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Mini-Review

Targeting of mRNAs Within the Glial Cell Cytoplasm: How to Hide the Message Along the Journey

Graciela L. Boccaccio*
Instituto de Investigaciones Bioquímicas "Fundación Campomar," IIB Buenos Aires, CONICET, IIB-FCEyN, University of Buenos Aires, Buenos Aires, Argentina

The subcellular targeting of mRNAs encoding myelin proteins to the oligodendrocyte processes is an accepted fact in myelin formation. How these messengers are kept silent during their movement to the subcellular domain where they are turned on remains a mystery. This review focuses on aspects of mRNA targeting and speculates on possible molecular mechanisms for the translational control of myelin-located mRNAs. J. Neurosci. Res. 62: 473–479, 2000. © 2000 Wiley-Liss, Inc.

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Extensive evidence supports the notion that messengers encoding the highly charged myelin proteins may be found in asymmetric distribution within the oligodendrocyte cytoplasm. A landmark in the field was established when, working with subcellular fractions from brain, Colman et al. (1982) found that isolated myelin membranes were enriched in mRNAs coding for myelin basic proteins. MBPs are a major component of CNS myelin and the localization of the corresponding transcripts since then has been studied both by in situ hybridization and subcellular fractionation approaches. It is now accepted that MBP mRNAs are translocated to the oligodendrocyte myelinating processes. The biological significance of such spatial restriction has been commented upon (reviewed in Brophy et al., 1993; de Vries et al., 1997; Boccaccio et al., 1999a). The property itself seems to reside in the strongly basic composition of those polypeptides, a feature shared with another molecule, the myelin oligodendrocyte basic protein (MOBP), whose mRNA is also segregated to the cell processes (Ainger et al., 1997; Gould et al., 1999). Transfection of several non-glial cell types and in vitro assays had led to the notion that MBPs are synthesized near the myelin membrane to avoid mislocalization and aberrant association with internal cellular membranes (reviewed in Brophy et al., 1993; Boccaccio and Colman, 1995). This simple model predicts that in myelinating cells MBP polypeptides would be located at the same subcellular regions where the messengers are restricted. Recent reports, however, have shown that the final location of the MBPs polypeptides depends on several factors. There are four major rodent MBP isoforms that differ in the splicing of the exons II and VI. The two isoforms containing the exon II are also detected inside the cell nucleus, and it is believed that they may participate in developmental regulation of the myelin formation process (Pedraza et al., 1997). Speculatively, the nuclear polypeptides observed at early stages might be translated from the fraction of mRNA that is present in the cell soma. Alternatively, it is possible that the restricted positioning of MBP messengers does not absolutely limit the movement of MBP polypeptides.

Active mRNA targeting has been well-documented in many cell types, ranging from yeast to neurons, oocytes and embryos (St Johnston, 1995; Steward, 1997; Hazelrigg, 1998; Mowry and Cote, 1999; Lasko, 1999). In glial cells, other mRNAs are differentially distributed besides the MBP and MOBP mRNAs. Carbonic anhydrase IV mRNA, and tau mRNA, the latter being also targeted to the proximal axonal region in neurons, also appear present in oligodendrocyte processes (references in Boccaccio et al., 1999a).

Several recent studies have helped underscore and define the molecular mechanisms supporting the transport of MBP mRNAs (Barbarese et al., 1995; Ainger et al. 1997; Carson et al., 1997; Barbarese et al., 1999; Munro et al., 1999). Briefly, mRNA cytoplasmic segregation seems to start inside the nucleus with the recognition by heterogeneous nuclear ribonucleoprotein A2 (hnRNPA2) of an 11-mer element, the hnRNPA2 response element (A2RE) located in the 3′UTR of the MBP message, followed by the formation of a transport competent ribonucleoparticle (RNP) that is thought to be translocated along microtubules by the action of kinesins. Once the

*Correspondence to: G.L. Boccaccio, Instituto de Investigaciones Bioquímicas "Fundación Campomar," Av. Patricias Argentinas 435, 1405 Buenos Aires, Argentina. E-mail: gboccac@iib.uba.ar

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final destination is reached, translation commences. This model has common elements with those proposed for mRNA targeting in cells as diverse as neurons, fibroblasts, yeast and oocytes, where different messengers are alternatively transported by kinesins, myosins or dyneins (Arn and MacDonald, 1998; Hazelrigg, 1998; Schnorrer et al., 2000).

An emerging notion is that the molecules required for RNA trafficking in quite different cell types may be conserved through evolution, at least in part. Indeed, the mRNA coding for the neural cytoskeleton associated protein tau is translocated at the vegetal pole of Xenopus oocytes; a neuroblast cell line supports the movement of the glial specific MBP mRNA, and the male germ line protamine mRNA is transported inside cultured oligodendrocytes (Ainger et al., 1993; Litman et al., 1996). Accordingly, certain *cis*-acting elements are conserved and homologous trans-acting factors have been identified in different cell types and species (Deshler et al., 1998; Hazelrigg, 1998; Kiebler et al., 1999; Lasko, 1999; Mowry and Cote, 1999; Norvell et al., 1999; Kiebler and DesGroseillers, 2000). It might be expected that the translation arrest during mRNA movement may share common elements among the different cell systems as well. Translation arrest is still an intriguing step of mRNA targeting. As we will see from the variety of emerging mechanisms presented below, the most detailed information is about maternal mRNAs.

Translation Arrest: Requirement For Transport?

Is translation "allowed" during mRNA transport, or not? Let's consider the prototype oligodendrocyte specific MBP mRNA. Cumulative direct and indirect evidence strongly suggests that MBP messengers remain translationally silent along the way. As discussed above, the unrestricted translation of these extremely basic polypeptides would allow the interaction with organelle membranes rather than specifically with compact myelin, likely interfering with intracellular functions. The argument that a very basic polypeptide has to be translated in a restricted place may also apply for the MOBP 81A mRNA, that shares transport elements with the MBP mRNAs and is also found to be concentrated in the myelinating processes (Ainger et al., 1997; Boccaccio et al., 1999a).

It is of interest to compare the observed mRNA particle transport speed with the polypeptide elongation rate. RNA moves in cultured cells at 1.2–4 μm/min (Ainger et al., 1993; Muslimov et al., 1997). This is enough to translate more than one full length MBP peptide at the average rate of 1 amino acid/sec across a distance as short as 50 nm. It is difficult to conceive of a moving polysome particle from which actively growing peptides, likely to be associated with chaperones, are emerging. The steric hindrance and the interaction with cellular components would impair the movement, and thus translation or at least peptide elongation has to be blocked. Therefore, it should be predicted that the messengers are translationally arrested during transport, despite the presence of translational elements in the granule (Barbarese et al., 1995). A less likely alternative is that translation is not actively blocked, but instead the mRNA is simply sequestered from the translation machinery inside the RNP. Once the translocation is completed, the engagement of mRNA into polysomes could help to keep the subcellular localization of certain mRNAs, likely by anchoring them to the cytoskeleton (Kleinman et al., 1993; Boccaccio et al., 1999b).

Translation Arrest: Is There a Developmental Switch?

Many targeted maternal mRNAs remain silent during early developmental stages and became active much later. In those cases, translation is an event temporally separated from transcription and transport. As an example, translation of the Drosophila bicoid mRNA is not spatially restricted, but is repressed until stages when the transcripts are properly located at the anterior pole.

It seems that the translation of MBP mRNAs is developmentally regulated. The first observation supporting the notion of a developmental switch is a lag between the appearance in the CNS of MBP mRNAs and MBP polypeptides (reviewed in Brophy et al., 1993; Ueno et al., 1994a). Furthermore, several glial cell lines that synthesize MBP mRNAs are unable to translate them into protein, but can be induced to do so when they are grown under certain conditions (Hayes et al., 1992; Dyer and Popko, 1993; Verity et al., 1993). In the glial cell line N20.1 that displays markers for immature oligodendrocytes, MBP transcription takes place, with a splicing pattern corresponding to early stages, but the polypeptides remain undetected (Verity et al., 1993). It has also been shown that the translation of a reporter construct carrying the MBP 3′UTR is impaired in N20.1 cells but not in nonglial cells (Ueno et al., 1994b), thus opening the possibility that repressor elements located in this mRNA region operate in immature oligodendrocytes. Furthermore, the MBP mRNAs are stimulated by steroids and it has been found that the 5′UTR is involved in this upregulation. In addition to the putative effect of the 3′UTR, this could add to the developmental regulation of this messenger (Verdi and Campagnoni, 1990). Investigation on MBP expression using the recent technology for culture and differentiation of multipotential neuroepithelial stem cells (Lee et al., 2000; Tang et al., 2000) will bring valuable knowledge to this issue.

A similar transcription-translation uncoupling seems to occur in certain myelin mutants where oligodendrocytes remain arrested in immature stages. Several mutants of the PLP gene such as *jimpy*, *jimpy*^{msd}, and *jimpy*^{rsh} and the *quaking* mutant shows diminished levels and translatability of MBP messengers, together with that of other myelin genes (Mitchell et al., 1992; see also Brophy et al., 1993). As discussed previously, some of those mutants also display a disrupted MBP mRNA distribution, resembling early stages where those messengers are abundantly detected in the cell body (Brophy et al., 1993). Simultaneously, the MBP transcripts do not seem to accumulate in the cell process in the N20.1 cell line (Verity et al.,

1993), again suggesting that at immature stages when mRNA localization is not yet completed, MBP synthesis is downregulated.

The molecular bases of the developmental regulation of MBP translation, as well as its putative role in keeping non-localized messengers silent remain to be determined. Obviously, this blockage does not operate at later myelinating stages when active transcription and translation occur simultaneously.

Translation Arrest Signal: Does It Share Elements With the Localization Signal?

Besides a developmental switch, other mechanisms for the active control of translation during mRNA transport operate in other systems. The simplest hypothesis of how translation can be coupled to localization is that the same RNA element(s) is controlling both processes. A similar principle exists in the well-known case of targeting of nascent protein chains to the ER. Here the recognition of the signal peptide by the SRP (signal recognition particle) initiates both the translation arrest and the ER-targeting of the polyribosome engaged in synthesis of ER-translated proteins. The translational control of Nanos mRNA located at the posterior pole of Drosophila oocytes is an example where this simple model of a bifunctional RNA signal seems to operate. Nanos is an important posterior determinant that has to be expressed accurately in time and space to guarantee the normal development of the embryo. Redundant elements named TCE (translation control element) or SER (Smaug responsive element) overlap the Nanos mRNA localization signal that span 540 bases of the 3′UTR (reviewed in Lasko, 1999). The TCE binds the repressor protein Smaug thus arresting translation (Lasko, 1999; Dahanukar et al., 1999; Smibert et al., 1999). It is speculated that at the posterior pole Smaug repressor action is blocked by the action of another protein, Oskar, that is also localized at the posterior. Although it is not clear how this occurs, a likely model is that Oskar binds to the repressor Smaug releasing it from the Nanos mRNA molecule thus allowing translation. In this way, only messengers properly located are allowed to direct Nanos protein synthesis. This is an important issue because the majority of Nanos mRNA remains unlocalized. Recently, Smaug has been cloned independently by the groups of Wharton and McDonald (Dahanukar et al., 1999; Smibert et al., 1999). Smaug is a novel RNA-binding protein and the region that interacts with target RNA does not shares homology with previously described RNA binding domains (Dahanukar et al., 1999). A relevant finding is that the mammalian homologue to the Drosophila Smaug has been reported and it is likely expressed in the brain (Kikuno et al., 1999), where a growing number of targeted mRNAs are known to occur in neurons and glial cells. Thus, a mechanism based in repression by proteins homologous to Drosophila Smaug could a priori operate in glial cells.

Other Drosophila maternal mRNAs localized asymmetrically are silenced by different mechanisms. As an example, the translation of Oskar mRNA, another posterior determinant that regulates the expression of downstream genes, does not share elements with the Nanos mRNA repression pathway described above. As in many other maternal messengers, distinct RNA elements located at the 3′UTR operate at different developmental times to target the messenger to distinct oocyte regions. A 242 nt fragment is essential for the final positioning of Oskar mRNA at the posterior pole. The Oskar mRNA translation is controlled by both the 3′ and 5′ UTRs. Silencing depends on the binding of the repressor Bruno to a consensus 9 nt sequence, the BRE (Bruno response element) (Lasko, 1999; Castagnetti et al., 2000). There are 4 copies of the BRE inside the element responsible for posterior localization and two more copies in a region not relevant for mRNA transport. The interaction with a derepressor element located at the 5′ end allows translation to proceed (Gunkel et al., 1998). It has been confirmed recently that this does not involve the 5′ CAP nor the poly A tail and thus, the molecular events directly conducive to translation have not been identified (Lie and Macdonald, 1999). A novel in vitro system that recapitulates the Drosophila embryo translational conditions (Lie and Macdonald, 1999; Smibert et al., 1999; Castagnetti et al., 2000) will add a biochemical approach to the genetic data on translational regulation of maternal messengers thus helping to elucidate the underlying molecular mechanisms. No elements of the Oskar translational control pathway were described until now to occur in mammals.

Several RNA binding proteins involved in transport could also participate in translational repression. The double strand RNA binding protein Staufen plays an important role in the positioning of maternal and neural messengers in Drosophila oocytes and neuronal precursor cells (reviewed in Kiebler and DesGroseillers, 2000). Since the finding of the human homologous protein, studies has been performed to evaluate its function in mRNA transport in neurons and oligodendrocytes (Boccaccio et al., 1999b; Kiebler et al., 1999, Kiebler and DesGroseillers, 2000). It was suggested that Drosophila Staufen may regulate translation of transported RNAs (Lasko, 1999; Micklem et al., 2000) and thus the capacity of the mammalian protein to inactivate targeted mRNAs in CNS cells should be investigated.

Another protein that acts in mRNA targeting in mammals is the Translin or TB-RBP (testis-brain RNA binding protein). Translin is involved in the repression of certain mRNAs as well as in the mRNA transport through the intercellular bridges in mammal male germ cells (Han et al., 1995; Morales et al., 1998). Both functions seem to depend on the recognition of consensus motifs in the target RNA named "Y" and "H" elements. Short sequences similar to these Y and H elements are present in targeted neuronal RNAs such as the microtubule associated protein 2 (MAP 2); tau; ligatin and α-calmodulin dependent kinase II (αCAMKII) mRNAs and in the non-coding transcript BC1 (Han et al., 1995; Morales et al., 1998; Severt et al., 1999). More relevant to this review, a Y element is also present in the 3′UTR of the

oligodendrocyte specific MBP mRNA (Han et al., 1995; Wu and Hecht, 2000). This opens the possibility of a general function of TB-RBP in the metabolism of targeted RNAs, likely transport or repression.

It has been convincingly demonstrated (Mayford et al., 1996) that the 3′UTR of the αCAMKII mRNA is enough to promote both mRNA dendrite targeting and localized translation. Evidence has been presented recently, however, that the Y element located in the coding region may also contribute to mRNA localization, thus directly involving TB-RBP in the transport mechanism (Severt et al., 1999). The messenger encoding the cytoskeleton associated protein tau is targeted to the proximal region of axons. An H element is located more than 200 bases upstream of the minimum region required for transport (fragment I in Behar et al., 1995). A larger fragment (designed B in Behar et al., 1995) including this motif seemed more efficient in promoting neurite localization. This may be interpreted either as the involvement of the TB-RBP in transport or in translation repression, because a silenced messenger could result a better cargo for the transport machinery. The polymerase III transcript BC1 is a non-coding RNA that has Y and H elements. Not surprisingly, TB-RBP recognizes them and associates to the BC1 RNA forming a RNP that is transported to dendrites (Muslimov et al., 1997). Kobayashi et al. (1998) has suggested that the presence of TB-RBP in this neuronal compartment suppress mRNA translation of dendritic mRNAs. Direct evidence of the role of Translin/TB-RBP in arresting transported messengers in neurons is lacking.

Is TB-RBP involved in the transport or repression of targeted mRNA in glial cells? Translin/TB-RBP is a quite ubiquitous protein. Its presence in astrocytes has been documented, but no data has been reported on oligodendrocytes. We have confirmed the presence of TB-RBP mRNA in isolated adult oligodendrocytes (Vazquez-Pianzola, Santa-Coloma, and Boccaccio, unpublished). It is perhaps relevant here that a partially purified TB-RBP from brains is able to bind to a MBP mRNA fragment containing the Y element (CTCAGCCCTGACTT) as judged by gel retardation assays (Han et al., 1995). A more recent study has confirmed the association of recombinant TB-RBP with MBP mRNAs by immunoprecipitation approaches (Wu and Hecht, 2000). The Y element is located 145 b upstream of the RNA transport signal in the murine MBP (Ainger et al., 1997), and does not promote by itself nor is required for transport of injected RNA (SalI truncated fragment in Ainger et al., 1997).

Thus, the TB-RBP binding site is outside the transport and localization signals, suggesting that it would participate in a step other than transport, likely translational control. Interestingly, other targeted messenger bearing RTS also carry Y or H elements, suggesting that in those cases transport is accomplished by RTS recognition factors while repression is mediated by TB-RBP. Examples of those messengers are the dendrite localized ARC mRNA and MAP2 mRNA, the protamine-2 mRNA transported through male germ cells bridges, and the rat opioid receptor B (Han et al., 1995).

If TB-RBP is a factor that mediates translation repression of transported MBP mRNAs, a reversible action is expected, because messengers located at the myelin membrane would be actively translated. This supposes either the dissociation from the mRNAs or at least inactivation of the repressor activity at the myelin compartment. An hypothesis is that this can be achieved by changes in the phosphorylation state of TB-RBP (Han et al., 1995). The participation of TB-RBP in mRNA transport is undoubtedly connected to the microtubule and microfilament binding capacity of the TB-RBP (Wu et al., 1999). In addition, Wu et al. (1999) identified recently several proteins that interact with TB-RBP and may therefore be involved either in transport or translation control.

Another protein class likely involved in the metabolism of targeted mRNA is the ELAV (embryonic lethal abnormal vision) family. ELAV proteins promote neurogenesis, by increasing the stability of certain mRNAs and as it was shown recently, the ELAV member Hel-N1 increases the translation of Neurofilament M mRNA (Antic et al., 1999). Neural ELAV proteins are found in the cytoplasm in mRNP complexes that associate with microtubules (alpha complexes). These in turn associate with polysomes and microfilaments to form a translational apparatus (beta complex), thus, neural ELAV interacts with both repressed and translated mRNAs (Antic and Keene, 1998). A 43 kDa protein that binds to the tau mRNA localization signal was recently identified as HuD, a member of this family of RNA binding proteins (Behar et al., 1995; Aranda-Abreu et al., 1999). It is unclear if the binding of HuD to the tau mRNA localization signal mediates the transport or translational control. At present, it has been confirmed that HuD promotes tau mRNA stability (Aranda-Abreu et al., 1999). Again, the localization signal appears as an element that couples different aspects of mRNA metabolism with transport.

It was confirmed recently that the mouse homologue to Hel-N1 is expressed in glial cell lines (Schramm et al., 1999). The RNA targets of ELAV proteins are variable arrangements of AU-rich sequences. Similar elements are scattered in the long MBP 3′UTR, opening the possibility that some member of the ELAV family interacts with this mRNA.

Are the MBP mRNA transport elements involved in translational regulation? Unexpectedly, the RNA element that binds hnRNPA2 and directs the transport is not a repressor but a translation enhancer that works in a cap-dependent cell-independent manner (Kwon et al., 1999). It could be speculated that it stimulates protein synthesis of localized messengers molecules. The hnRNPA2, however, was detected inside the nucleus and cell soma but not in compact myelin, the place where the translation of MBP mRNAs is supposed to occur actively and thus, the physiological relevance of this translation enhancement remains unclear. Interestingly, the actin zip-code binding

protein 1 (ZBP1) and the cognate Xenopus protein vera show homology with hnRNPE1, that blocks translation of certain mRNAs by interaction with their 3′UTR (Ostareck et al., 1997). A novel protein involved in the transport of maternal Xenopus mRNAs, the vegetal RNA binding protein 60 (VgRBP60) has high homology to hnRNPI, that is thought to participate in nuclear RNA metabolism (Cote et al., 1999). The effect of ZBP1/Vera in translation of targeted mRNA has not been assessed.

Finally, another aspect that links MBP mRNA targeting with translation resides in the RLS (RNA localization signal). This is a secondary structure element required for the correct localization of MBP mRNAs in the myelin compartment after their translocation along major oligodendrocyte process (Ainger et al., 1997). The direct effect of RLS in translation has not been tested, but it is intriguing that the RLS is no longer required for myelin localization when the transcript is devoid of coding regions (Ainger et al., 1997). This observation could suggest that the RLS is involved in a translational regulation event, likely de-repression that is in turn required for the movement to proceed inside the myelin compartment.

The majority of the *cis/trans* acting factors likely involved in translational control of transported mRNAs mentioned in this review interacts or are located at the 3′UTR. It is not a surprise that the 3′end may exert influences in the translatability of the messenger. It is well known that the poly A tail synergistically with the 5′CAP enhance translation initiation, likely by binding of the poly(A)binding protein (PABP) and eucaryotic translation initiation factor 4E (eIF4E) respectively, that in turn interact with the eIFG4 and eIF3 promoting ribosome binding (Preiss and Hentze, 1999). Furthermore, the physical interaction between the two Oskar mRNA ends described above is an example of a more general concept of the mRNA molecule as a closed loop. This has been documented by electronic microscopy (Preiss and Hentze, 1999).

Translation Activation by Cytoplasmic Polyadenylation

Finally, the last mechanism for the translational control of localized mRNAs to be discussed is cytoplasmic polyadenylation. Initially described for maternal mRNAs, localized or not, this strategy has been recently reported to occur in neurons and has been extensively reviewed (Wu et al., 1998, Richter, 1999, Wells et al., 2000). Briefly, a short sequence termed the cytoplasmic polyadenylation element (CPE) located at the 3′UTR is recognized by an activated CPE-binding protein (CPEB) thus triggering polyA elongation. Similar factors are apparently involved in mature neurons and oocytes. In Drosophila, the maternal bicoid mRNA localized at the anterior pole undergoes polyA elongation in a developmentally regulated manner, increasing from 50 to 150 nucleotides. The CPE motif is not apparent in the bicoid mRNA, suggesting that different signals for cytoplasmic polyadenylation exists. In Xenopus embryos, a motif located at the 3′UTR, the embryonic-type CPE (eCPE) promotes cytoplasmic polyadenylation by binding of a member of the ELAV family, the Elra (Wu et al., 1997) thus extending the action of this protein family to further aspects of mRNA metabolism.

It has recently been shown that in vertebrate neurons the dendritic αCAMKII mRNA is activated selectively upon synaptic stimulation by CPE-mediated cytoplasmic polyadenylation (Wu et al., 1998). Is this pathway operating in the targeting of oligodendrocyte mRNAs? It is relevant to mention that in the previous examples the uncoupling of translation and transport accomplishes a physiological role: only upon synaptic stimulation the product of the CAMKII is required and only after all the bicoid mRNA is properly located translation is launched. In both cases cytoplasmic polyA elongation is triggered by a signal transduction event. Such a dramatic scenario is not that of MBP mRNAs. Indeed, preliminary results would indicate that the MBP mRNA poly A tail would have at the adult myelin compartment the same length as in non-localizing pre-myelinating stages (Vazquez-Pianzola, Santa Coloma and Boccaccio, unpublished). It is likely that this mechanism of mRNA activation is reserved for stored messengers like maternal and certain dendritic mRNAs, where localization is completed much earlier than the beginning of translation.

CONCLUSIONS

Since the first observation leading to the notion of compartmentalized protein synthesis in polarized cells other than oocytes and embryos, substantial progress has been achieved in understanding the signals and factors involved in the mRNA transport. In contrast, how translation is coupled to the localization process is poorly understood. This is an important issue in the biology of myelin because the expression of myelin genes is both temporal and spatially restricted inside oligodendrocytes. We have discussed the few translational repression mechanisms known to regulate targeted mRNAs in other cell types as well as the chances that they are actively controlling MBP mRNA synthesis in the myelin compartment. The working model to be tested is that MBP mRNA would be developmentally silenced at early stages of myelination and that the further action of repressor proteins is required at later times of active myelin synthesis. These unknown factors may be related to repressor proteins described in other systems and likely would interact with the 3′UTR of myelin-located messengers. Until today, the messengers encoding MBPs and MOBPs, major myelin components and target of the autoimmune reaction in the demyelinating disease multiple sclerosis, are the prototype targeted oligodendrocyte mRNAs. The search for novel messengers located at the myelin would help to look for common elements putatively involved in their transport and translation. A considerable amount of work have still to be done to understand the cellular and molecular events underlying the selective restriction of protein synthesis at the myelin compartment.

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