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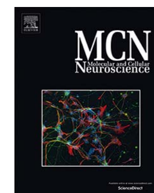

Neuron-specific alternative splicing of transcriptional machineries: Implications for neurodevelopmental disorders

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ABSTRACT

The brain has long been known to display the most complex pattern of alternative splicing, thereby producing diverse protein isoforms compared to other tissues. Recent evidence indicates that many alternative exons are neuron-specific, evolutionarily conserved, and found in regulators of transcription including DNA-binding protein and histone modifying enzymes. This raises a possibility that neurons adopt unique mechanisms of transcription. Given that transcriptional machineries are frequently mutated in neurodevelopmental disorders with cognitive dysfunction, it is important to understand how neuron-specific alternative splicing contributes to proper transcriptional regulation in the brain. In this review, we summarize current knowledge regarding how neuron-specific splicing events alter the function of transcriptional regulators and shape unique gene expression patterns in the brain and the implications of neuronal splicing to the pathophysiology of neurodevelopmental disorders.

1. Introduction

One of the long-standing questions in genetics is how cells achieve cell-type-specific gene expression. The major roles of DNA-binding transcription factors (TFs) in this process have been well established. Master TFs are often expressed in limited cell types and bind to their cognate DNA sequence at promoters and enhancers, thereby activating or repressing gene expression in a cell-type-specific manner (Deplancke et al., 2016). In multicellular organisms, DNA is organized into nucleosomes with the four core histones (Luger et al., 1997), which are generally refractory to actions of RNA polymerase II (Li and Reinberg, 2011). To relax the inherently closed chromatin structure, TFs recruit a variety of machineries, including histone-modification enzymes and chromatin-remodeling complexes.

Unlike master TFs, chromatin modifiers and remodelers tend to be ubiquitously expressed. More recent work has begun to reveal exceptions to this rule. Germ-cell-specific assembly of the preinitiation complexes (Goodrich and Tjian, 2010), neuron-specific micro-RNA circuitries (Yoo et al., 2011), and neuron-specific ATP-dependent chromatin-remodeling complexes (Staahl and Crabtree, 2013) provided earlier insights into how non-TF agents can contribute to cell-type-specific gene expression. While these mechanisms all rely on the cell-type-restricted presence of transcriptional regulators, recent evidence indicates that alternative splicing of ubiquitously-expressed factors can contribute to cell-type specific transcription, in particular, within neurons.

In this article, we discuss current views on how alternative splicing contributes to complexity of the brain, its link to neurodevelopmental disorders, and how neuron-specific splicing events can influence the roles of transcriptional machineries. A growing amount of literature has begun to support the idea that compromised function of the neuronal isoforms of transcriptional regulators may underlie multiple neurodevelopmental disorders.

2. Alternative splicing in the brain

Alternative splicing generates multiple proteins from a single pre-mRNA by including and/or excluding alternative exons, thereby diversifying cellular proteomes. In complex organisms, such as humans, alternative splicing events are estimated to occur in 92–94% of genes (Wang et al., 2008). Throughout vertebrate evolution, alternative splicing programs are notably most complex in the nervous system (Yeo et al., 2004; Chen and Manley, 2009; Barbosa-Morais et al., 2012; Merkin et al., 2012), suggesting that alternative splicing contributes to the complexity of brain anatomy, development, and function. Not only does the brain have a higher number of alternative splicing events relative to other tissues (Xu et al., 2002; Yeo et al., 2004; Pan et al., 2008), but conservation of the brain-specific alternative splicing

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program is especially prominent through vertebrate evolution suggesting functionality of spliced products (Barbosa-Morais et al., 2012; Merkin et al., 2012). Recent work has highlighted the neocortex, the center for higher-order cognitive processes, as a hotspot of alternative splicing events that influence cortical development, layering, and cell fate (McKee et al., 2005; Belgard et al., 2011; Zhang et al., 2014; Zhang et al., 2016). As will be discussed in detail below, dysregulation of this alternative splicing program leads to neurological disease (Licatalosi and Darnell, 2006).

3. Mechanisms and biological roles of neuron-specific alternative splicing factors

Alternative splicing is coordinated by *cis*-acting RNA elements and *trans*-acting RNA binding proteins that regulate intron excision. The spliceosome is the major molecular machinery, which controls intron excision and determines which pre-mRNA sequences are to be included or excluded from the mature mRNA. The core spliceosome is a large RNA-protein complex and involves the five subunits defined by the five RNA components, U1, U2, U4, U5, and U6, and the associated small ribonucleoproteins (RNPs). A large number of auxiliary proteins help the spliceosome recognize splice sites (Li et al., 2007; Chen and Manley, 2009; Wahl et al., 2009). While most spliceosome components are constitutively expressed, tissue-specific RNA-binding proteins direct spliceosome machinery to specific splice sites to generate tissue-specific splicing patterns. Neuron-specific alternative splicing is one such example controlled by the coordinate actions of many brain-specific RNA-binding proteins. Several recent review articles have comprehensively discussed the mechanisms of actions and roles in brain development of these splicing regulators (Raj and Blencowe, 2015; Lara-Pezzi et al., 2016; Vuong et al., 2016). Below, we provide a brief summary of the biological roles of key factors that are crucial in generating unique splicing patterns within neurons and also highlight the recent discovery of microexons. We highlight five key splicing factors, nSR100, NOVA, RBFOX family members, PTB, and Hu/ELAV family members, which have been well characterized. It should be noted that other factors including SAM68 family members, TDP-43, and MBNL, also contribute to neuron-specific alternative splicing as reviewed by others (Yap and Makeyev, 2013; Raj and Blencowe, 2015; Iijima et al., 2016).

3.1. Brain-specific spliceosome recruiting factor, nSR100

Neural-specific SR-related protein of 100 kDa, nSR100, was identified as a vertebrate and tissue-specific Serine/Arginine-repeat region containing splicing factor that activates inclusion of a large number of brain-specific exons (Calarco et al., 2009; Raj et al., 2014). nSR100 recognizes pyrimidine-rich motifs flanking the 3′ splice site and binds specifically with U2-RNP components to assist in early-acting spliceosome assembly (Raj et al., 2014).

Expression of nSR100 increases upon neuronal maturation (Irimia et al., 2014). In mammalian cell culture and zebrafish models, nSR100 is required for neurogenesis and neuronal differentiation (Calarco et al., 2009, Raj et al., 2014). An nSR100 haploinsufficient mouse model has impaired neurite outgrowth, altered neuronal excitability and synaptic transmission, and behavioral abnormalities that resemble autism spectrum disorder (Quesnel-Vallieres et al., 2015; Quesnel-Vallières et al., 2016).

3.2. Position-dependent splicing regulators

3.2.1. NOVA

Neuro-oncologic ventral antigen (NOVA) was the first described splicing factor that is responsible for neuron-specific exon content (Buckanovich et al., 1996; Yang et al., 1998; Jensen et al., 2000). NOVA was initially identified as an antigen produced in tumor tissues that lead to an autoimmune neurological disorder, paraneoplastic opsoclonus myoclonus ataxia (POMA) (Luque et al., 1991; Buckanovich et al., 1993). An initial survey of NOVA-target RNAs identified 34 transcripts regulated by NOVA in mice, but recent high-throughput methods suggest the regulatory network of NOVA may include as many as 700 gene transcripts (Ule et al., 2003; Zhang et al., 2010).

Compared to nSR100, NOVA plays more diverse roles in mRNA regulation. NOVA appears to control both alternative splicing (Ule et al., 2005) and selection of polyadenylation sites to generate brain-specific 3′-UTR of mRNAs through binding of YCAY clusters, which influences both U2 and U1 recruitment (Licatalosi et al., 2008). Interestingly, binding of NOVA near 5′ splice sites promotes exon inclusion through U2 recruitment; however, binding of NOVA near 3′ splice sites promotes exon skipping through inhibition of U1 binding (Ule et al., 2006; Licatalosi et al., 2008). The distinct actions at 5′ and 3′ splice sites are referred to as position-dependent control of splicing.

NOVA is expressed specifically in neurons (Buckanovich et al., 1996; Yang et al., 1998; Jensen et al., 2000), and NOVA targets transcripts encoding synaptic proteins that are important for synaptic plasticity (Ule et al., 2003; Ule et al., 2005). In human and mouse, the *NOVA1* and *NOVA2* genes encode highly homologous proteins, and mouse reverse genetics has provided insights into their interplay. *Nova1*-null mice exhibit progressive motor dysfunction, brain stem and spinal cord neuronal apoptosis, and death 1–2 weeks after birth (Jensen et al., 2000). *Nova2*-null mice display a specific deficit in long-term potentiation of slow inhibitory postsynaptic current in hippocampal CA1 neurons (Huang et al., 2005). *Nova1/Nova2*-double null mice are born, but are completely paralyzed and die shortly after birth (Ruggiu et al., 2009). These mouse models and human genetics studies establish pivotal roles of NOVA in plasticity and development of both central and peripheral nervous systems.

3.2.2. RBFOX

The RNA-binding protein FOX paralogs (RBFOX1, 2, and 3) are another major set of splicing factors that increase in expression during neuronal development and promote neuronal exon inclusion. RBFOX specifically recognizes UGCAUG motifs, which are found at both 5′- and 3′-regions of introns. Similar to NOVA, RBFOX exerts position-dependent splicing control (Auweter et al., 2006; Zhang et al., 2008). RBFOX binding in 3′ splice site regions inhibits exon inclusion, whereas binding in 5′ splice site regions enhances exon inclusion. Such context-specific function suggests the combinatorial involvement of other splicing regulators to select for the inclusion of neuron-specific exons (Zhang et al., 2008).

Several lines of evidence have indicated important roles of RBFOX family proteins in neuronal development and function. Expression of RBFOX1 was downregulated in post-mortem brains from autistic individuals, and RBFOX1 downregulation was associated with splicing dysregulation of genes relevant to synaptogenesis (Voineagu et al., 2011). Another study found specific regulation of a calcium channel alternative exon that alters the electrophysiological properties of this channel activation in neurons (Tang et al., 2009). Genome-wide mapping of protein-RNA interaction sites revealed that RBFOX1, 2, and 3 directly control splicing of genes that are up-regulated during brain development and whose dysregulation has been linked to autism (Weyn-Vanhentenryck et al., 2014).

3.3. Negative regulator of exon inclusion, PTB

While NOVA, nSR100, and RBFOX primarily promote inclusion of alternative exons (Ule et al., 2006; Zhang et al., 2008; Calarco et al., 2009), Polypyrimidine Tract-Binding protein 1 (PTB or PTBP1) is a well-known negative regulator of exon inclusion. PTB binds CU-rich regions causing a looping-out of the RNA, which prevents assembly of the spliceosome (Oberstrass et al., 2005). Furthermore, PTB suppresses expression of its neuron-specific paralog neural-PTB (nPTB, PTBP2) by excluding an exon within nPTB, whereby the absence of this exon leads

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