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The exon junction complex in neural development and neurodevelopmental disease

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Abstract

Post-transcriptional mRNA metabolism has emerged as a critical regulatory nexus in proper development and function of the nervous system. In particular, recent studies highlight roles for the exon junction complex (EJC) in neurodevelopment. The EJC is an RNA binding complex composed of 3 core proteins, EIF4A3 (DDX48), RBM8A (Y14), and MAGOH, and is a major hub of post-transcriptional regulation. Following deposition onto mRNA, the EJC serves as a platform for the binding of peripheral factors which together regulate splicing, nonsense mediated decay, translation, and RNA localization. While fundamental molecular roles of the EJC have been well established, the *in vivo* relevance, particularly in mammals, has only recently been examined. New genetic models and cellular assays have revealed core and peripheral EJC components play critical roles in brain development, stem cell function, neuronal outgrowth, and neuronal activity. Moreover, human genetics studies increasingly implicate EJC components in the etiology of neurodevelopmental disorders. Collectively, these findings indicate that proper dosage of EJC components is necessary for diverse aspects of neuronal development and function. Going forward, genetic models of EJC components will provide valuable tools for further elucidating functions in the nervous system relevant for neurodevelopmental disease.

Keywords

Exon junction complex; neocortex; neurogenesis; dosage; microcephaly; axon guidance

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Introduction

The exon junction complex (EJC) is an RNA binding complex which regulates diverse aspects of mRNA metabolism (Figure 1) (1–5). The EJC consists of three core components, EIF4A3 (DDX48), RBM8A (Y14/Tsunagi), and MAGOH (Mago Nashi) (Table 1). EIF4A3 binds RNA via its DEAD-box domain, and this interaction is stabilized by a MAGOH-RBM8A heterodimer and by a peripheral component, CASC3 (MLN51/Barentsz) (6,7). Core EJC proteins are deposited onto mRNA concomitant with splicing, and bind canonical sites 20–24 nucleotides upstream of exon-exon junctions, or to non-canonical sites across the mRNA (1,8). Recent cross-linking RNA immunoprecipitation experiments coupled with deep sequencing reveal EJCs bind to many but not all spliced mRNAs, suggesting EJC deposition is a regulated event (9–11). Though interactions with peripheral components, the EJC is able to influence mRNA metabolism throughout the transcript's lifecycle, beginning with nuclear splicing, and persisting until mRNA translation, nonsense mediated decay (NMD), or subcellular localization. Below we discuss functions of the EJC, with a focus on the role of components in the developing mammalian nervous system.

The EJC influences events in the nucleus, including splicing, as observed in recent transcriptome-wide studies in model organisms and mammalian cells. *Drosophila* orthologs of *Eif4a3*, *Rbm8a*, and *Magoh* are required for splicing of specific targets (*Mapk*), whereas *Casc3* is not (12,13). Splicing regulation is thought to occur via mechanisms in which EJCs define and influence the splicing of neighboring introns (14). Genomic studies in mammalian cells further support a global function for core EJC components in mRNA splicing (15). Wang et al. observed splicing defects with knockdown of *EIF4A3*, *RBM8A* and *CASC3* in HeLa cells. The observation that *CASC3* influences splicing in human cells but not *Drosophila*, could be due to species or cell specific differences. Wang et al. noted a change in the rate of transcript elongation by RNA polymerase II in EJC-depleted cells, and speculated that the EJC has an indirect role in splicing, in which loss of EJC components results in insufficient time for splicing to occur. Another important nuclear role of the EJC is to promote mRNA export. This is accomplished via EJC interactions with the TREX complex and other nuclear export factors, and has been shown to be especially relevant for short transcripts (16).

Once in the cytoplasm, the core EJC interacts with different peripheral factors to influence mRNA translation, NMD, and subcellular mRNA localization. It has been well documented that spliced mRNAs are translated at higher levels (17,18). This has been attributed in part to the EJC, which is bound to most spliced mRNAs (4,11). The EJC and pre-initiation ribosomal complexes are bridged via interactions with PYM (Partner of Y14 and Magoh) (19). The EJC can also enhance translation through interactions of EIF4A3 with SKAR (S6K1 ALY/REF-like Substrate) (20), which facilitates signaling of the translational regulator, mTOR. In the cytoplasm, the EJC also is promotes NMD, the process by which mRNA transcripts containing a premature termination codon (PTC) are recognized and degraded (16,21–23). In the presence of a PTC, ribosomes stall upstream of a bound EJC, which then recruits and activates NMD components (UPFs). CASC3 is involved in both translation and NMD (1,24). UPF3 (RENT3A/3B) and UPF2 (RENT2) utilize the EJC as a binding platform, and recruit UPF1 (RENT1) along with the decay-inducing (DECID)

complex to initiate transcript degradation (25). A third cytoplasmic role of the EJC is to control sub-cellular mRNA localization. This has been best exemplified in *Drosophila*, in which numerous studies have shown that EJC components are required for localization of *oskar* mRNA to the posterior pole of the oocyte (5,26–28).

Altogether, these studies illustrate molecular and biochemical functions of the EJC, primarily in model organisms, immortalized cells, and *in vitro*. However, the contribution of core and peripheral EJC components to the developing mammalian nervous system has only recently been investigated. Given that several core and auxiliary EJC components are implicated in neurodevelopmental disease, such studies are of clinical significance. Below, we discuss the expanding literature connecting the EJC to the development and function of the mammalian nervous system.

Roles of the EJC in embryonic neurogenesis

Several recent studies demonstrate that EJC components are required for proper brain development, and specifically for neurogenesis, whereby neurons are produced from neural stem cells (NSCs). At the onset of neurogenesis neuroepithelial cells are the predominant NSC, which primarily self-renew to amplify the progenitor pool (29). As neurogenesis proceeds, neuroepithelial cells are replaced by radial glia, which can self-renew or produce neurons either directly or indirectly via production of intermediate progenitors (IPs). Ultimately, the earliest born neurons reside in the deep cortical layers, while the later born neurons reside in more superficial layers, due to the inside-out pattern of neuronal migration (30). Disruption of neurogenesis can affect adult brain size and structure, causing disorders such as microcephaly (reduced brain size) or macrocephaly (increased brain size).

The first evidence implicating the EJC in cortical development came from studies of a germline mouse mutant in the core component Magoh. *Magoh* haploinsufficiency results in smaller body size, with a disproportionate microcephaly (31). This is associated with decreased thickness of all cortical layers. *Magoh* depleted cortices show fewer IPs, premature generation of neurons, and extensive apoptosis. A later study reported the generation of a conditional *Magoh* allele and found NSC-specific depletion of *Magoh* recapitulates the microcephaly phenotype (32). *Magoh* is highly enriched in dividing neural progenitors and also influences mitosis of various cell types including immortalized HeLa cells and neural crest-derived melanocytes (31,33). These findings indicated that NSC dysfunction, and specifically altered mitosis, may directly influence altered production of neurons and stem cells. Indeed, in a follow up study our group found that *Magoh* haploinsufficiency caused delayed mitotic progression of NSCs, which was directly associated with increased neuron production, reduced progenitor production, and increased apoptosis of progeny (34). Notably, pharmacological prolonging of mitosis recapitulated these *Magoh* mutant phenotypes. Taken together these genetic models establish a critical requirement of *Magoh* for cortical development, influenced by delayed mitotic progression of NSCs.

The protein partner of MAGOH is RBM8A, which is also highly enriched in neural progenitors (35). To formally test its requirement for cortical development, our group

generated a conditional floxed *Rbm8a* allele (35). *Rbm8a* conditional haploinsufficiency, induced with a NSC-specific *Emx1*-Cre, resulted in severe microcephaly. *Rbm8a* haploinsufficient brains contain fewer progenitors (NSCs and IPs), premature neurons, and increased apoptosis, similar to *Magoh* mutants. *Rbm8a* haploinsufficient NSCs also show cell cycle defects including increased cell cycle exit and increased mitotic index, also consistent with *Magoh* haploinsufficiency. Upon completion of neurogenesis, *Emx1*-Cre; $Rbm8a^{lox/+}$ mice displayed disorganized cortical layers, with preferential loss of upper layer neurons. Some of these results were independently corroborated by another group, who used shRNA knockdown of *Rbm8a* in neural progenitor culture (36). Consistent with our study, the authors find *Rbm8a* knockdown increases cell cycle exit and neuron production. Although both studies are concordant regarding outcomes of *Rbm8a* loss of function, there is some discrepancy in overexpression phenotypes. While our group did not observe overexpression phenotypes in the developing cortex, Zou et al. report reduced cell cycle exit and less neuron production upon overexpression. These differences could be due to the timing of the experiment, nature of overexpression, or brain region in which overexpression was examined. Taken together these data support a critical role of *Rbm8a* in embryonic neurogenesis and indicate that *Rbm8a* haploinsufficiency causes microcephaly.

Beyond core EJC components, peripheral NMD components are also implicated in stem cell maintenance and neuronal differentiation. Jolly et al. show that *Upf1*, *Upf3a*, and *Upf3b* are expressed in the developing neocortex (37). Moreover, they find that shRNA mediated depletion of *Upf3b* in mouse primary NSCs promotes progenitor proliferation, at the cost of reduced differentiation. Recent studies of *UPF3B* in NSCs also suggest NMD is required for neuronal maturation (38). Depletion of another NMD factor, *Upf1,* however, tells a different story (39). Lou et al. show that *Upf1* expression, along with several other NMD factors, is reduced in mouse cortical neurons and P19 neuronal cells as neuronal differentiation proceeds. Consistent with this expression pattern, *Upf1* promotes proliferation, whereas its downregulation induces differentiation. The authors find that NMD functions in stem cells by preferentially destabilizing anti-proliferative factors. Altogether, these studies suggest the regulatory role of NMD components in neurogenesis is complex. Perhaps the roles of NMD are divergent at different stages of neurogenesis, or individual NMD factors have distinct outcomes on specific NMD targets.

This literature supports an essential role for core and peripheral EJC components in neurogenesis, and raise many interesting questions. Are other core EJC components, *Eif4a3* and *Casc3*, also required for neurogenesis and brain size? MAGOH is the only core EJC component with a recognized homolog, MAGOHB, which is virtually identical at the protein level (40). Thus it is interesting to consider the role of MAGOHB in brain development as well. How do core EJC components induce progenitor defects and mitosis defects at a molecular level? Translation and NMD dysfunction are likely relevant, given the requirements of UPF factors. Splicing defects are also predicted to contribute to the apoptosis of *Magoh* and *Rbm8a* mutant brains, given that EJC-mediated alternative splicing of *Bcl-X* promotes apoptosis in non-neuronal cells (41). It is also intriguing to consider if the EJC mediates RNA localization and transport in NSCs, particularly given the elaborate bi-polar morphology of radial glial cells. Future studies which address these important questions will be of interest.

Roles for EJC components in post-mitotic neurons

Beyond embryonic neurogenesis, there is mounting evidence implicating EJC components in the cell biology of post-mitotic neurons. After their generation, neurons extend their axons via growth cones, in order to form synapses with target neurons. A recent study by Colak et al. finds that the peripheral EJC components, UPF1, UPF2, and SMG1, localize within growth cones of commissural neurons (neurons with contralaterally targeted axons) (42). Consistent with this localization, neurons in which *Upf2* is conditionally deleted or in which a UPF1 dominant-negative construct is expressed, exhibit disorganized axonal trajectories and aberrant axon guidance. Conditional *Upf2* loss from neurons caused increased accumulation of the axonal guidance receptor *Robo3.2*, which the authors establish as a NMD substrate, providing a molecular mechanism to explain the *Upf2* and *Upf1* phenotypes. Two additional studies have shown the NMD factor *Upf3b* also influences axon outgrowth and neurite branching (37,38). Together these findings argue that peripheral EJC components are important for establishing proper neuronal connectivity in the developing brain. Given these findings, one might predict that core EJC components also impact axon outgrowth, although this has not yet been reported.

Beyond neurite outgrowth, EJC components are also required for neuronal activity. Giorgi et al. discovered that EIF4A3 is associated with UPF1 in messenger ribonucleoprotein (mRNP) complexes in dendrites of hippocampal neurons (43). The authors went on to demonstrate that mRNA for *Arc,* an immediate early gene which regulates synaptic plasticity, is degraded via NMD. Loss of *Eif4a3* or *Upf1* led to accumulation of *Arc* and increased the amplitude of miniature excitatory post-synaptic currents (mEPSCs), consistent with the established role of *Arc* in AMPA receptor trafficking (44). A later study implicated *Eif4a3* in *Arc* regulation in the context of novel environment exploration in rats (45). This study argued that *Eif4a3* is relevant for spatial learning, which may be due to regulation of *Arc* mRNA. These findings indicate that the EJC is relevant for synaptic plasticity, which suggests it could have a potential role in learning and memory.

Rbm8a has also been implicated in regulating neuronal activity and mouse behavior. Overexpression of *Rbm8a* in the adult mouse hippocampus alters anxiety and autism-like behaviors (46). The authors note reduced depression-like behaviors in a forced swim test, which they suggest may be attributed to increased adult neurogenesis in the dentate gyrus. Behavioral changes were also accompanied by a reported increase in mEPSC frequency observed in primary neuronal culture, which the authors speculate is likely due to increased synapse formation. The authors also saw that RBM8A binds to a number of important neuronal targets transcripts including *GluR1*, *CaMKII*, and *Egr1* (43). Interestingly RBM8A did not bind some mRNAs reported to associate with EIF4A3, such as *Arc.* This difference could be due to neuron-specific differences or could imply EJC components differentially regulate target mRNAs.

Overall, these studies provide compelling evidence that the EJC influences post-mitotic neuronal functions, including axonal targeting, neurite outgrowth, and synaptic plasticity. Similar to the field of neurogenesis, many interesting questions remain to be addressed including whether all core and peripheral EJC components are similarly required for

development and maintenance of neurons, and what are the molecular mechanisms at play. Are EJC mRNA targets different in distinct neuronal subtypes or in response to external cues? More research is needed to thoroughly understand how EJC components work together or separately to control neuronal activity and modulate behavior.

Disruption of EJC function is associated with human disease

The aforementioned studies provide a functional basis for understanding how the EJC contributes to neurological disorders. As described below, recent genetic studies demonstrate significant associations between copy number variations and point mutations in core and auxiliary EJC components and neurodevelopmental pathologies.

Nguyen et al. performed a search for CNV variants of NMD factors in a cohort of patients with intellectual disability (47). This study compared CNV data from over 57,000 patients with neurodevelopmental disorders against over 20,000 controls. The authors find a significant association between intellectual disability and loss of *RBM8A*, *UPF2*, and *UPF3A*. Significant gains were also seen in *RBM8A*, *EIF4A3*, *RNPS1*, *UPF2* and *SMG6* in patients. Notably, other EJC factors, including *MAGOH* and *CASC3*, displayed elevated frequencies of CNVs in patients with neurodevelopment presentations, however these correlations did not achieve statistical significance. Pathological manifestations were diverse, but most commonly included intellectual disability and aberrant brain formation. To understand the underlying defects associated with *UPF2* dosage, Rosenfeld et al. performed RNA-seq of *UPF2* deletion patient cells, finding similar transcriptomic alterations to those previous reported in *UPF3B* loss of function (48). As a result, the authors suggest that dosage alterations in NMD genes is a contributing factor to neurodevelopmental disorders. This finding fits well with studies of mouse models described above, which also demonstrate that haploinsufficiency for EJC components has deleterious impact upon brain development.

The idea that EJC dosage is relevant for neurodevelopmental disease is also supported by studies of the 1q21.1 chromosomal region, which includes *RBM8A.* Multiple studies find that patients harboring deletions of the proximal portion of chromosomal region 1q21.1 present with increased incidence of intellectual disability, epilepsy, autism, and schizophrenia (49–53). Additionally, nearly half of the patients reported in one study had brain size abnormalities, including macrocephaly and microcephaly (50). These clinical observations are consistent with studies of the *Rbm8a* mouse model, suggesting that microcephaly associated with 1q21.1 deletions may be due to neurogenesis aberrations and influenced by *RBM8A* loss (35). Further evidence implicating *RBM8A* as a disease gene came from studies of the disorder thrombocytopenia with absent radius syndrome (TAR syndrome). While TAR syndrome primarily presents as a disorder of the limbs and blood, it is associated with increased incidence of neurodevelopment phenotypes (54). TAR syndrome arises from a 1q21.1 deletion in combination with a SNP within the regulatory region *RBM8A* (55,56). This mutation causes hypomorphic reduction of *RBM8A* expression, indicating that the *Rbm8a* haploinsufficient mouse may be a suitable model for understanding this disorder (35).

EIF4A3 has also been linked to a developmental autosomal recessive disorder termed Richieri-Costa-Pereira (RCP) syndrome (57). Favaro et al. report a cohort of patients in Brazil which present with dysmorphic craniofacial and limb features. A striking 50% of the patients are reported to have learning and language deficits. This is consistent with a role of *EIF4A3* in neurodevelopment and function, although whether this is due to a direct role in the brain or indirect result of craniofacial malformation is still unknown. The causative mutation is an expansion of repeat sequences within the non-coding 5' UTR of *EIF4A3.* This leads to hypomorphic expression of *EIF4A3*. Generation of *Eif4a3* mouse models will be valuable for exposing neurological mechanisms by which *EIF4A3* mutation causes RCP syndrome.

Point mutations within the NMD component, *UPF3B,* cause diverse neurological diseases, including intellectual disability, autism and schizophrenia. Tarpey and others showed *UPF3B* loss of function is associated with X-linked disability (58). In this study several patients also displayed macrocephaly, consistent with alterations during cortical development. Additional studies found that *UPF3B* mutations are linked to intellectual disability, which can present with and without autism. Follow up studies extended the clinical manifestations, identifying renal dysplasia and broad developmental delay (59). Several other studies have found familial associations between *UPF3B* mutations and schizophrenia (60–62). Together these studies support a strong link between *UPF3B* and diverse presentations of neurological disorders.

The above studies demonstrate that mutations of EJC components are increasingly associated with neurological disease. It is interesting to consider why the human brain is so vulnerable to perturbations of EJC-mediated processes, even as most of these components are expressed fairly ubiquitously. One potential explanation is the wide prevalence of alternative splicing in the nervous system, which may make NMD alterations more prominent (see review, (63). The EJC also plays a role in mRNA localization, which is known to be prevalent in the developing nervous system. As we learn more about *in vivo* roles of EJC components in the nervous system, we may gain new insights into the striking relationship between EJC factors and neurodevelopmental disease.

Conclusions

Taken together both human genetics studies and mouse models strongly support a key role of EJC components in embryonic neural development and the etiology of neurodevelopmental disorders. Several studies support impaired NMD as a critical factor, however the contribution of other established roles of the EJC (splicing, mRNA localization, and translational efficiency) remain to be fully explored. The further characterization of EJC functions in neurogenesis will be of paramount importance for understanding microcephaly and macrocephaly in patients. Potential functions of the EJC in other aspects of neural development need to be addressed, including functions in production of different neuronal subsets, glia, and comprehensive roles in adult neurogenesis. The generation of *in vivo* models provides a powerful tool to probe the requirements of the core and peripheral EJC factors in various aspects of development. The current models reveal important insights into the etiology of neurodevelopmental disease, as described throughout this review. Going

forward, use of mammalian models will be useful to gain detailed insights into autonomous functions of EJC components in the developing nervous system and disease.

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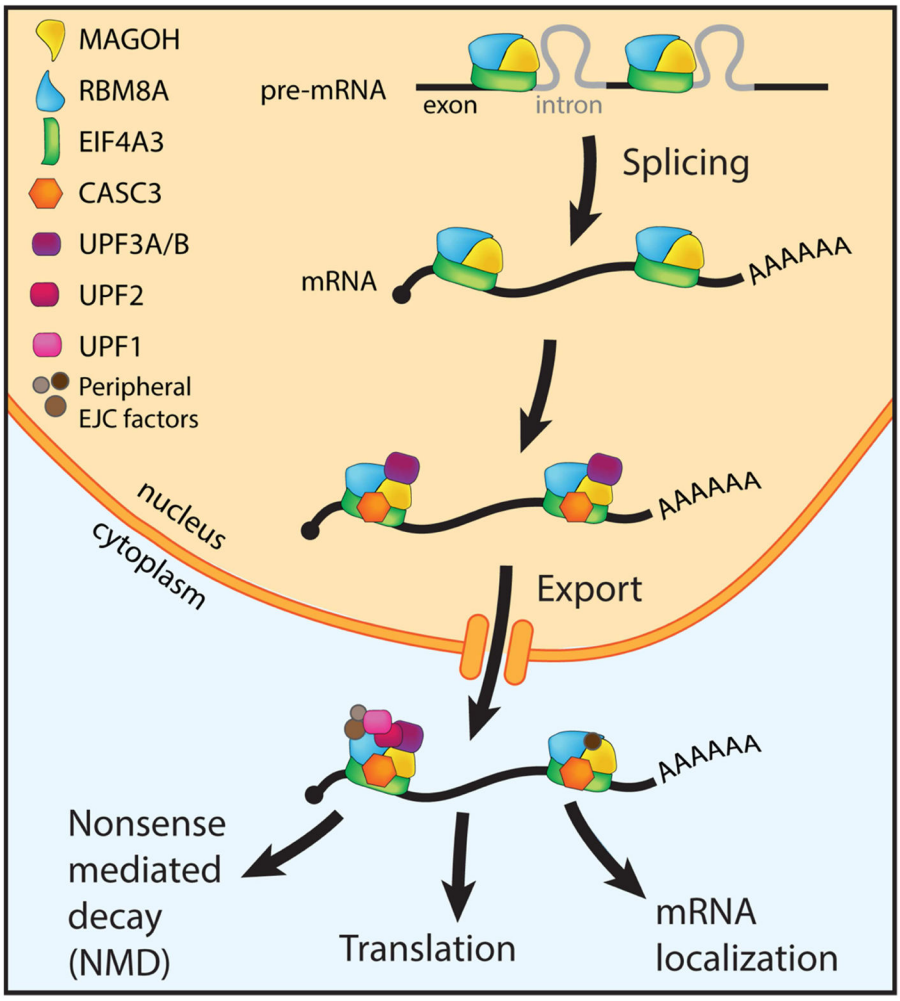

Figure 1. Schematic representation of functions of the exon junction complex

Core EJC components, MAGOH, RBM8A, and EIF4A3, are indicated along with peripheral EJC components, including UPF1, UPF2, UPF3A, and UPF3B. The EJC binds to RNA concomitant with splicing, and function in alternative splicing, nonsense-mediated decay, translation, and RNA localization.

Table 1

Core and peripheral EJC components discussed in review.

EJC Component (Alternative Names)	Biological Function Nervous System	Molecular Function	Tools Employed	Human Neurological Disorder	Human Mutation	Human Refs.
EIF4A3 (DDX48)	Neuronal Activity	NMD Translation Localization Splicing	RNAi	Richieri-Costa-Pereira syndrome Intellectual disability	Noncoding mutation CNV-gain	(47,57)
RBM8A (Y14/Tsunagi)	Neurogenesis Neuronal Activity	NMD Translation Localization Splicing	cKO Mouse RNAi Over-expression	1q21.1 del/dup, TAR syndrome Intellectual Disability Altered Brain Size Autism, Seizures	LOF CNV-gain, loss	(47,49–53,55,56)
MAGOH (Mago Nashi)	Neurogenesis	NMD Translation Localization Splicing	cKO Mouse Germline Mouse RNAi	Not Reported	CNV-gain *, loss *	(47)
MAGOHB	Unknown	Unknown	RNAi	Not Reported	Not Reported	
CASC3 (MLN51/Barentsz)	Unknown	NMD Translation Localization Splicing	RNAi	Not Reported	CNV-gain *, loss *	(47)
UPF1 (RENT1)	Neurogenesis Neuronal Activity	NMD	Germline Mouse	Not Reported	CNV-gain *	(47)
UPF2 (RENT2)	Axon Guidance Neurite Outgrowth	NMD	cKO Mouse	Intellectual Disability	CNV-gain, loss	(47)
UPF3A (RENT3A)	Unknown	NMD	RNAi	Intellectual Disability	CNV-gain *, loss	(47)
UPF3B (RENT3B)	Differentiation Neurite Outgrowth	NMD	RNAi	Intellectual Disability Autism Schizophrenia	LOF CNV-gain *, loss *	(47,58–62)

* Nyugen et al. found evidence of CNVs in patients with ID which did not achieve significance