

Staufen: a common component of mRNA transport in oocytes and neurons?

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Mammalian homologues of Staufen, a protein involved in localizing mRNAs during oogenesis and early central nervous system development in Drosophila, have been identified recently.

The mammalian staufen gene encodes a protein containing several conserved double-stranded mRNA-binding domains and is expressed in hippocampal neurons. The mammalian Staufen protein forms granules that are transported to the distal dendrite during neuronal maturation. The Staufen granules colocalize with ribonuclear particles that transport mRNA to the dendrites. These findings might provide clues to a mechanism of mRNA transport conserved in mammalian neurons and Drosophila oogenesis.

The establishment of a specific localization of mRNA is a common mechanism for partitioning information and for establishing polarity in oocytes and somatic cells¹⁻³. In *Drosophila* oocytes, localization of *bicoid*, *nanos* and *oskar* mRNAs is a prerequisite for the establishment of protein gradients that define the anterior and posterior domains of the developing embryo⁴. In *Xenopus*, *VegT* mRNA is localized to the vegetal pole of the egg, which is a necessary step in endoderm formation⁵. In *Drosophila* somatic cells, mRNA localization has been observed in neuroblasts of the developing nervous system⁶ and this also occurs in neurons and oligodendrocytes in mammals^{2,7}. The molecular characterization of the mammalian homologue of the *Drosophila* double-stranded RNA-binding protein Staufen⁸⁻¹⁰ has potentially revealed a mechanism that is common to both mRNA localization in mammalian cells, particularly in neurons, and mRNA trafficking in insect oocytes and neuroblasts.

Staufen functions in mRNA localization in *Drosophila* oocytes

The *staufen* gene was identified initially as a maternal factor required for the correct formation of the anteroposterior axis in the *Drosophila* embryo^{11,12}.

The anterior and posterior domains of the *Drosophila* embryo are defined by two oppositely localized mRNAs, whose protein products diffuse from either pole to establish a gradient¹³. The anterior signal is generated by localized *bicoid* mRNA at the anterior pole, which generates freely diffusible Bicoid protein from the anterior pole after fertilization^{14,15}. A similar gradient of Nanos protein is established on the posterior side of the embryo by the posterior group genes *oskar*, *staufen*, *vasa*, *valois* and *tudor*¹⁶⁻¹⁸. An important step in the formation of the Nanos gradient is the localization of *oskar* mRNA to the posterior pole of the oocyte¹⁷. The localization of *oskar* and *bicoid* mRNAs was found to depend on *staufen*. The Staufen protein colocalizes with *oskar* mRNA at the posterior pole of the *Drosophila* oocyte and is present with *bicoid* mRNA at the anterior pole of the egg and early embryo (Fig. 1a,b)^{12,19}. The maternal component of the Staufen protein is thus a necessary element in the localization of mRNAs responsible for establishing anterior and posterior patterning in *Drosophila*.

Staufen and asymmetric cell divisions in the developing nervous system

The function of *staufen* is not limited to oogenesis and early embryonic patterning. Zygotic Staufen in *Drosophila* is expressed throughout the developing nervous system and participates in establishing asymmetry by localizing *prospero* mRNA in neuroblasts (Fig. 1c-e)²⁰⁻²⁴. During embryonic development of the central nervous system (CNS), neuroblasts delaminate from the epithelial layer and begin to divide asymmetrically several times to produce a small ganglion mother cell (GMC) and a neuroblast at each division⁶. Staufen colocalizes with Prospero protein and mRNA in neuroblasts^{20,21}. The proper positioning of both Prospero and Staufen depends on Inscuteable and Miranda, which colocalize with Staufen, Prospero and *prospero* mRNA at the apical cortex during interphase^{22,24-27}. At metaphase, Miranda, Staufen, Prospero and *prospero* mRNA are relocated to the basal cortex, whereas Inscuteable remains at the apical cortex. Staufen interacts directly with both Miranda and Inscuteable *in vitro*, and Staufen is mislocalized in both *miranda* and *inscuteable* mutants. In *staufen* mutant embryos, *prospero* mRNA is mislocalized, but the other protein components involved are localized normally. GMC specification does not require Staufen protein function, indicating that Staufen is involved in a backup mechanism in proper *prospero* mRNA localization to ensure that high levels of Prospero are maintained during the rapid neuroblast/GMC divisions²⁰.

The interaction of Staufen with mRNA

In addition to *in vitro* and *in vivo* studies of the interaction of Staufen with mRNA, deletion analysis of the *Drosophila* Staufen protein has provided insights into the mechanism of the interaction. Extensive studies have determined the elements necessary for *bicoid* mRNA localization²⁸⁻³⁰. Injection of full-length *bicoid* mRNA or *bicoid* 3' UTR into *Drosophila* embryos was shown to recruit Staufen to form

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granules that move to the cortex during formation of the syncytial blastoderm¹⁹. The 3' UTR of *bicoid* was analysed further by injecting a series of deletion derivatives to determine the nucleotides necessary for the formation of Staufen–RNA granules. Three distinct regions of the *bicoid* 3' UTR are required for the formation of Staufen–RNA granules, and these regions coincide with predicted extensive stem–loop structures in the mRNA^{19,28–30}. Extensive stem–loop structures are, however, not sufficient to form Staufen granules *in vivo*. Other RNAs with extensive stem–loop structures, such as *VAI* mRNA, poly(rI–rC) and the antisense *bicoid* 3' UTR, do not cause formation of Staufen–RNA granules *in vivo*. These studies indicate a specific role for secondary structure of the *bicoid* 3' UTR in recruiting Staufen; however, evidence of a direct interaction has not yet been shown. Further biochemical studies are needed to confirm this direct interaction, and complete characterization of the contents of Staufen–RNA granules will solidify these conclusions.

The Staufen protein contains five double-stranded RNA-binding domains (dsRBDs) that appear to bind individually to dsRNA nonspecifically³¹. The proposed interaction between Staufen and the 3' UTR of *bicoid* mRNA could be conferred by the combined stem–loop structures of the 3' UTR in conjunction with the positions of the dsRBDs. Other cofactors present in the oocyte might be involved in the localization of *oskar* mRNA to the posterior pole by Staufen. The 3' UTR of *oskar* mRNA shows no homology to the *bicoid* 3' UTR, and does not form Staufen–RNA granules when injected into *Drosophila* embryos¹⁹. The oocyte might contain elements necessary to mediate the correct localization of *oskar* mRNA by Staufen, but which are no long present in the embryo. *Prospero* mRNA has not yet been analysed to determine which regions are necessary for its interaction, but, like *oskar*, *prospero* might require unidentified cofactors to mediate its interaction with Staufen. In both *Drosophila* oocytes and embryonic neuroblasts, Staufen is associated with macromolecular complexes containing mRNAs. Identification of molecules contained in these complexes, either by genetic interaction or biochemical analysis, should contribute to our understanding of the different levels of regulation of the interaction between Staufen and mRNA.

Staufen is a member of a conserved family of dsRNA-binding proteins

The role of Staufen as an RNA-binding protein responsible for the localization of mRNAs in diverse

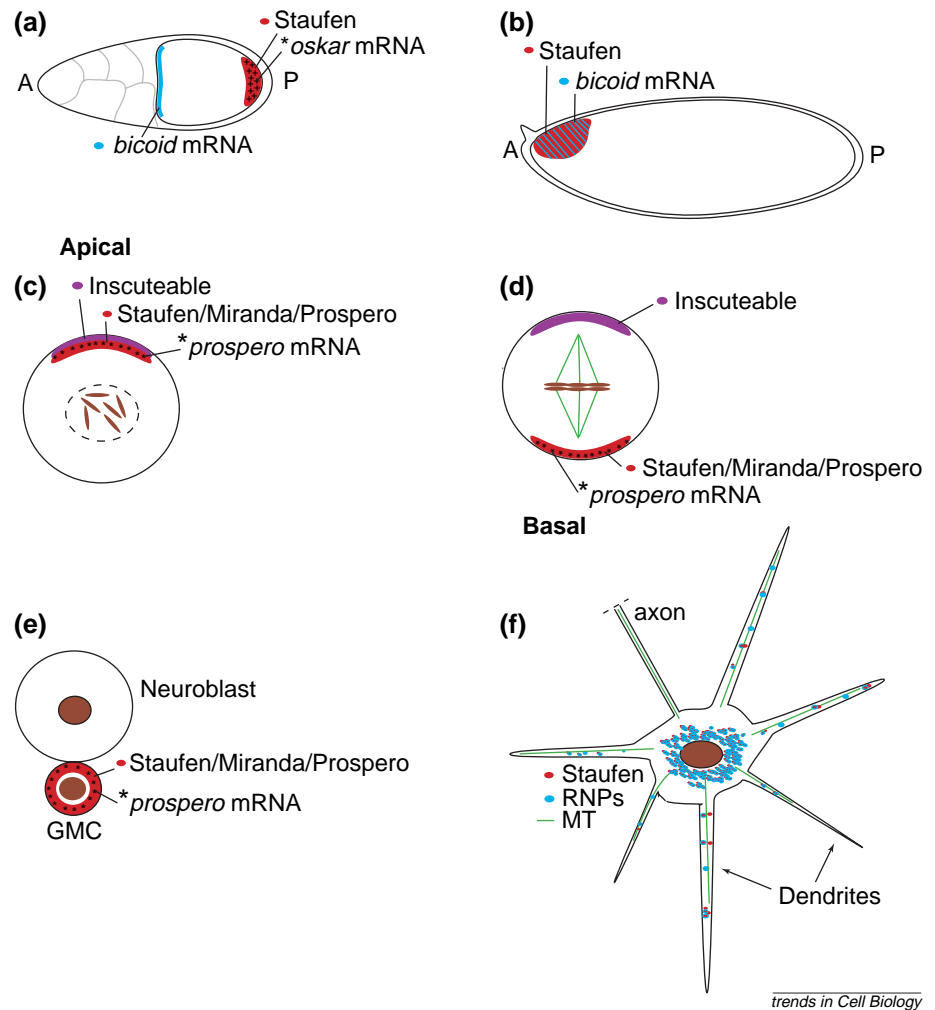


FIGURE 1

Localization of Staufen in *Drosophila* oocytes (a), eggs (b), neuroblasts (c–e) and in mammalian neurons (f). During Stages 9 and 10 of the maturing oocyte (a), Staufen (red) colocalizes with *oskar* mRNA (*) and is responsible for its localization at the posterior pole (P). *bicoid* mRNA (blue) is distributed along the anterior (A) region of the oocyte. In the fertilized egg (b), Staufen colocalizes with *bicoid* mRNA and is responsible for its localization at the anterior pole. During asymmetric divisions of embryonic neuroblasts in the *Drosophila* central nervous system (c–e), Staufen is part of a complex (red) containing Miranda, Prospero, *prospero* mRNA (*) and Inscuteable (purple) at the apical cortex during prophase (c). Staufen is responsible for the localization of *prospero* mRNA and interacts directly with Inscuteable and Miranda at the apical cortex. During mitosis (d), Staufen, Miranda, Prospero and *prospero* mRNA are relocated to the basal cortex of the neuroblast. Inscuteable remains at the apical cortex and is responsible for the apical–basal orientation of the spindle and the correct positioning of the complex at the basal cortex. Following mitosis (e), Staufen, Miranda, Prospero and *prospero* mRNA are segregated to the basal ganglion mother cell (GMC). In the neuroblast, Inscuteable is degraded. In mammalian neurons (f), Staufen (red) forms granules in both the cell body and dendrites, and these granules colocalize with ribonuclear particles (RNPs: blue), which have a similar distribution. In the dendrites, not all RNPs contain Staufen, but Staufen and RNP translocation is microtubule (MT: green) dependent.

cell types in *Drosophila* has led to the search for homologues in other organisms. Recently, several groups have identified the mammalian homologue of *staufen* in the rat, mouse and human^{8–10}. The *Caenorhabditis elegans* genome also contains an uncharacterized open reading frame that shows similarity to human and mammalian *staufen* (Fig. 2)¹⁰. Analysis of the mammalian Staufen dsRBDs indicates that these regions are functional homologues; however, the mammalian protein is missing the first RBD, which is found in both the *Drosophila* and

TABLE 1 – GENES INVOLVED IN mRNA LOCALIZATION IN *DROSOPHILA*

Gene	Role in mRNA localization	Mammalian homologue	Refs
<i>staufen</i>	Required for the proper localization of <i>oskar</i> , <i>bicoid</i> and <i>prospero</i> mRNAs during oogenesis, early embryogenesis and neurogenesis, respectively.	mStaufen	8–10, 12, 20, 21
<i>oskar</i>	Localized mRNA participates in the establishment of the posterior pole of the oocyte.	None	16, 17, 32
<i>bicoid</i>	Localized mRNA establishes a bicoid protein gradient that defines the anterior pole of the embryo.	None	14, 15
<i>inscuteable</i>	Interacts with Staufen at apical cortex of neuroblasts during interphase, required for basal positioning of Staufen, Prospero, <i>prospero</i> mRNA and Miranda, as well as spindle orientation during mitosis.	None	21, 24, 25
<i>prospero</i>	Homeo-domain transcription factor required for differentiation of ganglion mother cell.	prox1	20–23
<i>miranda</i>	Linker protein required for correct localization of Staufen, Prospero and <i>prospero</i> mRNA to the basal cortex during neuroblast mitosis.	None	22–24, 27

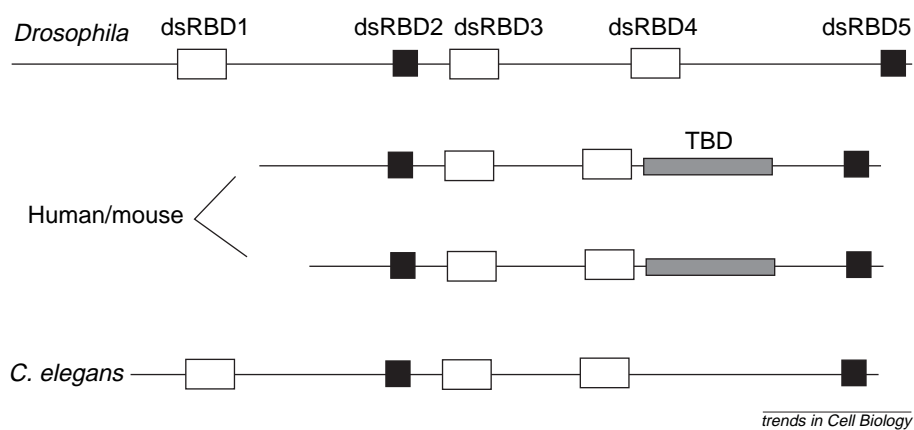


FIGURE 2

Structure of *Drosophila staufen* and the mammalian (human and mouse) and *Caenorhabditis elegans* homologues. The *Drosophila* gene contains two short (black boxes) and three long (white boxes) domains that bind to double-stranded RNA. The human and mouse homologues contain only four double-stranded RNA-binding domains (dsRBDs) and a tubulin-binding domain (TBD: grey boxes). The mammalian gene is expressed as two splice variants differing in their N-terminal domain. The *C. elegans* gene contains five dsRBDs, and, like the *Drosophila* gene, contains no TBD¹⁰.

C. elegans staufen^{9,10}. Mammalian *staufen* contains a putative microtubule-associated protein (MAP-1B)-binding domain (MBD) that is lacking in both the *C. elegans* and *Drosophila* proteins¹⁰. The *Drosophila* N-terminal portion of the protein is also absent from the mammalian homologue³². No mammalian homologue to *bicoid* has been identified, and no specific mammalian mRNA has yet been shown to interact with Staufen. Deletion mapping of the mammalian Staufen protein indicates that dsRBDs 2 and 3 are responsible for the interaction with *Drosophila bicoid* mRNA in an *in vitro* binding assay¹⁰, whereas deletion of the MBD abolishes the interaction of mammalian Staufen with microtubules *in vitro*¹⁰.

The human *staufen* gene maps to band 20q13.1 on the long arm of chromosome 20 (Ref. 33) and is present in up to four splice variants encoding two protein isoforms of approximately 60 and 65 kDa that differ in their N-terminal region^{8–10}. The *staufen* gene is expressed in most tissues, including the gonads, heart, liver, pancreas, nervous system and muscle^{8–10}.

The intracellular localization of ectopically expressed Staufen has been studied in COS cells and endogenous Staufen in neurons using specific antibodies^{8–10}. One aspect of the localization of Staufen in cells is the variety of subcellular structures with which it colocalizes; mammalian Staufen colocalizes with markers of the rough endoplasmic reticulum (RER)^{8–10}, in addition to microtubules and polysomes. Biochemical studies indicate that Staufen cosediments with polysomes, supporting the immunolocalization studies. There is no indication to date that Staufen localization in cells requires polysomes or the RER, and several of these observations are based on overexpression of Staufen in cultured cells, and therefore should be interpreted with caution. The colocalization of Staufen with the RER and polysomes indicates a possible role in translational control of mRNAs, but this has not yet been demonstrated. The importance of

the MBD is difficult to ascertain; the localization of Staufen in *Drosophila* oocytes¹⁹ and mammalian neurons³⁴ is microtubule dependent, yet the *Drosophila* protein lacks the MBD. Perhaps other microtubule-binding proteins, such as motor proteins, are necessary for the *in vivo* interaction in both *Drosophila* and mammalian cells.

The potential role of mammalian Staufen in mRNA localization in neurons

Localization of mRNAs at the synapse has been proposed as a mechanism for establishing synaptic memory and maintaining synaptic plasticity^{35,36}. Targeting of specific mRNAs at synapses might create specific postsynaptic domains through local translation of these localized mRNAs². These differentiated synaptic domains could provide a mechanism for establishing synaptic memory. A required step in generating synaptic domains is transportation of mRNAs from the soma to the distal dendrite. The study of the dynamics of mRNA transport in developing hippocampal neurons using the fluorescent

nucleic acid dye SYTO14 showed that mRNA formed granules in the soma of the developing neuron and that, during maturation, these granules would gradually be restricted to the dendrites, and excluded from the axon³⁷. In this context, the evidence that Staufen is expressed in neurons and colocalizes with mRNA granules provides a potential mechanism for transport of mRNAs to the dendrite (Fig. 1f)⁸. At the ultrastructural level, these mRNA granules are associated with polyribosomal structures³⁷. The distribution of Staufen protein in developing hippocampal neurons was investigated to determine whether it was involved in mRNA granule transport in these cells^{8,34}. Ultrastructural analysis of the post-synaptic region shows that Staufen is closely associated with tubular structures resembling the ER and is enriched in regions where microtubules are present. When compared with the distribution of mRNA-containing particles, Staufen is often found in perfect colocalization with these ribonuclear particles (RNPs), but not all RNPs contain Staufen. Staufen was not found to colocalize with ribosomes by immunoelectron microscopy⁸, in contradiction to an *in vitro* study⁹ that showed that Staufen co-sediments with intact polysomes in sucrose gradients. More direct studies of the interaction of Staufen with polysomes will have to address this discrepancy because it has important implications for the potential involvement of Staufen in translational control of localized mRNAs.

Both Staufen and RNA-containing granules move in a microtubule-dependent way along the dendrite^{34,37}. In early dendrites, the movement is primarily anterograde, but, as the neuron matures, both anterograde and retrograde transport are observed. The dynamics of Staufen recruitment to the dendrite was studied using hippocampal neurons transfected transiently with a Staufen–GFP fusion protein and visualized by time-lapse fluorescence microscopy³⁴. The distribution of Staufen–GFP was compared with that of SYTO-14-labelled RNPs in living neurons. Staufen was found to accumulate in large and small granules in the soma and dendrites. The movement of Staufen–GFP granules was very similar to that seen in labelled RNPs³⁴. As in the transport of RNPs, Staufen–GFP recruitment and translocation are dependent on the presence of intact microtubules; treatment with nocodazole leads to an increase in cytosolic Staufen and a decrease in the percentage of Staufen granules³⁴.

Based on these observations, an attractive model can be proposed for the function of Staufen in developing and mature neurons. In the developing neuron, Staufen might be responsible for the formation of large RNPs that transport specific mRNAs along microtubules to the elaborating dendrite. This mRNA transport might contribute to dendrite morphogenesis by providing mRNAs for local protein synthesis. In the fully differentiated neuron, Staufen would continue to function in transporting specific mRNAs to the synapse to produce synaptic micro-environments through local protein synthesis. Local protein synthesis has been proposed as a mechanism of establishing synaptic memory.

Although the studies cited above broadly support this model, specific experiments addressing several aspects of the role of Staufen need to be undertaken. If Staufen is binding to and transporting mRNAs, which specific mRNAs are being transported to the dendrite and what is the role of these mRNAs? The current studies have not shown that Staufen interacts with any specific mammalian mRNAs, and although mammalian homologues of the *Drosophila* genes *bicoid* and *oskar* have not been characterized, a mammalian *prospero* homologue, *prox1*, is expressed in the mouse nervous system during development³⁸ (Table 1). *Prox1* mRNA would be a potential candidate for localization by Staufen in mammalian neurons, but this question has not yet been addressed experimentally. Although Staufen appears to colocalize with the RER, it is unclear whether this implicates Staufen as part of the translational machinery. Is Staufen transporting mRNAs to the RER at the distal dendrite to be translated, or does the colocalization of Staufen with the RER indicate that the RER itself might be transported along the dendrite³⁵? Are there additional components of the mRNA localization machinery that might be shared between oocytes and neurons? The Staufen–RNA granules might contain other molecules (such as in the *Drosophila* oocyte) that could mediate the interaction of Staufen with both mRNA and subcellular structures. Potential candidates include components of the translation machinery, and molecular motors such as kinesins that might be involved in the translocation of Staufen along microtubules³⁹. Finally, the potential role of Staufen in early mammalian embryonic development has yet to be determined, and could be addressed by analysis of the phenotype of knockout mutant embryos.

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We thank Salim Abdelilah, Bingwei Lu, Claudia Petritsch and Kimberly Raab-Graham for critical reading of the manuscript.

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Seeing the light

Perhaps as a result of our status as complex metazoans, humans tend towards a 'mechanistic' view of stimulus response – the stimulus is detected by one machine (eyes, for example), processed by another (the brain) and used to instruct all the other machines in the body. Recently, this view has been challenged by the discovery of peripheral circadian rhythms. In this situation, the 'other machines' – peripheral organs such as the heart or kidneys – maintain their own internal clock in addition to receiving information from the central sensors (eyes). These peripheral clocks control rhythmic oscillations in the expression of particular genes, such as *Clock*. In addition, peripheral clocks can be adjusted ('entrained')

to match stimuli detected by the principal sense organs, so that, when one travels, for example, the peripheral clocks adjust to local time.

Now Whitmore *et al.* have taken this view a step forward by showing that peripheral organs can entrain their circadian rhythm directly, without the signal having to be detected via the central nervous system¹. By removing hearts and kidneys from zebrafish kept in one light–dark regime and culturing the dissected organs in a different light–dark regime, the group show that these organs can respond to the new conditions and shift the expression of *Clock*. This shift is extremely rapid, with a complete reversal of the expression pattern being achieved within two days of

entering the new regime. Moreover, a similar effect can be observed even in an immortalized zebrafish cell line, suggesting that individual cells have the ability to perceive and respond to a changing light stimulus.

This elegant demonstration of decentralized light detection in vertebrates will undoubtedly stimulate some intense research into the identity of the receptors responsible and raises the exciting prospect of a much more 'systemic' view of stimulus detection.

1 Whitmore, D. *et al.* (2000) Light acts directly on organs and cells in culture to set the vertebrate circadian clock. *Nature* 404, 87–91



Hitting the wall: how microtubules interact with the cell cortex

This month's headlines were contributed by

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Proper orientation of the mitotic spindle is a key feature of polarized cell division. In processes such as plant morphogenesis and vertebrate embryogenesis, polarized cell growth

is responsible for the spatial positioning of newly formed tissue. In order for cells to propagate in a particular direction, their spindles must be aligned along a particular axis at the

beginning of mitosis such that mother and daughter cells are positioned properly at the end of cytokinesis.

The baker's yeast, *Saccharomyces cerevisiae*, serves as an excellent