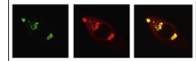


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Review

The structure and function of actin cytoskeleton in mature glutamatergic dendritic spines



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ABSTRACT

Dendritic spines are actin-rich protrusions from the dendritic shaft, considered to be the locus where most synapses occur, as they receive the vast majority of excitatory connections in the central nervous system (CNS). Interestingly, hippocampal spines are plastic structures that contain a dense array of molecules involved in postsynaptic signaling and synaptic plasticity. Since changes in spine shape and size are correlated with the strength of excitatory synapses, spine morphology directly reflects spine function. Therefore several neuropathologies are associated with defects in proteins located at the spines. The present work is focused on the spine actin cytoskeleton attending to its structure and function mainly in glutamatergic neurons. It addresses the study of the structural plasticity of dendritic spines associated with long-term potentiation (LTP) and the mechanisms that underlie learning and memory formation. We have integrated the current knowledge on synaptic proteins to relate this plethora of molecules with actin and actin-binding proteins. We further included recent findings that outline key uncharacterized proteins that would be useful to unveil the real ultrastructure and function of dendritic spines. Furthermore, this review is directed to understand how such spine diversity and interplay contributes to the regulation of spine morphogenesis and

Abbreviations: ABPs, actin-binding proteins; A β , amyloid-beta peptide; AD, Alzheimer's disease; AMPARs, α -amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptors; APP, amyloid precursor protein; ASD, autistic spectrum disorders; AVC, amorphous vesicular clumps; BDNF, brain-derived neurotrophic factor, BDNF; CAMs, cell adhesion molecules; CA1-4, cornu ammonis; CaMKII, Ca²⁺/calmodulin-dependent protein kinase II; chemLTP, chemical LTP protocol; CNS, central nervous system; Eph, ephrins; EM, electron microscopy; FRAP, fluorescence recovery after photobleaching; FXS, Fragile X syndrome; GABA, gamma-aminobutyric acid; GEF, guanine nucleotide exchange factor; GPCRs, G-protein coupled receptors; HD, Huntington's disease; KO, knock-out; LTD, long-term depression; LTP, long-term potentiation; MAGUKs, membrane-associated guanylate kinase homologs; MAPs, microtubule-associated proteins; mGluRs, metabotropic glutamate receptors; mRNA, messenger ribonucleic acid; mRNP, messenger ribonucleoprotein; MTT, multiple trace theory; NMDARs, N-methyl-D-aspartate receptors; NGLs, neuroligins; NTD, N-terminal domain; NXNs, neurexins; PD, Parkinson's disease; PSD, postsynaptic density; RNAi, ribonucleic acid interference; SA, spine apparatus; SER, smooth endoplasmic reticulum; shRNA, short hairpin ribonucleic acid; siRNA, small interfering ribonucleic acid; SINE, short interspersed repetitive element; SNARE, Nethylmaleimide-sensitive factor attachment protein receptor complex; SYNPO, synaptopodin; UPR, unfolded protein response

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dynamics. It highlights their physiological relevance in the brain function, as well as it provides insights for pathological processes affecting dramatically dendritic spines, such as Alzheimer's disease.

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1. Introduction

The brain function relies on the organization of the neuronal circuitry, which is a vastly interconnected network of synapses. Synapses mediate neuronal communication primarily via neurotransmitters, which are endogenous chemical compounds that can be released from the pre- to the postsynaptic compartment. In general terms, they are composed of a varicosity or bouton from a presynaptic neuron that contains coated vesicles filled with neurotransmitters and communicates with the postsynaptic neuron, usually through a dendritic spine.

Throughout evolution, the vertebrate brain has acquired differential morphological modifications to achieve more complex functions. Thus, vertebrates developed spiny neurons to produce higher levels of cortical processing (Sala et al., 2008). Dendritic spines are membranous protrusions arising from the dendritic shaft, which are considered to be the locus of the vast majority of excitatory synapses in the central nervous system (CNS), accounting for almost the 90%. They are preferentially located on peripheral dendrites of neocortical and hippocampal pyramidal neurons, as well as in the striatum and in cerebellar Purkinje cells. Nevertheless, they can be also found on proximal dendrites or even on the

soma. Each spine receives inputs typically from one excitatory synapse, although spine-type synapses with inhibitory axons have also been described. In addition, there are smooth or aspiny neurons with dendrites carrying few or no spines that are immunopositive for gamma-aminobutyric acid (GABA) (Roussignol et al., 2005). However, for the purposes of the present work we focus on hippocampal spiny neurons, since they are key structures in learning and memory formation and they provide biochemical compartments that locally control and integrate signaling inputs into complex neural networks (Bourne and Harris, 2008).

During the last decades, different speculative hypothesis have been developed in order to grasp why excitatory axons choose to contact spines, since there are also aspiny neurons that form synapses directly on the dendritic shaft. Initially, three principal hypotheses were postulated to explain the function of spines (Lee et al., 2012).

The first one implies that spines connect axons to enhance synaptic connectivity and provide proper synaptic transmission, making the neuronal matrix more distributed.

The second one proposes that spines are electrically favorable, since spine neck morphology can impact the kinetics and propagation of synaptic potentials, allowing input-specific plasticity. In the third place, it is postulated

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