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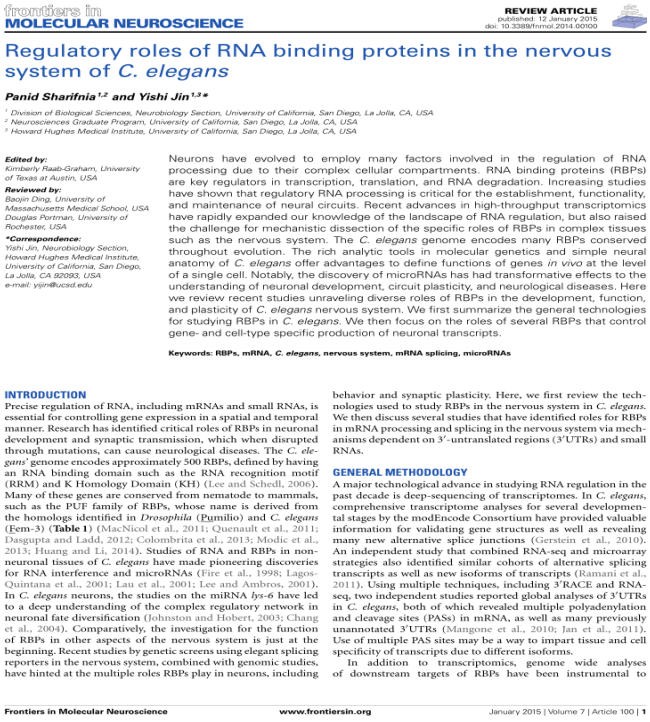

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Regulatory roles of RNA binding proteins in the nervous system of *C. elegans*

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Neurons have evolved to employ many factors involved in the regulation of RNA processing due to their complex cellular compartments. RNA binding proteins (RBPs) are key regulators in transcription, translation, and RNA degradation. Increasing studies have shown that regulatory RNA processing is critical for the establishment, functionality, and maintenance of neural circuits. Recent advances in high-throughput transcriptomics have rapidly expanded our knowledge of the landscape of RNA regulation, but also raised the challenge for mechanistic dissection of the specific roles of RBPs in complex tissues such as the nervous system. The *C. elegans* genome encodes many RBPs conserved throughout evolution. The rich analytic tools in molecular genetics and simple neural anatomy of *C. elegans* offer advantages to define functions of genes *in vivo* at the level of a single cell. Notably, the discovery of microRNAs has had transformative effects to the understanding of neuronal development, circuit plasticity, and neurological diseases. Here we review recent studies unraveling diverse roles of RBPs in the development, function, and plasticity of *C. elegans* nervous system. We first summarize the general technologies for studying RBPs in *C. elegans*. We then focus on the roles of several RBPs that control gene- and cell-type specific production of neuronal transcripts.

Keywords: RBPs, mRNA, *C. elegans*, nervous system, mRNA splicing, microRNAs

INTRODUCTION

Precise regulation of RNA, including mRNAs and small RNAs, is essential for controlling gene expression in a spatial and temporal manner. Research has identified critical roles of RBPs in neuronal development and synaptic transmission, which when disrupted through mutations, can cause neurological diseases. The *C. elegans*' genome encodes approximately 500 RBPs, defined by having an RNA binding domain such as the RNA recognition motif (RRM) and K Homology Domain (KH) (Lee and Schedl, 2006). Many of these genes are conserved from nematode to mammals, such as the PUF family of RBPs, whose name is derived from the homologs identified in *Drosophila* (Pumilio) and *C. elegans* (Fem-3) (**Table 1**) (MacNicol et al., 2011; Quenault et al., 2011; Dasgupta and Ladd, 2012; Colombrita et al., 2013; Modic et al., 2013; Huang and Li, 2014). Studies of RNA and RBPs in non-neuronal tissues of *C. elegans* have made pioneering discoveries for RNA interference and microRNAs (Fire et al., 1998; Lagos-Quintana et al., 2001; Lau et al., 2001; Lee and Ambros, 2001). In *C. elegans* neurons, the studies on the miRNA *lys-6* have led to a deep understanding of the complex regulatory network in neuronal fate diversification (Johnston and Hobert, 2003; Chang et al., 2004). Comparatively, the investigation for the function of RBPs in other aspects of the nervous system is just at the beginning. Recent studies by genetic screens using elegant splicing reporters in the nervous system, combined with genomic studies, have hinted at the multiple roles RBPs play in neurons, including behavior and synaptic plasticity. Here, we first review the technologies used to study RBPs in the nervous system in *C. elegans*. We then discuss several studies that have identified roles for RBPs in mRNA processing and splicing in the nervous system via mechanisms dependent on 3′-untranslated regions (3′UTRs) and small RNAs.

GENERAL METHODOLOGY

A major technological advance in studying RNA regulation in the past decade is deep-sequencing of transcriptomes. In *C. elegans*, comprehensive transcriptome analyses for several developmental stages by the modEncode Consortium have provided valuable information for validating gene structures as well as revealing many new alternative splice junctions (Gerstein et al., 2010). An independent study that combined RNA-seq and microarray strategies also identified similar cohorts of alternative splicing transcripts as well as new isoforms of transcripts (Ramani et al., 2011). Using multiple techniques, including 3′RACE and RNA-seq, two independent studies reported global analyses of 3′UTRs in *C. elegans*, both of which revealed multiple polyadenylation and cleavage sites (PASs) in mRNA, as well as many previously unannotated 3′UTRs (Mangone et al., 2010; Jan et al., 2011). Use of multiple PAS sites may be a way to impart tissue and cell specificity of transcripts due to different isoforms.

In addition to transcriptomics, genome wide analyses of downstream targets of RBPs have been instrumental to

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