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Mechanisms and cellular roles of local protein synthesis in mammalian cells

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Summary

After export from the nucleus it turns out that all mRNAs are not treated equally. Not only is mRNA subject to translation, but through RNA binding proteins and other *trans*-acting factors, eukaryotic cells interpret codes for spatial sorting within the mRNA sequence. These codes instruct the cytoskeleton and translation apparatus to make decisions about where to transport and when to translate the intended protein product. Signaling pathways decode extra-cellular cues and can modify transport and translation factors in the appropriate cytoplasmic space to achieve translation locally. Identifying regulatory sites on transport factors as well as novel physiological functions for well known translation factors have provided significant advances in how spatially controlled translation impacts cell function.

Introduction

Spatial regulation of translation within the cytoplasm results in the accumulation of newly synthesized proteins in discrete locations of the cell. The most widely studied mechanism to spatially restrict protein synthesis is through active sorting of the template for translation within the cytoplasm, often termed mRNA localization [1]. mRNA localization allows cells the flexibility to determine the exact place and time of protein synthesis in the absence of *de novo* transcription providing a mechanism to quickly respond to changes in their extra-cellular environment. The information required for localization is contained within the mRNA sequence. There are many potential mechanisms to explain how a nucleic acid sequence distributes an mRNA within the cytoplasm [1]. It is possible that sequences within the mRNA interact directly with cytoskeletal elements [2], although most current models for localization suggest that mRNA sequences interact with subsets of RNA binding proteins, forming a Localizing Ribonucleo-Protein (L-RNP) complex. The L-RNP localizes through interactions with cytoskeletal elements either directly or indirectly. Therefore, in addition to carrying the information required for protein synthesis, an mRNA contains sequences whose purpose is to select the appropriate complement of *trans*-acting factors to achieve proper spatio-temporal regulation of translation.

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Many localized mRNAs are translationally repressed, and it has been hypothesized that this is to prevent ectopic synthesis during transport [1]. Localized mRNAs need to associate with localizing factors as well as reversible translational repressors that are responsive to spatial cues in the cytoplasm. To ensure repression in the cytoplasm, translational regulatory factors join the mRNA as soon as it is synthesized in the nucleus [3]. The activities of these localization and translational repression factors need to be coordinated to achieve the proper timing of events and can be contained within a single factor or provided by interacting factors. As a consequence, a great deal of study has been devoted to the formation and function of the components of RNP complexes. Global analysis of mRNA associated with RNP components has observed that many of them associate with multiple functionally related mRNAs [4]. Thus the cell's ability to respond to extra-cellular signals may be coordinately regulated through RNPs by initiating the translation of many members of a multi-protein complex at the same time and place [4]. This central role of RNP complexes in spatial control of translation will be illustrated through one well-known mammalian mRNA localization factor, ZBP1. Other systems, such as yeast and *Drosophila* operate through parallel mechanisms and will not be detailed here due to space restrictions [5,6].

ZBP1 is a Src dependent translational repressor

ZBP1 is an RNA binding protein isolated from chick embryo fibroblasts based on its affinity for a *cis*-acting 54 nucleotide cytoplasmic localization element within the 3′UTR of β-actin mRNA known as the zipcode [7]. The zipcode sequence was necessary and sufficient for peripheral targeting of RNA [8]. ZBP1 functions as a translational inhibitor by preventing 80S ribosomal complex formation [3]. Importantly, Src phosphorylation of ZBP1 at tyrosine 396 resulted in translational derepression [3]. A non-phosphorylatable ZBP1 mutant prevented translational derepression resulting in decreased peripheral actin and aberrant neurite outgrowth [3]. Interestingly, β-actin translation sites were redistributed to the perinuclear cytoplasm in myoblast cells containing a transfected β-actin mRNA lacking the zipcode, supporting the hypothesis that interaction between ZBP1 and the zipcode prevents precocious translation [9]. IMP1 (the human ortholog to ZBP1) RNP complexes, biochemically isolated from HEK293 cells contain exon junction complex components and lack eIF4E, eIF4G, and 60S ribosomal subunits suggesting that IMP1 associated mRNAs have not undergone translation [10]. In addition, a mouse ortholog of ZBP1 represses the translation of insulin-like growth factor II mRNA in a developmentally regulated manner [11]. Altogether these data demonstrate that an interaction between ZBP1 and the zipcode is required to regulate β-actin mRNP complexes at the level of localization and translation. In this case, the localization and translational repression activities for β-actin mRNP complexes are present within a single *trans*-acting factor, and phosphorylation of this factor coordinates these activities.

β-actin mRNA is targeted in a Rho-dependent manner

In chicken embryo fibroblasts, β-actin mRNP complex targeting to the cell periphery was induced with serum or PDGF implicating signal transduction pathways in this process [12]. Inhibiting tyrosine kinase activity prevented PDGF induced β-actin RNP complex targeting [12]. Rho GTPases were similarly involved in localization as Rho inhibitors and a dominant negative RhoA reduced serum induced peripheral targeting of β-actin mRNP complexes while peripheral targeting increased in the presence of constitutively active RhoA [13]. In addition, ROCK inhibition reduced β-actin mRNP complex targeting while overexpression of p160ROCK increased targeting [13]. These data indicate RhoA and its downstream effector ROCK are required for β-actin mRNP complex targeting to discrete cytoplasmic sites. Consistent with the hypothesis that functionally related mRNAs may be coordinately regulated, all seven mRNAs of the Arp 2/3 complex are targeted to cellular protrusions in what is thought

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to be a Rho GTPase dependent manner [14]. Thus RhoA and ROCK signaling is required for peripheral targeting of RNP complexes.

ZBP1, adhesion and metastasis

ZBP1 levels in motile tumor cells collected in an *in vivo* collection assay were reduced 10 fold compared to the levels in cells remaining in the tumor, inversely correlating ZBP1 levels with metastatic potential [15,16]. Contrasted with this, high levels of IMP1 correlated with poor prognosis in ovarian carcinomas and with metastasis in colon cancer [17,18]. Given ZBP1's role as a translational regulator and localization factor, it is not surprising that ZBP1 expression could result in disparate effects since different substrate mRNAs can be found within ZBP1 containing RNP complexes in different cell backgrounds. Thus ZBP1 may act as an RNA regulon serving to integrate signals required for mRNA targeting and local translation of RNP complexes containing functionally related transcripts [4,19].

Areas with high RhoA activity and high Src activity are likely sites of ZBP1 RNP complex translational derepression establishing a local translation signature for ZBP1 containing RNP complexes [3,13] This local translation signature is found at cell-cell and cell-substrate adhesion complexes suggesting that ZBP1 mediated local β-actin translation may occur at these sites. In fact, full-length β-actin mRNA is locally translated and accumulated at cell-cell contacts in myoblast cells. In contrast, β-actin mRNA lacking the zipcode caused mislocalization of β-actin translation sites resulting in a significant reduction in the amount of N-cadherin targeted to adherens junctions [9]. Several studies support a role for ZBP1 mediated local translation in regulating cellular adhesions[9,20-23]. Depletion of IMP1 from HeLa adenocarcinoma cells resulted in a decrease in cell-cell contacts, reduced invadopod formation and delayed cell spreading [20], and a ZBP1 paralog was found at spreading initiation centers following replating in culture [21]. Moreover, β-actin, N-cadherin, β-catenin and other members of adherens junction complexes contain putative zipcode sequences suggesting that all of these mRNAs may be coordinately regulated. These data provide a physiological context for localized translation and may explain how ZBP1 functions as a metastasis suppressor in certain cell types [16,22]. Loss of ZBP1 expression in these cells may weaken cell-cell contacts at the level of adherens and tight junctions resulting in cells that no longer have an intrinsic polarity and are not attached as strongly to their neighbors making it easier for these cells to orient and move toward chemo-attractant gradients that entice cells to move out of the tumor.

Localized translation in Neurons

The mammalian nervous system has emerged as a particularly influential system for studies of localized translation and significant progress in our understanding the impact of spatially regulating translation has come from studies in neurons. At least two events in differentiated neurons have been proposed to involve localized translation within distinct domains of the cytoplasm. The first role for localized mRNA translation in developing neurons is within the growth cones of axons and is involved in axon guidance in response to guidance cues as well as during axon regeneration after injury [24-26]. Interestingly, the ZBP1 dependent localization system may play a role in this process similar to the one it plays in cell motility since β-actin mRNA and the Xenopus ZBP1 homolog, Vg1RBP/Vera, have both been recently demonstrated to localize to growth cones of Xenopus retinal axons [24,25]. Previously it was also demonstrated that ZBP1 and localization of β-actin mRNA played a role in dendritic spine formation of rodent hippocampal neurons [27,28].

A second role for localized translation in neuron cytoplasm is in synaptic plasticity (Fig. 1). Early studies examining the long-term changes that occur at synapses following stimulation recognized that new protein synthesis was required for later phases of these changes to occur [29,30]. Modification of specific translation factors in response to synaptic activity have been

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defined recently and these studies have begun to reveal the molecular mechanisms by which activity influences translation in neurons. There have been two major avenues of investigation into the influence of synaptic activity on the translation machinery, one focused on the targeting of mRNAs specifically to the axons or dendrites of neurons and the other focused on the regulation of the general translation machinery due to synaptic activity. These two pathways likely operate together to achieve local protein synthesis within the processes of neurons.

Targeting mRNA to active synapses

In mature neurons, specific targeting of mRNAs to distinct locations within the cytoplasm provides the cell with a very powerful way to rapidly affect the concentration of particular proteins at regions of the neuron quite distal to the nucleus, a particularly important function when the lengths of some neuronal processes can reach several orders of magnitude over the length of the cell soma [31,32]. Based on global analyses of mRNA content within the processes of neurons it is clear that not all cellular mRNAs are present at these distal sites [33-35]. Because the mRNA content within neurites is not equivalent to the population of mRNA present within the whole cell, it is reasonable to hypothesize that mRNAs are under active sorting mechanisms in the neuronal cytoplasm.

Recruitment of individual mRNAs directly to active synapses has not been demonstrated directly, but many results indicate that synaptic activity influences the distribution of mRNA as well as mRNA binding factors within the processes of neurons [27,36-39]. Several RNA binding proteins demonstrate enrichment within microscopically observable punctate structures, both in fixed cells as well as in living cells using fluorescent protein chimeras [40, 41]. Fluorescent mRNAs capable of transport into neuronal processes can be found in similar formations after microinjection, and general RNA staining dyes also show punctate staining [42,43]. Based on all of these observations, RNPs have been proposed to transport within entities that have been called RNA granules [40]. The heterogeneous nature of these RNA containing entities within the cytoplasm has made it challenging to gather information on specific mRNA transport pathways by studying them. Despite this, it is abundantly clear that synaptic activity influences the distribution and motility of these entities, and based on this it has been proposed that mRNA localizes to active synapses through the RNA binding factors and activities associated with RNA granules.

Micro RNAs (miRNAs) are a very recent addition to the repertoire of *trans*-acting factors that are involved in recognizing mRNA sequence. miRNAs are endogenous small RNAs (21 nt) that have complementarity to sites within subsets of mRNAs and as a result provide sequence specific binding to those mRNAs [44]. miRNA targeted mRNAs are post-transcriptionally silenced, through translational repression and perhaps enhanced mRNA turnover [45]. The miRNAs are part of a much larger multi-protein complex, and the mRNA-miRNA interaction functions to target this complex to an mRNA [45]. Several RNA binding proteins implicated in the transport of mRNA as well as translational control and stability of mRNA have been found among the components of these miRNA-associated complexes [46]. Moreover, components of miRNA RNP complexes are found in processes and at synapses, and one particular interaction (miR134-Limk1 mRNA) is important for controlling the size of dendritic spines in a synaptic activity sensitive mechanism [47,48]. Although it has not been shown that mRNA-miRNA interaction functions to localize mRNAs to the processes of neurons, this is evidence that mRNA-miRNA interactions might repress translation of mRNAs that do get localized.

Global activity, local effect

Recent work involving the translation machinery in neurons has also provided novel insights into how regulation of the general machinery may participate in spatial control of translation

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within the cytoplasm. The example most relevant to neuron function in learning and memory comes from studies of GCN2, an eIF2α kinase. eIF2α phosphorylation status appears to play a central role in controlling expression of the CREB-antagonizing ATF4 transcription factor [49,50]. ATF4 acts to repress memory formation that is stimulated by CREB mediated transcription, and GCN2$^{-/-}$ mice make less ATF4, therefore memory formation is enhanced [49]. The effect of GCN2 ablation in this process being due to eIF2α is supported by mice harboring a mutated eIF2α allele, that prevents the inhibitory GCN2 phosphorylation, also showing enhanced memory formation [50]. This suggests an attractive model for spatial control of translation where at the activated synapses in the neuronal memory circuit, local changes in eIF2α phosphorylation lead to the effects on ATF4 protein production. It has not been demonstrated directly that eIF2α is only modified locally or that ATF4 is translated at active synapses. However, given the strong spatial partitioning of synapses within the cytoplasmic volume of a neuron it is feasible that controlling a general factor by local activation from individual synapses can provide spatial control of translation of specific mRNAs. Recent publications have also explored responsiveness of the general translation machinery to synaptic activity suggesting that multiple mechanisms of translational control may be impacted by synaptic activity [51-54].

Concluding Remark

In this review we examined data on the physiological consequences of mRNA localization and local translation in both somatic and neuronal cells. Emerging evidence indicates that RNP complexes containing translational silencing factors are key mediators of a cell's initial response to extracellular environmental changes. In certain carcinoma cells, ZBP1 mediated regulation of β-actin translation sites may be required to prevent progression to metastasis. In neurons, regulated local translation occurs within growth cones to impact guidance as well as at synapses to effect plasticity in learning and memory. These examples underscore the importance of mRNA targeting and local translation on the physiology of multiple cell types.

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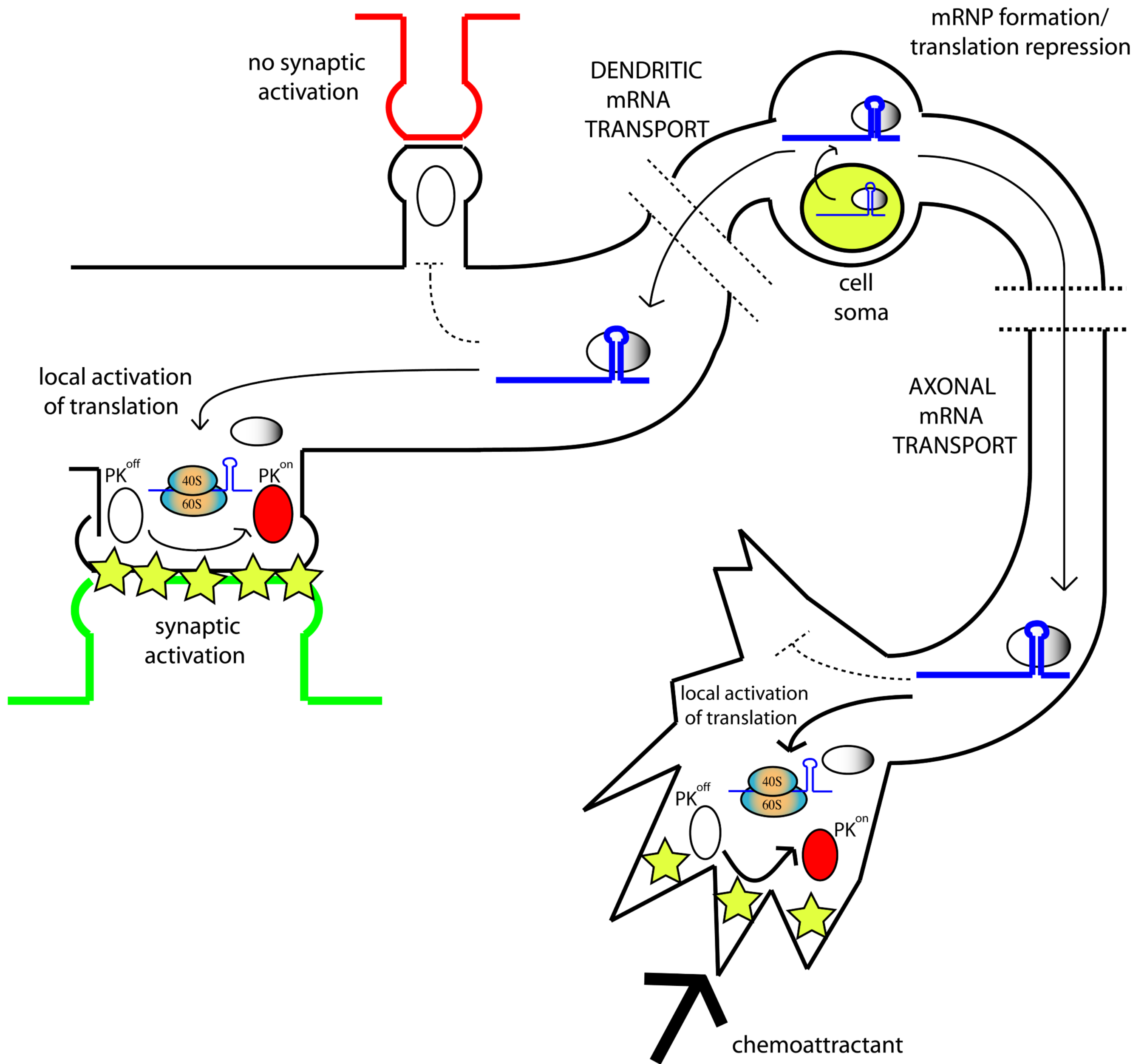

Figure 1. Spatial control of mRNA translation in neurons

Localizing mRNA to be transported to the neuronal processes begins RNP (L-RNP) formation within the nucleus, helping to ensure stringent translational repression. In the cell soma after export the mRNA (blue line) and associated RNA binding proteins (gray circle) form the L-RNP. In one pathway, an L-RNP is actively transported along the axon (axonal mRNA transport) to the growth cone where guidance cues activate local signal transduction pathways (yellow stars). This activates kinases (open circle; inactive kinase, red circle; activated kinase) that modify components of the transport and/or translation machinery, resulting in local translation (represented by 40S and 60S ribosomal subunits) of the mRNA toward the direction of the guidance cues to aid in navigation of the growth cone. In another pathway an L-RNP is actively transported into the dendrites (dendritic mRNA transport). At the post-synaptic region of activated synapses (green pre-synaptic terminal) synaptic activity activates signal

transduction pathways, activating kinases that modify components of the transport and/or translation machinery, resulting in local translation of the mRNA in the vicinity of the guidance cues. The lack of activated kinases at non-stimulated synapses (red pre-synaptic terminal) does not cause translational de-repression at these sites.

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