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A Proposed Role for Interactions between Argonautes, miRISC, and RNA Binding Proteins in the Regulation of Local Translation in Neurons and Glia

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The first evidence of local translation in the CNS appeared nearly 40 years ago, when electron microscopic studies showed polyribosomes localized to the base of dendritic spines. Since then, local translation has been established as an important regulatory mechanism for gene expression in polarized or functionally compartmentalized cells. While much attention has been placed on characterizing the local transcriptome and regulatory “grammar” directing mRNA localization in neurons and glia, less is understood about how these cells subsequently de-repress mRNA translation in their peripheral processes to produce a rapid translational response to stimuli. MicroRNA-mediated translation regulation offers a possible solution to this question. Not only do miRNAs provide the specificity needed for targeted gene regulation, but association and dynamic interactions between Argonaute (AGO) with sequence-specific RNA-binding proteins may provide a molecular switch to allow for de-repression of target mRNAs. Here, we review the expression and activity of different AGO proteins in miRNA-induced silencing complexes in neurons and glia and discuss known pathways of miRNA-mediated regulation, including activity-dependent pre-miRNA maturation in dendrites. We further detail work on AGO and RNA-binding protein interactions that allow for the reversal of miRNA-mediated translational silencing, and we propose a model for how intercellular communication may play a role in the regulation of local translation.

Introduction
The potential importance of local translation in CNS function was first postulated nearly 40 years ago, when polyribosomes were found to localize to the base of dendritic spines (Steward and Levy, 1982). Local translation has since been found to be an evolutionarily conserved cellular mechanism for the spatiotemporal regulation of protein translation, allowing cells to form functionally independent compartments or processes (Lécuyer et al., 2007; Besse and Ephrussi, 2008; Holt et al., 2019). Thus, the evolution of regulated local translation in the nervous system is proposed as an elegant biological solution to allow the distal processes of these cells to respond to external cues in an independent, yet rapid, manner (Ainger et al., 1993; Sakers et al., 2017; Holt et al., 2019).

Much of our early understanding of local translation came from studies of neurons. Several studies have provided strong evidence that essential neuronal processes, including synaptic plasticity, are dependent on highly regulated local translation (Kang and Schuman, 1996; D. O. Wang et al., 2009; Holt et al., 2019). Along with the finding that polyribosomes localize to the base of dendritic spines, early studies found that transcripts, such as β-actin, CaMKIIa, and Arc, were localized in growth cones and dendrites (Burgin et al., 1990; Bassell et al., 1998; Steward et al., 1998; Rangaraju et al., 2017). These studies led to further questions regarding whether local translation allows independent processes to produce a specific response to external stimuli. To address this, approaches, such as blocking the activity of mini excitatory synaptic events in a subset of dendrites (Sutton et al., 2004), stimulating individual dendritic lamina (Farris et al., 2014), or even specific dendritic spines with two-photon glutamate uncaging (Tanaka et al., 2008; Govindarajan et al., 2011), have been used. In support of such specificity, these studies found that selectively blocking dendritic stimulation or activation of individual spines indeed produced an independent response involving local translation, and that different transcripts responded differently to such stimulation (Farris et al., 2014).

In addition to neurons, several groups have shown that local translation occurs in other cells of the CNS with specialized domains, including oligodendrocytes (Müller et al., 2013) and astrocytes (Boulay et al., 2017; Sakers et al., 2017; Mazaré et al., 2020). To further understand this phenomenon, many groups have focused on defining the local transcriptome of distal processes and defining cis-elements within these localized transcripts sufficient for directing their transcription. Such studies have provided much insight into unique regulatory features found in the untranslated regions (UTRs) of neuronal and astrocytic mRNAs,
of the brain: A cell type-specific RNA-Seq database shows that each AGO displays distinct expression patterns in the different cell types of the brain (Yoo et al., 2009). The repression of gene expression (Peters and Meister, 2007) is achieved by the recruitment of a multiprotein complex by direct binding a member of the Argonaute (Ago) subfamily of proteins to form the miRNA-induced silencing complexes (miRISC). The loaded miRNA guides this complex to a complementary sequence in the 3′ UTR of a target mRNA to mediate the repression of gene expression (Peters and Meister, 2007). At ~21 nucleotides long, miRNAs offer versatile mechanisms for specific translational regulation. Yet, their potential role in the regulation of local translation in cells of the CNS remains largely uncharacterized. In this review, we assess the distinct expression patterns and functional characteristics of the core components of miRISC, as well as known roles of miRNA-mediated local translation regulation in the context of the CNS as a model for how specificity might be achieved. We then evaluate dynamic interactions between miRISC and RNA binding proteins (RBPs) to propose another layer to the model in which local translation is regulated through these interactions. We lastly speculate a potential role for intercellular communication in this regulation and end with the questions for future research directions.

Argonautes and miRNAs: big roles for the small actors
A model describing the regulation of local translation should address several important questions: (1) How do cells regulate which transcripts are translocated to distal processes? (2) How are cells able to repress translation during localization and subsequently de-repress the translation of these mRNAs in response to stimuli? (3) How are cells able to shut off translation of specific mRNAs when signaling indicates they are no longer necessary? Translational repression by miRISC offers a simple solution to these questions.

AGO proteins, the core of miRISC, constitute a subfamily of highly conserved, RNA-directed proteins present throughout all domains of life (Swarts et al., 2014). The mammalian genome encodes four distinct AGOs (Ago1-Ago4) characterized by four conserved domains: the N-terminal domain, PAZ domain, MID domain, and PIWI domain (Fig. 1a) (Peters and Meister, 2007; Müller et al., 2020). The PIWI domain, which has structural similarities to RNase H, harbors the catalytic tetrad (Yuan et al., 2005; Müller et al., 2020). However, despite the argonaute subfamily of proteins being considered the core effectors of miRISC activity, only AGO2 is believed to have retained endonuclease activity because of the apparent necessity of both the DEDH catalytic tetrad (the residues directly partaking in the catalytic activity) and two N-terminal motifs (Liu et al., 2004; Müller et al., 2020), and is thus the most commonly studied. This has left much to be understood about functional differences between

Figure 1. The mammalian genome encodes four Argonaute proteins. a, The Argonautes are a highly conserved subfamily of proteins: AGOs are characterized by four conserved domains: an N-terminal domain, PAZ domain, MID domain, and PIWI domain. The catalytic triad located in the PIWI domain is responsible for the endonuclease activity of AGO2; however, this activity is also dependent on two motifs in the N-terminal domain, which are only both present in AGO2 (Müller et al., 2020). b, Argonautes 1-4 have distinct expression patterns in different cell types of the brain: A cell type-specific RNA-Seq database shows that each AGO displays distinct expression patterns in the different cell types of the brain (Zhang et al., 2014), c, Argonautes 1-4 have distinct expression patterns in hippocampal astrocytes during development. An astrocyte-maturation RNA-Seq database shows that each AGO displays unique expression patterns throughout development in mouse hippocampus (Clarke et al., 2018). Figures made in www.BioRender.com.
AGO2 and the remaining AGO proteins, as well as whether different AGO proteins are used for distinct pathways of regulation.

Studies in stem cell lines have shown that the mammalian Ago protein subfamily displays significant functional overlap (Su et al., 2009), while other findings suggest that miRNAs do not preferentially sort with different AGO proteins (D. Wang et al., 2012). Despite this, there is also evidence supporting important functional differences between the subfamily members. For example, AGO1 and AGO4 have been found to localize in the nucleus to mediate siRNA-directed transcriptional regulation (D. H. Kim et al., 2006; Chalertpet et al., 2019), while AGO3 has been found to localize in P-bodies, and likely functions in a cytoplasmic translational repression pathway (Azuma-Mukai et al., 2008). Thus, further investigation into the unique roles of the different AGO proteins may lead to a greater understanding of gene regulation, and possibly a novel pathway of local translation regulation.

It was previously believed that the AGO proteins are ubiquitously expressed in most adult tissue (Sasaki et al., 2003); however, in-depth RNAseq analysis shows distinct expression patterns in different cell types of the brain (Fig. 1b) (Zhang et al., 2014) and at different developmental time points (Fig. 1c) (Clarke et al., 2018). In mice, for example, AGO1 appears to be the most abundant AGO in astrocytes, neurons, and oligodendrocyte progenitor cells (Zhang et al., 2014). In maturing astrocytes, AGO1 is also highly expressed in the hippocampus during all developmental time points, although the expression levels decrease between P7 and P32, while the other AGOs display relatively similar patterns of expression throughout development (Clarke et al., 2018). AGO2, on the other hand, is strongly expressed in neurons and astrocytes, while poorly expressed in myelinating oligodendrocytes. Interestingly, AGO3, which is only modestly expressed in those cell types, has relatively high expression levels in newly formed oligodendrocytes. Last, AGO4 is poorly expressed in all CNS cell types (Zhang et al., 2014). Several aspects of AGO expression remain unclear, such as whether the relatively high expression of AGO3 in young oligodendrocytes is functionally significant, or whether the distinct expression patterns of AGO1-AGO4 in specific cell types of the CNS reflect an important biological phenomenon. Interestingly, the SFARI gene database, a centralized database with genotypic and phenotypic information on families affected by autism spectrum disorder, lists AGO1, AGO2, and AGO4 as strong candidates for autism spectrum disorder risk genes (Iossifov et al., 2014; Takata et al., 2018; Sakaguchi et al., 2019; Lessel et al., 2020), suggesting an important role in the regulation of neurodevelopment for these members.

While little is known about the distinct functions of the different AGO proteins in cells of the CNS, more is understood about a second essential component of miRISC: miRNAs themselves. Within the brain, miRNA expression is finely tuned in developmental stage-specific, brain region-specific, and cell type-specific patterns (Krichevsky et al., 2003; Bak et al., 2008; Pomper et al., 2020). Moreover, certain miRNAs are selectively enriched within axonal or dendritic compartments of neurons, suggesting a potential role in the regulation of local translation (Schartt et al., 2006; Natera-Naranjo et al., 2010; O’Carroll and Schaefer, 2013; De Rubeis et al., 2014; Rocchi et al., 2019). Despite the common belief that miRNA-mediated translational silencing leads directly to mRNA degradation, it is becoming increasingly apparent that the actual activity of miRISC depends on factors, such as mRNA/miRNA seed-sequence complementarity and the composition of proteins within the complex (Navalpuri et al., 2020). Therefore, understanding the heterogeneity in miRISC function is essential to uncover its potential role in regulating local translation.

The canonical model of miRNA targeting posits that the seed region of the miRNA, centered around nucleotides 2-8, directs miRISC to the 3’ UTR of target transcripts. Perfect complementarity between the miRNA and target transcript is largely believed to direct mRNA cleavage by AGO2 (Fig. 2a) (Yekta et al., 2004; Bartel, 2009); however, mRNA destabilization before degradation by other factors was found to be the dominant pathway of miRISC activity under steady-state conditions (Eichhorn et al., 2014). In such cases, imperfect seed-sequence complementarity and different miRISC:protein interactions mediate various mechanisms destabilizing mRNA, such as deadenylation and decapping, often followed by transcript degradation (Fig. 2b) (Filipowicz et al., 2008). Yet, this work
was largely performed in HeLa cells and cultured neutrophils, which may exhibit different steady-state mechanisms than postmitotic cells in vivo. Furthermore, the dynamic properties of the distal processes of neurons and glia, which are often responding to external signals and cues, are not well modeled by cultured cell lines. Thus, miRNA-mediated transcript destabilization and degradation may not be the dominant pathway active in distal processes in the CNS. Indeed, miRISC also functions to repress mRNA translation in a manner decoupled from transcript destabilization and degradation (Nawalpuri et al., 2020). In this pathway, the association of mRNAs with miRISC and various RBPs may impede proper assembly of the translation initiation complex or preclude a transition to the elongation stage (Filipowicz et al., 2008; Nawalpuri et al., 2020). Of importance, because mRNAs are not degraded in this pathway, reversal of this translational repression may provide an elegant mechanism for the spatiotemporal control of protein expression, potentially serving as the foundation of a model for initiating local translation regulation. Likewise, new recruitment of miRISC to mRNA in peripheral processes in response to other cues could also serve to end local translation.

Studies in neurons have indeed described important roles for miRNAs in regulating local protein synthesis in synaptic compartments. For example, the first dendritically localized miRNA to be characterized, miR-134, has been shown to have a role in negatively regulating dendritic spine size through repression of Limk1 translation (Schratt et al., 2006). Moreover, the authors found that this repression was reversed on treatment with BDNF, suggesting that miR-134-mediated repression plays a partial role in activity-dependent regulation of translation. Interestingly, miR-134 is clustered with over 50 other miRNAs (miR379-410 cluster) that have been found to have activity-dependent transcriptional regulation (Fiore et al., 2009). From this cluster, the authors found miR-134, -329, and -381 to be important for activity-dependent dendritic outgrowth. Several additional miRNAs found to be abundant in synapses, including the let-7 family, miR-125b-5p, and miR-128-3p, have also been found to be dysregulated in CNS pathologies (Epple et al., 2021). Thus, individual miRNAs as well as miRNA clusters may serve as essential regulators of local translation for normal CNS function.

Another intriguing layer of regulation comes from the activity-dependent localization or processing of precursor miRNAs (pre-miRNAs) enriched in the distal processes of cells to locally regulate target gene expression. Pre-miRNAs arise from the nuclear processing of primary miRNAs (pri-miRNAs) by Drosha, followed by exportation to the cytoplasm where processing by Dicer generates the mature miRNA (Bernstein et al., 2001; Lee et al., 2003). In neurons, it has been found that several pre-miRNAs are selectively enriched in dendrites, but may have differing effects on gene expression on neuronal stimulation (Sambandan et al., 2017; Zampa et al., 2018). For example, the study by Sambandan et al. (2017) found that pre-miR-181a, a dendritically enriched pre-mRNA, was actively processed by Dicer on neuronal stimulation. Furthermore, they found that the mature miR-181a produced a local downregulation of a target gene, CamkIIa (Fig. 3a) (Sambandan et al., 2017). Alternatively, the study by Zampa et al. (2018) found that neuronal stimulation led to an increased accumulation of pre-miR-134 in the dendritic spines, where it was independently processed by Dicer to form a functional miRNA. Interestingly, this caused an increase in overall dendritic protein expression because miR-134, discussed earlier, also represses locally translated Pumilio 2 (Pum2) mRNA, an RBP known to bind and repress gene expression (Fig. 3b) (Zampa et al., 2018). Together, these studies suggest that activity-dependent miRNA maturation may serve as an additional mechanism for regulation of local translation.

Argonaute and RBP interactions: molecular switches for gene expression

Because of the inherent necessity for fine-tuned, stimulus-dependent protein expression in cells of the CNS, additional levels of local translation regulation have emerged. RBPs are well-characterized regulators of mRNA transport and translation (Wells, 2006). Furthermore, analysis of locally translated mRNAs has revealed an enrichment of key RBP binding motifs, such as Fragile X Mental Retardation Protein (FMRP) and Zipcode Binding Protein (ZBP) in neurons (Ouwenga et al., 2017; Tushev et al., 2018), and QKI in astrocytes (Sakers et al., 2017), suggesting an important regulatory role for certain RBPs in local translation. The interactions between core miRISC components and associated RBPs are of particular interest in understanding this complex regulation because, not only does a combination of miRNAs and RBPs provide additional sequence specificity necessary to tightly regulate which transcripts are locally translated, but these dynamic interactions also provide a potential mechanism by which distal processes of cells can produce a rapid, stimulus-dependent translational response.

Work done in neurons and oligodendrocytes has shown that interactions between RBPs and AGO in miRISC may act as a “molecular switch” regulating translational repression. FMRP is one such RBP that has been extensively studied because of its known role in the neurodevelopmental disorder Fragile X Syndrome (Garber et al., 2008). FMRP has been shown to be an essential regulator of translation by stalling translating ribosomes (Darnell et al., 2011), and it has been proposed to regulate local translation of a variety of synaptic proteins in opposition to glutamate receptor activation (Dölen and Bear, 2008). Later work has highlighted interactions with miRISC. For instance, Kute et al. (2019) were interested in understanding the role of FMRP and the RNA helicase Moloney Leukemia Virus 10 (MOV10), in NMDAR activity-mediated translational regulation within neurons. NMDAR activation had previously been shown to rapidly induce translation of specific genes, such as αCamK II and Arc/Arg3.1 (Scheetz et al., 2000; Bloomer et al., 2008); however, the factors causing this rapid translational response downstream of NMDAR signaling were unclear. Using synaptoneurosomes and polysome fractionation, Kute et al. (2019) found MOV10 incorporated in miRISC under basal conditions, but on stimulation, MOV10 remained bound to the mRNA and dissociated from miRISC to associate with polysomes. Furthermore, they found that these associations were dependent on the presence and phosphorylation state of FMRP (phosphorylation of FMRP promotes the dissolution of MOV10 from FMRP:miRISC), leading them to propose a mechanism in which the phosphorylation status of FMRP functions as a molecular switch regulating translation downstream of NMDAR signals (Fig. 4a). Interestingly, previous work by Muddashetty et al. (2011) showed that the dephosphorylation of FMRP following Class I mGluR activation was necessary for the dissociation of AGO from PSD-95 mRNA to allow translation, supporting a model in which dynamic interactions between different RBPs and miRISC can be finely tuned to provide a specific translational response to different upstream signals.
Other exciting insight into stimulus-dependent de-repression of local translation by RBPs associated with AGO2 has come from studies in oligodendrocytes. Myelin basic protein (MBP) has been well characterized as a locally translated protein in myelinating oligodendrocyte processes (Colman et al., 1982; Ainger et al., 1993; Müller et al., 2013). The RBP HNRNPA2 has been found to bind a specific sequence of the 3’ UTR of Mbp to mediate cytoplasmic transfer and subsequent localization (Hoek et al., 1998). However, it was unclear how Mbp translation was temporarily repressed during localization and activated in response to local triggers. Müller et al. (2013) found that an interaction between AGO2 and HNRNPA2 was key in orchestrating this complex translational regulation. Previous work had found that neuronal stimulation activates Fyn kinase in oligodendrocytes, which then phosphorylates HNRNPA2 to cause the release of Mbp mRNA for translation (White et al., 2008). However, Müller et al. (2015) found that AGO2 was also a downstream target of Fyn kinase. They postulate that the
phosphorylation of AGO2 by Fyn kinase decreases its affinity for a small noncoding RNA (snRNA), the group previously uncovered as an inhibitor of Mbp translation (Bauer et al., 2012), subsequently causing the release of Mbp mRNA from miRISC to allow local translation (Fig. 4b). While it is currently unclear whether the phosphorylation of HNRNPA2, AGO2, or both is essential for the stimulus-dependent release of Mbp for translation, these studies provide further evidence supporting a role of RBP and miRISC interactions in the regulation of local translation.

In addition to HNRNPA2, Fyn kinase has other significant downstream targets that make promising candidate RBPs essential for relying HNRNPA2 signals from neurons to regulate local translation in glia. One such RBP is quaking (QKI). A study by Sakers et al. (2017) characterized the transcriptome of peripheral astrocyte processes (PAPs) in mouse cortices. To do so, they used synaptosome isolation in conjunction with a translating ribosome affinity purification (TRAP) method using astrocyte-specific, Aldh1L1 TRAP mice (Fig. 5a). Of interest, they found that the PAP transcriptome was enriched for 3' UTRs containing QKI RBP response elements (Sakers et al., 2017), and subsequently found that QKI was important for translational regulation of proteins with functions at or near the cell surface, suggesting a functional role in local translation regulation (Fig. 5b) (Sakers et al., 2017, 2021). QKI has intriguingly also been found to be a downstream target of Fyn kinase, phosphorylation of which was found to attenuate binding to Mbp mRNA, and was reported to interact with AGO2 during localization to stress granules in glia (Zhang et al., 2003; Lu et al., 2005; Y. Wang et al., 2010). While this interaction has not been further characterized in mammals, Akay et al. (2013) reported that the Caenorhabditis elegans QKI homolog, GLD-1, interacts with various miRISC pathways. Thus, future work focusing on potential interactions between QKI and miRISC may uncover a mechanism for the regulation of local translation in astrocytes and other glia.

While these as well as other (Kedde et al., 2010; Friend et al., 2012; Cottrell et al., 2018) studies show that the dynamic interactions between RBPs and AGO may function as a "molecular switch" for local translation regulation, much remains to be understood about the complex pathways and interactions between various RBPs and miRISC components. For example, while motif analysis has provided insight into RBPs with probable roles in regulating local translation (Ouwenga et al., 2017; Sakers et al., 2017; Tushev et al., 2018), a systematic analysis of RBPs involved in local translation in the major cell types of the CNS would provide further insight into the molecular mechanisms underlying this regulation. One possibility, proposed by S. Kim et al. (2021), is that RBPs may open up local mRNA secondary structures, thus allowing AGO2 to access the target site and repress translation until cellular stimuli allow for the release of the mRNA. Indeed, it is likely that multiple mechanisms underlie these complex pathways of translational regulation; thus, the field of local translation would benefit from further investigation into the interactions between miRISC and RBPs, and how these interactions can serve as a "molecular switch" regulating gene expression.

Intercellular communication in the regulation of local translation

The interactions between miRISC and different RBPs provide a dynamic model for the regulation of local translation in which cells can rapidly respond to cues of activity based on the phosphorylation status of different proteins. This model can also incorporate another layer of regulatory control in the distal processes of neurons and glia: intercellular communication.

It is well recognized that neurons and glia can release extracellular vesicles, such as exosomes or microvesicles. However, because it was originally believed these vesicles were unwanted materials released by the cells, the study of intercellular communication has become increasingly appreciated, as extracellular vesicles have been found to carry cargo, such as lipid signaling molecules, protein, and, interestingly, miRNAs (Budnik et al., 2016; Lizarraga-Valderrama and Sheridan, 2021). Indeed, in recent years, the role of extracellular vesicles in mediating intercellular communication has become increasingly appreciated, as extracellular vesicles have been found to carry cargo, such as lipid signaling molecules, protein, and, interestingly, miRNAs (Budnik et al., 2016; Lizarraga-Valderrama and Sheridan, 2021).

To further understand the role of exosomes in mediating neuron-astrocyte communication, Men et al. (2019) developed exosome reporter mice. After confirming neuron-derived exosomes could be internalized by astrocytes, they then characterized the miRNA profiles of these exosomes using miR-microarray hybridization. From this, they found a noticeable difference between the miRNA profile of neurons and neuron-derived exosomes, suggesting there exists a regulatory mechanism for miRNA-loading of exosomes. Of particular interest, they found miR-124-3p was enriched in neuron-derived exosomes. Previous work by the group showed that exosomal miR-124 mediated the upregulation...
of the glutamate transporter, GLT-1, translation in astrocytes (Morel et al., 2013), which has been characterized as a locally translated protein in PAPs (Sakers et al., 2017). Furthermore, they showed that this upregulation was indeed an indirect translational effect: miR-124-3p inhibited the expression and activity of two miRNAs (miR-132 and miR-218) known to suppress GLT-1 translation (Fig. 6a). Thus, while more work is needed to characterize the potential local activity of this translational...
regulation in vivo, exosomal communication within the CNS may offer yet another level of dynamic regulation of local translation.

Such regulation of local translation by exogenous miRNAs may also provide a better model for understanding the role of glia in the progression of neurodegenerative diseases, such as ALS. For instance, as discussed above, miR-124-3p was found to also increase levels of GLT-1 by suppressing the inhibitory activity of miR-218 and miR-132. Of importance, GLT-1 downregulation has been implicated in ALS progression and severity (Rothstein et al., 1995). The work by Morel et al. (2013) showed that exogenously delivered miR-124 was able to increase the expression of GLT-1 in an ALS mouse model compared with control. Intriguingly, while using mRNA Tagging and Affinity-purification (miRAP) to determine miRNAs associated with AGO2 in a cell type-specific manner, Hoye et al. (2017, 2018) also discovered that miR-218 is released in RNP complexes, rather than in exosomes, by dying motor neurons in an ALS mouse model. Furthermore, they found that these RNPs were taken up by astrocytes and inhibit translation of GLT-1, driving astrogliosis. The proposed model is that miR-218 import-mediated loss of astrocytic GLT-1, which normally allows astrocytes to clear excess glutamate from synapses, promotes excitotoxicity on remaining motor neurons. While they did not probe which proteins were complexed with miR-218, AGO:miRNA complexes have been found circulating in plasma (Arroyo et al., 2011), suggesting that AGO may also be directly involved in this process (Fig. 6b). As miR-218 is not expressed in mature astrocytes of healthy mice or ALS mouse models (Hoye et al., 2018), understanding the role exogenous miRNAs play in the dysregulation of local translation during disease may provide an avenue for identifying potential therapeutic targets in ALS and other neurodegenerative diseases.

There are other avenues of intercellular communication with potential interesting implications in regulating local translation, namely, endogenous retroelements, such as ARC and PEG10. Arc, a retrotransposon and immediate-early gene with known, activity-dependent local translation in dendritic spines, is largely involved in the endocytic trafficking of AMPARs (Chowdhury et al., 2006; Bloomer et al., 2008). However, it was more recently discovered that ARC protein can spontaneously oligomerize to form virus-like particles that enclose arc mRNA, as well as non-coding RNAs, to mediate intercellular communication (Ashley et al., 2018; Pastuzyn et al., 2018). In a similar manner, PEG10, a different retrotransposon essential for embryo development (Ono et al., 2006), has also been found to form virus-like particles that packages its own mRNA in neurons (Segel et al., 2021). Much remains unclear about these retroelement-derived proteins and their resulting virus-like particles, including how they may mediate intercellular communication or synaptic plasticity (Gallo et al., 2018). Future research on the regulation of local translation and intercellular communication would greatly benefit from further understanding of ARC and PEG10 virus-like particles, such as whether glial cells are able to take up these particles, if these particles contain distinct mRNA, miRNA, or other ncRNA profiles that may suggest a regulated form of intercellular communication, and whether this mechanism may provide a potential platform for therapeutic RNA delivery (Segel et al., 2021).

Conclusions and Perspectives

Over the past several decades, great progress has been made in characterizing the ability of morphologically complex cells to direct the localization of a subset of transcripts to distal processes for future translation. Local translation has been found to be essential for many functions of the cells of the nervous system, such as synaptic plasticity (D. O. Wang et al., 2009; Holt et al., 2019). Yet, many of the mechanisms and trans-regulatory elements underlying the regulation of this process remain unclear.

The diversity and versatility of miRISC-mediated translational repression offer a promising model for many reasons. First, cells must be able to discriminate between transcripts designated for translocation to distal processes and transcripts remaining in the soma. While cis-elements in the 3′ UTR often serve as “zipcode motifs,” RBP target motifs alone contain limited information content; thus, coregulation with miRISC may provide the high sequence specificity needed for accurate discrimination of several miRNAs sharing RBP target motifs, but differing miRNA seed sequences. Second, cells must be able to repress translation of localized transcripts during the process of translocation while preventing degradation. The heterogeneity of miRISC function depends largely on factors, such as seed-sequence specificity and RBP partners, allowing for translational repression to occur independent of mRNA degradation. Third, cells must be able to de-repress translation either on delivery to the distal process or in response to other cellular stimuli. As the studies discussed above have shown, post-translational modifications, such as phosphorylation, to RBPs or AGO allow for dissociation of the mRNA from the inhibitory complex, thus providing a molecular switch controlling gene expression. Fourth, cells need mechanisms to shut off translation of specific miRNAs in response to other signaling cues or when the response has subsided. Local maturation of pre-miRNAs by Dicer in response to stimuli provides such a mechanism by allowing direct translational repression of a target gene (Fig. 3a) or more complex translational regulation by repressing the expression of a repressive RBP, such as PUM2 (Fig. 3b).

As much of this work has been done in neurons, understanding the dynamic interactions between miRISC and RBPs in other cell types, such as glia, will provide further insight into this biologically essential phenomenon. Astrocytes, for example, are necessary for the regulation of synaptogenesis and synapse maturation, and play a key role in neurodevelopment and neurodegeneration (Sloan and Barres, 2014; Chung et al., 2015). With a single astrocyte making contact with up to 2 million different synapses in humans (Obereith et al., 2009), it is essential for PAPs to translationally respond independent of signals received by other processes. Yet, much remains to be understood about this translational regulation in astrocyte processes. For example, while astrocyte-derived exosomes have been found to have a unique miRNA profile (Jovičić and Gitler, 2017), much less is known about the presence and profile of miRNAs functioning in PAPs. Thus, future work on neurodevelopmental and neurodegenerative disorders would greatly benefit from further characterizing the mechanisms regulating local translation in both neurons and glial cell types.

References


