The dynamics of spine morphology is due to the actin cytoskeleton concentrated highly in spines. Filopodia, which are thin and headless protrusions, are thought to be precursors of dendritic spines. Drebrin, a spine-resident side-binding protein of filamentous actin (F-actin), is responsible for recruiting F-actin and PSD-95 into filopodia, and is suggested to govern spine morphogenesis. Interestingly, some recent studies on neurological disorders accompanied by cognitive deficits suggested that the loss of drebrin from dendritic spines is a common pathognomonic feature of synaptic dysfunction. In this review, to understand the importance of actin-binding proteins in spine morphogenesis, we first outline the well-established knowledge pertaining to the actin cytoskeleton in non-neuronal cells, such as the mechanism of regulation by small GTPases, the equilibrium between globular actin (G-actin) and F-actin, and the distinct roles of various actin-binding proteins. Then, we review the dynamic changes in the localization of drebrin during synaptogenesis and in response to glutamate receptor activation. Because side-binding proteins are located upstream of the regulatory pathway for actin organization via other actin-binding proteins, we discuss the significance of drebrin in the regulatory mechanism of spine morphology through the reorganization of the actin cytoskeleton. In addition, we discuss the possible involvement of an actin–myosin interaction in the morphological plasticity of spines.

Keywords: Spine formation; Spine morphology; Actin; Actin-binding protein; Drebrin; Synaptic activity; Actin–myosin interaction

Contents

* Corresponding author. Tel.: +81 27 220 8050; fax: +81 27 220 8053.
E-mail address: tshirao@med.gunma-u.ac.jp (T. Shirao).

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1. Introduction

Neurons show characteristic morphological changes during development. They extend axons and terminate on small protrusions of various shapes on a dendrite, which are called dendritic spines. Dendritic spines are the postsynaptic receptive regions of most excitatory synapses (Harris and Kater, 1994). Because morphological studies of spines by the autopsy of dementia patients demonstrate the correlations between brain dysfunction and abnormal spine morphology (Purpura et al., 1982; Wisniewski et al., 1991; Irwin et al., 2000), it has been believed for a long time that spine morphology is crucial for understanding higher brain functions, such as learning and memory. Although synaptic function cannot be elucidated directly from spine shapes, the regulatory mechanisms of spine morphogenesis and the dynamics of spine morphology will provide essential information on the developmental and regulatory mechanisms of higher brain functions.

Spines have not yet been observed to emerge on dendrites of immature neurons. Instead, immature neurons have many thin headless protrusions, called dendritic filopodia, on their dendrites (Fig. 1A). Newly born filopodia lack the postsynaptic machinery necessary for matured synaptic function.

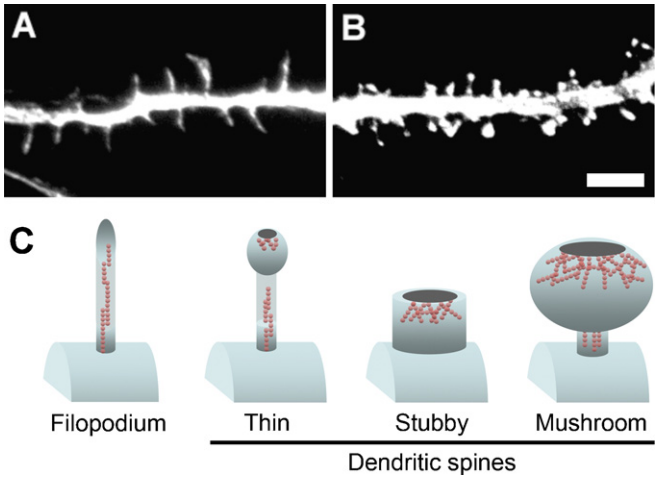

Fig. 1. Morphology of dendritic protrusions, filopodia and spines. Dendrites of GFP-transfected hippocampal neurons cultured for 7 days (A) and 21 days (B). At the immature stage (7 days), dendritic protrusions are very thin and long; these protrusions are called dendritic filopodia. In contrast, at the mature stage (21 days), dendrites are covered by dendritic spines, which commonly have an expanded head and a narrow neck. Scale bar, 5 μm. (C) Schematic representation of morphologies of filopodium and three types of dendritic spine: thin type, stubby type and mushroom type. Gray disks represent the PSD structure and chains of red circles represent F-actin.

When the brain receives much information on circumstances, the number of filopodia rapidly decreases and the number of bulbous spines simultaneously increases (Fig. 1B). Dendritic spines are fully equipped with postsynaptic machineries, such as neurotransmitter receptors, scaffold proteins anchoring the receptors, intracellular signaling molecules, and actin-binding proteins endowing the actin cytoskeleton with spine-specific characteristics (Fig. 2). Hence, dendritic spines can respond to extracellular signals and show morphological plasticity.

Because filopodia and spines are similar in terms of the presence of small protrusions (0.5–8 μm) on dendritic shafts and of the lack of microtubules and intermediate filaments (Kaech et al., 1997, 2001), there are occasionally some confusions in terminology which lead to the difference between dendritic filopodia and dendritic spines. In this review, the term ‘‘filopodia’’ will apply to all thin headless protrusions on dendritic shafts, and the term ‘‘spine’’ will apply to all other protrusions on dendritic shafts. In addition, filopodia at the tips of axonal and dendritic growth cones are excluded from ‘‘filopodia’’ in this review, because they differ from dendritic filopodia (Fiala et al., 1998; Portera-Cailliau et al., 2003) in terms of their mobility and fine structures.

Dendritic spines observed in fixed brain tissue shows various shapes, and are generally classified into three types: the thin type having a slender neck and a small head, the mushroom type having a short neck and a relatively large head, and the stubby type having no neck (Fig. 1C). In living neurons, spine shapes easily interchange between the above three types. In other words, spine morphologies are snapshots of dynamic morphological changes. Therefore, not only the spine morphology but also its dynamic change should be elucidated to understand synaptic functions.

What machineries are involved in the motility and dynamics of dendritic spines? Luo et al. (1996) were the first to suggest the significance of actin cytoskeleton in spine formation. The overexpression of a constitutively active Rac1, a regulatory signal of the actin cytoskeleton, facilitates spine formation. Three years later, we showed the enlargement of the spine by the overexpression of a neuron-specific actin-binding protein, drebrin A, in cultured neurons (Hayashi and Shirao, 1999). This is the first observation demonstrating that the manipulation of a single actin-binding protein in neuron alters spine morphology. Numerous findings related to actin organization in dendritic spines have rapidly emerged after these initial studies, which clearly demonstrated that the actin cytoskeleton plays a pivotal role in spine morphology (for review, see Shirao and Sekino, 2001; Ethell and Pasquale, 2005).