Tutorial Paper

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RNA-Binding Proteins in Metazoans

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Abstract

RNA-binding proteins (RBPs) are the proteins which associate with RNAs in cells and play an important role in post-transcriptional process to create the spatiotemporal diversity of proteome in muticellular organisms. They recognize specific sequence in the RNA stretch and are tissue-specific transcription of alternative splicing. In all metazoans, RBPs regulate and control gene expressions by promoting or repressing mRNA targets in many tissues; examples include brain, heart, gonads bone and muscle. Therefore, the aim of present paper is the subject to document and summarize the recent information and basic mechanisms of RBPs in metazoans.

Keywords: RNA-binding proteins, alternative splicing, metazoans

1. Introduction

Alternative pre-messenger RNA splicing of post transcriptional process plays a crucial role in the gene expression of animals [1, 2]. It has been considered to be a main precursor of proteomic diversity in metazoans and limited the number of genes [3] (Fig. 1). Recently, it is known that an alternative splicing which creates different genes is controlled by RNA-binding protein (RBP) regulators [4]. RBPs are the proteins that specifically bind to either single- or double-strand RNA stretches to form ribonucleoprotein complexes *via* RNA recognition motif [5]. They regulate exons or flanking introns, leading to promote or suppress the exon targets [4].

In metazoans, many studies have been reported the finding of RBPs and their mechanisms such as Fox-1, Sam68, a2bp1 and CG32062 [4, 6] (Table 1). RBPs may coordinate with other RBPs for regulating gene expression and are tissue-specific alternative splicing in animals [7]. Furthermore, RBP regulations on gene expression depend on the developmental periods of embryonic and adult stage [6]. Therefore, the present review is the aim to document current literature of RBP information in metazoans, and basic mechanisms will be summarized in this review.

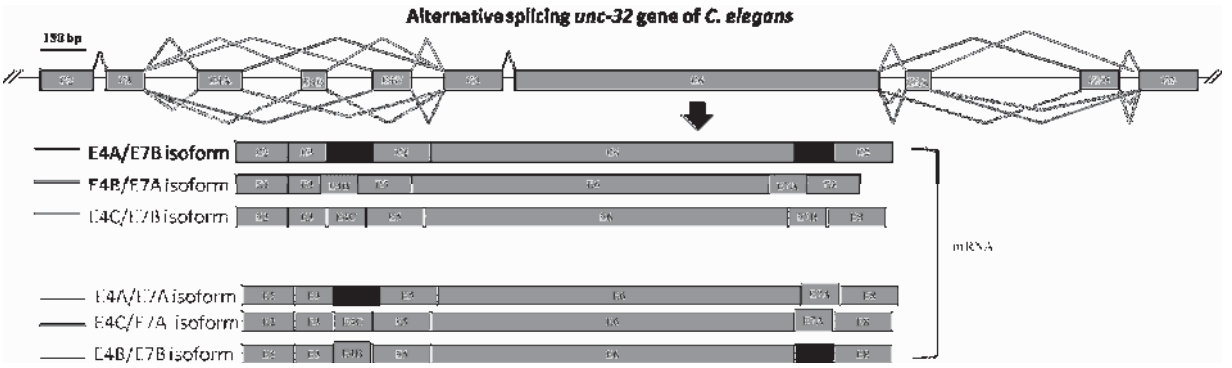

Fig. 1. A schematic diagram of alternative splicing *unc-32* gene producing 6 mRNA isoforms in nematode [8].

Table 1. Examples of RNA-binding proteins from human, mouse, zebrafish, common fruit fly and round worm. (Adapted from Kuroyanagi [4]).

Protein	Species	Gene symbol
Fox-1	Human (*H. sapiens*)	*A2BP1*
Fox-1	Mouse (*M. musculus*)	*A2bp1*
Sam68	Mouse	*Sam68* [9]
a2bp1	Zebrafish (*D. rerio*)	*a2bp1*
CG32062	Common fruit fly *D. melanogaster*	*CG32062*
FOX-1	Round worm (*C. elegans*)	*fox-1*
ASD-1	Round worm	*asd-1*

2. Promoting and repressing mechanism on gene expression by RBP

RBPs regulate gene expressions *via* the specific target of RNA stretch. Kuroyanagi [4] reported that Fox-1 family of RBP recognized the UGCAUG sequence of intron to alternatively splice exons. In promoting, RBP enhances inclusion of exons by acting through specific sequence on RNA intron of the downstream (Fig. 2a). Conversely, in repressing, RBP inhibit exon inclusion *via* specific sequence in the upstream of flanking intron (Fig. 2b) [10].

3. RBPs coordinately regulate with other RBPs

In post-transcriptional process, RBP may coordinate with another protein *via* intronic target as a stable complex for regulating alternative splicing expression of gene. This complex may interplay either positive or negative regulation for enhancing or limiting number of genes [11]. For instance, Fox-1 and SUP-12 coregulated tissue-specific alternative splicing of *egl-15* gene by mediating specific sequence of intronic flanking. Fox-1 and SUP-12 recognized UGCAUG and GUGUG stretches, respectively. Those protein complexes repressed exon5B in exon inclusion of *egl-15* pre-mRNA (Fig. 3) [7].

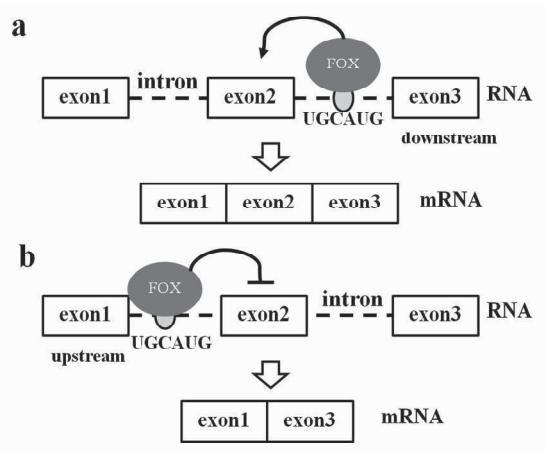

Fig. 2. Schematic diagram of alternative splicing by Fox of RBP regulator. **a.** Fox promotes the inclusion of exon1, 2 and 3 by binding to UGCAUG specific sequence of intron in downstream. **b.** Fox represses exon2 in upstream (Adapted from [4]).

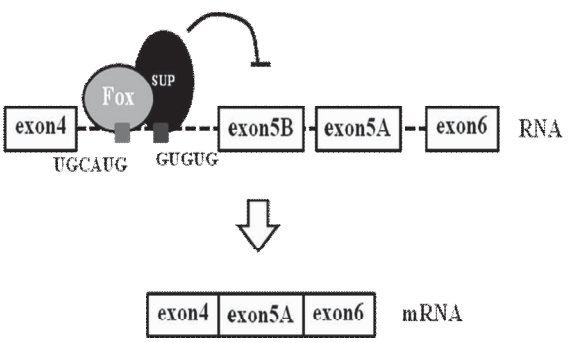

Fig. 3. Schematic illustration of alternative splicing pattern by coordinating Fox-1 and SUP-12. Both Fox and SUP repress exon inclusion of *egl-15* gene to creating 4/5A/6 isomer of mRNA. Those protein specifically recognize UGCAUG and GUGUG stretches in flanking intron, respectively [7].

4. RBP regulations on gene expression depending on the developmental periods

RBPs may regulate alternative splicing by switching of mutually exclusive developmental period from larval stage to adult stage. Ohno *et al*. [6] demonstrate that RNA-binding protein ASD-2 regulated the *let-2* gene of *C. elegans* on the developmental stage by switching alternative splicing exon inclusion from embryonic stage to adult stage. ASD-2 regulated *let-2* gene *via* specific target of intron which altered the exon 9 form in larval stage to the exon 10 form in adult stage (Fig. 4).

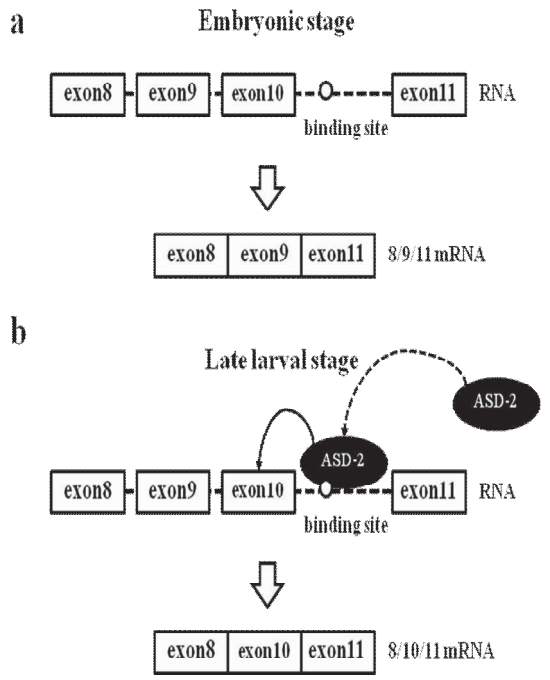

Fig. 4. Schematic illustration of alternative splicing *let-2* gene regulated by ASD-2. **a.** In embryonic stage, *let-2* gene alternately splice exon9 to 8/9/11 mRNA form without ASD-2 regulation. **b.** In late larval stage, ASD-2 promote exon10 to 8/10/11 mRNA form [4, 6].

5. Conclusion

It is summarized that RNA-binding proteins play a key role in an important step of postransciptional alternative splicing mRNA for creating the huge proteomic diversity in metazoan. The regulation patterns are different in tissues and stages of development. RNA-binding proteins precisely act on RNA stretches by binding specific sequences to for controlling gene expression. Therefore, we believe that the present review help to understand the basic mechanism of RNA-binding protein regulation in alternative splicing and apply to utilize those model for molecular biology. Furthermore, the knowledge of RNA-binding protein may develop a medical tool for detection or diagnosis of molecular disease.

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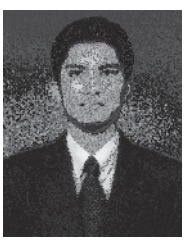

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