Mini-Review

Local Protein Synthesis and Spine Morphogenesis: Fragile X Syndrome and Beyond

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Behavioral experiences can modulate neural networks through changes in synaptic morphology and number. In contrast, abnormal morphogenesis of dendritic spines is associated with cognitive impairment, as in Fragile X syndrome. Dendritic or synaptic protein synthesis could provide the specificity and speed necessary for spine morphogenesis. Here, we highlight locally translated proteins shown to affect synaptic morphology (e.g., Fragile X mental retardation protein).

Key words: **synaptic plasticity, CaMKII; FMRP; Rho GTPases; Fmr1 knock-out mice; synaptogenesis; learning and memory; metabotropic glutamate receptor; Rac1; SHANK-HOMER; dendritic spine; PSD-95**

Behavioral experiences can modulate the function of individual synapses or entire neural networks through changes in synaptic morphology and number (Bailey and Chen, 1983; Black et al., 1990). Recent *in vivo* imaging studies have shown that experience or activity can induce morphogenesis (or changes in shape or motility) of postsynaptic spines, sites for excitatory synapses (Majewska and Sur, 2003; Zuo et al., 2005). Abnormal spine morphogenesis, in contrast, is associated with cognitive impairment, as in Fragile X syndrome (FXS) and other disorders (Purpura, 1974; Hinton et al., 1991). Reactive spine morphogenesis likely requires rapid availability of macromolecules, and dendritic or synaptic protein synthesis could provide specificity and speed. Although direct evidence tying local protein synthesis to spine morphogenesis is scarce, we review the available indirect evidence with an emphasis on locally translated proteins, including the Fragile X mental retardation protein (FMRP), that have known effects on synaptic morphology.

Markers of translation [polyribosomal aggregates (PRAs)] have been observed near synapses during peak developmental synaptogenesis (Steward and Falk, 1986), and local protein synthesis is regulated by intrinsic and extrinsic signals (Schuman et al., 2006). Greenough et al. (1985) found that PRAs were localized to dendritic spines in the visual cortex of rats exposed to a complex environment, a paradigm that alters the number, shape, and size of synapses (Grossman et al., 2002). Induction of long-term potentiation (LTP), an electrically induced change in synaptic strength, also moves PRAs from dendritic shafts into spines (Ostroff et al., 2002). Furthermore, only spine synapses that contained PRAs were larger after stimulation, suggesting that local translation was important for this morphogenesis.

Another model of synaptic activation involves administration of neurotransmitter receptor agonists. Weiler et al. (1997) used synaptoneurosomes (synapses dissociated from cell bodies) to show that stimulation of metabotropic glutamate receptors (mGluRs) triggers rapid aggregation of polyribosomes and translation of proteins (including FMRP). Vanderklish and Edelman (2002) recently reported elongation of dendritic spines after stimulation of mGluRs. Preincubation with a translation inhibitor blocked elongation, but it remains unclear whether the protein synthesis required is specifically dendritic.

Translation inhibitors have been used for many years to establish the importance of protein synthesis for memory, synaptic morphogenesis, and cortical function (Agranoff and Klinger, 1964; Kleim et al., 2003). Failure to synthesize specific proteins can profoundly affect synapse morphology. For example, patients with FXS (characterized by the absence of FMRP) exhibit elevated spine density in the neocortex as adults and an abundance of spines with morphologies commonly observed early in development (Hinton et al., 1991; Irwin et al., 2001). This phenotype is also seen in the neocortex and hippocampus of adult mice lacking FMRP (*Fmr1* knock-out mice), suggesting a deficit in synaptic maturation (Galvez and Greenough, 2005; Grossman et al., 2006).

One emphasis of recent research has been to differentiate possible roles of local from somatic protein synthesis in specific forms of synaptic plasticity (Pfeiffer and Huber, 2006). Studies using isolated dendrites have demonstrated that local translation is both necessary and sufficient for establishment and maintenance of LTP (Cracco et al., 2005; Vickers et al., 2005). Similarly, Schuman and colleagues (Kang and Schuman, 1996; Aakalu et al., 2001) demonstrated that local protein synthesis is important for synaptic potentiation after administration of the neurotrophin BDNF and, more recently, have visualized dynamics of local

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translation associated with synaptic potentiation. In the future, these techniques and others in which protein synthesis is restricted to the soma of intact neurons (Miller et al., 2002; Bradshaw et al., 2003) can delineate the necessity for local protein synthesis in spine morphogenesis.

Locally translated proteins important for spine morphology

Specific proteins and biochemical pathways have been associated with spine morphogenesis (Tada and Sheng, 2006); many of these pathways lead ultimately to actin rearrangement in the spine cytoskeleton. Rho GTPases such as Rac1, for example, are upstream modulators of actin polymerization. Their activity is regulated by environmental signals such as visual input, and stimulation of these Rho GTPase pathways affects spine morphology and stability (Sin et al., 2002; Tashiro and Yuste, 2004). Proteins that are important for spine formation and remodeling and that are locally translated can be grouped into two broad functional categories: (1) direct or indirect "regulators" of spine formation and remodeling and (2) "plastic structural elements" that integrate structurally into the synapse, thus influencing synaptic physiology and potentially altering the capacity for future morphogenesis. Although evidence directly linking local synthesis of specific proteins to spine changes is sparse, proteins from both of these categories are linked to pathways that can affect spine morphogenesis (Fig. 1).

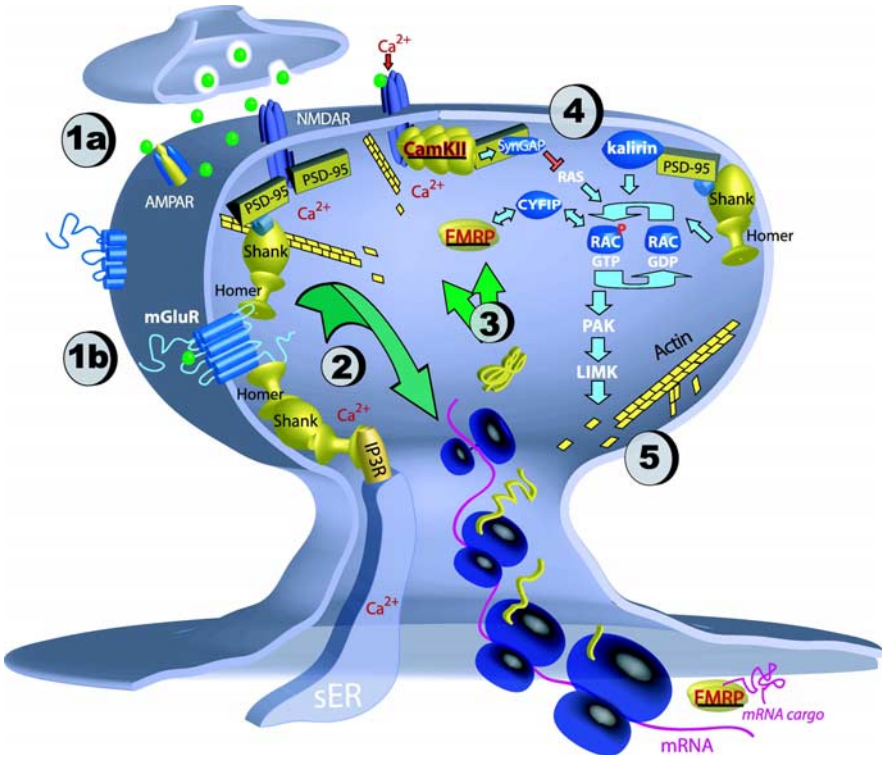

Figure 1. Synaptic stimulation can act via ionotropic glutamate receptors (AMPA/NMDA; 1a) and mGluRs (1b) and can initiate translation (2) of locally synthesized proteins (3; shown in yellow), including regulators (underlined red text) and plastic structural elements (black text). Both broad categories of proteins can interact with a Rho GTPase pathway (4; simplified here for illustration purposes), affecting morphology through rearrangement of actin filaments (5). Locally synthesized proteins can thereby interact to assemble or reorganize the spine, regulating function and affecting future spine morphogenesis (see text for details). NMDAR, NMDA receptor; AMPAR, AMPA receptor; PAK, α-p-21-activated kinase; LIMK, LIM-kinase; IP_3R, IP_3 receptor; sER, smooth endoplasmic reticulum.

Regulators

Many locally synthesized proteins can potentially influence other proteins or signaling cascades involved in morphogenesis. For example, local translation of kinases or phosphatases could rapidly shift the equilibrium among pathways operating within the spine. Synthesis of RNA-binding proteins would have longer-term effects (Wells, 2006).

FMRP. The *Fmr1* mRNA is found in neuronal somata, dendrites, and spines. Activation of mGluRs localizes *Fmr1* to dendrites and initiates translation of FMRP in synaptoneurosomes (Weiler et al., 1997; Antar et al., 2004). Activity-induced translation of FMRP could affect spine morphology via interactions with its protein binding partners, including cytoplasmic FMRP interacting protein 1 (CYFIP1) (Schenck et al., 2003). In *Drosophila*, CYFIP and FMRP may regulate Rac1, and in mice, FMRP may also regulate other members of this actin-polymerization cascade (Kobayashi et al., 1998; Castets et al., 2005). Inhibition of Rac1 results in longer spines and decreased spine head size, as well as reduced head morphing and reduced spine stability (Tashiro and Yuste, 2004).

In addition to being synthesized at synapses, FMRP binds mRNA and ribosomes and seems to regulate mRNA transport and synaptic protein synthesis (Weiler et al., 1997; Khandjian et al., 2004). Weiler et al. (2004) found that stimulating mGluRs in synaptoneurosomes rapidly initiated translation in wild-type but not *Fmr1* knock-out mice, indicating that FMRP is important for neurotransmitter-activated protein synthesis. FMRP could affect spine morphogenesis through regulation of "cargo" mRNA, such as Map1B mRNA, shown recently to colocalize with FMRP near synapses (Antar et al., 2005). Map1B binds both actin and microtubules, and microtubule stability seems to be increased in *Fmr1* knock-out mice (Lu et al., 2004). Whereas these observations indicate that FMRP is important for initiating translation at synapses, FMRP may also inhibit constitutive protein synthesis elsewhere in the cell (Laggerbauer et al., 2001; Li et al., 2001). Together, these findings support a dual role for FMRP: delivery of protected mRNAs to synaptic locations and release of mRNAs for activity-dependent translation (Davidovic et al., 2005; Weiler, 2005).

Thus, at least three mechanisms may contribute to the abnormal spine morphology in FXS: (1) loss of protein–protein interactions leading to disruption of morphogenesis pathways; (2) dysregulated local synthesis of proteins important for morphogenesis; and (3) mislocalization of mRNA cargoes, any number of which could be critical for spine morphogenesis. These cargoes include Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII) (discussed below), calbindin, the α-glucocorticoid receptor, and cadherins (for more complete lists, see Sung et al., 2000; Brown et al., 2001; Miyashiro et al., 2003). Abnormal transport and translation of FMRP cargoes may underlie many other symptoms of FXS, as well (Markham et al., 2006).

CaMKII. CaMKII makes up a substantial proportion of the postsynaptic density (PSD) and may function both as a regula-

tory kinase and a scaffolding molecule for recruiting synaptic proteins (Merrill et al., 2005). Local protein synthesis appears to play a significant role in the regulation of dendritic CaMKII; its mRNA is observed throughout apical dendrites of hippocampal neurons, and mice missing dendritic targeting regions of α-CaMKII mRNA have reduced levels of the protein in their PSDs (Martone et al., 1996; Miller et al., 2002). The dynamics of local CaMKII translation remain unclear but may involve association of FMRP with CaMKII mRNA through the small RNA BC1 (Zalfa et al., 2003). Introducing phosphorylated CaMKII causes immediate formation of long, thin filopodia and shorter dendritic spines; in contrast, preventing CaMKII phosphorylation inhibits morphological changes that follow LTP induction (Jourdain et al., 2003). In mice in which CaMKII is restricted from dendrites, late-phase LTP and spatial memory are impaired, as are associative fear conditioning and object-recognition memory (Miller et al., 2002).

The proposed roles of CaMKII in spine morphogenesis are threefold. (1) It phosphorylates signaling proteins, potentially activating or repressing morphogenesis pathways. For example, CaMKII phosphorylates SynGAP (synaptic GTPase-activating protein), a regulator of the RAS-Rac1 actin-polymerization pathway (Song et al., 2004). (2) CaMKII acts as a regulator of protein translation through activation of cytoplasmic polyadenylation element-binding protein (CPEB) (Atkins et al., 2004) and could therefore, like FMRP, wield influence on morphogenesis through mRNA targets. (3) CaMKII may act as a plastic structural element by accumulating at the PSD in response to neuronal stimulation (Otmakhov et al., 2004), and by binding nearby synaptic proteins. For example, the NR2B subunit of NMDA receptors, which are important for spine morphogenesis, may be recruited to synapses by CaMKII (Zhou et al., 2004; Robison et al., 2005). Additional studies restricting CaMKII to the somata (Miller et al., 2002) should examine spine morphology to determine whether local synthesis of CaMKII is required for normal morphogenesis.

Plastic structural elements

Local synthesis of synaptic structural elements used by rapidly developing or remodeling spines can replenish pools of raw material. They may also provide a substrate for future morphological change, or plasticity. For example, mRNA for the cytoskeletal protein β-actin is localized to dendrites in an activity-dependent manner (Tiruchinapalli et al., 2003). Upregulation of β-actin mRNA stimulates the formation of dendritic filopodia, whereas exclusion of β-actin mRNA from dendrites disrupts the production of filopodia (Eom et al., 2003). Activity-induced remodeling of actin filaments provides a dynamic scaffold for localization of additional kinases and receptors (Ouyang et al., 2005), potentially affecting postsynaptic responses and the capacity of the spine to exhibit future morphogenesis. The concept of plastic structural elements is consistent with the idea of "metaplasticity" and may enable "synapses to integrate a response across temporally spaced episodes of synaptic activity" (Abraham and Tate, 1997).

PSD-95. PSD-95 is a locally synthesized scaffolding molecule, the expression levels of which increase after stimulation of mGluRs (Todd et al., 2003; Lee et al., 2005). Overexpression of PSD-95 in cultured hippocampal neurons leads to synapse maturation, clustering of glutamate receptors, and increased spine density and size (El-Husseini et al., 2000). PSD-95 can also bind and recruit to the PSD essential synaptic components, many of which independently affect spine shape (e.g., NMDA receptors, Homer, and others) (Kim and Sheng, 2004). Furthermore, PSD-95 binds and targets to synapses kalirin-7, a regulator of Rac1 signaling and spine morphogenesis (Penzes et al., 2001). Finally, the mGluR-induced increase in PSD-95 appears to require FMRP (Todd et al., 2003), suggesting that in FXS, deficits in local translation of PSD-95 may lead to abnormal spine morphogenesis and may affect spine responsiveness to future signals.

SHANK and Homer. SHANKs are scaffolding elements that bind indirectly to PSD-95 and F-actin (Boeckers et al., 2002). The mRNAs for SHANK1 and SHANK3 are localized to dendrites, and SHANK has dramatic effects on spine morphogenesis, inducing development of spines on non-spiny neurons (Bockers et al., 2004; Roussignol et al., 2005). It interacts with actin-associated proteins such as cortactin and appears to assemble NMDA receptors and mGluRs at spines (Boeckers et al., 2002). SHANK may exert some of its synaptic effects by binding the locally synthesized adapter protein Homer2 and together recruiting synaptic components such as IP_3 receptors, PSD-95, and F-actin to the spine (Sala et al., 2001; Schratt et al., 2004). Homer can cluster mGluRs at plasma membranes and can interact with Rho GTPase pathways (Shiraishi et al., 1999; Kammermeier, 2006), thus potentially affecting postsynaptic responses to neurotransmitter signals. Together, the SHANK–Homer2 complex increases the density of mushroom and multi-synapse spines (Sala et al., 2001). In mice lacking FMRP, phosphorylation of Homer protein is impaired, as is its association with mGluRs; lower levels of PSD-associated mGluRs in *Fmr1* knock-out mice suggest that Homer dysregulation contributes to the spine phenotype of FXS (Giuffrida et al., 2005).

These examples of regulators and plastic structural elements represent some of the locally synthesized proteins that influence spine morphogenesis. As new candidates appear [e.g., AMPA receptor subunit GluR1 (Smith et al., 2005) and β-thymosin (van Kesteren et al., 2006)], our understanding of the dynamics between local protein synthesis and spine morphogenesis will continue to develop.

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