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Chapter 2

Post-Transcriptional Mechanisms of Neuronal Translational Control in Synaptic Plasticity

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Abstract

The dynamic complexity of synaptic function is matched by extensive multidimensional regulation of neuronal mRNA translation which is achieved by a number of post-transcriptional mechanisms. The first key aspect of this regulatory capacity is mRNA distal trafficking through RNA-binding proteins, which governs the transcriptomic composition of post-synaptic compartments. Small non-coding microRNA and associated machinery have the capacity to precisely coordinate neural gene networks in space and time by providing a flexible specificity dimension to translational regulation. This RNA-guided subcellular fine-tuning of protein synthesis is an exquisite mechanism used in neurons to exert control of synaptic properties. Emerging evidence also implicates brain-enriched long non-coding RNA and novel circular RNA in posttranscriptional regulation of gene expression through the modulation of both mRNA and miRNA functions, thereby exemplifying the complex nature of neuronal translation. Herein, we review current knowledge of these regulatory systems and analyse how these mechanisms of transcriptomic regulation may be linked together to achieve high-order spatiotemporal control of post-synaptic translation.

Keywords: translation, mRNA trafficking, messenger ribonucleoprotein, microRNA, P-bodies, circular RNA

1. Introduction

The early phases of long-term potentiation (LTP) and long-term depression (LTD) are characterised by post-translational modification and trafficking of AMPA glutamate receptors, modifying reactivity of the post-synaptic membrane following an appropriate inducing stimulus [1]. While this is an effective means of altering synaptic transmission in the short term, consolidation of these changes into late-phase synaptic plasticity requires a substantially

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deeper response, driven by novel transcription and translation of messenger RNA (mRNA) [2]. Translation is a particularly interesting aspect of this system as discrete foci of polyribosomes have been observed in dendritic spines engaging in protein synthesis, indicating a role for localised distal translation in dendritic function which has since proven critical in synaptic plasticity, and indeed, learning and memory [2–5].

Considering the importance of dendritic translation in strengthening alterations to the post-synaptic compartment, the role of mRNA in connecting neuronal transcription and distal translation is crucial and understandably subject to significant modulation. To this extent, neurons exploit a variety of post-transcriptional regulatory mechanisms to ensure an array of over 2500 unique, dendritically localised mRNAs are only translated when appropriate [5]. At present, it is clear that a variety of mRNA-binding proteins (RBPs) act to selectively distribute mRNAs to individual dendritic spines and may additionally act as enhancers or inhibitors of translation. Non-coding RNA, specifically microRNA (miRNA), provides a potent and specific dimension to translational control, which themselves may be regulated by other novel, brain-enriched, non-coding RNA.

Despite extensive investigation of neuronal mechanisms of translation control, we still lack a clear understanding of how these systems work both individually and synergistically to regulate the localisation and appropriate timing of translation. This chapter therefore explores recent advances in the field of neuronal post-transcriptional translational regulation, with particular focus on miRNA and how these small non-coding RNAs interact with a variety of intermediates to exert precise control over neuronal protein synthesis.

2. Intracellular trafficking supplies dendrites with mRNA

2.1. Cis-acting factors

Neuronal subcellular compartments such as dendritic spines rely on distal trafficking of mRNA from the soma to provide a stockpile of transcripts for protein synthesis. Considering the functional similarity and close proximity of these compartments, precise localisation of mRNA is critical for modulation of the dendritic transcriptome, which influences translation in response to stimuli such as synaptic transmission. This raises a key question; how can thousands of unique mRNAs successfully localise in functionally similar subcellular neuronal compartments?

Part of the answer lies within the mRNA itself as its 3′ UTR is encoded with *cis*-acting sequences known as localisation elements (LE), which signal the desired site of transcript localisation. LEs were initially observed in chicken embryonic myoblasts whereby isoform-specific 3′ UTR sequences were shown to direct the accumulation of α-actin and β-actin in peripheral and perinuclear regions, respectively [6]. Dendrite-specific LEs have since been identified in key mediators of synaptic plasticity, including AMPA receptors, MAP2, αCaMKII and BDNF [7–10], indicating LEs play a critical role in the post-synaptic localisation of specific mRNAs. The AMPA receptor is a particularly interesting example as “flip” and “flop” splice variants have been shown to respectively localise in dendrites and the soma [7], revealing alternative

splicing may serve to edit LE expression and subcellular localisation through removal of undesirable LEs in specific transcript splice variants. Furthermore, MAP2 long and short 3′ UTR variants generated by alternative polyadenylation have been shown to, respectively, target the dendrites and soma [9], implicating polyadenylation as another possible mechanism through which LE expression may be altered.

Following the discovery of LEs, a subset of studies has focussed on identifying a mechanistic basis through which these sequences facilitate selective mRNA trafficking. Considering the role of proteins in physically transporting mRNA (covered next), a distinct possibility is "digital" LEs form secondary structures to facilitate "analogue" recognition by RNA-binding proteins (RBP) [11]. This proposed mechanism of LE function is strongly supported by the identification of 3′ UTR stem-loop LEs required for the transport of K10, ASH1 and Oskar mRNAs in non-neuronal models [12–14]. In the context of synaptic function, a 5′ UTR stem-loop motif has recently been shown to direct sensorin mRNA to the synapse in *Aplysia*, both demonstrating the role of stem-loops in moderating synaptic mRNA localisation and revealing that LEs may not be purely confined to the 3′ UTR [15].

2.2. Trans-acting factors

While encoding mRNAs with LEs constitutes an elegant mechanism by which transcripts may be directed to subcellular compartments, neurons require an efficient physical mechanism of mRNA distribution to ensure all dendrites and their spines are adequately supplied with transcripts. Such a system is provided by a specialised group of RBPs, the neuronal microtubule network and associated motor proteins, all of which act in concert to facilitate mRNA trafficking from the soma to far distal regions of the neuron.

Current evidence heavily implicates neuronal messenger ribonucleoprotein (mRNP) granules as the primary vehicles of neuronal mRNA trafficking as observed through their translocation in neurites and mRNA/protein enrichment [16, 17]. These granules are composed of aggregated mRNA-RBP complexes, which are hypothesised to form upon *cis-trans* interaction between RBPs and target mRNA LEs (**Figure 1**), conferring specificity to this system while additionally providing a means of translationally repressing mRNAs during transport [18, 19]. At present, the neuronally enriched fragile X mental retardation protein (FMRP) and Staufen family proteins are the chief candidate RBPs involved in neuronal mRNA trafficking as evidenced by their enrichment within mRNP granules while complexed with a variety of plasticity-relevant mRNAs including CaMKIIα, MAP1b, β-actin and poly(A)-binding protein (PABP) [20–25]. An important aspect of these studies is that neuronal RBPs clearly target a variety of unique mRNAs, therefore suggesting RBPs recognise a number of different LEs, or alternatively, LEs for the same subcellular compartment share similar structural properties. Regardless, the key advantage of this system is the need for relatively few unique RBPs relative to the number of mRNAs requiring transport. In contrast to this observation, zipcode-binding protein 1 (ZBP1) specifically engages in activity-dependent trafficking of β-actin mRNA to the axon and dendrites through recognition of a 54nt LE within the 3′ UTR [26, 27]. While other binding partners may exist, it is possible that ZBP1 acts as a highly specific mediator of β-actin expression due to the high demand for this protein in neuronal cytoskeletal remodelling [28].

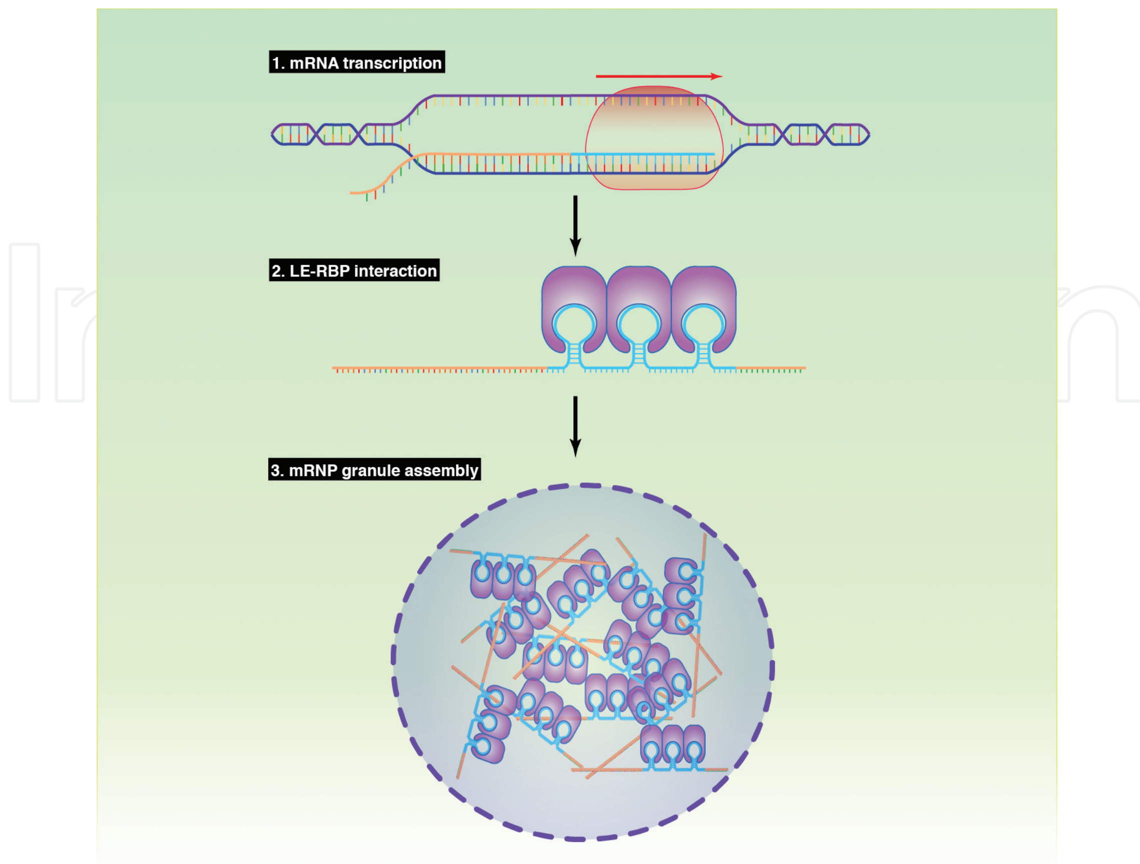

Figure 1. Assembly of neuronal messenger ribonucleoprotein granules. (1) During transcription, mRNAs are inherently encoded with cis-acting localisation elements in the 3′ UTR. (2) These sequences form secondary structures such as stem-loops, facilitating recognition by RNA-binding proteins. (3) Aggregation of multiple mRNA-RBP complexes results in the formation of neuronal mRNP granules, which transport mRNAs to distal locations in a translationally repressed state.

The overall significance of RBPs in neuronal mRNA trafficking is further exemplified by their hypothesised role as adaptors, linking transcripts to motor proteins for distal transport via microtubules. Supporting this view, mRNP granule-associated FMRP has been shown to directly interact with KIF3c and KIF5 kinesin motor protein subunits [22, 29], while similarly, ZPB1 directly binds the tail domain of KIF11 while complexed with β-actin mRNA [30]. The role of microtubules in this process has been further elucidated by the observed microtubule-dependent translocation of Staufen granules to the dendrites in response to synaptic activity as seen through GFP-fusion experiments [31]. It is interesting to note that Dynein is another candidate motor protein involved in mRNA microtubular trafficking; however, its role is currently only described in *Drosophila* embryonic extracts [32].

2.3. “Synaptic Tag and Capture” and “Sushi Belt” theories

Evidence pertaining the activity-dependent migration of neuronal mRNP granules to the dendrites implies that these granules bear functional significance in the regulation of activity-dependent translation [31, 33]. However, despite our extensive knowledge of neuronal mRNA trafficking, it is still unclear how specific neuronal mRNP granules are successfully delivered

to individual dendritic spines following stimuli such as synaptic transmission. A commonly accepted model regarding this question was initially proposed in 1997 by Frey and Morris, who presented the "Synaptic Tag and Capture" theory in the context of LTP [34, 35] which has since received significant attention, and indeed, refinement [36–38]. At the core of this theory, strong synaptic stimuli capable of inducing late-phase LTP "tags" specific dendritic spines, signalling for the uptake of plasticity-related proteins and mRNAs from dendritic shafts and the soma [34]. While evidence obtained since the original proposal of this model has supported synaptic tag and capture, the identity of the tag, whether a single molecule or state of the synapse, has yet to be elucidated [38].

More recently, Doyle and Kiebler [18] have proposed an alternate "Sushi Belt" theory of dendritic mRNA trafficking with stronger emphasis on neuronal mRNP granules. This theory suggests that mRNPs constitutively circulate dendritic shafts through microtubules and motor proteins, analogous to a sushi conveyor belt. Application of a potentiating stimulus to any particular spine "tags" it, resulting in recruitment of mRNP granules to that spine through the action of dynamic microtubules when novel translation is required. Importantly, this theory accounts for both basal and activity-dependent mRNP transport in addition to anterograde and retrograde mRNP translocation, which has previously been observed [16]. Considering current knowledge of mRNA dendritic transport, however, it remains a distinct possibility that facets from both of these models may likely underlie the true mechanism behind both basal and activity-dependent neuronal mRNA trafficking.

3. microRNAs specifically and potently regulate post-synaptic translation

MicroRNAs (miRNAs) are a class of short, ~22nt non-coding RNAs that function as target-specific guides in the degradation and translational repression of mRNA. Since their initial discovery in 1993 [39, 40], the role of miRNA in providing combinatorial specificity to translational regulation has been highlighted through the discovery of more than 3700 unique miRNA participating in over 366,000 experimentally supported miRNA-target interactions [41]. Profiling studies have further identified the CNS as a source of significant miRNA enrichment whereby a subset of miRNA and associated factors regulate synaptic plasticity and are subject to activity-dependent turnover, indicating a key role in the maintenance of synaptic function [42]. Consequently, dysregulation of miRNA function is thought to contribute to the pathogenesis of complex neurological diseases, in particular, neuropsychiatric conditions characterised by impairments in learning and memory [43].

3.1. miRNA biogenesis and target interaction

miRNAs are derived from the transcription and processing of miRNA genes (**Figure 2**) located in a diverse array of genomic locations, including coding, non-coding and intergenic regions [44, 45]. Transcription of miRNA genes by RNA polymerase II yields primary miRNA (pri-miR), which house one (monocistronic) or multiple (polycistronic) miRNA species and are post-transcriptionally supplemented with 5′ methylguanosine cap and 3′ poly(A)

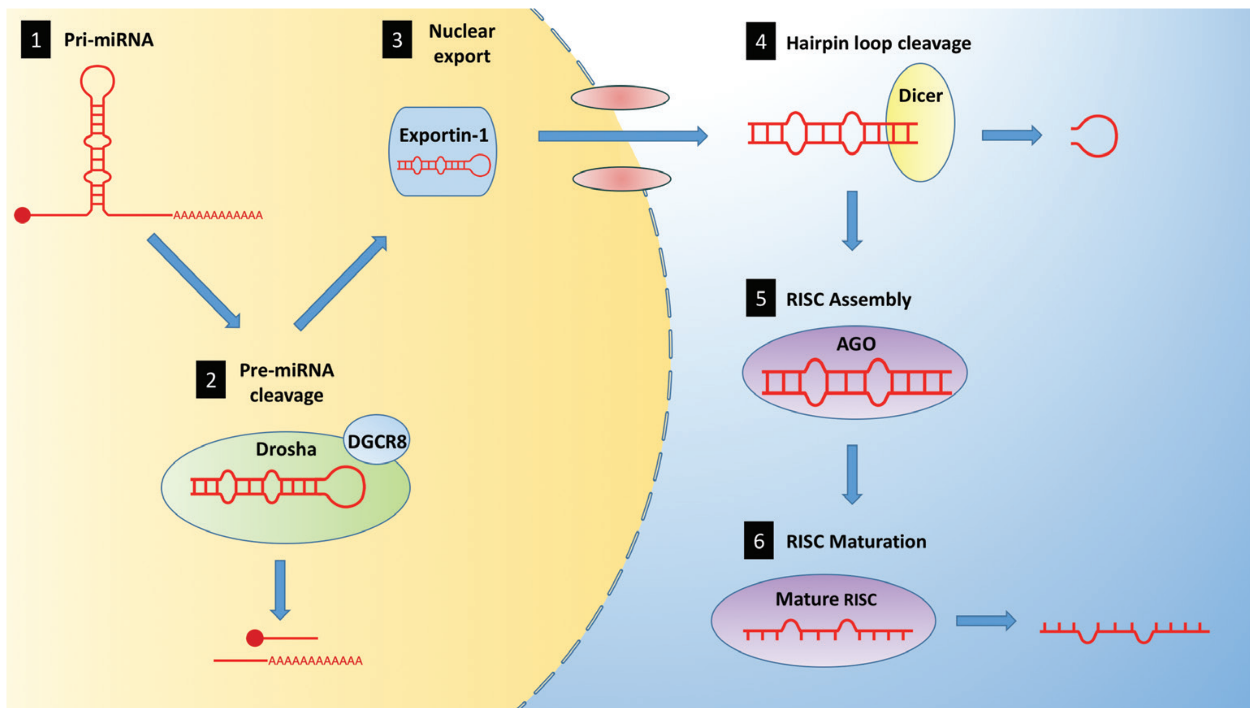

Figure 2. miRNA biogenesis. (1) Transcription of miRNA genes yields pri-miRNA, which adopt a hairpin secondary structure and contain 5′ cap and 3′ poly(A) tail similarly to mRNA. (2) These structures are cleaved from the pri-miRNA by Drosha and cofactor DGCR8, yielding a ~70nt pre-miRNA which is (3) transported to the cytosol through exportin-5. (4) Further processing by dicer cleaves the pre-miRNA hairpin loop, leaving a miRNA duplex which is (5) loaded into one of four human argonaute proteins. (6) The RISC is considered mature following selection of a guide strand and subsequent ejection of the passenger strand.

tail structures [46–48]. Complementary base pairing between the miRNA sequence and its antisense counterpart forms a secondary hairpin structure which is liberated from the primary transcript via cleavage, mediated by the nuclear microprocessor Drosha and co-factor DGCR8 [49]. The resultant ~70nt miRNA precursor (pre-miR) is exported to the cytoplasm through the action of Exportin-5 in a Ran-GTP-dependent manner [50, 51] wherein the cytoplasmic RNase III Dicer cleaves the hairpin loop structure from this pre-miR [52, 53]. This produces a ~22nt double-stranded miRNA duplex which associates with one of four orthologues of the Argonaute (AGO) protein family, thereby forming an immature RNA-induced silencing complex (RISC) [54]. Maturation of this complex is achieved through positive selection of a 5′ uridine containing "guide" [55] strand from the miRNA duplex and subsequent ejection of the antisense "passenger" strand from the RISC [56–58]. Incomplete Watson-Crick base complementarity between the miRNA seed region (nucleotides 2–8) and miRNA recognition elements encoded in the mRNA 3′ UTR (and occasionally, 5′ UTR and CDS) subsequently acts as a targeting mechanism for the RISC, facilitating translational repression and degradation of specific mRNAs [59–62]. This redundancy in miRNA-mRNA interaction is a particularly critical characteristic of miRNA function as it enables a single miRNA to regulate a many unique transcripts, eliminating the need for excessively large numbers of very specific miRNA.

3.2. miRNA regulation of gene expression

3.2.1. 5′ to 3′ exonucleic decay

The initial stages of cap-dependent mRNA translation are primed by interaction between 5′ bound eukaryotic initiation factors (eIF) and 3′ poly(A)-binding proteins (PABP), which both circularise mRNA for efficient translation and promote assembly of a translation initiation complex in the 5′ UTR [63]. The mRNA 5′ methylguanosine cap and 3′ poly(A) tail are therefore considered as two critical *cis*-acting factors in translation initiation and are thus ideal targets for translational repression and degradation by miRNA and the RISC [64].

An extensive body of research has since revealed that the RISC induces activation of the 5′ to 3′ mRNA decay pathway to facilitate degradation of target mRNAs. The first step of this pathway is characterised by recruitment of the PAN2-PAN3 and CCR4-NOT deadenylation complexes to target mRNA, which trigger sequential cleavage of the 3′ poly(A) tail [65, 66]. Co-immunoprecipitation and structural analysis suggest that the RISC indirectly recruits these deadenylation factors through the action of GW182 proteins, which bind both AGO family members in addition to the PAN3 and NOT1/9 deadenylase subunits [67–70]. Erosion of the poly(A) tail subsequently stimulates the removal of the 5′ methylguanosine cap via DCP2 and associated decapping factors, recruited to the target mRNA via CCR4-NOT [71]. The exposed mRNA is then subject to 5′ to 3′ digestion by XRN1 exonuclease [71].

3.2.2. Inhibition of active translation

RISC-mediated degradation of mRNA has long been recognised as the canonical mechanism through which miRNAs specifically modulate the transcriptome and therefore translation. Emerging evidence suggests the RISC may also function to repress translation through a number of mechanisms (**Figure 3**), foremost of which is inhibition of active translation. This form of translational repression arose as a potential facet of RISC function following the initial discovery of miRNA in association with polysomes [72]; however, no evidence was uncovered regarding a link between miRNA binding and arrest of active translation. A similar discovery has also been observed for the dendrite-abundant translational repressor FMRP, which has been shown to form translationally active complexes with ribosomes in mouse cortical preparations [73]. Further studies have identified CDS-bound phosphorylated FMRP is associated with stalled ribosomes, leading to the current hypothesis that FMRP halts active protein synthesis through binding actively translating ribosomes [74–76]. This holds significance for neuronal miRNA function since FMRP has been shown to interact with AGO1 [77], AGO2 [78], MOV10 (RISC RNA helicase) [79] and specific microRNAs [80], raising the possibility that miRNA and the RISC may act as a targeting mechanism for FMRP. Considering these interactions together in conjunction with the dendritic enrichment of FMRP, miRNA- and FMRP-mediated stalling of actively translating ribosomes could constitute an exciting dimension to miRNA function particularly relevant to synaptic translation.

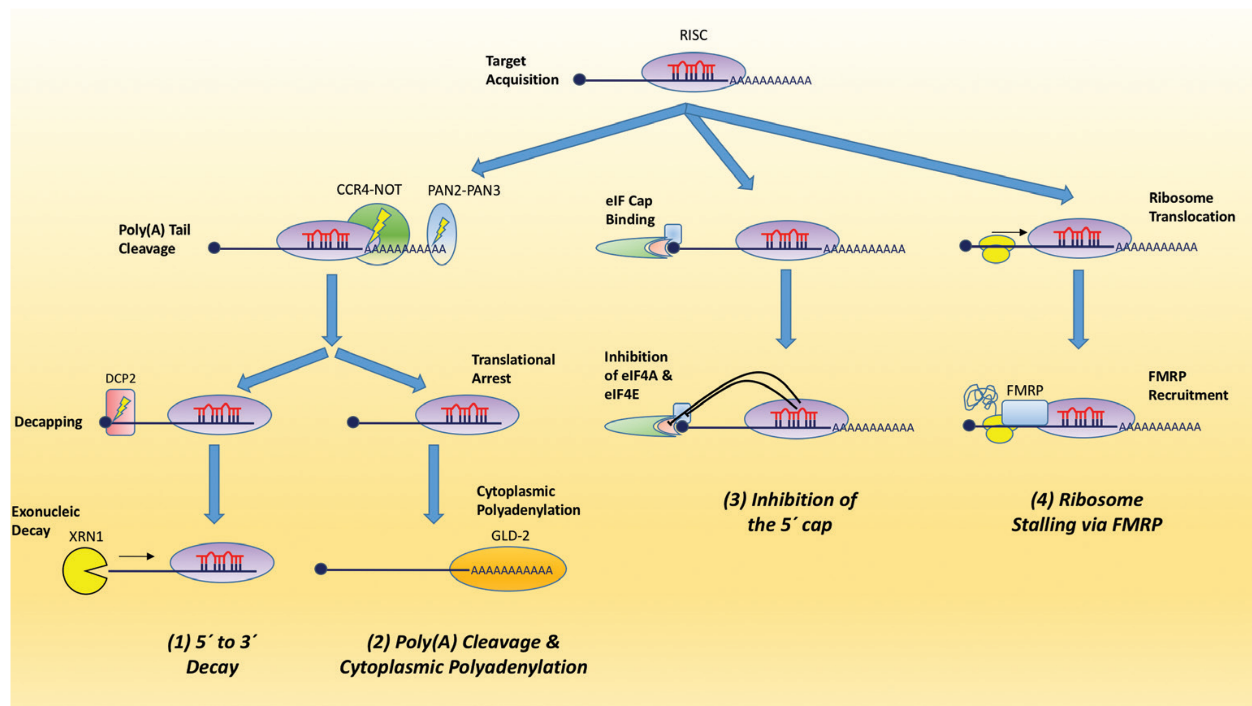

Figure 3. Mechanisms of miRNA-mediated translational repression. The RISC acquires target mRNAs through complementary base pairing, triggering one of a number of repressive pathways. (1) Transcript degradation is stimulated through RISC recruitment of deadenylase complexes to cleave the mRNA poly(A) tail, followed by decapping and exonuclease decay. (2) Cleavage of the poly(A) tail reduces the capacity for target mRNA to act as a substrate for protein synthesis, leading to translational repression likely reversible by cytoplasmic poly(A) polymerases. (3) The RISC may additionally stimulate dissociation of eIFs from the mRNA 5′ cap, or alternatively, (4) recruit FMRP to halt active synthesis through ribosome stalling.

3.2.3. Poly(A) tail erosion and cytoplasmic polyadenylation

While RISC induction of mRNA decay constitutes an effective mechanism through which translation may be fine-tuned for cellular needs, in the neuronal context, this mechanism relies heavily on both transcriptional activity and mRNA trafficking to maintain transcriptomic supply at dendrites. Consequently, a system by which the translational competency of mRNAs could be modulated during periods of quiescence and in response to plasticity-inducing stimuli would significantly relieve pressure applied by RISC degradation of transcripts. A major candidate mechanism through which this may be achieved is modulation of mRNA poly(A) tail length, since this structure and associated PABPs facilitate 5′–3′ interactions required for translation initiation [63]. The manipulation of reporter mRNA in HeLa cultures [81] and cell-free systems [82] has indeed revealed let-7 translational arrest of reporter luciferase depends on the expression of a poly(A) tail, emphasising the role of the poly(A) tail as a conduit through which translational competency may be altered by miRNA. A requirement for such a system to exist, however, is the functional decoupling of poly(A) tail erosion and mRNA decay. Recent studies illustrate that this occurs in embryonic culture systems such that deadenylated targets of miRNA, including miR-35-42, miR-51-56 and miR-155, have been shown to accumulate in a stable manner [83, 84], suggesting miRNA-mediated poly(A) tail cleavage does not necessarily instigate mRNA decay.

This potential dimension to miRNA function becomes particularly interesting in the neural context, as cytoplasmic polyadenylation has the potential to reinstate the translational activity of poly(A) deficient mRNAs. Poly(A) polymerase GLD-2 is a promising contender for this function due to its neuronal enrichment, cytoplasmic localisation and participation in translational enhancement via poly(A) tail extension [85, 86]. In addition to these features, GLD-2 function increases the abundance and stability of poorly translated mRNAs and is also required for the induction of LTP, suggesting that cytoplasmic polyadenylation could play a significant role in synaptic plasticity [85, 87, 88]. Regardless, the role of GLD-2 and deadenylase counterpart PARN (poly(A)-specific ribonuclease) in bidirectional regulation of poly(A) tail length and neuronal translation as part of the cytoplasmic polyadenylation complex illustrates the significance of cytoplasmic polyadenylation in neuronal translational control [85].

3.2.4. Inhibition of translation initiation

Further emerging evidence implicates miRNA and the RISC in direct inhibition of translation initiation through interaction with 5′ cap-bound eIFs responsible for mediating ribosomal assembly in the mRNA 5′ UTR [63]. At present, AGO1-RISC has been shown to indirectly stimulate disassociation of eIF4E via GW182, and eIF4A through a mechanism independent of GW182, inhibiting the assembly of an eIF4F translation initiation complex [89, 90]. While it is clear that this interaction acts to prevent translation of target mRNAs, there is uncertainty regarding whether this is another mechanism of translationally arresting mRNA or simply a precursor to mRNA degradation. The recent discovery of an RNA-independent association between CCR4-NOT subunit NOT1 and eIF4A2 RNA helicase involved in RISC degradation of target mRNA [91] suggests the latter is likely but does not rule out the possibility of eIF interference as a means of transcript repression.

3.3. microRNAs in synaptic function

Considering the array of confirmed and emerging miRNA functions, miRNA degradation and/or repression of transcripts constitutes an effective mechanism for fine-tuning highly dynamic translation at the post-synaptic compartment. While miRNAs are thought to be largely stable mRNA species, new evidence suggests that miRNAs are subject to activity-dependent synthesis and rapid turnover in dendritic spines [42]. Dendritic synthesis of miRNA became particularly apparent following the discovery of pre-miRs [92] and their inactive processing enzyme Dicer at the post-synaptic density (PSD) whereby activity-dependent stimulation of Calpain I was sufficient to induce Dicer function [93]. These data were supported by the detection of mature miRNA species enriched in mouse forebrain synaptoneurosomes [92]. Activity-dependent degradation of miRNA has also recently been observed in mouse retinal neurons; however, the exact mechanism of degradation remains elusive [94]. Interestingly, exosome release may act as a means of post-synaptic miRNA clearance, as MAP1B-enriched neuronal exosomes released in response to depolarisation have recently been shown to contain miRNA (miR-638, miR-149*, miR-4281 and let-7e) normally downregulated by depolarisation in the dendritic compartment [95].

Supporting the critical role of miRNA in synaptic function, microarray analysis and deep-sequencing have revealed that subsets of miRNA are subject to differential expression up to 24-h post-induction of hippocampal synaptic plasticity [96, 97]. These data have since been extended through the development of a conditional *Dicer 1* knockout in the adult mouse forebrain shown to result in enhanced LTP, learning and memory [98]. Reflecting on these discoveries, it is perhaps not surprising that a number of neuron-enriched miRNA have been described in terms of the regulation of synaptic function.

Arguably the most studied miRNA in the context of synaptic function, miR-132 is widely regarded for its role in the regulation of synaptic plasticity in brain regions such as the visual cortex [99] and hippocampus [100]. Following neuronal activity, miR-132 is subject to a rapid increase in CREB-mediated (cAMP response element-binding protein) transcription, resulting in stimulation of dendritic growth and branching through suppression of p250GAP (p250 GTPase activating protein) [101, 102]. These modifications to dendritic morphology are characterised by expression of stubby, mushroom-like dendritic spines which act to potentiate synaptic transmission [80]. miR-132 expression additionally directs the upregulation of NR2A, NR2B and GluR1 glutamate receptor subunits following BDNF stimulation [103], revealing this miRNA may direct synaptic plasticity through guiding both morphological and physiological change. A particularly interesting aspect of miR-132 function, however, is its relationship with FMRP, which provides novel insight regarding potential interplay between miRNA and FMRP homologues. Specifically, miR-132 effects on dendritic morphology are abolished following FMRP knockdown, uncovering a functional relationship between these molecules likely to be responsible for miR-132-associated regulation of plasticity-relevant transcripts [80]. A similar relationship has been observed for miR-125b whereby FMRP deficits inhibit miR-125b negative regulation of both dendritic spine morphology and NR2A [80], further supporting the role of FMRP in neuronal miRNA function.

Aside from miR-132, several recent studies have implicated a variety of other neuron-enriched or specific miRNAs in the modification of synaptic function. miR-134 is a key example which modulates dendritic spine volume through the regulation of *Limk1* expression, resulting in dendritic spine volume deficits when miR-134 is overexpressed [104, 105]. This function of miR-134 in the negative regulation of dendritic spine morphology is reflected in the impairment of mouse contextual fear learning following miR-134 overexpression in the CA1 hippocampus; however, post-transcriptional miR-134 regulation of the CREB transcription factor appears to significantly contribute to this deficiency [106]. Another miRNA involved in the inhibition of synaptic plasticity is miR-137 which decreases dendritic complexity and length through downregulation of mind bomb-1 ubiquitin ligase while additionally inhibiting presynaptic vesicle release [107, 108]. miR-137 also directly influences AMPA receptor expression through the regulation of GluA1, leading to synaptic silencing and deficits in hippocampal learning when overexpressed in mice [109].

Considering these examples alone, it is evident that miRNAs modulate a variety of synaptic characteristics through post-transcriptional regulation of a number of unique mRNA species, emphasising the importance of miRNA in coordinating a number of gene expression networks to fine-tune synaptic plasticity. Moreover, miRNA species appear to provide the basis through which the induction of plastic alterations to the synapse may be bidirectionally

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regulated. This not only implicates specific miRNA species such as miR-132 in the enhancement of synaptic plasticity, but also additionally implies miRNA including miR-134 and miR-137 act as a breaking mechanism to prevent excessive potentiation or depression of individual synapses. Despite this extensive understanding of miRNA function, many are yet to be fully characterised in relation to synaptic and indeed neuronal function.

4. P-bodies and mRNP granules: linking mRNA transport, translation and repression

miRNA regulation of gene expression is sequestered within subcellular granules known as processing bodies (P-bodies), proposed to form through aggregation of translationally arrested mRNA and mRNA degradation machinery [110]. These granules were initially described as cytoplasmic “speckles” termed GW-bodies, observed as aggregates of GW182 complexed with mRNA [111]. P-bodies have since been characterised as foci of mRNA degradation due to their enrichment of translationally repressive RBPs such as Argonaute proteins, DCP1 & DCP2 decapping enzymes, Pat1 & edc3 decapping factors and XRN1 exonuclease [110]. Considering these granules are both enriched at the post-synaptic density and actively migrate to post-synaptic compartments following neuronal activity [112–114], P-bodies are currently heavily implicated in post-synaptic translational regulation.

Neuronal mRNP granules similarly form by the aggregation of messenger RNPs to provide a vehicle for mRNA distal transport while maintaining mRNAs in a translationally arrested state [18]. Interestingly, *Drosophila* Staufen and FMRP mRNP granules are enriched with homologues of mRNA decay machinery including DCP1, XRN1 and AGO2 [24], demonstrating these granules bear similarity to P-bodies. In conjunction with this observation, an exciting interaction between these granules has recently been reported whereby 50% of dendritic P-bodies have been shown to dock with neuronal mRNPs [113], raising the prospect that these granules exchange their contents.

Drawing from these observations, a fascinating scenario is the potential for neuronal RNP granules to unload their mRNA and mRNA degradation cargo to P-bodies for repression until translation is appropriate, thereby acting as a means of mRNA storage with the potential for degradation if specific transcripts are not required. In support of this possibility, mapping of mRNA localisation during yeast glucose starvation and tetracycline transcriptional suppression indicates mRNA can associate with polysomes from P-bodies [115], revealing mRNA may be subjected to translation following sequestration in P-bodies. Adding to this evidence, cationic amino acid transporter–1 mRNA has recently been observed undergoing release from miR-122 repression and subsequently associating with polysomes from P-bodies during cellular stress [116], further implicating miRNA in repressing translation without necessarily instigating mRNA decay. While the potential underlying mechanisms driving mRNA de-repression in P-bodies remains unclear, *Drosophila* GLD-2 poly(A) polymerase has been observed to co-localise with FMR1 in neuronal mRNP granules [87] and may therefore be delivered to P-bodies, lending to the possibility of cytoplasmic poly(A) tail lengthening in de-repressing mRNA.

In addition to their mRNA, P-bodies themselves respond to cellular stimuli as synaptic input induces as much as a 60% decrease in dendritic P-body abundance [113], while artificial stimulation of cap-dependent translation decreases P-body biogenesis in PNS sensory neurons [117]. Overall, these observations imply that these repressive granules could dissociate in a pro-translational environment to release a collection of mRNAs for novel protein synthesis. A subset of dendritic P-body-like granules containing miRNAs repressed mRNAs and lacking XRN1, which respond to synaptic activation may represent a subcategory of P-bodies specifically designed for such a purpose [112]. Stress granules, which contain translationally stalled mRNAs, translational enhancers (such as eIFs and PABPs) and interact with P-bodies, are another key candidate for mRNA storage; however, their functional relevance is limited to periods of exposure to stressful cellular stimuli [118].

5. Emerging non-coding RNAs in post-transcriptional regulation of synaptic translation

5.1. Long non-coding RNA

Long non-coding RNA (lncRNA) is a broad category of >200nt non-coding transcripts characterised by widespread genomic distribution and involvement in a variety of regulatory functions [119]. Like miRNA, lncRNAs inhabit a range of genomic regions including intergenic, telomeric and gene regulatory sequences [119]. Protein-coding genes have also been identified as a source of lncRNA expression wherein these RNA may reside in antisense, overlapping, intronic or bidirectional configurations relative to protein-coding sequences [120]. From these genes, lncRNAs are transcribed by RNA polymerase II following which many are subject to posttranscriptional modifications including alternative splicing, 5′ capping and polyadenylation [121]. Despite this similarity to mRNA, recent studies have revealed the genomic origin of lncRNA dictates the functional role of individual lncRNA species, which may serve as regulators of translation, transcription and epigenetic modifications, or act as miRNA precursors or sponges [120, 122]. Translational regulation is a particularly interesting aspect of lncRNA function due to the range of emerging post-transcriptional mechanisms through which this may be achieved. This holds significance in the context of neuronal function as the adult brain has recently been identified as a source of substantial lncRNA enrichment, reflected in the discovery of 849 (of 1328 examined) lncRNAs subject to specific patterns of expression in mice [123]. Accordingly, a number of lncRNAs have exhibited roles in the regulation of synaptic translation and synaptic function, adding further complexity to the nature of neuronal translation.

The rodent lncRNA *Bc1* and its primate orthologue *BC200* are prime examples of neuronal lncRNAs, which modulate post-synaptic translation of plasticity-associated mRNA, including Arc, CaMKII and MAP1B [124]. Current studies indicate that *Bc1*/*BC200* instigates translational repression at somatodendritic compartments through inhibition of eIF4A and eIF4B activity at the mRNA 5′ cap, thereby suppressing translation initiation [125]. In conjunction with this observation, *BC200* alone has been shown to contain *cis*-acting adenine-rich elements which

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potentially facilitate interaction with PABPs [126], indicating this lncRNA may additionally interfere with 5′ to 3′ mRNA interactions required for translation initiation. FMRP may further contribute to the multidimensional nature of *Bc1/BC200* lncRNA function as oligonucleotide masking of an mRNA recognition motif within the *Bc1* lncRNA primary sequence inhibits FMRP interaction with MAP1B mRNA [124]. This suggests that *Bcl* lncRNA may potentially act as a guide in FMRP association with plasticity-associated mRNA analogous to miRNA and the RISC; however, the exact functional mechanism of these relationships is yet to be elucidated.

In addition to *Bc1/BC200*, other emerging lncRNAs have been implicated in synaptic regulation through multiple post-transcriptional mechanisms. lncRNA Malat1 is one such example, which modulates synaptic density through positive regulation of neuroligin 1 and SynCAM1 mRNA expression and alternative splicing of CaMKIIB [127]. Interestingly, this occurs within nuclear speckles, known for their role as sites of mRNA storage and processing, revealing this lncRNA modulates synaptic properties from the nucleus via a post-transcriptional mechanism [127]. lncRNA Tsx has additionally been shown to enhance short-term hippocampal memory in mice through an elusive mechanism, suggesting a role for this lncRNA in the regulation of synaptic plasticity [128].

Considering these examples together, it is evident that current understanding of the exact mechanisms through which various lncRNAs post-transcriptionally modulate synaptic properties is limited. Despite this gap in the literature, lncRNAs appear to bidirectionally regulate post-synaptic translation, suggesting lncRNAs may act to fine-tune protein synthesis rather than strongly influence gene expression networks. Supporting this theory, mRNAs with roles in synaptogenesis including *CamkIIa* and *Dag1* have been observed in complex with their antisense lncRNA counterparts in synaptoneurosomes of the adult mouse forebrain [129]. This further raises the possibility that lncRNAs could block translation via binding target mRNAs while additionally inhibiting miRNA-mediated mRNA decay through masking miRNA recognition elements. This distinct prospect further underscores the complex and multidimensional nature of post-transcriptional lncRNA function in the regulation of synaptic properties and emphasises the need for extensive characterisation of individual lncRNA species.

5.2. Circular RNA

Circular RNAs (circRNAs), as their name implies, are a class of circular long non-coding RNAs produced by exonic or intronic splicing which lack 5′ cap and 3′ poly(A) tail structures and exhibit exonuclease-resistance [130]. Unlike miRNA and RBPs which generally serve to regulate translation through direct modulation of mRNA characteristics, emerging evidence implicates circRNA as miRNA sponges, serving as a regulatory mechanism by which miRNA translational regulation may be dampened. A well-characterised example is the brain-enriched circRNA ciRS-7 (also known as CDR1as) which contains as many as 74 conventional seed-binding sites for miR-7 that allow this circRNA to function as a more potent miRNA sponge than traditional anti-miRs used for miRNA knockdown [131, 132]. While this circRNA demonstrates highly specific miRNA sponging, it is unclear whether this is a unique example or common among other species. For comparison, circHIPK3 and circRNA mlb, respectively, knockdown 9 and 2 unique miRNA [133, 134].

circHIPK3 is a particularly interesting example as overexpression of this species triggers a reduction of midbrain size in developing zebrafish [133], indicating circRNA may exert substantial influence over neuronal structure and function. Considering this, the function of this RNA class bears significant implications in the neuronal context since circRNAs exhibit substantial brain enrichment and accumulate during nervous system development and with age [135, 136]. circRNA may also act to fine-tune plasticity-associated translation as evidenced through their subcellular enrichment within dendritic compartments of cortical pyramidal neurons and interneurons, and differential expression of at least 42 distinct species during bicuculline-induced synaptic plasticity [134]. Together, these studies therefore implicate circRNA in both neuronal development and plasticity and provide an exciting added dimension to neuronal translational control. Further characterisation of individual circRNA will no doubt be integral in both determining the status of miRNA sponging as a primary circRNA function and the functional significance of these RNA in neuronal structure and function.

6. Towards a unified model of neuronal post-transcriptional regulation of translation

Since the initial discovery of extrasomatic neuronal translation, it has become evident that a number of regulatory systems fine-tune neuronal protein synthesis in an exquisitely coordinated manner to control structural and physiological characteristics associated with synaptic plasticity. Since these regulatory systems are continually exhibiting varying degrees of overlap, deciphering the mechanisms through which these systems both function in isolation and interact is of critical importance in revealing the intricate details of neuronal post-transcriptional regulation of translation.

A key example is the interplay between neuronal transport mRNP granules and P-bodies at the post-synaptic compartment [113]. The possibility of mRNP granules delivering cargo to P-bodies is an enticing prospect further exemplified by the potential for P-bodies to isolate and store repressed mRNAs for translation under suitable conditions [115]. What remains to be considered is the potential for P-bodies to export cargo to neuronal mRNP granules, perhaps acting as a means of mRNA recycling especially interesting in the context of the proposed "Sushi Belt" theory of neuronal mRNA transport [18]. As P-bodies, neuronal mRNP granules, polysomes and stress granules display multiple degrees of functional interaction, an overlying mechanism of mRNA transport, storage, repression and translation is likely at play to exert considerable influence over the available pool of translatable mRNA at the post-synaptic compartment.

With regard to miRNA function in the neuronal context, an increasing body of evidence underscores the fact that miRNAs are not simply mediators of mRNA decay. For neurons in particular, the existence of reversible systems of translational repression would present an energetically favourable mechanism of translational control capable of reducing total reliance on novel transcription and extra-somatic mRNA trafficking to dendrites. Indeed, the role of cytoplasmic poly(A) polymerases such as GLD-2 in enhancing activity-dependent translation [85] shows potential for cytoplasmic poly(A) tail modulation as a reversible mechanism

of neuronal translational control, warranting investigation of the theoretical decoupling of miRNA repression and degradation of mRNA in the neuronal context. Furthermore, uncovering the functional relevance of FMRP in mediating miRNA ribosome stalling will likely reveal a neuron-specific aspect to miRNA function which may prove critical in characterising the role of FMRP in the biogenesis of neuronal disease. Further miRNA studies in conjunction with high-throughput ribosome profiling [137], poly(A) tail sequencing [138] and co-immunoprecipitation sequencing will prove critical in revealing the existence and functional significance of these repressive systems in coordinating post-synaptic neuronal translation.

From the presented examples miR-132, miR-134 and miR-137, plasticity-relevant miRNA species clearly regulate dynamic morphological and physiological changes at the post-synaptic compartment through interaction with a variety of targets. However, it is important to note that these miRNA constitute well-described examples subject to intensive research. Additional miRNAs, such as miR-9, miR-22, miR-124 and miR-188, among others [139], have all displayed an association with synaptic plasticity and therefore stress the need for further characterisation of specific miRNA and how together they exquisitely coordinate gene expression networks in regulation of synaptic plasticity. This holds true for lncRNAs, which appear to regulate synaptic plasticity via an assortment of posttranscriptional mechanisms [119], stressing the need for further investigation of individual lncRNA species and the mechanisms through which they act. Considering the potential role of circRNA in regulating miRNA [131–134] and their post-synaptic enrichment, emphasis should no doubt be additionally placed on characterising these non-coding RNA in the context of neuronal translational control. Expression of circRNA is likely to partially account for the distinct complexity of neuronal translation and could act as novel therapeutic target or biomarker in neurological disease.

Continual advancement in high-throughput technology and analysis will substantially further our ability to characterise and integrate these regulatory systems into a unified model of neuronal posttranscriptional regulation of neuronal translation. Increasing our knowledge of this aspect of the central dogma of molecular biology in the neuronal context will subsequently facilitate characterisation of the molecular events underlying synaptic plasticity, fuelling our understanding of learning and memory.

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