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Review

ELAV proteins along evolution: Back to the nucleus?

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ABSTRACT

The complex interplay of post-transcriptional regulatory mechanisms mediated by RNA-binding proteins (RBP) at different steps of RNA metabolism is pivotal for the development of the nervous system and the maintenance of adult brain activities. In this review, we will focus on the highly conserved ELAV gene family encoding for neuronal-specific RBPs which are necessary for proper neuronal differentiation and important for synaptic plasticity process. In the evolution from *Drosophila* to man, ELAV proteins seem to have changed their biological functions in relation to their different subcellular localization. While in *Drosophila*, they are localized in the nuclear compartment of neuronal cells and regulate splicing and polyadenylation, in mammals, the neuronal ELAV proteins are mainly present in the cytoplasm where they participate in regulating mRNA target stability, translation and transport into neurites. However, recent data indicate that the mammalian ELAV RBPs also have nuclear activities, similarly to their fly counterpart, being them able to continuously shuttle between the cytoplasm and the nucleus. Here, we will review and comment on all the biological functions associated with neuronal ELAV proteins along evolution and will show that the post-transcriptional regulatory network mediated by these RBPs in the brain is highly complex and only at an initial stage of being fully understood. This article is part of a Special Issue entitled 'RNA and splicing regulation in neurodegeneration'.

Contents

Abbreviations: RBP, RNA-binding protein; elav, embryonic lethal abnormal vision; miRNA, microRNA; rbp9, RNA-binding protein 9; fne, found in neurons; ARE, AU-rich element; UTR, untranslated region; RRM, RNA recognition motif; PABP, polyA-binding protein; eiF4A, eukaryotic initiation factor 4A; CARM1, coactivator-associated arginine methyltransferase 1; PKCα, protein kinase C α; SMN, survival of motoneurons; TDP-43, TAR DNA-binding protein 43; CGRP, calcitonin gene-related peptide; TIA-1, T-cell intracellular antigen-1; TIAR-1, TIA-1-related protein; AUBF, adenosine–uridine binding factor; TTP, tristetrapolin; AUF1, AU-binding factor 1; KSRP, KH-type splicing regulatory protein; GAP-43, growth-associated protein 43; FMRP, fragile X mental retardation protein; ZBP1, zipcode binding protein1; CPEB, cytoplasmic polyadenylation element binding; HDAC2, histone deacetylase 2; CPSF160, cleavage and polyadenylation specificity factor 160 subunit; CstF64, cleavage stimulation factor 64 subunit.

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Introduction

Gene expression can be tightly controlled at the transcription level which represents the first step in the flow of information from genome to proteome (Spitz and Furlong, 2012). However, post-transcriptional regulation of gene expression operates at another important step by controlling the flow of information from transcriptome to proteome and includes a variety of mechanisms differentially regulating splicing, polyadenylation, mRNA transport and stability, and degradation and translation of a given transcript. Because of the multi-faceted aspects of post-transcriptional regulation, the dynamic interplay of all these regulatory processes (also known as "ribonome") determines the fate

of transcripts and has a great impact on the final composition of the active proteome within a cell (Mansfield and Keene, 2009). Post-transcriptional regulatory mechanisms also have the advantage of allowing a dynamic and fast response to changes in environmental conditions, which require a rapid adjustment of the whole proteome profile. This biological aspect is particularly relevant in highly polarized cells such as neurons, where protein content in specific subcellular compartments, such as growth cone, axons and dendrites, must be dynamically controlled and modulated in embryogenesis for proper neuronal differentiation as well as in adult brain for neuronal plasticity programs and cell homeostasis (Martin and Ephrussi, 2009).

The active players in post-transcriptional regulation of gene expression are RNA-binding proteins (RBP) and non-coding RNA molecules, including microRNA (miRNA), that act synergistically or in competition with each other to determine the fate of a target transcript endowed with multiple *cis*-acting motifs (Goldie and Cairns, 2012). These *cis*-acting signatures are specifically recognized by RBPs and miRNAs and the final balance of all the bound *trans*-acting factors allow a fine-tuned spatial and temporal control of fate and translatability of the target mRNAs.

In the brain, several RBPs are known to play pivotal roles in neural development and maintenance and, among these, are the ELAV proteins, highly phylogenetically conserved RBPs which show a neuronal-restricted expression pattern (Okano and Darnell, 1997). This review will focus on this gene family highlighting the functional changes that occurred during evolution from *Drosophila* to humans, and will also present and comment on the recently emerged multi-faceted activities of these proteins in the mammalian brain.

The elav gene family in *Drosophila*

In *Drosophila*, the elav gene family encodes RBPs specifically expressed in the nervous system and includes three paralogous genes, elav (embryonic lethal abnormal visual system), rbp9 (RNA binding protein 9) and fne (found in neurons) (Campos et al., 1985; Kim and Baker, 1993; Samson and Chalvet, 2003). Within the nervous system, these three RBPs are mainly expressed in neuronal cells, although rbp9 is also expressed in other tissues, such as testes and ovaries (Good, 1995; Kim-Ha et al., 1999) (Table 1). They have a conserved structure with three RNA recognition motifs (RRM) that recognize and bind RNA targets, although with different specificities (Samson and Chalvet, 2003), differentially regulating post-transcriptional RNA processing.

The elav gene was the first member of the family to be identified through the characterization of lethal embryonic fly mutants with an abnormal visual system phenotype, indicating that the function provided by the gene is essential during embryogenesis and for proper neuronal differentiation (Campos et al., 1985; Robinow et al., 1988). The ELAV protein localizes in the nucleus of neurons and is expressed at all stages of neural development, as it is also involved in the maintenance of the adult nervous system (Robinow and White, 1991; Yao et al., 1993). Importantly, ELAV has been shown to regulate the neural-specific splicing of three genes, including armadillo, neuroglian and the vital gene erect wing (ewg) (Koushika et al., 1996, 2000). The ectopic expression of ewg, encoding for the human homologue of the transcription factor NRF-1, has been shown to rescue elav lethality and the associated synaptic growth defects (Haussmann et al., 2008). Rbp9, the second identified member of the elav gene family, encodes a nuclear RBP which is expressed in neuronal cells in the mid-pupal stage after morphogenesis of the adult nervous system, although its mRNA is present earlier, at the third larval instar (Kim and Baker, 1993). It is also present in the cytoplasm of cystocytes and oocytes during oogenesis, where it was shown to negatively regulate the stability of bag-of-marbles (Bam) mRNA, a developmental regulator of germ cells (Kim-Ha et al., 1999). Contrarily to the elav gene, no gross neural developmental defects have been observed in Rbp9-null fly mutants, but reduced locomotor activities, shorter lifespan and female sterility, probably due to a failure in cystocyte differentiation (Kim et al., 2010; Kim-Ha et al., 1999). Fne is the last identified member of the elav gene family and its pattern of expression in all neurons of the central and peripheral nervous system during *Drosophila* development recapitulates that of elav, although with a delayed onset of its embryonic expression (Samson and Chalvet, 2003). However, in contrast to ELAV and RBP9 that are mainly nuclear, FNE protein is localized in the cytoplasm of neuronal cells, suggesting different molecular functions (Samson and Chalvet, 2003). FNE was observed to have a role in courtship behavior and in the development of the adult mushroom bodies involved in olfactory learning and memory, specific functions that are non-overlapping with the ones of the other two members of the family (Zanini et al., 2012). Similarly to rbp9, fne-null

Table 1
Expression pattern and post-transcriptional activities of elav gene family members.

Organism	Homologue	Cellular localization	Tissue distribution	Functions
Drosophila	ELAV	Nucleus	Nervous system	Splicing Polyadenylation
	RBP9	Nucleus (neuron) Cytoplasm (oocyte)	Nervous system, ovary, testis	Splicing Negative regulation of mRNA stability (oocyte)
	FNE	Cytoplasm	Nervous system	Polyadenylation Negative regulation of mRNA stability
Mammals	HuB/Hel-N1	Cytoplasm	Nervous system, ovary, testis	Positive regulation of mRNA stability Translation enhancement Splicing Polyadenylation
	HuC	Cytoplasm	Nervous system	Positive regulation of mRNA stability Translation enhancement Splicing Polyadenylation
	HuD	Cytoplasm	Nervous system	Positive regulation of mRNA stability Translation enhancement Splicing Polyadenylation
	HuA/HuR	Nucleus	Ubiquitous	Positive/negative regulation of mRNA stability Translation enhancement/repression mRNA transport into dendrites Splicing Polyadenylation