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Control of CNS functions by RNA-binding proteins in neurological diseases

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Abstract

Purpose of Review—This review summarizes recent studies on the molecular mechanisms of RNA binding proteins (RBPs) that control neurological functions and pathogenesis in various neurodevelopmental and neurodegenerative diseases, including autism spectrum disorders, schizophrenia, Alzheimer's disease, amyotrophic lateral sclerosis, frontotemporal dementia, and spinocerebellar ataxia.

Recent Findings—RBPs are critical players in gene expression that regulate every step of posttranscriptional modifications. Recent genome-wide approaches revealed that many proteins associate with RNA, but do not contain any known RNA binding motifs. Additionally, many causal and risk genes of neurodevelopmental and neurodegenerative diseases are RBPs. Development of high-throughput sequencing methods has mapped out the fingerprints of RBPs on transcripts and provides unprecedented potential to discover new mechanisms of neurological diseases. Insights into how RBPs modulate neural development are important for designing effective therapies for numerous neurodevelopmental and neurodegenerative diseases.

Summary—RBPs have diverse mechanisms for modulating RNA processing and, thereby, controlling neurogenesis. Understanding the role of disease-associated RBPs in neurogenesis is vital for developing novel treatments for neurological diseases.

Keywords

RNA binding proteins; neurodevelopmental disorder; neurodegeneration

Introduction

Neurodevelopment requires the functions of different proteins at different developmental stages. It involves in diverse transcriptional and post-transcriptional events, such as RNAs transportation, alternative splicing, stabilization, degradation and translation. RNA-binding proteins (RBPs) have a critical role in regulating these processes (Figure 1). Abnormalities of RBPs in the early stages of neural system development may affect neuronal migration,

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Conflict of Interests

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synaptic plasticity and neurobehavioral functions that lead to neurodevelopmental and neurodegenerative diseases [1].

Autism spectrum disorders (ASD) and schizophrenia (SCZ) are two major neurodevelopmental disorders with strong genetic backgrounds. Multiple risk genes for ASD and SCZ involve RBPs. RNA processing defects are observed in several neurodegenerative diseases, including amyotrophic lateral sclerosis (ALS), frontotemporal dementia (FTD), spinocerebellar ataxia (SCA) and Alzheimer's disease (AD) [2–9]. Thus, we will focus on their diverse functions in regulating RNAs as a variety of etiologies of neurodevelopmental and neurodegenerative diseases.

RBPs in ASDs

FMR1

The inherited neurodevelopmental disorder fragile X syndrome (FXS) features intellectual deficits and autistic behaviors [10]. FXS is the well-known leading monogenic cause of ASD [11]. The increased trinucleotide repeats at the 5' untranslated region of *FMR1* lead to a decrease in levels of fragile X mental retardation protein (FMRP). Local translation at the synapse is important for neuronal plasticity [12]. As an mRNA-binding protein, FMRP modulates mRNA localization and local translation at the synapse [13]. It represses polypeptide elongation of protein synthesis by stalling polyribosomes [14]. Loss-of-function of FMR1 significantly impairs local protein translation and plasticity. In addition, FMR1 serves as a sequence-context-dependent N6-methyladenosine (m6A) reader that indicates the m6A modification regulates mRNA stability [15].

The FXS mouse model (*Fmr1*^{-y}) shows hyperactive ERK and mTOR signaling. Chronic metformin treatment selectively downregulates the ERK and mTOR signaling pathway and rescues core autistic phenotypes in this mouse model [11]. Metformin treatment also corrects the phenotypes of increased spine density and exaggerated metabotropic glutamate receptor (mGluR)-dependent long-term depression (LTD), providing an exciting drug target for FXS. Using translating ribosome affinity purification (TRAP) and RNA-seq, excessively translating mRNAs were identified in CA1 pyramidal neurons of the *Fmr1*^{-y} mouse model [16]. The muscarinic acetylcholine receptor 4 (M4) is excessively translated and consequently suppresses mGluR-induced LTD of synaptic transmission. VU0152100, a positive allosteric M4 modulator, enhances the effects of cholinergic agonists on M4 that significantly reduce the audiogenic seizures [16], suggesting a potential pathway to reverse FXS-associated phenotypes.

ELAV-like RBPs

Neuronal ELAV-like RBPs are involved in several neurological disorders [17]. The combination of crosslinking-immunoprecipitation and RNAseq (CLIP-seq) has identified more than 8000 targets that bind to ELAV-like RBPs. They regulate RNA splicing and abundance [18]. Knockdown of *ELAVL2* in primary human neurons alters mRNA alternative splicing, including *RBFOX1* and *FMR1*, which are well-known ASD risk genes [19]. The CUGBP ELAV-like family member 4 (*CELF4*) gene encodes an RNA-binding

protein. Haploinsufficiency of *CELF4* was found in ASD patients [20]. Similarly, *CELF4* mutant mice show complex seizure disorders [21]. *CELF4* regulates excitatory neurotransmission by stabilizing mRNA and supporting synaptic local translation [22]. It regulates about 30% of potential ASD risk genes at pre- and postsynaptic sites.

RBFOX1

RBFOX proteins are a family of RNA-binding proteins that contain a single high-affinity RNA recognition domain. RBFOX proteins bind to UGCAUG motifs to regulate RNA processing in neurons, muscle and heart [23]. *RBFOX1* has been associated with neurodevelopmental disorders, such as ASD and epilepsy [24, 25]. Alternative splicing of *RBFOX1* generates different protein isoforms localized to either the nucleus or cytoplasm. The nuclear isoform regulates mRNA splicing. Downregulation of nuclear Rbfox1 delays neuronal migration in the brains of embryonic day 14.5 mice [26]. CLIP-seq shows that targets of Rbfox1 in mouse brains enriched in regulating brain development and ASD risk genes [27]. Unlike nuclear Rbfox1, cytoplasmic Rbfox1 predominantly regulates mRNA stability and translation. CLIP-seq results at single-nucleotide resolution indicate that cytoplasmic Rbfox1 binds to 3'-UTR of mRNA targets and increases their abundance [24]. The Rbfox1-bound genes control synaptic activity and calcium signaling.

Exon junction complex

The exon junction complex (EJC) is an RNA-binding protein complex that controls pre-mRNA splicing, maturation, translation and nonsense-mediated mRNA decay (NMD) [28]. The core protein components are eIF4AIII, MAGOH, RBM8A and BTZ [29, 30]. Intact pre-mRNA splicing plays an important role in the development of the central neural system, and multiple NMD factors contribute to neuro-developmental disorders [31].

RBM8A is highly expressed in the neural progenitor cells (NPCs) of the subventricular zone at embryonic brain. Downregulation of *RBM8A* at embryonic day 13 promotes the neuronal migration in the neocortex and decreases the proliferation of NPCs. Upregulation of *RBM8A* suppresses the neuronal migration and increase the NPCs dividing [32]. Consistently, haploinsufficiency of *eIF4AIII*, *MAGOH* and *RBM8A* in NPCs of the dorsal telencephalon reduce cortical area and volume of mouse brains [33–35]. Conditional deletion of *TP53* in NPCs recovers the microcephaly phenotype in the embryonic state [33]. In adult mice, abnormal *RBM8A* expression in the dentate gyrus leads to anxiety behaviors [36].

NMD is an mRNA surveillance mechanism that eliminates mRNAs containing premature termination codons. UPF1, UPF2, UPF3A and UPF3B are required for activation of NMD in eukaryotes [37]. *UPF3B* mutations are found in patients with ASD, SCZ or attention-deficit hyperactivity disorder [38–41]. Knockdown of *UPF3B* increases proliferation of neural progenitor cells and decreases primary axon growth. *UPF3B*-null mice have fewer dendritic spines and less neural activity. The mutant UPF3B mice are deficient in the prepulse inhibition and fear learning tests [42]. Interestingly, *UPF3A*, an assumed redundant paralog of *UPF3B*, has an antagonistic function against the NMD pathway [43]. In the nervous system, besides regulating NMD, UPF1 facilitates mRNA transport and local translation for

synaptic plasticity [44]. Downregulation of UPF1 decreases *MAP1B* mRNA in neurites. STAU2, another RBP, physically interacts with UPF1 to regulate mRNA transportation. Thus, RBPs controlling NMD are important in protecting neuronal development from inaccurate mRNA splicing and incorrect synaptic localization.

Methyl-DNA-binding proteins

Epigenetic regulators, such as *MECP2* and DNA methyl-transferases (DNMTs), contain well-characterized methyl-DNA-binding domain (MBD) and modulate DNA methylation and control gene expression. Abnormal copies of *MECP2* gene affect neuronal development and lead to neurodevelopmental disorders. *MECP2* deletions cause Rett's syndrome [45], whereas *MECP2* duplication leads to similar autistic behaviors and intellectual disability. Conditionally overexpressed *MECP2* in a mouse model can be behaviorally corrected by removing one *MECP2* allele or using antisense oligonucleotides to silence *MECP2* [46], suggesting that gene dosage is important for brain development. Intriguingly, some MBD proteins and DNMTs, including *MECP2*, interact with RNA and form an RNA-protein complex [47]. The RNA-binding motifs in these proteins are different from their MBDs. These data suggest that MBD-containing proteins and DNMTs associate with RNAs to participate in DNA methylation [48]. *MBD1* and *MECP2* dysfunction affect adult neurogenesis and the hippocampal functions [49–51].

Other RBPs in ASDs

Heterogeneous nuclear ribonucleoproteins (hnRNPs) are a family of RBPs that control variant transcriptional and translational events. Abnormalities of hnRNPs are associated with different neurological diseases and cancers [52]. Missense mutation of *hnRNPH2*, which localizes in the X chromosome, associates with autistic behaviors and ataxia in females [53]. *HnRNPU* deletion was reported in patients carrying copy number variations with infantile spasms, seizures and brain malformation [54, 55].

The growth cone responds to axonal guidance cues to reach a targeted region and form synapses. This process involves local mRNA translation to generate rapidly appropriate responses. The RBPs, hnRNPK and PCBP1, join with mRNA and Mena (ENAH), an actin-regulatory protein, to form an RNP complex [56]. CLIP data show that Mena-bound mRNAs modulate axon guidance. *DYRK1A* (Dual Specificity Tyrosine Phosphorylation Regulated Kinase 1A), a Down syndrome and ASD risk gene, is guided by the Mena complex for the synaptic local translation. Janus kinase and microtubule-interacting protein 1 (*JAKMIP1*) is an RBP that involves in RNP translation.

JAKMIP1 is highly expressed in glutamatergic neurons in developmental brains [57]. Differential expression of *JAKMIP1* has been observed in ASD patients [58]. Protein interactome analysis indicates that *JAKMIP1*'s binding partners participate in translational regulation [59]. *JAKMIP1* knockout mice show autistic behaviors, such as social deficits, repetitive behavior and impaired vocalization [59]. Translation initiation factors, such as EIF4E, regulate local translation in the synapse. De novo mutations of *EIF4E* have been associated with autistic behaviors [60].

RBPs in SCZ

Disrupted in Schizophrenia 1

SCZ is a devastating mental disorder with high genetic risk. *Disrupted in Schizophrenia 1* (*DISC1*) was first identified in a big Scottish family with high incidences of mental diseases [61]. The chromosomal translocation within the *DISC1* gene locus is associated with SCZ [62]. *DISC1* associates with many proteins and is important in neurogenesis and neural plasticity [63, 64]. It modulates Wnt pathway and regulates NPC proliferation and neuronal migration/differentiation by inhibiting GSK3 β activity [65–69]. Interactome screens indicate that *DISC1* physically interacts with several RNA-binding proteins [70]. Their targets involve RNA-transporting granules and synaptic plasticity, such as the *ITPR1* gene.

ZNF804A

ZNF804A was the first SCZ risk gene identified by genome-wide association studies (GWAS) [71]. Several follow-up GWASs replicated that result and also confirmed the association of rs1344706 with SCZ in different populations [72–80]. In addition to common variants, the SGENE-plus consortium reported rare copy number variants (CNVs) at the *ZNF804A* locus in psychotic patients, including a deletion in a SCZ patient, a deletion in a patient with an anxiety disorder, and a duplication in a BD patient [74], but none in controls. Interestingly, chromosome duplication, deletion, inversion and translocation at the *ZNF804A* locus were found in patients with autism [81, 82] and developmental delay [83, 84]. Consistent with the reproducible genetic association of risk SNP in *ZNF804A* with SCZ, neuroimaging and neuropsychological studies provide mounting evidence that *ZNF804A* risk allele modulates human brain structures and functions [85–111].

ZNF804A contains a zinc-finger domain that may have DNA and RNA binding ability. Although it has been proposed to function as a transcription factor [112], using RNA immunoprecipitation sequencing (RIP) and interactome analysis, we found that *ZNF804A* binds to RNAs [113]. *ZNF804A* is highly expressed in the prenatal central nerve system. Knockdown of *ZNF804A* affects translation, as well as neural migration toward the neocortex in mouse embryonic stage [113]. Suppression of *ZNF804A* expression in human NPCs and primary rat cortical neurons reduces neurite formation and dendritic spine formation [114], supporting the important function of *ZNF804A* in brain functions.

Quaking

Quaking (QKI) is a member of the signal transduction and activation of RNA (STAR) protein family and the hnRNP K homology (KH)-type family [115]. QKI binds to its downstream mRNAs carrying a conserved QKI response element (QRE). QKI regulates several RNA processes, including alternative splicing, micro-RNA processing, mRNA stabilization and translation. Differential splicing of *QKI* mRNA produces several isoforms. Decreased QKI-7 and QKI-7b variants were observed in 55 SCZ patients [115]. These isoforms are regulated by hnRNP C1/C2 [116]. *QKI* variants are also expressed in astrocytes. Downregulation of QKI-7 in astrocytes decreases glial fibrillary acidic protein (GFAP) expression. A typical antipsychotic medication, haloperidol, increases QKI-7 and

GFAP expression, suggesting that QKI-7 coordinates with GFAP to regulate the function of astrocytes [117]. This study proposes a new potential link of RNA processing with SCZ.

A recent GWAS identified 108 genetic loci associated with SCZ [79]. SCZ shares many risk genes with intellectual disability and ASDs. Interestingly, *de novo* mutations in SCZ enriched in glutamatergic postsynaptic proteins related to activity-regulated cytoskeleton-associated protein (ARC) and N-methyl-D-aspartate receptor (NMDAR) complexes. Many transcripts of these complexes are targets of FMRP [118]. Interestingly, FMRP is also a substrate of glycogen synthase kinase 3 β (GSK3 β) [119]. Inhibition of GSK3 β has antipsychotic and mood stabilization effects as GSK3 β is the target of psychoactive drugs to treat mental illnesses.

RBPs in ALS/FTD

ALS and FTD are two diseases with similar symptoms and pathogenesis [120]. Recent evidence indicates that disrupting RNA homeostasis is a leading cause of ALS/FTD [121]. Mutations in several RBPs have been identified in ALS/FTD patients.

STAU1

Staufen 1 (*STAU1*) is an RNA binding protein responsible for RNA transportation, localization, translation and the ribonucleoprotein formation [122]. Gershoni-Emek *et al.* observed altered localization of synaptic STAU1 in an ALS SOD1^{G93A} mouse model, probably due to interrupted retrograde transportation from the synapses [123].

TDP-43

TAR DNA-binding protein 43 (*TDP-43*, also called *TARDBP*) is a causal gene for ALS [124]. It encodes an RBP involved in transcription, mRNA splicing, stability and transportation [125]. Cytoplasmic mislocalization and decreased nuclear expression are associated with TDP-43 mutation. Both mislocalization and downregulation of expression contribute to the cellular toxicity [126, 127]. Though the protein has been associated with ALS for almost two decades, until recently, studies revealed that an oligomeric form of TDP-43 is functional in the nucleus, and this state is essential for its role in RNA metabolism [128]. Additionally, TDP-43 has been reported to regulate ER-mitochondria communication and Ca²⁺ homeostasis, probably through regulating GSK3 β signaling pathway [129]. Using motor neurons derived from human induced pluripotent stem (iPS) cells, Alami *et al.* reported that anterograde axonal transportation of mRNAs was reduced with ALS-causing mutations of TDP-43 [130].

Fused in Sarcoma

Fused in sarcoma (*FUS*), another ALS/FTD risk gene, shares many common pathophysiological characteristics with *TDP-43* [124]. They are both involved in RNA processing and neuronal development [131]. Specifically, FUS binds to nascent mRNA and modifies alternative splicing [131]. A recent microarray study suggested that these two proteins share some downstream targets, including splicing and expression regulation [132]. In fibroblasts derived an ALS patient, FUS formed nuclear aggregates [133]. Patel *et al.*

reported that FUS undergoes a dynamic liquid-like phase transition *in vivo*, and converted to aggregates upon aging. This transition to aggregates is accelerated with the disease-related mutation in prion-like domains [134]. This could be the mechanism for other age-related diseases involving proteins carrying prion-like domains. Later in the same year, Murakami and colleagues reported a similar phenotype that mutant FUS generates irreversible hydrogels from liquid droplets [135]. ALS-associated FUS mutations often show higher cytoplasmic expression than wildtype controls [136], and the nuclear-localization of FUS seems to not be required for protein aggregation and neuronal toxicity [137].

When ALS-associated mutant FUS aggregates are formed, other ALS-associated RNA-binding proteins are sequestered in the same complex, including SMN1, hnRNPA1, hnRNPA2, STAU-1 [138, 135]. By using an *in vitro* fluorescent molecule tracking assay, Murakami *et al.* claimed that irreversible FUS assemblies trap cargo RNPs, which leads to cellular toxicity. Specially among the affected proteins, *SMN1* is the major causal gene for spinal muscular atrophy (SMA). Sun *et al.* reported that the interaction of FUS with SMN protein is increased in ALS-associated FUS mutation [139]. At the same time, the mutated FUS has reduced interaction with U1-snRNP, through which it affects global mRNA splicing [139, 140]. FUS also regulates translation. Specifically, Yasuda *et al.* observed that FUS promotes translation preferentially within cell protrusions, and the translation process is not halted by FUS-positive granules [141]. Fragmentation of the Golgi apparatus has been observed in ALS [142, 143], and FUS disease mutation induces Golgi fragmentation [144]. Although FUS is associated with both ALS and FTD, Suárez-Calvet and colleagues identified a difference: mono-methylated arginine occurs exclusively in FTL-D-FUS mutations, which makes the protein bind more tightly to the nuclear import receptor, transportin-1, but not in ALS-FUS mutations [145].

C9ORF72

The hexanucleotide “GGGGCC” repeat expansion in the noncoding region of the *C9ORF72* gene is another common genetic cause for ALS/FTD. Donnelly *et al.* reported an alteration in gene expression profiles and sequestration of GGGGC binding RBP, ADARB2, in nuclear aggregates of patient-derived iPS cells with *C9ORF72* repeats [146]. Other ALS-associated RBPs, including FUS, TDP-43 and HNRNPA1, were not identified in the same complexes [146]. However, another study did find inclusion of other RBPs, including SF2, SC35 and HNRNPH, and HNRNPH was identified as a binding partner with the hexanucleotide expansion [147]. Aggregation results in increased sensitivity to glutamate toxicity [146] and enhanced apoptosis [147]. Besides interrupting RNA processing, ATM-mediated chromosomal break repair was disrupted by the expansion, suggesting another possible cause of neurodegeneration by repeat expansion [148]. Unbiased yeast screening revealed karyopherins and other nucleocytoplasmic transport proteins are involved in the cytotoxicity [149]. Several potential drug targets have been reported that might help prevent neurodegeneration associated deficits, including inhibiting SRSF1-dependent nuclear export of *C9ORF72* repeat transcripts [150] and antisense intervention [146].

GLE1

Recent exome screening studies linked mutations in gene *GLE1* with ALS [151]. GLE1 expresses two isoforms in human cells, GLE1A and GLE1B [152]. GLE1A regulates translation, and is localized to stress granules (SG) upon stress and regulates SG assembly and disassembly [153]. GLE1B is an mRNA export factor associated with nuclear pore complex [152, 154]. GLE1 mutations lead to dysregulation at nuclear pore complexes and cause human lethal congenital contracture syndrome-1 (LCCS1) [155, 156]. In zebrafish, *Gle1* knockout results in defective Schwann cell development [157]. The ALS-linked GLE1 allele was reported to encode a protein that has the function of both GLE1A and GLE1B, which may affect the normal regulatory roles of GLE1 [158].

RBP in SCA

SCAs are a group of over 35 progressive neurodegenerative diseases. At least six of them (SCA1, SCA2, SCA3, SCA6, SCA7 and SCA17) are caused by a polyglutamine expansion encoded by CAG repeats [159]. Two of the risk proteins, polyglutamine expansion within the ataxin-1 protein (ATXN1) and ATXN2, causing SCA1 and 2, respectively, have been identified as RBPs.

ATXN1

The ATXN1 mutation causes SCA1 [160]. The binding ability of this RBP is disrupted by the expanded polyglutamine [161]. ATXN1 regulates neuronal proliferation *in vitro* and *in vivo* [162, 163]. By modulating the GSK3 β -mTOR pathway, ATXN1 regulate energy homeostasis in the mouse cerebellum [164]. On the other hand, the RAS-MAPK-MSK1 pathway modulates ATXN1 protein levels and its associated toxicity [165]. Meanwhile, ATXN1 expression level is negatively regulated by PUMILIO1 (PUM1), which is also an RBP, by modulating ATXN1 RNA stability [166]. By increasing the expression of ATXN1, *Pumilio1* haploinsufficiency leads to SCA1-like neurodegeneration [166]. Transcriptome profiles of ATXN1 transgenic mouse cerebellum of several ages and genotypes revealed that upregulation of cholecystokinin (CCK) may play a protective role against Purkinje cell death [167]. Intracellular expression of HMGB1 prolongs lifespan in mutant *Atxn1* knock-in mice by repairing mitochondrial DNA damage, which may serve as a potential treatment for SCA1 [168].

ATXN2

Abnormal polyglutamate expansion in ATXN2 results in SCA2 [169, 170] and ALS [171]. ATXN2 regulates metabolism through modulating the mTOR pathway [172–174]. It belongs to the like-Sm (LSm) protein family that regulates multiple aspects of RNA metabolism [175]. It directly interacts with poly(A)-binding protein, cytoplasmic 1 (PABPC1), and possibly regulates translation and mRNA stability partly through its binding partners [176, 177]. Meanwhile, PAR-CLIP revealed that ATXN2 also targets a group of genes in a PABPC1-independent manner and helps to maintain mRNA stability, including genes involved in posttranscriptional processes and metabolic processes [178]. For example, *TDP-43* is targeted by ATXN2 [178]. Crossing *Ataxin-2* knockout mice to *TDP-43* transgenic mice showed drastic reducing in TDP-43 aggregation [179]. In cell culture,

ATXN2 with an intermediate length of polyglutamate repeats promotes mutant FUS translocation and stimulates Golgi fragmentation and apoptosis caused by mutant FUS [144]. The same *ATXN2* mutant also enhances neuronal toxicity caused by *C9ORF72* depletion [180]. Mitochondria dysfunction is associated with ALS [181]. ATXN2 was identified as a transcriptional regulator upstream of PINK1, a key regulator for mitochondrial stress response [182]. By positively regulating the translation of circadian rhythm maintenance gene, Period (PER), ATXN2 modulates circadian cycle in *Drosophila* [183, 184]. Antisense oligonucleotides (ASO) of *Ataxin-2* effectively improve motor functions in several SCA mouse models, suggesting ASO as a potential treatment for ATXN2-associated human neurodegenerative diseases [179, 185].

RNA metabolism in AD

The neurofibrillary tangle caused by microtubule-associated protein, tau, is a well-known pathological feature of AD. Though there is still a controversy on whether tau is an RBP or not, it has been reported decades ago that RNA facilitates the formation of paired helical filaments of tau [186]. A study using a *Tau*-knock-out mouse model suggests that RNA-integrity in neurons is affected under heat-shock with tau deficiency [187]. Recently, using PAR-iCLIP, Zhang *et al.* found that the major associated RNAs of tau are tRNAs [188]. Intriguingly, mixing tau and RNA *in vitro* created dynamic liquid droplets, which may be the mechanism underlying tau pathology [188]. Besides direct association with RNA, tau interacts with RBPs. Vanderweyde *et al.* reported that TIA-1 modulates tau pathology, and synergistically, they promote neuronal death [189]. Besides tau, other AD-associated proteins have been suggested to be regulated by RNA. Faghihi *et al.* reported that the concentration of β -secretase 1 (BACE1) antisense RNA is elevated in both post-mortem human brains and Tg19959 mouse [190]. The elevation was associated with BACE1 mRNA stability and A β accumulation [190]. Knockdown of this RNA transcript induces neuronal differentiation [191].

Conclusion

In the human genome of ~20,000 protein coding genes, about 7.5% directly associate with RNA and regulate different RNA processes. Many RBPs are implicated in human diseases and only a small fraction of RBPs are summarized in this review (Table 1). The rapid development of next-generation sequencing-based methods, such as RIP- and CLIP-based methods, ribosome profiling, *in vivo* RNA secondary structure profiling, and small and long RNA-seq, will help define the regulation of each RBP in the whole RNA network. However, many details of RNA regulatory mechanisms and their disease relevance remain to be determined. These studies will reveal novel targets and pathways that potentially facilitate new therapeutic development.

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Figure 1.

Overview of RBPs regulating mRNA life-cycle. The RBPs discussed in the review are marked with their involvement in post-transcriptional processes. Note that the proteins in color are the proteins that are associated with ASD (red), SCZ (purple), ALS/FTD (blue) and SCA (green).

Table 1

List of RBPs in brain functions and neurological disorders

RNA BINDING PROTEIN	ASSOCIATED NEUROLOGICAL DISEASES	FUNCTION IN RNA REGULATION	NERUONAL FUNCTION	REFERENCES
FMRI	ASD Fragile × syndrome	RNA localization Local translation Repress polypeptide elongation	Neural activity dendritic spine formation	10–16
ELAVL2	ASD	Splicing RNA abundance		18–19
CELF4	ASD	Stabilizing mRNA Local translation	Excitatory neurotransmission	21–22
RBFOX1	ASD Epilepsy	Slicing RNA stability Translation	Neuronal migration Synaptic activity Calcium signaling	23–27
RBM8A	ASD TAR syndrome	Splicing NMD Translation	Neural progenitor cells proliferation Neuronal migration	32–36
UPF3B	ASD Schizophrenia ADHD	Splicing NMD Translation	Neural progenitor cells proliferation Axonal growth	38–42
UPF1A	ASD	RNA transportation NMD Local translation	Synaptic plasticity	44
MECP2	Rett syndrome ASD	DNA methylation	Neurogenesis Hippocampal functions	45–51
HNRNPS	ASD Mental retardation Infantile spasms and seizures	Splicing RNA transport	synapses formation Axonal growth	53–56
JAKMIP1	ASD	Translation	glutamatergic neuron activity	57–59
DISCI	Schizophrenia	Physically interact with RNA-binding proteins that regulate NPC proliferation and neuronal migration	Neurogenesis Neural plasticity	61–70
ZNF804A	ASD Schizophrenia Anxiety disorder Bipolar disorder	Translation	Neuronal migration Proliferation Neurite formation Dendritic spine formation	71–114
QKI	Schizophrenia	Splicing Micro-RNA processing mRNA stabilization Translation	Astrocytes property	115–117
STAU1	ALS/FTD	RNA transportation Localization Translation	Synaptic formation	122–123
TDP-43	ALS/FTD	Splicing RNA stabilization Transportation	Anterograde axonal transportation Neurodegeneration	124–130
FUS	ALS/FTD	Splicing RNA granules formation Translation	Nuclear aggregates Golgi fragmentation Apoptosis	131–145
C9ORF72 (HEXANUCLEOTIDE EXPANSION)	ALS/FTD	Nuclear granules formation	sensitivity to glutamate toxicity Neurodegeneration	146–150
GLE1	ALS	Translation Stress granules formation RNA exportation	Nuclear pore complexes formation Neuronal death	151–158
ATXN1	SCA1	Transcription	Polyglutamine toxicity Neural proliferation	162–168
ATXN2	SCA2	RNA stability Translation	Polyglutamine toxicity Neural proliferation	169–185