Journal of Neurochemistry

JNC

JOURNAL OF NEUROCHEMISTRY | 2014 | 128 | 473–475

doi: 10.1111/jnc.12488

EDITORIAL HIGHLIGHT

Spikar speaks to spines and nuclei

Chiara Verpelli,* Michael J. Schmeisser† and Carlo Sala*,‡

*CNR Institute of Neuroscience and Department of Biotechnology and Translational Medicine, University of Milan, Milan, Italy

†Institute for Anatomy and Cell Biology, Ulm University, Ulm, Germany

‡Neuromuscular Diseases and Neuroimmunology, Foundation Carlo Besta Neurological Institute, Milan, Italy

Read the full article *'Spikar, a novel drebrin-binding protein, regulates the formation and stabilization of dendritic spines'* on page 507.

Understanding how dendritic spines are formed and generated is a fundamental question for neurobiologist and scientist in general.

Filamentous (*F*)-actin is the main cytoskeletal component of dendritic spines and highly contributes to forming three-dimensional scaffolds in the spine neck and head (Shirao and González-Billault 2013). Thus, a number of acting binding proteins have been found to positively or negatively regulate actin polymerization in spines and thereby modulate their formation, shape and plasticity. Among them, drebrin A was one of the first molecules to be proposed as a regulator of spine actin and spine morphology (Hayashi *et al.* 1996; Hayashi and Shirao 1999).

Indeed Hayashi and Shirao showed, more than 10 years ago, that in cultured cortical neurons the over-expression of a cDNA encoding the adult isoform drebrin (drebrin A) increases the length of dendritic spines (Hayashi and Shirao 1999). On the contrary, drebrin knockdown in cultured neurons decreases spine and filopodia densities (Takahashi *et al.* 2006), the density of excitatory synapses and also the function of inhibitory synapses (Ivanov *et al.* 2009). Drebin activity in spines primarily depends on its *F*-actin interaction, but also on its interaction with other actin-regulatory proteins, such as profilin, myosin, gelsolin, and Ras (Mammoto *et al.* 1998; Biou *et al.* 2008). Important questions were still open regarding drebrin function in spines and synapses. Interestingly, although consistent data have been produced in cultured neurons, drebrin knock-out mice have dendritic spines with normal morphology, but present with altered homeostatic plasticity, suggesting that drebrin might control a subset of actin involved in synaptic plasticity (Aoki *et al.* 2009). Therefore, the downstream signaling cascades connecting drebrin-induced actin remodeling and the plasticity of dendritic spines remain to be better defined.

Yamazaki *et al.* (2013) have now identified a novel drebrin-binding protein that was called spikar for its spine and karyoplasm (nuclear) localization (Fig. 1). Spikar, which was identified by yeast two hybrid screening using the N-terminal region of drebrin as bait, is a multi-domain protein formed by a Plant Homeo Domain, a Bromo domain, a nuclear receptor recognition sequence, a PWWP domain, a coiled-coil domain and a MYND domain. The protein sequence also contains a nuclear localization sequence (NLS) to target the protein to nuclei. Furthermore, the interaction with drebrin is important for spikar localization to dendritic spines and occurs between the N-terminal region of spikar and the actin-depolymerizing factor homology domain of drebrin, thus without interfering with the specific binding of *F*-actin to the central domain of drebrin (Hayashi and Shirao 1999; Grintsevich *et al.* 2010). However, the C-terminal region of spikar that does not bind to drebrin also contributes to the accumulation of spikar in dendritic spines.

In cell nuclei, spikar can work as transcriptional co-activator and similarly to the BS69 protein, it can potentiate TRβ1-mediated transcription of thyroid hormone response element in the presence of its ligand, triiodothyronine, and activate transcription mediated by the glucocorticoid receptor and estrogen receptor α.

In addition, Yamazaki *et al.* (2013) clearly showed that spikar has an impact on dendritic spines independently of its nuclear activity, because a mutant of spikar lacking the NLS is able to increase dendritic spine number when over-expressed in cultured neurons. The effect of spikar on dendritic spines is complementary to the effect of drebrin: while drebrin regulates spine morphology but not the number of dendritic spines, the over-expression of spikar determines

Received October 10, 2013; accepted October 10, 2013.

Address correspondence and reprint requests to Carlo Sala, CNR Institute of Neuroscience and Department of Biotechnology and Translational Medicine, University of Milan, Milan, Italy.
E-mail: c.sala@in.cnr.it

Abbreviation used: NLS, nuclear localization sequence.

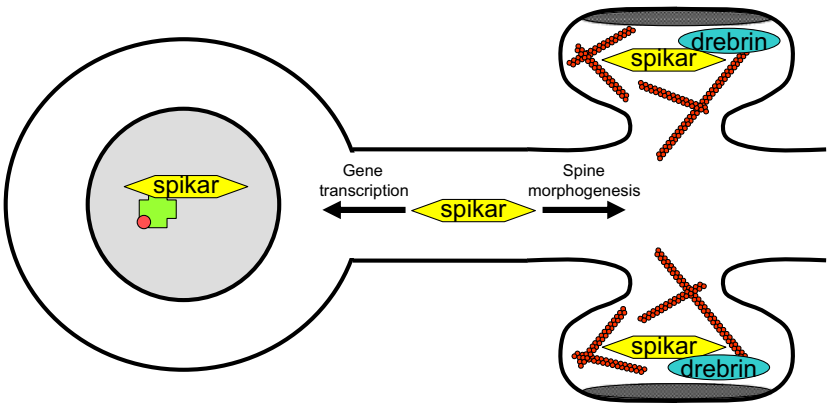

Fig. 1 The cartoon shows a schematic representation of spikar activity on dendritic spines number and gene transcription as co-activator of nuclear receptors.

an increase of spine density by affecting *de novo* formation and the retraction of existing spines.

On the other hand a number of data suggest that spikar activity on dendritic spines is depending on the binding to drebrin in synapses. In the absence of drebrin, the dendritic localization of spikar is impaired, and in dendritic spines, the level of over-expressed spikar is proportional to the level of drebrin.

Furthermore, the over-expression of spikar protein lacking the NLS does not increase spine density in neurons devoid of drebrin. These data suggest that drebrin-mediated anchoring of spikar at dendritic spines is necessary for increasing spine density. Importantly only the extranuclear spikar regulates spine density indicating that gene transcription induced by nuclear spikar is not required for spine formation.

Thus, the artificial separation between dendritic and nuclear functions of spikar reveals a double role of spikar. The predominant function of endogenous spikar still remains open though. Does synaptic activity regulate the double function of spikar?

Looking in the literature, other synaptic/nuclear proteins have been described to shuttle between the synapse and the nucleus and to regulate the transcription of genes involved in synaptic morphology and plasticity. Abi-1, just to mention one example, binds to ProSAP2/Shank3 (Boeckers *et al.* 2002), a major scaffold protein of the post-synaptic density, and is translocated to nuclei from synapses upon NMDA receptor stimulation where it can turn on the transcription of a number of E-box-containing genes (Proepper *et al.* 2007). Indeed knocking down Abi-1 by RNAi changes both dendrite morphology, by increasing the branching, and spine structure that becomes more similar to an immature shape suggesting that Abi-1 can regulate dendrite and synapse formation working as a synapto-nuclear messenger specifically controlling gene transcription (Proepper *et al.* 2007).

Interestingly, spikar seems to regulate gene transcription mediated by the glucocorticoid and estrogen receptors both of which are expressed in the hippocampus and are strongly involved in synaptic function and plasticity although the molecular pathways involved have not completely been revealed (Saldanha *et al.* 2011). There is no question about the fact that future studies should now clarify if spikar is a link between acting binding proteins of dendritic spines and steroid mediated transcription in the contest of synaptic plasticity.

Acknowledgements

This work was financially supported by Comitato Telethon Fondazione Onlus, grant GGP11095, PRIN 2012 and Ministry of Health in the frame of ERA-NET NEURON. The authors have no conflict of interest to declare.

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