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Molecular mechanisms of dendritic spine development and remodeling

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Abstract

Dendritic spines are small protrusions that cover the surface of dendrites and bear the postsynaptic component of excitatory synapses. Having an enlarged head connected to the dendrite by a narrow neck, dendritic spines provide a postsynaptic biochemical compartment that separates the synaptic space from the dendritic shaft and allows each spine to function as a partially independent unit. Spines develop around the time of synaptogenesis and are dynamic structures that continue to undergo remodeling over time. Changes in spine morphology and density influence the properties of neural circuits. Our knowledge of the structure and function of dendritic spines has progressed significantly since their discovery over a century ago, but many uncertainties still remain. For example, several different models have been put forth outlining the sequence of events that lead to the genesis of a spine. Although spines are small and apparently simple organelles with a cytoskeleton mainly composed of actin filaments, regulation of their morphology and physiology appears to be quite sophisticated. A multitude of molecules have been implicated in dendritic spine development and remodeling, suggesting that intricate networks of interconnected signaling pathways converge to regulate actin dynamics in spines. This complexity is not surprising, given the likely importance of dendritic spines in higher brain functions. In this review, we discuss the molecules that are currently known to mediate the exquisite sensitivity of spines to perturbations in their environment and we outline how these molecules interface with each other to mediate cascades of signals flowing from the spine surface to the actin cytoskeleton.

Contents

Abbreviations: ADF, actin depolimerizing factor; AMPA, α-amino-3-hydroxy-5methyl-4-isoxazole propionate; Arp2/3 complex, actin-related 2/3 complex; BDNF, brain-derived neurotrophic factor; CaMKII, calcium/calmodulin-dependent protein kinase II; CREB, cyclic AMP response element binding protein; Ena/VASP, enabled/vasodilator-stimulated phosphoprotein; FDG1, faciogenital dysplasia gene 1; GABA, gamma-aminobutyric acid; GFP, green fluorescent protein; GIT1, G protein-coupled receptor kinase-interacting protein 1; GK, guanylate kinase; GKAP, guanylate kinase-associated protein; GPI, glycosylphosphatidylinositol; GRIP1, glutamate receptor interacting protein-1; GTP, guanosine triphosphate; GTPase, guanosine triphosphatase; IP3kinA, inositol 1,4,5-triphosphate 3-kinase A; IRS p53, insulin receptor substrate p53; IP3, inositol 1,4,5-triphosphate; LTD, long-term depression; LTP, long-term potentiation; MAGUK, membrane-associated guanylate kinase; MAP kinase, mitogen-activated protein kinase; Mena, mammalian enabled; N-CAM, neuronal cell adhesion molecule; NMDA, *N*-methyl-D-aspartate; N-WASP, neural-Wiskott–Aldrich syndrome protein; Pak1, p21-activated kinase; Pick1, protein interacting with C kinase-1; PIP_2, phosphatidylinositol 4,5-bisphosphate; βPIX, Pak-interacting exchange factor; PKA, protein kinase A; PKC, protein kinase C; PP1, protein phosphatase 1; PSD-95, postsynaptic density protein 95; RGD, arginine–glycine–aspartate; ROCK, Rho associated kinase; Shank, Src homology 3 domain and ankyrin repeat-containing; SNK, serum-inducible kinase; SPAR, spine-associated Rap GTPase-activating protein; WAVE, WASP family verprolin-homologous protein; WIP, WASP-interacting protein

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1. Introduction

More than 100 years ago, Santiago Ramon y Cajal discovered that "the surface of Purkinje cell dendrites appears bristling with thorns or short spines" and proposed that "such spines could be the points where electrical charge or current is received" (Ramon and Cajal, 1888, 1899). Cajal visualized neurons with a silver impregnation method developed by Golgi (1873) and observed them using the optical microscopes available in the late 19th century. Many years later, the efforts of investigators using more advanced imaging technologies proved that Cajal's hypothesis was indeed correct (Gray, 1959). Today, it is well established that most excitatory synapses are formed between axon terminals and small protrusions on the surface of dendrites known as "dendritic spines" (Harris, 1999; Hering and Sheng, 2001) (Fig. 1). Dendritic spines represent the postsynaptic component of most excitatory synapses and some inhibitory synapses. Spines are present on different populations of neurons in the brain, and have been best characterized in pyramidal neurons of the hippocampus and neocortex as well as in Purkinje cells of the cerebellum.

The prototypical dendritic spine consists of a bulbous head connected to the dendritic shaft by a narrow neck (Sorra and Harris, 2000) (Fig. 1). However, spines come in a wide range of sizes and shapes, even within the same brain region. Stubby spines without a neck and filopodial spines without a head are found side by side with mushroom-shaped spines with a large and sometimes irregularly shaped head (Yuste and Bonhoeffer, 2004)