RNA-binding proteins and neural development: a matter of targets and complexes

François Agnès[CA] and Muriel Perron

Embryologie Moléculaire et Expérimentale, UMR 8080 CNRS-Université Paris-Sud, Bat 445, 91405 Orsay Cedex, France

[CA]Corresponding Author: francois.agnes@ibaic.u-psud.fr

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RNA-binding proteins control multiple steps of nuclear and cytoplasmic RNA processing including alternative splicing, stabilization, transport and translational repression of RNAs. Here we present existing evidence showing that RNA-binding proteins expressed in the nervous system are required in many steps of its development and play multiple roles during the life of a neuron. We describe emerging views based on recent studies strongly suggesting that RNA-binding proteins cooperate actively within neurons in large multifunctional complexes to regulate the flow of information encoded in ribonomes in a coordinated fashion. *NeuroReport* 15:2567–2570 © 2004 Lippincott Williams & Wilkins.

INTRODUCTION

During development of the nervous system, cells constantly have to make decisions. Gene expression must be therefore tightly regulated for a progenitor to adopt a particular fate or a neuron to acquire its complex and dynamic architecture. Spatial and temporal control of gene expression within neural cells is achieved at the transcriptional and post-transcriptional levels. While transcription sets the transcriptome of a given cell at a given time, post-transcription tunes gene expression within differentiating cells by modulating the diversity, the level and the localization of mRNAs. 2–8% of the total number of genes in animal genomes encode RNA-binding proteins [1]. Among them, sequence-specific RNA-binding proteins can be distinguished from other RNA-binding proteins controlling the general splicing, export and translation machinery of RNAs, because they bind specific RNA targets. For convenience, we will refer to sequence-specific RNA-binding proteins as RBPs. RBPs control multiple steps of nuclear and cytoplasmic RNA processing including alternative splicing, stabilization, transport and translational repression of RNAs. RBPs expressed in the developing nervous system include for instance ELAV/Hu, FMRP, Nova, ZBP, CPEB, Musashi, Staufen and QKI. The molecular function of these RBPs is mediated through their ability to bind, via their RNA-binding domains (RRM, KH domain, RGG box, DRBD), specific sequences (Zipcode, ARE, CPE, U-rich), or structural motifs (G quartet, A-form double helix RNA) located in target pre-messenger or messenger RNAs (reviewed in [2–4]).

In this review, we first present evidence showing that RBPs are required in many steps of neural development and that a given RBP plays multiple roles during neuronal differentiation. Second, we describe the emerging view that ribonomes, representing subsets of RNAs, are post-transcriptionally regulated by RBPs and discuss target sequence specificity. Third, several recent studies will be presented, supporting a model where RBPs cooperate actively within neurons in large multifunctional complexes to regulate in a coordinate fashion the flux of information from the nucleus to distal parts of the cell.

RNA-BINDING PROTEINS CONTROL MULTIPLE ASPECTS OF NERVOUS SYSTEM DEVELOPMENT

The developing nervous system produces an extraordinarily high number of diverse neurons and glia from a limited number of precursors. Neural cell diversity is generated via asymmetric division of neuroblasts occurring in a stem cell fashion. Mutant analyses have shown that several RBPs are involved in cell fate decisions during this step of neural development. In *Drosophila*, Staufen and Musashi are required during asymmetric division of neural precursors [5,6]. In mice, Musashi proteins seem to be involved in self-renewal and maintenance of CNS stem cell populations [7]. Recently, a *Xenopus* RNA-binding protein, Xseb4R, has been involved in neural cell fate decisions since altering its level in retinoblasts affects retinal cell type distribution [8]. Together, these data suggest that post-transcriptional gene regulation in early phases of neural development may be crucial for generating cell diversity.

Among eukaryotic cells, neurons acquire by far the most complex and dynamic architectures. These hyperpolarized cells extend axons and many dendrites that navigate over long distances and establish numerous and plastic synapses with their targets. The ELAV/Hu proteins and the fragile X protein, FMRP, are involved in neurite growth and guidance in the embryonic and adult developing nervous system. While over-expression of Hu induces neurite outgrowth [9], treatment of neuronal cells with antisense oligodeoxynucleotides directed against HuD blocks their induction [10]. In *Drosophila* embryos, commissural neurons lacking ELAV do grow but their axons fail to cross the midline (F.A., unpublished data). The *Drosophila* FMRP is also required for

normal neurite extension, guidance, and branching as well as axonal development in the mushroom bodies [11,12]. Dendrite morphogenesis requires the function of some RBPs as well, as shown by *Drosophila nanos*, *pumilio* and *FMRP* mutants displaying high-order dendritic branching defects [13,14]. Few RBPs acting in differentiating glia have been described. QKI for example has been shown to be important in oligodendrocytes for their myelinization [15].

Interestingly, RBPs involved in neural development are also involved in adult behavior. For example, ELAV/Hu proteins are involved in spatial learning and memory in rodents [16,17]. Staufen together with Pumilio is important for long-term memory in *Drosophila* [18]. The learning and cognitive impairments in Fragile X FMRP are thought to be due to the key role of FMRP in synaptic growth, structure, and long-term plasticity elucidated with knockout mice and mutant flies (reviewed in [19]). FMRP has also been shown to be involved in courtship and circadian rhythm in *Drosophila* [20,21].

Neuronal viability requires RBPs as evidenced by *Nova-1* mutant mice, which die postnatally from a motor deficit associated with apoptotic neuronal death [22]. Together, these data show that RBPs are virtually involved in all steps of neural development, but also that a number of RBPs are involved in multiple aspects of a neuron's life, acting during its differentiation and contributing to its physiological function. Because the absence of FMRP is responsible for the Fragile X syndrome and because Hu and Nova auto-antibodies induced in cancers cause neurological paraneoplastic syndromes in man (reviewed in [23]), understanding the role of these RBPs during normal neural development is of great interest in designing therapeutic strategies for patients suffering from these neuropathologies.

NEURAL RNA-BINDING PROTEINS AND THEIR TARGETS: THE RIBONOMIC ERA

For a decade, many efforts have been made to identify neuronal RPB targets. It has become clear that RBPs bind to many RNA targets *in vitro*, suggesting that they are involved in many aspects of neuron differentiation. For instance, Gao *et al*. demonstrated that the HuB RNA targets encode cell-cycle regulators, transcription factors and other early-response gene products in agreement with the involvement of ELAV/Hu proteins in various functions of neural development [24]. In *Drosophila*, functional *in vivo* binding sites for ELAV have been defined in *neuroglian* and *erect-wing* pre-mRNAs [25,26]. The past few years have seen a rapid expansion in the identification of the *in vivo* RBP targets based on novel protocols combining immuno-precipitation of ribonucleoprotein (RNP) complexes coupled with genomic technologies [27–30]. Consistent with the abnormal neuron phenotypes found in both fragile X patients and the *Fmr1*-knockout mouse, several FMRP mRNA targets encoding proteins involved in axon guidance or synaptic functions have been identified using micro-arrays [29] (reviewed in [31]). The work of the Keene and Darnell laboratories has led to the concept that multiple nuclear and cytoplasmic subsets of pre-mRNAs and mRNAs (ribonomes) encoding products involved in the same regulatory pathways are being coordinately regulated by RBPs during neuron differentiation (reviewed in [32]). For example, Nova protein binds to a subset of pre-mRNAs that encode components of inhibitory synapses [30]. Therefore, as proposed by Keene, there might be, in the developing neuron, ribonucleoprotein infrastructures regulating the flow of genetic information between the genome and the proteome, representing posttranscriptional operons, in which RBPs would play pivotal roles [1,33].

RBPs bind RNA through one or more specific RNA-binding domains (RRM, KH, RGG box). For example, ELAV/Hu proteins bind ARE-containing RNA sequences and FMRP bind G-quartet-containing RNA sequences [31,34] but also interacts with U-rich RNAs in a yeast-three hybrid system [35]. While numerous *in vivo* mRNA targets have been identified for Hu and FMRP proteins, none has yet been shown to be a common target of these distinct RBPs. In a general manner, RBPs recognize and bind *in vivo* specific mRNA targets and non-overlapping ribonomes (references therein), reinforcing the idea that RBPs regulate specific mRNA subsets. However, the zipcode of the chicken β-actin mRNA, which is a target of ZBP-1, binds *in vitro* at least six other RBPs, including HuC [36], suggesting that a single mRNA may be post-transcriptionally regulated by multiple RBPs. Moreover, a single RBP may be involved in multiple steps of RNA processing as revealed by the discovery that *Hrp48*, which regulates alternative splicing [37], is also involved in the transport as well as the translational repression of *oskar* mRNA in *Drosophila* oocytes [38,39]. In neurons, SMN (survival of motor neuron), another RBP which functions as part of a multiprotein complex playing an essential role in the assembly of snRNPs in the nucleus (reviewed in [40]), has been shown to modulate axon growth and localization of β-actin mRNA in growth cones of motor neurons [41]. These data raise the possibility that SMN, beside its role in the nucleus, regulates specific mRNAs or ribonomes in the cytoplasm, reinforcing the idea that RNA processing in the nucleus and cytoplasm are intimately coupled. In support of this, Hachet and Ephrussi have demonstrated that splicing of *oskar* RNA in the nucleus is a prerequisite for its proper cytoplasmic localization in *Drosophila* oocytes [42]. Altogether, these data suggest that in differentiating neurons, ribonomes may be coordinately regulated by multiple RBPs in macromolecular RNP complexes at all steps of RNA processing.

NEURONAL RNA-BINDING PROTEINS CO-OPERATE WITHIN LARGE MOTILE MULTIFUNCTIONAL RNP COMPLEXES

In growth cones and synapses, the most distal tips of neurons, signals are translated into local responses. How are functions sent to appropriate sub-cellular locations? Recent studies have demonstrated that axons and growth cones, like dendrites and synaptic spines, contain all the machinery for protein translation and that local protein synthesis plays a functional role (reviews in [43–47]). Therefore, the ability of these distal structures to translate mRNAs may provide their rapid and adjustable responsiveness to external cues. Local expression of proteins in growth cones and synaptic boutons imposes a controlled translocation of mRNAs within axons and dendrites. How are mRNAs transported in these neurites and how are their repression, stability and translation controlled?

mRNAs are found in RNP granules that can translocate along microtubules (reviewed in [48]). Although the granules have been directly visualized in neurons, relatively little is known about their components. Recent studies show

that RBPs are found in these moving granules, where they may play distinct roles. Some granules are highly enriched in Staufen [49], which is required for dendritic RNA targeting [50] and may represent the core component of these granules [51]. HuD has been identified as a component of tau RNA-containing RNP granules [52], possibly acting as an mRNA-stabilizing protein. FMRP, which has also been found in motile RNA-containing granules within neurites of PC12 cells [53], may repress the translation of its RNA targets during their transport. Moving RNP granules contain densely packed clusters of translationally dormant ribosomes and may represent reservoirs of silent mRNA maintained in a repressed state until reaching appropriate subcellular destinations [49]. Recent work, aiming at characterizing the FMRP complex, led to unexpected results. The *Drosophila* FMRP (FMR1) forms a complex that includes Argonaute2 (AGO2) and Dicer, two proteins that mediate RNA interference (RNAi) [54,55]. Mammalian FMRP interacts with microRNAs [55,56], which are small non-coding RNAs involved in translation repression [57]. Together, these findings suggest that FMRP may regulate translational repression of its targets via microRNAs and an RNAi-related apparatus.

Other biochemical studies, aiming at identifying components of neuronal granules, have shown that distinct RBPs are part of the same RNP granules. For instance, Staufen and FMRP, or HuD and ZBP1 can be isolated together in the same RNP complexes [58,59]. Moreover, these RBP-containing RNP complexes also contain motor proteins such as dynein and kinesin and components of the cytoskeleton such as myosin [58–60]. These data indicate that RBP-containing granules are transported within neurons in a microtubule-dependent manner. Novel, live cell-imaging techniques have indeed allowed visualization of such cytoskeletal-based active transport of FMRP and SMN in neuronal processes [53,61].

Together, these data support a model where RBPs are part of large multifunctional motile RNP complexes coordinately regulating the stability, transport and repression of mRNAs until they reach their appropriate location within neurons. Because, the decision for a neural precursor to generate a certain cell type or a growth cone to change its trajectory depends on the correct localization of mRNAs, it will be interesting to determine if the concept of organized post-transcriptional regulation of ribonomes represents a general mode of gene regulation in neural cells, in which RBPs would process RNAs in a coordinated fashion.

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