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Synaptic activity regulated mRNA-silencing *foci* for the fine tuning of local protein synthesis at the synapse

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Abbreviations: AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; CamKII, Ca^{2+}/calmodulin-dependent protein kinases II; CPEB, cytoplasmic polyadenylation element binding protein; FMRP, fragile X mental retardation protein; FUS/TLS, fused in sarcoma/translated in liposarcoma; mGlutR, metabotropic glutamate receptor, NMDA, N-Methyl D-aspartic acid; PBs, processing bodies; RBP, RNA-binding protein; RNG105, RNA granule protein 105; RNP, ribonucleoprotein; S-*foci*, Smaug1 foci; SGs, stress granules; SyAS *foci*, synaptic activity-regulated mRNA silencing *foci*; TDP43, TAR DNA-binding protein 43; ZBP1, zip code-binding protein 1

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The regulated synthesis of specific proteins at the synapse is important for neuron plasticity, and several localized mRNAs are translated upon specific stimulus. Repression of mRNA translation is linked to the formation of mRNA-silencing *foci*, including Processing Bodies (PBs) and Stress Granules (SGs), which are macromolecular aggregates that harbor silenced messengers and associated proteins. In a recent work, we identified a kind of mRNA-silencing *foci* unique to neurons, termed S-*foci*, that contain the post-transcriptional regulator Smaug1/SAMD4. Upon specific synaptic stimulation, the S-*foci* dissolve and release mRNAs to allow their translation, paralleling the cycling of mRNAs between PBs and polysomes in other cellular contexts. Smaug 1 and other proteins involved in mRNA regulation in neurons contain aggregation domains distinct from their RNA binding motifs, and we speculate that self-aggregation helps silencing and transport. In addition to S-*foci* and PBs, other *foci* formed by distinct RNA binding proteins, such as TDP-43 and FMRP among others, respond dynamically to specific synaptic stimuli. We propose the collective name of synaptic activity-regulated mRNA silencing (SyAS) *foci* for these RNP aggregates that selectively respond to distinct stimulation patterns and contribute to the fine-tuning of local protein synthesis at the synapse.

Local translation at the synapse is key for neuronal activity. Hundreds of mRNAs encoding highly diverse proteins involved in distinct structures and processes are transported from the cell soma to the dendrites and synapses with distinct localization patterns. Adding significance to this exquisite spatial distribution, the translation of these transcripts is regulated by synaptic activity, thereby providing a precision mechanism for the local production of specific proteins in response to local changes. Dendritically localized mRNA molecules may remain silent most of the time, and become active upon specific stimulus.[1] An emerging concept is that mRNA repression is linked to the formation of mRNA-silencing *foci*. Processing Bodies (PBs) and Stress Granules (SGs) are the founding members of this novel family of cellular structures, which are cytoplasmic supramolecular aggregates of repressed RNA and inhibitory proteins. PBs are ubiquitous and SGs are specific of the stress response. SGs are rapidly assembled during the global translational silencing triggered by cell stress. Both PBs and SGs are dynamic and dissolve when the associated mRNAs engage in translation according to cellular needs.[2-4]

Recently, we identified a mRNA-silencing *foci* specific of neurons. These *foci* contain Smaug1/SAMD4, a translational repressor initially identified in the Drosophila embryo, and that we found expressed in the mammalian CNS.[5,6] Smaug proteins are novel mRNA regulators and they recognize their targets by a unique strategy, involving a SAM domain that binds a number of related motifs collectively termed SRE (Smaug Recognition Element).[7] Smaug1 *foci* are distinct from PBs and other neuronal RNA granules hitherto described, and were named S-*foci*. Both in neurons as

well as in transfected cell lines, the integrity of the S-*foci* inversely correlates with that of polysomes, as expected for mRNA-silencing *foci*. The S-*foci* dissolve when mRNAs are trapped into polysomes. Conversely, S-*foci* formation is enhanced when mRNAs are released from polysomes. Drosophila Smaug also forms mRNA silencing *foci* when expressed in mammalian cells.[5,6]

The S-*foci* are present at dendrites and remarkably associated to the post-synapses. Up to 60% of the dendritic spines of mature hippocampal neurons contain S-*foci*. An important finding is that these neuron-specific mRNA silencing *foci* respond to synaptic activation. The S-*foci* dissolve and release target mRNAs to allow their translation upon stimulation of the N-Methyl D-aspartate (NMDA) receptor. The response is rapid and maximal dissolution occurs between 1 to 5 min after stimulation. The effect is transient and after massive dissolution the S-*foci* begin to reassemble, provided that polysomes are allowed to disengage after the translation pulse. These observations suggest that mRNAs cycle between S-*foci* and polysomes, thus paralleling the cycling of mRNAs between PBs and polysomes in other cellular contexts (**Fig. 1A and B**).[6]

The S-*foci* apparently do not respond to α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor stimulation. The S-*foci* enter a round of relaxation and re-assembly upon stimulation of metabotropic glutamate receptors (mGlutR), with a distinctive time-course, thus allowing the transient release of mRNAs followed by translation (Luchelli and Boccaccio, unpublished) (**Fig. 1C and D**).[6] Both NMDAR and

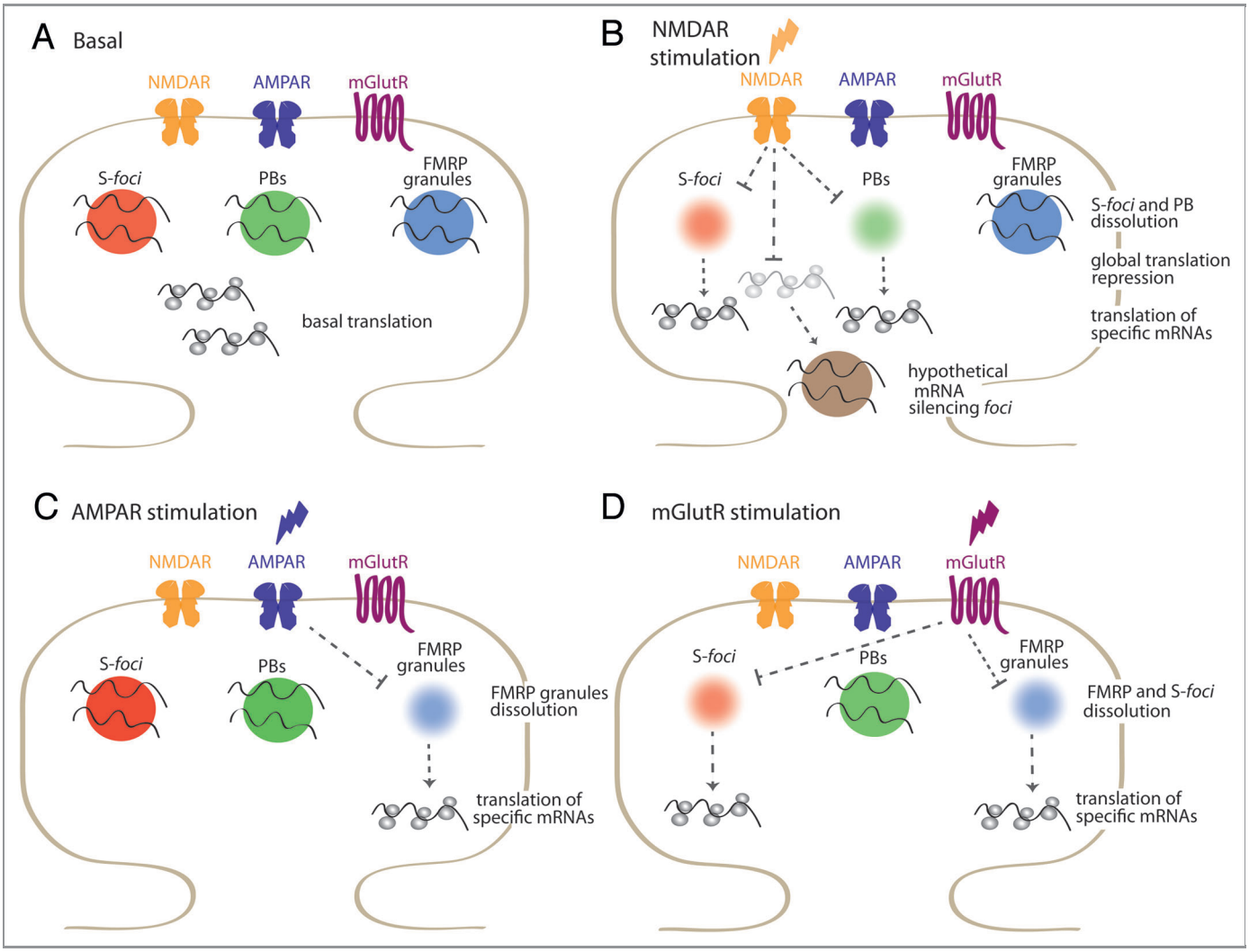

Figure 1. SyAS-*foci* and translational regulation at the synapse. (A) Several mRNA-silencing *foci*, including S-*foci*, PBs and FMRP granules, among others, are present in dendrites and dendritic spines. S-*foci* are different from FMRP granules and PBs. The three kind of SyAS-*foci* may coexist in a single dendritic spine. (B-D) Distinct SyAS-*foci* respond to specific stimuli, dissolving and releasing specific mRNAs. Stimulation of NMDAR or mGlutR affect S-*foci* and FMRP granules, and activates the translation of CamKIIα, among others.[6] About half of synapse-localized CamKIIα mRNA is associated to S-*foci* under resting conditions and is released upon NMDA stimulation and S-*foci* dissolution.[6] In addition, CamKIIα mRNA is as well regulated by FMRP and PBs,[30] opening the possibility of multiple regulation by distinct pathways. NMDAR stimulation provokes a global silencing, and the translation of a number of transcripts, including Kv1.1 mRNA among others, is repressed.[6,36]

mGlutR activation trigger the local synthesis of a number of proteins involved in synapse remodelling, including CamKIIα, a key signaling molecule.[8] Current evidence indicates that the mRNA encoding CamKIIα is associated to S-*foci* and released upon NMDAR activation. Molecular abrogation of Smaug1 by RNAi strategies leads to a dramatic alteration of dendritic spine morphology and excitability. Deregulation of CamKIIα mRNA undoubtedly contributes to these defects.[6] In addition, we speculate that Smaug1 regulates other mRNAs. Supporting this notion, the Drosophila molecule controls the stability and translation of hundreds of maternal mRNAs during early development, and the SAM domain accommodates a number of variations on the cognate RNA motif.[7,9-13] A profound remodelling of the transcriptome occurs during neuron development and synapse formation. A large number of neuronal mRNAs encoding different cell functions and that are expressed early during neuron maturation show a decrease after the onset of synaptogenesis.[14] Thus, paralleling the role of Drosophila Smaug as a major determinant of the maternal-to-zygotic transition, we speculate that mammalian Smaug1 is a major mRNA regulator during synaptogenesis, a stage when Smaug1 expression is maximal.[6] Among other candidates, nanos 1—homologous to Drosophila nanos, which is the best characterized Smaug target in the fly—is likely to be regulated by mammalian Smaug1. Drosophila nanos is under Smaug control in the embryo and in peripheral neurons, where it affects the dendritic arbour.[15-17] Nanos is also a translational repressor, and is recruited to mRNAs by its partner Pumilio. Both in mammalian and fly neurons, Pumilio affects dendritogenesis and/or synaptogenesis.[15,16,18-21] Thus, the relevance of the Smaug -Nanos/Pumilio post-transcriptional regulatory pathway is likely to be conserved from the insect to the mammalian CNS.

The molecular mechanism for mRNA repression by mammalian Smaug1 is unknown, but is expected to be similar to that of Drosophila Smaug, which operates at several levels. Drosophila Smaug blocks translation initiation and induces mRNA decay by triggering deadenylation.[10-12,22] Both mechanisms are likely to occur in the mammalian counterpart. Deadenylation is frequent in neuronal mRNAs, and the mRNA encoding CamKIIα, which is repressed in S-*foci*, is activated by cytoplasmic polyadenylation.

Whether aggregation of Smaug1 in discrete structures is required for efficient mRNA repression is unknown. Several proteins involved in general mRNA silencing have distinct oligomerization domains.[2-4] Among others motifs, regions enriched in glutamine (Q) and asparagine (N), which have a propensity to assemble into ordered aggregates, are frequent in PB components.[2-4] None of these oligomerization domains are present in Smaug1. We found that Smaug1 aggregation is independent of RNA binding and of the presence of PBs.[6] All this indicates that S-*foci* formation is not a consequence of mRNA repression, and allows the speculation that aggregation is important for Smaug1 function. Supporting this, granule formation is conserved in Drosophila Smaug. Like Smaug1 in hippocampal neurons, the fly molecule is found in *foci* in the embryo[22] and in large RNP complexes that can be isolated biochemically.[23] In addition, Drosophila Smaug forms *foci* when expressed in mammalian cells.[5] Self-aggregation is a common theme in several RNA binding proteins relevant to RNA regulation in neurons. Drosophila FMRP has a Q/N rich domain that mediates protein-protein interaction and that is important for the establishment of short-term memory.[24] The active form of Cytoplasmic Polyadenilation Element Binding protein (CPEB) from Aplysia forms small aggregates that bind CPE-containing mRNAs, thus stimulating their cytoplasmic polyadenylation.[25] Orb2, the Drosophila homolog, forms amyloid-like oligomers and neurons with Orb2 oligomers are the site for long-term memory storage.[26] RNG105, a post-transcriptional repressor found in dendritic RNA granules bears a coiled-coil region that is necessary for both translational repression and aggregation. Loss of RNG105 results in aberrant synapse formation and degeneration of neuronal networks.[27] Mammalian Pumilio forms granules in both neurons and cell lines,[19] and Drosophila Pumilio and its nematode ortolog PUF-9 localize to microscopically visible aggregates when expressed in yeast cells.[21] Pumilio bears a Q/N rich segment at the N-terminus. This prion-like region is important for recruitment of mammalian Pumilio 2 to SGs[19] and regulates postsynaptic Pumilio function in the fly.[21] Messenger RNAs translated at the synapses travel long distances from the cell soma, and they move packaged in granules. We speculate that self-aggregation of Smaug1 and other translational repressors may facilitate the transport of their target mRNAs.

Simultaneously with the activation of mRNAs stored in the S-*foci*, we and others have shown that NMDAR stimulation triggers a global translational silencing.[1,6] Using the FUNCAT strategy,[28] we found that in a few minutes, the protein synthesis rate in the surroundings of the stimulated synapses is reduced to half of the normal values (**Fig. 1A and B**). This rapid translation shut down is akin to the acute translation repression upon cellular stress, and whether it involves the assembly of specific mRNA silencing *foci* remains to be investigated. SGs form in neurons immediately upon stress induction, but not upon NMDAR stimulation[6] (Luchelli and Boccaccio, unpublished), leaving the point unanswered.

In addition to the S-*foci*, which are exclusive of mature neurons, PBs also appears to play a role in translation regulation upon synaptic activity. Neuronal PBs diverge from those present in cell lines, and PB components that usually colocalize in a single kind of *foci* in cell lines are found in separate *foci* in dendrites.[29-31] Synaptic activity affects the dynamics and integrity of dendritic PBs,[31-33] and the speculation is made that this allows the release of mRNAs and their incorporation into polysomes. PBs and several neuronal RNA granules containing FMRP (FragileX Mental Retardation Protein), FUS/TLS (fused in sarcoma/translated in liposarcoma), TDP43 (TAR DNA-binding protein 43), Staufen, Pumilio, ZBP1 (zip code-binding protein 1) and others, are motile and believed to contribute to RNA transport. We anticipate that many of them will behave as mRNA-silencing *foci* and will respond to

synaptic stimulation with enhanced assembly or dissolution to control the availability of specific transcripts. We propose the name of synaptic-activity regulated mRNA silencing *foci* (SyAS-*foci*) to these structures. Supporting these speculations, in addition to S-*foci* and PBs, the dynamics of a number of RNA granules is affected by neuronal activity. FMRP forms granules that dissolve upon AMPAR stimulation, which does not affect the integrity of the S-*foci*.[6,34] Depolarization enhances TDP43 granules in dendrites.[35] RNG105 granules shrink and DCP1a-containing PBs are enhanced upon BDNF exposure.[32] All this suggests that local translation upon stimulation by specific neurotransmitters or neurotrofins involves the concerted regulation of distinct SyAS-*foci* (**Fig. 1A–D**).

Our recent results show that Smaug1 knockdown severely disrupts spine morphology and neuron excitability, thus resembling the phenotype associated to Fragil X Mental Retardation Syndrome, a serious neurological disease provoked by altered expression of FMRP. Deregulation of Pumilio, Staufen or RNG105 provokes similar effects.[2,18,27] S-*foci* are distinct from the RNA granules containing these molecules, suggesting that Smaug1 and these non-related RNA binding proteins act in parallel pathways. Collectively, these observations emphasize the relevance of translation regulation by a plethora of SyAS-*foci* in neuron development and homeostasis.

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