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The Role of Mammalian Staufen on mRNA Traffic: a View from Its Nucleocytoplasmic Shuttling Function

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ABSTRACT. **The localization of mRNA in neuronal dendrites plays a role in both locally and temporally regulated protein synthesis, which is required for certain forms of synaptic plasticity. RNA granules constitute a dendritic mRNA transport machinery in neurons, which move along microtubules. RNA granules contain densely packed clusters of ribosomes, but lack some factors that are required for translation, suggesting that they are translationally incompetent. Recently some of the components of RNA granules have been identified, and their functions are in the process of being examined, in attempts to better understand the properties of RNA granules. Mammalian Staufen, a double-stranded RNA binding protein, is a component of RNA granules. Staufen is localized in the somatodendritic domain of neurons, and plays an important role in dendritic mRNA targeting. Recently, one of the mammalian homologs of Staufen, Staufen2 (Stau2), was shown to shuttle between the nucleus and the cytoplasm. This finding suggests the possibility that Stau2 binds RNA in the nucleus and that this ribonucleoprotein particle is transported from the nucleus to RNA granules in the cytoplasm. A closer study of this process might provide a clue to the mechanism by which RNA granules are formed.**

Key words: Staufen/RNA transport/RNA granule/CRM1/exportin-1/exportin-5/nuclear export

Introduction

Local protein synthesis in neuronal dendrites is required for some forms of synaptic plasticity, for example, neurotrophin-induced hippocampal synaptic plasticity (Kang and Schuman, 1996). The discovery of the localization of ribosomal clusters at the bases of dendritic spines in neurons provided the first indication that protein synthesis occurs in neuronal dendrites independent of neuronal soma (Steward and Levy, 1982). Since then, a large body of experimental evidence has been reported that support the dendritic protein synthesis hypothesis (reviewed in Steward and Schuman, 2001). The essential components of the translation machinery, including ribosomes, tRNAs and initiation and elongation factors, and the endoplasmic reticulum and Golgi apparatus, which are implicated in posttranslational modifications, have been shown to be present in dendrites, as revealed by immunocytochemical analysis (Tiedge and Brosius, 1996; Gardiol *et al*., 1999).

For local translation, mRNA must be localized in dendrites beforehand. mRNA at dendrites was first identified in the developing rat brain, in which microtubule-associated protein 2 (MAP2) mRNA was visualized using *in situ* hybridization (Garner *et al*., 1988). In the past twenty years, it has been reported that many types of mRNAs are delivered to dendrites in neurons (Eberwine *et al*., 2002). Some of them, for example, MAP2 and calcium/calmodulin-dependent protein kinase II α (CaMKIIα) mRNAs have been shown to be delivered to dendrites, depending on a cis-acting dendritic targeting element (DTE) in their 3'-untranslated regions (UTR) (Blichenberg *et al*., 1999; Mayford *et al*., 1996; Mori *et al*., 2000; Blichenberg *et al*., 2001). Two trans-acting proteins, MARTA1 and MARTA2, that specifically interact with DTE in MAP2 mRNA have been identified (Rehbein *et al*., 2000). However, the issue of whether MARTA1 or MARTA2 are required for the dendritic target-

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Abbreviations: MAP2, microtubule-associated protein 2; CaMKIIα, calcium/calmodulin-dependent protein kinase II α; DTE, cis-acting dendritic targeting element; dmStau, *Drosophila melanogaster* Staufen; dsRBD, double-stranded RNA-binding domain; Stau1, Staufen1; Stau2, Staufen2; NLS, nuclear localization signal; Exp-5, Exportin-5; RanGTP, GTP-bound form of RanGTPase; NES, nuclear export signal; RNP, ribonucleoprotein particle; NMD, nonsense-mediated mRNA decay; SMD, Stau1-mediated mRNA decay.

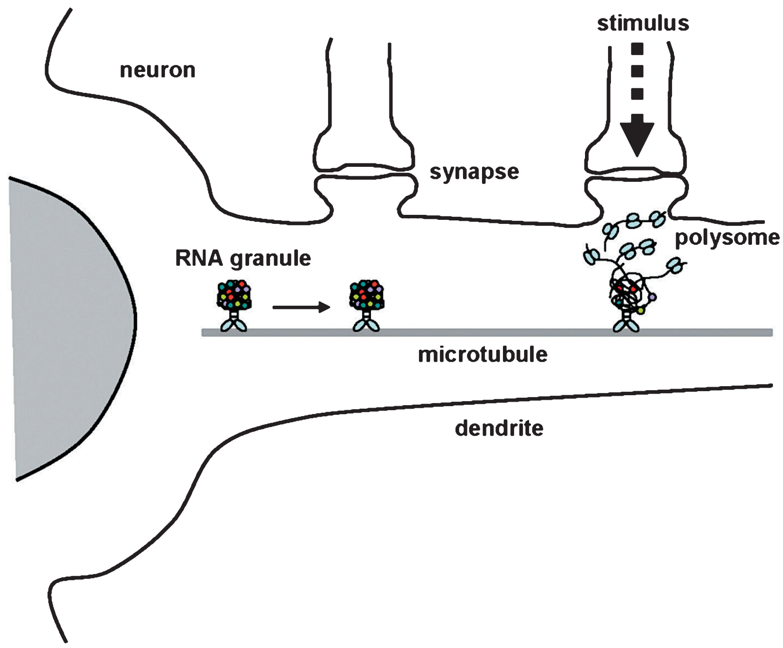

Fig. 1. Dendritic mRNA transport by RNA granules. Some mRNAs are included in RNA granules, RNA transport machineries in neuronal dendrites. RNA granule is a macromolecular structure composed of numerous factors including ribosomes, RNA-binding proteins and motor proteins, and moves along microtubules in dendrites. RNA granules lack some essential factors for translation, and, as a result, are translationally incompetent. A stimulus such as depolarization induces the release of some mRNAs from RNA granules to translationally active polysomes.

ing of MAP2 mRNA is currently unclear.

Various mRNAs including MAP2 mRNA and CaMKIIα mRNA are present in RNA granules, dendritic RNA transport machinery (Blichenberg *et al.*, 1999; Mayford *et al.*, 1996) (Fig. 1). RNA granules were originally identified as motile macromolecular structures in neurons, which move along microtubules within dendrites (Knowles *et al.*, 1996). The RNA granules were then isolated and shown to contain densely packed clusters of ribosomes (Krichevsky and Kosik, 2001). RNA granules transported by KIF5, a member of the kinesin super family proteins, were recently isolated, and a total of 42 proteins were identified as components (Kanai *et al.*, 2004). It has been shown that RNA granules do not include some factors that are essential for translation and tRNAs, indicating that they are translationally incompetent. Studies have shown that, after KCl depolarization, some RNAs including CaMKIIα mRNA and 18S rRNA are released from the RNA granule fraction to the translationally active polysome fraction (Krichevsky and Kosik, 2001). From these results, RNA granules are believed to act as a local storage pool for mRNAs that are held in translational arrest until they are stimulated for local protein synthesis (Krichevsky and Kosik, 2001). Thus, the function and components of RNA granules have recently been watched with keen interest. In this minireview, we focus on the function of mammalian Staufen, a component of RNA granules.

Staufen

Staufen was originally identified as a factor involved in the localization of two maternal RNAs, *bicoid* mRNA and *oskar* mRNA, in Drosophila embryo, and is therefore required for the correct formation of the anteroposterior axis (St Johnston *et al.*, 1991). *Drosophila melanogaster* Staufen (dmStau) consists of five double-stranded RNA-binding domains (dsRBDs) (Fig. 2). During oogenesis, dmStau colocalizes with *oskar* mRNA, and is responsible for posterior localization. On the other hand, dmStau is required for *bicoid* mRNA to become anchored at the anterior pole of fertilized eggs. The anterior localization of *bicoid* mRNA depends on the stem-loop structure in the 3'-UTR, which specifically binds to dmStau (Ferrandon *et al.*, 1994).

Two proteins that are encoded by distinct genes, Staufen1 (Stau1) and Staufen2 (Stau2), have been identified as mammalian homologs of Staufen (DesGroseillers and Lemieux, 1996; Buchner *et al.*, 1999). At least two ($Stau1^{63}$ and $Stau1^{55}$) and four ($Stau2^{62}$, $Stau2^{59}$, $Stau2^{56}$ and $Stau2^{52}$) splice isoforms exist for Stau1 and Stau2, respectively (Fig. 2) (Mallardo *et al.*, 2003; Monshausen *et al.*, 2004). Each isoform of Stau1 or Stau2 contains conserved dsRBDs. *In vitro*, the dsRBD of Staufen reportedly binds optimally to RNA stem-loops containing 12 uninterrupted base pairs (Ramos *et al.*, 2000). The dsRNA-binding capacity of the dsRBDs of Stau1 or Stau2 was investigated using the 3'-UTR of *bicoid* mRNA as a probe, and the dsRBD2 of

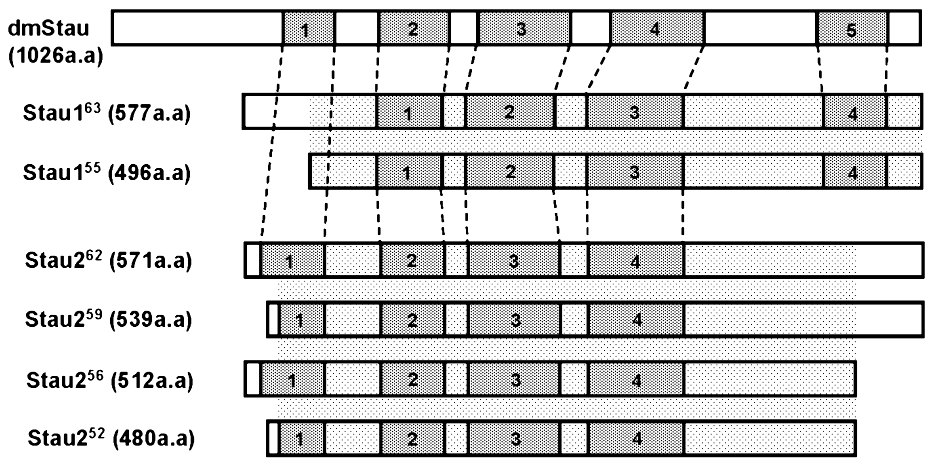

Fig. 2. Schematic representation of Staufen proteins. Mammalian homologs of *Drosophila melanogaster* Staufen (dmStau), Stau1 and Stau2 are composed of conserved dsRBDs. At least two and four splice isoforms for Stau1 and Stau2, respectively, have been identified, as denoted by molecular mass with number of amino acids (a.a). Dark grey boxes indicate the dsRBDs. Conserved dsRBDs are linked by dotted lines. A common domain among the splice isoforms for Stau1 or Stau2 is covered with a translucent grey box.

Stau1 or the dsRBD3 of Stau2, which is conserved from the dsRBD3 of dmStau, was shown to be the major dsRNA-binding determinant (Wickham *et al*., 1999; Duchaine *et al*., 2002). Furthermore, it is known that Stau1 is ubiquitously expressed, whereas Stau2 is mainly expressed in the brain (Wickham *et al*., 1999; Duchaine *et al*., 2002).

The function of Staufen in dendritic RNA transport

In neurons, Stau1 and Stau2 are located in the somatodendritic compartment and associate with RNA granules (Kiebler *et al*., 1999; Tang *et al*., 2001). Interestingly, however, Stau1 and Stau2 do not co-localize with each other in distal dendrites, suggesting that these proteins are located in distinct RNA granules (Duchaine *et al*., 2002), although it is not known whether different RNA granules include different sets of mRNA. It is noteworthy that knockdown of Stau1 by RNAi inhibits the transport of CaMKIIα 3'-UTR as a reporter mRNA to distal dendrites (Kanai *et al*., 2004). On the other hand, the overexpression of wild-type Stau2 but not the truncated mutant Stau2, which cannot become localized in distal dendrites, increases the amount of poly (A^+) mRNA in dendrites (Tang *et al*., 2001). These results indicate that Stau1 and Stau2 play an important role in mRNA transport as a component of RNA granules. At this time, however, no specific mRNAs have been identified that bind directly to Stau1 or Stau2 in RNA granules.

Stau2 shuttles between the nucleus and the cytoplasm

Although Staufen is predominantly localized in the cytoplasm, it was recently shown that Stau2 is able to shuttle between the nucleus and the cytoplasm (Macchi *et al*., 2004; Miki and Yoneda, 2004). The nuclear import of Stau2 depends on the region between dsRBD3 and dsRBD4 (Fig. 3A), in which a bipartite basic-type nuclear localization signal (NLS) was identified by computer prediction and mutational analysis (Macchi *et al*., 2004), although the nuclear import factor that recognizes the NLS remains to be identified.

Interestingly, two distinct pathways for the nuclear export of Stau2, an exportin-5 (Exp-5)-dependent one and a CRM1/exportin-1-dependent one appear to be operative. Exp-5 is a member of the importin β family of proteins, preferentially recognizes minihelix-containing RNAs in a GTP-bound form of RanGTPase (RanGTP)-dependent manner, and exports them from the nucleus (Gwizdek *et al*., 2003). The minihelix motif is often found in RNA polymerase III transcripts and consists of a double-stranded stem of over 14 nucleotides with a base-paired 5' end and a 3–8 nucleotide protruding 3' end that is able to tolerate some mismatches and bends (Gwizdek *et al*., 2001). MicroRNA precursors and adenovirus VA1 RNA, in which a minihelix motif is included, were shown to be good substrates for nuclear export by Exp-5 (Gwizdek *et al*., 2003; Yi *et al*., 2003; Lund *et al*., 2004; Bohnsack *et al*., 2004). The substrate of Exp-5 is not restricted to RNAs. Interleukin enhancer binding factor 3, which contains dsRBDs, is exported from the nucleus, depending on minihelix-containing RNA and RanGTP (Brownawell and Macara, 2002; Gwizdek *et al*., 2004). Moreover, eukaryotic elongation factor 1A can inter-

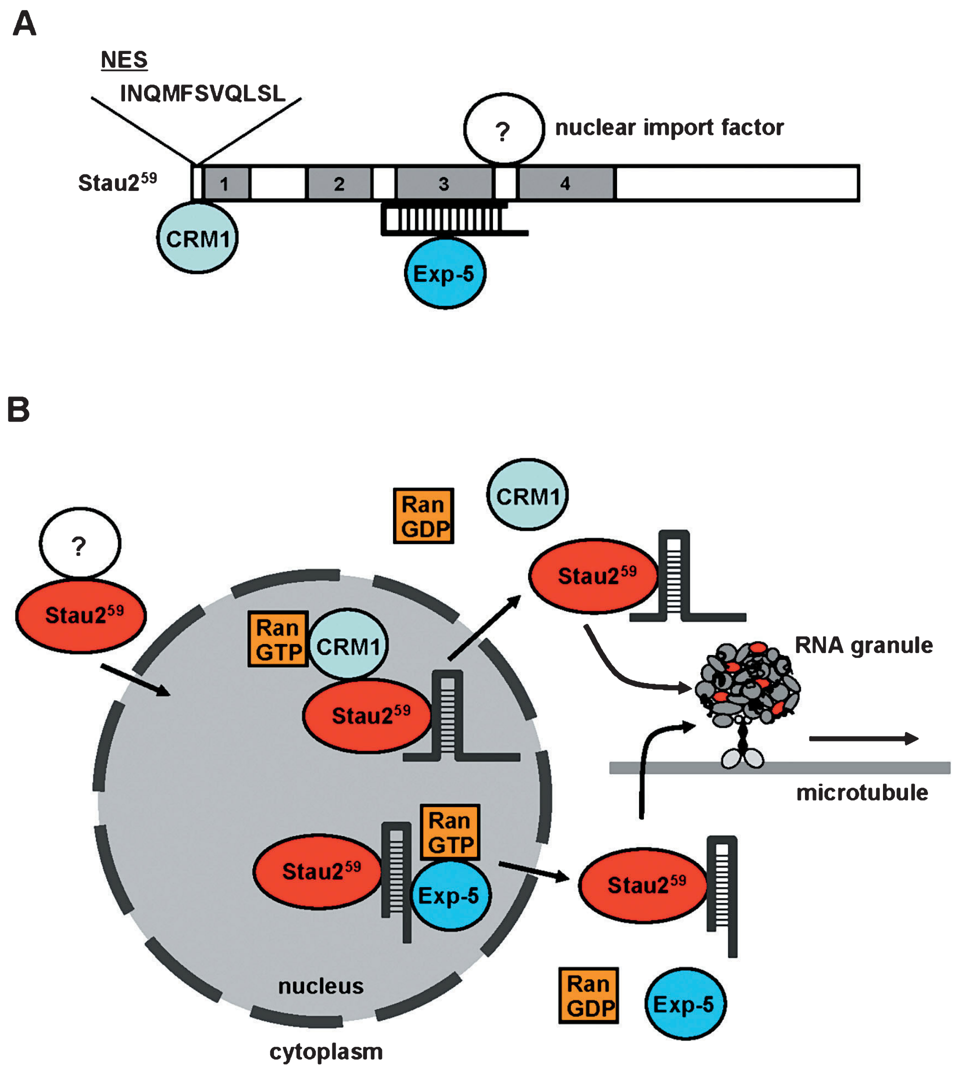

Fig. 3. Nucleocytoplasmic shuttling of Stau2. (A) Schematic representation of Stau2^{59} and its transport factors. The nuclear import of Stau2^{59} is mediated by the NLS between RBD3 and RBD4, although the import receptor remains unidentified. Stau2^{59} is exported from the nucleus via two distinct pathways, Exp-5-dependent one and CRM1-dependent one. Exp-5-dependent pathway is mediated via RBD3, which interacts with Exp-5 in a dsRNA-dependent manner. The CRM1-dependent pathway is mediated by the NES sequence "INQMFSVQLSL" at N-terminal domain. (B) Model for nuclear RNA export in which Stau2 may act as an export adaptor. In the Exp-5-dependent pathway, minihelix-containing RNA that bridges between Stau2 and Exp-5 is exported. In the CRM1-dependent pathway, other sets of RNA that are able to bind to Stau2 but not to Exp-5 may be exported. After export, Exp-5 or CRM1 dissociates as a result of GTP hydrolysis by Ran, and the Stau2-RNA complex then enters the RNA granule for dendritic transport.

act with Exp-5, depending on tRNA, and is exported from the nucleus by Exp-5 (Bohnsack *et al.*, 2002; Calado *et al.*, 2002). CRM1 also belongs to the importin β family of proteins. Proteins exported from the nucleus by CRM1 contain a nuclear export signal (NES), which is frequently composed of a stretch of characteristically spaced hydrophobic amino acids, such as leucine and isoleucine, as was originally reported for the protein kinase inhibitor and human immunodeficiency virus type 1 Rev proteins (Wen *et al.*, 1995; Fischer *et al.*, 1995).

Exp-5-dependent nuclear export is a common pathway for all Stau2 isoforms. Stau2 interacts with Exp-5 through dsRBD3 in a dsRNA and RanGTP-dependent manner (Fig. 3A) (Macchi *et al.*, 2004). In addition, it has recently been reported that Stau2^{59} is also exported via a CRM1-dependent pathway (Miki and Yoneda, 2004). CRM1 recognizes the NES at the N-terminal of Stau2^{59}, which is created by alternative splicing (Fig. 3A).

Stau1, which is predominantly localized in the cytoplasm, was reported to be localized in the nucleolus (Le *et al.*, 2000), suggesting that Stau1 also shuttles between the nucleus and the cytoplasm. Although the mechanism has not yet been investigated in detail, the RBD2 of Stau1 has been shown to interact with Exp-5 (Brownawell and Macara, 2002).

A putative role of Stau2 as an adaptor protein for nuclear RNA export

Based on the RNA-binding activity and the nucleocytoplasmic shuttling properties of Stau2, the possibility that Stau2 binds RNA in the nucleus and becomes incorporated into RNA granules in the cytoplasm cannot be excluded; in other words, Stau2 might act as an adaptor protein for nuclear RNA export (Fig. 3B). In fact, through the Exp-5-dependent pathway, Stau2 is exported from the nucleus while binding some RNA, because the interaction between Stau2 and Exp-5 requires a dsRNA (Macchi *et al*., 2004). Although an *in vivo* RNA target bridging both of the two proteins has not yet been identified, a minihelix-containing RNA appears to be a candidate. However, it should be noted that miRNAs and tRNAs are not included in RNA granules (Krichevsky and Kosik, 2001; Kim *et al*., 2004).

On the other hand, $Stau2^{59}$, which can be exported by CRM1, possibly acts as a nuclear export adaptor for other sets of RNAs, for example, mRNAs. Although it is well known that bulk nuclear mRNA export is not mediated by CRM1 but by Tap/NXF1 (Gruter *et al*., 1998; Kang and Cullen, 1999; Katahira *et al*., 1999; Herold *et al*., 2000; Braun *et al*., 2001), some reports have suggested that the CRM-dependent nuclear export of some cellular mRNAs occurs (Brennan *et al*., 2000; Yang *et al*., 2001). Therefore, although the possibility that $Stau2^{59}$ may be exported from the nucleus by CRM1 without binding any RNA cannot be excluded, it is likely that some mRNAs are exported from the nucleus via $Stau2^{59}$ in a CRM1-dependent manner.

In addition, Kiebler *et al*. (2005) proposed an interesting model in which, before nuclear export, Stau2 comes into the nucleolus for the assembly into ribonucleoprotein particles (RNPs) or for the maturation of the RNPs, because nuclear-localized Stau2 as a result of the inhibition of nuclear export accumulates to high levels in the nucleolus (Kiebler *et al*., 2005). Furthermore, it has recently reported that Stau2 interacts with the nuclear pore protein p62, with Tap and with the exon-exon junction complex proteins Y14-Mago heterodimer, providing a plausible hypothesis that Stau2 links nuclear RNA processing and cytoplasmic RNA localization in neurons (Monshausen *et al*., 2004).

Future directions

Although Staufen is a component of RNA granules and plays some role in dendritic RNA transport in neurons, the issue of how Staufen is transported into RNA granules is unknown. Where is the Staufen RNP, which is thought to be a core structure of RNA granules, formed? The nucleocytoplasmic shuttling activity of Staufen may well provide a hint. The most important issue in addressing this problem is the identification of a natural RNA target that is exported from the nucleus while bound to Staufen. In addition, to find the interacting partner of Staufen in the nucleus must be an important clue for why Staufen shuttles between the nucleus and the cytoplasm or how Staufen is involved in RNA transport.

Another possible role of Staufen in the cytoplasm was recently reported in which Stau1 mediates mRNA decay (Kim *et al*., 2005). Kim *et al*. (2005) showed that Stau1 binds to the 3'-UTR of ADP-ribosylation factor 1 mRNA and recruits Upf1, a protein that is involved in nonsense-mediated mRNA decay (NMD), to degrade the mRNA. The issue of whether a similar pathway exists for Stau2 also should be elucidated. It will be interesting to determine if SMD occurs at local sites in neuronal dendrites, because it may be involved in the regulation of mRNA after local translation.

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