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Review

Roles for RNA-binding proteins in development and disease

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ABSTRACT

RNA-binding protein activities are highly regulated through protein levels, intracellular localization, and post-translation modifications. During development, mRNA processing of specific gene sets is regulated through manipulation of functional RNA-binding protein activities. The impact of altered RNA-binding protein activities also affects human diseases in which there are either a gain-of-function or loss-of-function causes pathogenesis. We will discuss RNA-binding proteins and their normal developmental RNA metabolism and contrast how their function is disrupted in disease.

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1. Introduction

RNA-binding proteins (RBP) regulate RNA processing at multiple levels including alternative splicing, mRNA stability, mRNA localization and translation efficiency. As proteins highly involved in regulation, the expression of RBPs tends to be highly regulated. One mechanism of regulating the activities of RBPs in nuclear and cytoplasmic compartments is through changes in cellular localization. In the nucleus, some RBPs function as alternative splicing regulators often during development and/or in a tissue specific manner (Blencowe, 2006; Grabowski, 2011; Johnson, 2003; Wang et al., 2008). There are a growing number of examples in which alternative splicing changes have functional consequences (Giudice et al., 2014; Grabowski, 2011). In the cytoplasm, RBPs can function in the regulation of mRNA localization, mRNA stability or regulate the efficiency with which specific mRNAs are translated. As with the regulation of alternative splicing, regulation of cytoplasmic RNA processing events commonly occur during development (Jambor et al., 2015; Pilaz and Silver, 2015). The functions of RBPs can be disrupted in disease as either a primary cause of disease or a consequence. Understanding the normal roles of RBPs during periods of physiological change, such as during development, can reveal important aspects of function that are directly relevant to the pathogenic mechanisms and consequences in disease.

In this minireview, we discuss two sets of RBPs that control developmental transitions that are mis-regulated in disease: CUG-BP, Elav-like family (CELF) and Muscleblind-like (MBNL) proteins that have pathogenic roles in myotonic dystrophy (DM) and *f*used in sarcoma (FUS) and TAR DNA-binding protein (TDP-43) proteins that have pathogenic roles in amyotrophic lateral sclerosis (ALS). These RBPs are sequestered, hyperactive, or aggregated in the disease states. In the case of DM, the activities of both CELF and MBNL proteins revert to fetal patterns thereby promoting fetal mRNA processing of their targets in adult tissue. In neurons affected in ALS, FUS and TDP-43 are depleted from the nucleus and aggregate in the cytoplasm. Mutations in the *FUS* or *TARDBP* genes have a direct role in ALS pathogenesis; evidence also indicates that aggregation of FUS and TDP-43 causes both a loss-of-function and a gain-of-function. Currently, it is unknown if TDP-43 and FUS mRNA processing targets revert back to embryonic patterns; although it is clear there is mis-regulation of mRNA processing in ALS directly due to TDP-43 and FUS aggregation.

2. CELF and MBNL in DM

The CELF family contains six paralogs in humans and mice (CELF1-6), which can be subdivided into two groups containing CELF1-2 and CELF3-6 based on phylogenic analysis (Dasgupta and Ladd, 2012). Structurally, CELF proteins contain three RNA recognition motifs (RRMs) in which RRMs 1 and 2 are adjacent near the N-terminus, RRM3 is near the C-terminus and a unique domain of ~200 residues separates RRM2 and RRM3 (Ladd et al., 2004). CELF proteins bind preferentially to G/U-rich RNA sequence motifs (Faustino and Cooper, 2005; Marquis et al., 2006) and have well-established nuclear and cytoplasmic functions. In the nucleus, CELF proteins regulate alternative splicing to promote exon exclusion of some targets or inclusion of others (Kalsotra et al., 2008). Minigene and CLIP-seq studies have demonstrated that CELF proteins directly bind to pre-mRNAs, typically within introns, to promote the regulated splicing pattern (Daughters et al., 2009; Ladd et al., 2001; Wang et al., 2015). In the cytoplasm, CELF proteins affect mRNA translation or mRNA stability by binding the 3′ UTR of the regulated mRNA (Blanc and Davidson, 2003; Subramaniam et al., 2008; Vlasova and Bohjanen, 2008; Zhang et al., 2008).

The MBNL family consists of three paralogs: MBNL1-3 (Kanadia et al., 2003a). MBNL proteins bind RNA through two pairs of zinc finger domains, which consist of CCCH amino acid residues (Begemann et al., 1997). MBNL proteins bind to YGCY motifs, preferring UGCU (Du et al., 2010; Goers et al., 2010). As regulators of alternative splicing both CELF and MBNL proteins typically bind to the introns downstream or upstream of an alternative exon to promote inclusion or exclusion, respectively (Kalsotra et al., 2008; Wang et al., 2012). In the cytoplasm, MBNL affects mRNA localization or stability by binding the 3′ UTR of target mRNAs (Llamusi et al., 2013; Masuda et al., 2012).

CELF and MBNL have overlapping targets for alternative splicing and mRNA stability, and are most often antagonistic regulators of these common targets (Masuda et al., 2012; Wang et al., 2015). As splicing regulators, CELF and MBNL proteins promote the opposite effects on splice site or exon usage. Global analysis of CLIP-seq data shows that CELF and MBNL proteins overlap with thousands of 3′ UTR targets and affect mRNA stability (Wang et al., 2015). CELF-bound mRNA targets are degraded while MBNL1 binding leads to mRNA localization to the membrane for translation (Wang et al., 2015).

2.1 *Development*

During development, changes in the abundance and localization of CELF and MBNL proteins have been shown to promote global splicing transitions (Kalsotra et al., 2008). CELF and cytoplasmic MBNL protein levels are high in embryonic mouse skeletal muscle and CELF protein levels decrease while MBNL localizes to the nucleus during postnatal development (Kalsotra et al., 2008; Lin et al., 2006). CELF protein levels also drop during mouse heart postnatal development while MBNL protein levels increase (Kalsotra et al., 2008). Therefore in both striated muscles, the nuclear activities of CELF and MBNL proteins change in opposite directions. Studies of the developmental effects of CELF and MBNL proteins have focused on alternative splicing transitions in striated muscle. There are also likely to be important cytoplasmic effects during development that remain to be identified. The genes that undergo the developmental splicing transition are enriched for vesicular trafficking, among other functional categories, and induced CELF1 expression in transgenic mice reverts a subset of vesicular trafficking genes to the fetal splicing pattern (Giudice et al., 2014). MBNL proteins have been shown to maintain the differentiated state in cells