Dysregulated A to I RNA editing and non-coding RNAs in neurodegeneration

Minati Singh*
Department of Internal Medicine, University of Iowa, Iowa City, IA, USA

INTRODUCTION

Environmental signals provoke changes in gene expression in a mechanism that includes epigenetic-mediated gene regulation (Kubota et al., 2012; Miyake et al., 2012). Epigenetic regulation of gene expression has key roles in development, stress responses, and plasticity of the central nervous system (CNS). Epigenetic modifications include RNA editing and chromatin remodeling (i.e., histone modifications), and DNA methylation (Zhou et al., 2008; Luco and Misteli, 2011; Luco et al., 2011). In the CNS, evidence demonstrates that long non-coding RNAs (lncRNAs) are directed to the sites of action in the genome, suggesting that lncRNAs may provide key links between neural development, nervous system function, and neurodegenerative diseases. This review includes a summary of seminal findings regarding the impact of RNA editing by ADAR (adenosine deaminase that act on RNA) on biological and pathological processes, which may be further modified by non-coding RNAs (ncRNAs). The most common RNA editing in the mammalian central nervous system is a base modification, where the adenosine residue is base-modified to inosine (A to I). Studies from ADAR (adenosine deaminase that act on RNA) mutants in Caenorhabditis elegans, Drosophila, and mice clearly show that the RNA editing process is an absolute requirement for nervous system homeostasis and normal physiology of the animal. Understanding the mechanisms of editing and findings of edited substrates has provided a better knowledge of the phenotype due to defective and hyperactive RNA editing. A to I editing is catalyzed by a family of enzymes known as ADARs. ADARs modify duplex RNAs and editing of duplex RNAs formed by ncRNAs can impact RNA functions, leading to an altered regulatory gene network. Such altered functions by A to I editing is observed in miRNAs, microRNAs (miRNA) but other editing of small and long ncRNAs (lncRNA) has yet to be identified. Thus, ncRNA and RNA editing may provide key links between neural development, nervous system function, and neurodegenerative diseases. This review focuses on the impact of dysregulated A to I editing and ncRNAs in neurodegeneration.

Keywords: RNA editing, ADARs, non-coding RNAs, microRNAs, small RNAs, PIWI-interacting RNAs (piRNAs), long non-coding RNA

RNA editing is an alteration in the primary nucleotide sequences resulting from a chemical change in the base. RNA editing is observed in eukaryotic mRNA, transfer RNA, ribosomal RNA, and non-coding RNAs (ncRNA). The most common RNA editing in the mammalian central nervous system is a base modification, where the adenosine residue is base-modified to inosine (A to I). Studies from ADAR (adenosine deaminase that act on RNA) mutants in C. elegans, Drosophila, and mice clearly show that the RNA editing process is an absolute requirement for nervous system homeostasis and normal physiology of the animal. Understanding the mechanisms of editing and findings of edited substrates has provided a better knowledge of the phenotype due to defective and hyperactive RNA editing. A to I RNA editing is catalyzed by a family of enzymes known as ADARs. ADARs modify duplex RNAs and editing of duplex RNAs formed by ncRNAs can impact RNA functions, leading to an altered regulatory gene network. Such altered functions by A to I editing is observed in miRNAs, microRNAs (miRNA) but other editing of small and long ncRNAs (lncRNA) has yet to be identified. Thus, ncRNA and RNA editing may provide key links between neural development, nervous system function, and neurodegenerative diseases. This review includes a summary of seminal findings regarding the impact of ncRNAs on biological and pathological processes, which may be further modified by RNA editing. NcRNAs are non-translated RNAs classified by size and function. Known ncRNAs include miRNAs, smallRNAs (smiRNAs), PIWI-interacting RNAs (piRNAs), and lncRNAs play important roles in splicing, DNA methylation, imprinting, and RNA interference. Of note, miRNAs are involved in development and function of the nervous system that is heavily dependent on both RNA editing and the intricate spatiotemporal expression of ncRNAs. This review focuses on the impact of dysregulated A to I editing and ncRNAs in neurodegeneration.

Keywords: RNA editing, ADARs, non-coding RNAs, microRNAs, small RNAs, PIWI-interacting RNAs (piRNAs), long non-coding RNA
FIGURE 1 | Diagram showing the broad impact of dysregulated ADARs in altering A to I editing, producing defective RNAs and altering gene expression in neurodegeneration.

enzymes recognizes these duplex structures and process them by different mechanisms (Simpson and Emeson, 1996; Bass, 2002; Heale et al., 2009). Intersection of RNA editing in the RNA interference process is observed in both plants and animals (Luciano et al., 2004; Blow et al., 2006; Nishikura, 2006; Heale et al., 2009). Editing is induced by a variety of small ncRNAs such as endogenous small interfering RNAs (siRNAs), PIWI-interacting RNAs (piRNAs), and short transcripts that sit adjacent to promoter (i.e., promoter-associated RNAs; Han et al., 2007) and transcription initiation RNAs (Mehler, 2008). Furthermore, targeted RNA editing in the 3′ untranslated region (UTR) can affect stability, translation, or localization of miRNAs (Kursten and Goodwin, 2003; Sue and Kuchka, 2011; Irimia et al., 2012). Taken together, these findings support the hypothesis that there is cross talk between RNA editing and the silencing machinery (Scadden and Smith, 2001; Blow et al., 2006; Nishikura, 2006; Ohman, 2007; Heale et al., 2009).

DYSREGULATED A–I EDITING IN NEURODEGENERATION

Adenosine (A) to inosine (I) conversion in mRNA transcripts (A to I RNA editing) is catalyzed by a family of enzymes known as ADARs. Since inosine has the same base pairing properties as guanosine (G), the transcription and translational machinery recognizes I as a G. Hence, a silent mutation is created at the level of mRNA. In general, A to I editing most frequently targets repetitive RNA sequences located within the introns and 5′ and 3′ UTR to alter both sequence and structure of RNA. A to I editing is widespread and essential for normal life and development (Valente and Nishikura, 2005; Horsch et al., 2011). The ADAR gene family and A-to-I RNA editing deregulation, which results in uncorrected forms of hyper- or hypoeediting, has been implicated in a spectrum of neurodevelopmental, neurodegenerative, and neuropsychiatric disorders, strongly suggesting diverse roles in post-transcriptional gene regulation (Valente and Nishikura, 2005).

A to I RNA editing of targeted substrates in the nervous system can alter functional properties of proteins, silence constitutive activity, and modulate RNA translation, localization, and stability (Paul and Bass, 1998; Bass, 2002). In addition to changing codons in mRNA, A to I editing also has the capacity to modulate splicing sites, small nucleolar RNA (snoRNA) precursors, endogenous antisense RNAs, microRNA (miRNA) target diversity, mRNA and ncRNA processing, and ribonucleoprotein complex targets (Rueter et al., 1999; Bass, 2002; Levanon et al., 2004; Blow et al., 2006).
itol hexaphosphate (IP6) buried within its enzyme core (Macbeth 1996; Chen et al., 2000). ADAR2 has been found to contain inosine expression. Taken together, these data identify unique modulatory forms of ADARs. Specifically, the p150 long cytoplasmic maturation comes from studies showing environmentally responsive central roles of RNA editing in brain evolution as well (Bass, 2002). ADAR2 activity can be modulated by sequestration in the nucleolus and nucleoplasmin shuffling (Desterro et al., 2003; Sansam et al., 2003), and ADAR mRNA itself is subject to self-editing, known as auto-editing, which restricts its function in the adult Drosophila and mice (Baer et al., 1999; Keegan et al., 2005; Feng et al., 2006).

In mammals, ADARs are differentially expressed during organogenesis (Paspal et al., 2005; Jacobs et al., 2009). ADAR3 is restricted to the brain, whereas ADAR2 and ADAR1 are ubiquitously expressed but preferentially expressed in the CNS (Bass, 2002). During progressive stages of nervous system maturation, RNA editing also displays complex and dynamic profiles of subcellular localization and spatiotemporal expression (Bass, 1999; Paspal et al., 2000; Sansam et al., 2003; Jacobs et al., 2009). Furthermore, both the behavioral state and genetic background can modify RNA editing (Englander et al., 2005). Changing environmental signals including inflammation and feedback regulation also modifies the activity and molecular profiles of ADARs (Bass, 2002; Yang et al., 2003; Valente and Nishikura, 2005). The potential central roles of RNA editing in brain evolution as well as gene-environmental interactions during nervous system neural maturation come from studies showing environmentally responsive forms of ADARs. Specifically, the p150 long cytoplasmic isoform of ADAR1, which selectively targets endogenous antisense RNA pathways, is interferon-inducible, and ADAR3 exhibits selective regional, developmental, and mature nervous system expression. Taken together, these data identify unique modular structures of ADARs (Melcher et al., 1996; Chen et al., 2000). ADAR2 has been found to contain inositol hexaphosphate (IP6) buried within its enzyme core (Macbeth et al., 2005). Moreover, amino acids that coordinate IP6 in ADAR2 are also conserved in adenosine deaminases that act on transfer RNAs (ADATs), and IP6 is required for ADAT activity (Macbeth et al., 2005), thereby linking ADAR2 to cell signaling pathways. Multiple isoforms of ADAR1 and ADAR2 exist in the cell (Bass, 2002). ADAR1 displays preferential tissue-specific promoter utilization, whereas ADAR2 exists as multiple spliced isoforms generated by alternative splicing, which results in expression of a broad array of protein species with unique enzymatic properties and remarkably conserved molecular activity (George et al., 2005; Kawahara et al., 2005). ADARs are normally found as functional dimers that can either homo- or heterodimerize with their own isoforms (Chihketh et al., 2006; Poulson et al., 2006; Valente and Nishikura, 2007). However, dimerization of ADAR3 requires additional CNS environmental cues (Cho et al., 2003). Different ADARs can also edit multiple different sites on the same RNA species, resulting in diverse functional outcomes (Valente and Nishikura, 2005). Studies with transgenic mouse embryos that are deficient in both ADAR and ADARB1 activity revealed that deficiency of ADARB1 leads to accumulation of specific miRNAs and corresponding targets, thereby suggesting an important role for ADARs in mRNA biogenesis (Luciano et al., 2004; Yang et al., 2006; Ohman, 2007; Heale et al., 2009; Alon et al., 2012; Vesely et al., 2012). Furthermore, ADARs binding alone can affect miRNA biogenesis and function and RNA interference in the nervous system (Heale et al., 2009; Pato et al., 2012). The biological roles of ADAR3 are particularly interesting due to its broad substrate specificity (binding single-stranded as well as double-stranded RNA) and localization that is restricted to brain regions and post-mitotic neurons (Melcher et al., 1996; Chen et al., 2009). ADAR3 can act as a dominant negative regulator for both ADAR1 and ADAR2 activity in vitro, thereby suggesting that correct expression levels of ADARs are required for optimal editing. Furthermore, ADAR3 can form heterodimers with both ADAR1 and ADAR2, providing mechanistic insight into the functional complexity associated with these enzymes in the brain (Chen et al., 2000).
Brain region-specific changes at the Q/R editing site of the GluR-B transcript have been described in both AD and HD (Akbarian et al., 1995a,b; Wright and Vissel, 2012). The pathology of sporadic ALS, a progressive neurodegenerative disease of spinal motor neurons (62–100% relative to controls with 100% expression of spinal motor neurons (Flomen and Makoff, 2011). On the other hand, ALS patients also have decreased editing of the Q/R site in GluR-B transcripts. 

Pharmacological studies provide a clear role for serotonin in psychiatric disorders such as schizophrenia, depression, and anxiety (Kennett et al., 1997; Martin et al., 1998). Editing of the 5HT2CR mRNA is involved in the pathophysiology of psychotic and neuronal cell death characteristic of this disease (Akbarian et al., 1995a,b). Collectively, these observations suggest a differential deregulation of A to I editing in ALS likely leads to disturbances in the Ca++ permeability and neuronal cell death characteristic of this disease (Akbarian et al., 1995b).

Dysregulated miRNAs in neurodegeneration

The biological significance of edited miRNAs remains unknown. However, the possibility of a role in RNA interference is likely (Haramati et al., 2010; Hansen et al., 2012). RNA editing regulates precursor miRNAs that play a role in the biogenesis and function of certain miRNAs, which are abundantly edited by ADARs (Alous et al., 2012; Vosly et al., 2012). Several pri-miRNAs are A to I edited, which can prevent processing at either stages or modify the targets of the final RISC complex (Kawahara et al., 2007). The fact that neural defects including tremors and neurodegeneration are present in ADAR-knockout Drosophila melanogaster makes a strong case for requirement of regulated A to I editing for normal behavior and nervous system functioning (Pollardino et al., 2008; Keegan et al., 2005; Jeppson and Reeman, 2010).

Non-coding RNAs, such as miRNAs, siRNAs, and pRNA all guide effector Argonaut proteins to either genomic loci or target RNAs in a sequence-specific manner (Mattick, 2003; Mattick and Makunin, 2005; Pang et al., 2006). Development and neural cell differentiation are regulated by brain-specific miRNAs (Haramati et al., 2010; Hansen et al., 2012). In the adult brain at various time points, miRNAs are known to regulate neural function and synaptic plasticity. Expression of miRNAs are tightly regulated during developmental processes, cell proliferation, neuronal gene expression, brain morphogenesis, neural cell fate, apoptosis, and stem cell division (Mattick, 2005; Mattick and Makunin, 2008; Matzke et al., 2005; Mehler, 2008; Gliem et al. and Zamore, 2009). The brain displays both temporal and region-specific miRNA expression, and the most abundant miRNA expression is observed in cerebellum and cerebral cortex (Haramati et al., 2010; Hansen et al., 2012). Depending on where miRNAs are localized, distinct miRNAs are also involved in memory formation (Hansen et al., 2012).

MicroRNAs can be derived from either the introns or exons of both protein-coding and ncRNAs transcribed by RNA polymerase II. Processed small hairpin RNAs or double-stranded RNA precursors give rise to miRNAs that are generally 21–23 nucleotide long (Bartel, 2004). miRNAs that contain 21–23 nucleotide regulatory sequences inhibit translation of targeted mRNA by base pairing with the targeted regions in the mRNA (Pal-Bhadra et al., 2002; Kuersten and Goodwin, 2003; Nishikura, 2006; Carell and Sontheimer, 2009). A number of miRNAs are associated with neurodevelopmental diseases, with the most abundant miRNA expression observed in cerebellum and cerebral cortex (Haramati et al., 2010; Hansen et al., 2012). Depending on where miRNAs are localized, distinct miRNAs are also involved in memory formation (Hansen et al., 2012).

MicroRNAs can be derived from either the introns or exons of both protein-coding and ncRNAs transcribed by RNA polymerase II. Processed small hairpin RNAs or double-stranded RNA precursors give rise to miRNAs that are generally 21–23 nucleotide long (Bartel, 2004). miRNAs that contain 21–23 nucleotide regulatory sequences inhibit translation of targeted mRNA by base pairing with the targeted regions in the mRNA (Pal-Bhadra et al., 2002; Kuersten and Goodwin, 2003; Nishikura, 2006; Carell and Sontheimer, 2009). A number of miRNAs are associated with neurodevelopmental diseases, with the most abundant miRNA expression observed in cerebellum and cerebral cortex (Haramati et al., 2010; Hansen et al., 2012). Depending on where miRNAs are localized, distinct miRNAs are also involved in memory formation (Hansen et al., 2012).
et al., 2012). Increased expression of micro-21 is linked to glioblastoma (Wang et al., 2012). Deregulated DICER expression, which is associated with neurofibromatosis 2 syndrome (Chen et al., 2012), is involved in microRNA processing and in learning disability. Tourette’s syndrome is associated with sequence variations in micro-189, which targets SLIT (axonal growth-controlling protein SLIT) in a mechanism that includes alterations in the micro-189 binding site in SLIT and Trk-like family member 1 (SLITRK-1) mRNA (Abelson et al., 2005), a protein that is essential for neuronal growth, guidance, and neurite branching. Deregulated mir-175 expression has been linked to the X-linked mental retardation (MRX3), which resembles an early onset PD. In Waisman syndrome, disruption of the 3′ UTR of fibroblast growth factor 20 (FGF20) by a mutation alters the recognition site of mir-433, which results in increased translation of FGF20 and is correlated with increased alpha-synuclein expression (Doutte et al., 2003; Wang et al., 2008; Harraz et al., 2011). All together these studies suggest that alterations in mRNA expression lead to dysregulated neuronal functioning.

**Dysregulated Small Nucleolar RNAs in Neurodegeneration**

While a role for ADARs in other ncRNAs has not been reported, ncRNAs form secondary structures that might be recognized by ADARs. Thus, it is possible that RNA editing or ADAR binding might alter structure and function of other ncRNAs described in the following sections. SnoRNAs range from 60 to 300 nucleotides in length and guide site-specific modification of nucleotides in target RNAs by base pairing with short regions of target RNA. SnoRNAs can be divided into two major classes: the box C/D snoRNAs, which guide 2′-O-ribose-methylation, and H/ACA snoRNAs that guide pseudouridylation of target RNAs (Kiss et al., 2002, 2004). Another group known as orphan snoRNAs because of their unknown functions have been identified. Targets include ribosomal RNA (rRNA; small nuclear snoRNAs), and miRNAs (Pang et al., 2006). Mammalian snoRNAs are derived from introns of protein-coding genes, non-protein coding RNAs and protein coding RNAs.

** Dysregulated Long Non-Coding RNAs in Neurodegeneration**

Numerous brain-specific lncRNAs are alternatively spliced, developmentally regulated, and are physiologically responsive (Furuno et al., 2006; Kapranov et al., 2007). IncRNAs that are derived from the mammalian genome are both polyadenylated and non-polyadenylated (Mattick and Gagen, 2002; Huang et al., 2012; Song et al., 2012). Imprinting and antisense transcription of IncRNAs that host genes for miRNAs and snoRNAs that are localized to the nucleus of nervous tissue suggest that these IncRNAs may be involved in gene regulation (Furuno et al., 2006). The transcription patterns of IncRNAs are in complex intergenic, overlapping, and antisense patterns relatively adjacent protein-coding genes (Satoh, 2012; Tran et al., 2012). The functions of numerous IncRNAs are not known but studies suggest that they play an important role in cell identifying the neuronal and glial cells in the CNS (Mercey et al., 2010).

Patients with HD have widespread changes in their brain gene regulatory networks (Ideler and Sharon, 2008). These changes include non-protein coding RNAs and protein coding RNAs. Seven IncRNAs in the human brain are specifically dysregulated in HD (Johnson, 2012). New findings suggest that, besides protein-coding genes, ncRNAs also contribute to neurodegenerative processes. Evidence for a role for ncRNAs in HD comes from the genome-wide data where novel, non-coding targets of REI-silencing transcription factor (REST) were discovered (Buckley et al., 2010; Johnson et al., 2010). A human accelerated region 1 (HAR1) specifically is transcribed in the nervous system. REST is targeted to the HAR1 locus that is recognized by specific DNA regulatory motifs and results in potent transcriptional repression. Abrupt nuclear localization of the master transcriptional repressor REST disrupts the gene regulatory networks in
Adenosine deaminase that act on RNA have the ability to spectrum of spliced and unspliced larger ncRNAs of unknown Reik, 2006). These imprinted loci usually generate a complex hyperactivity disorder, bipolar disorder, and Tourette’s syndrome neurological diseases caused by disruptions in imprinted loci: PWS genes in regulating distinct brain signaling systems and in mediating RNAs to reciprocally imprinted neighboring protein-coding genes associated with imprinted loci that include the production of antisense misfolded proteins in neurons, and induction of the endoplasmic results in mischarged tRNAs, intracellular accumulation of the “editing” domain of a specific aminoacyl-tRNA synthetase to change codon recognition. Interestingly, a mutation in act in concert with ADATs to modify transfer RNAs (tRNAs) in regulating gene expression for normal functioning of the nervous system.

DYSREGULATED IMPRINTED NON-CODING RNAs IN NEURODEGENERATION

Imprinted genes are known to play essential roles in both neu-ral development and adult CNS functioning. Alterations in their expression profiles are linked to a spectrum of complex neurode-velopment and neuropsychiatric disorders (Costa, 2005; Davis et al., 2005). These allele-selective genes exhibit preferential and exquisite cell-specific patterns of expression within the brain and are frequently processed from larger transcriptional units that encompasses multiple tandem repeats of snoRNAs and miRNAs (Sleutels et al., 2009; Costa, 2005; Davis et al., 2005; Lewis and Relk, 2006). These imprinted loci usually generate a complex spectrum of spliced and unspliced larger ncRNAs of unknown function (Sleutels et al., 2009; Costa, 2005; Davis et al., 2005; O’Neill, 2005; Furuno et al., 2006). Additional ncRNAs are associated with imprinted loci that include the production of antisense RNAs to reciprocally imprinted neighboring protein-coding genes (Sleutels et al., 2009; Davies et al., 2005). The role of imprinted genes in regulating distinct brain signaling systems and in mediating brains-behavior relationships can be deduced from spectrum of neurological diseases caused by disruptions in imprinted loci: PWS and Angelman syndromes, autism, schizophrenia, attention deficit hyperactivity disorder, bipolar disorder, and Tourette’s syndrome (Davies et al., 2004, 2005, 2006; Wang et al., 2006b).

DYSREGULATED TRANSFER AND RIBOSOMAL RNAs IN NEURODEGENERATIVE DISEASE

Adenosine deaminase that act on RNA have the ability to act in concert with ADATs to modify transfer RNAs (tRNAs) to change codon recognition. Interestingly, a mutation in the “editing” domain of a specific aminoacyl-tRNA synthetase results in mischarged tRNAs, intracellular accumulation of misfolded proteins in neurons, and induction of the endoplasmic reticulum-mediated unfolded protein stress response with associated neurodegeneration (Lee et al., 2006). tRNAs and tRNAs are implicated in a broad array of neural developmental and mature CNS functions. Not surprisingly, therefore, mutations in these two classes of ncRNAs underlie a range of neurode-velopment, neurodegenerative, and neuropsychiatric diseases. Such examples include chronic progressive external ophthalmoplegia (CPEO), Kearns–Sayre syndrome (KSS: CPEO with retinal degeneration), mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke (MELAS) syndrome that manifests in mitochondrial encephalopathy with stroke-like syndromes and migraine headaches, myoclonic epilepsy with ragged red fibers (MERRF) syndrome that results in myoclonus epilepsy, mito-chondrial myopathy, cerebella ataxia (Dimauro, 2004; Dimauro and Davidson, 2005; Fattal et al., 2006), and motor neuron disease (Borchelt et al., 2016). Other tRNA-mediated neuropsychiatric diseases include schizophrenia, psychosis, delirium, personality disorders, major depressive disorders, and anxiety disorders (Fattal et al., 2006). Besides tRNA-associated diseases, deregulated rRNA is also implicated in RNA oxidation of vulnerable neurons in AD (Honda et al., 2005).

DYSREGULATED RNA TRINUCLEOTIDE EXPANSIONS IN NEURODEGENERATION

The expansion of trinucleotide repeats caused by RNA-mediated mechanisms is associated with neurodegenerative diseases (Gallo et al., 2005; Gatchel and Zoghbi, 2005). Dramatically expanded (>200) CGG repeats in the 5′ UTR of the Fmrt1 gene results in fragile X syndrome. The related disease is also associated with smaller (60–200) trinucleotide repeat expansion called frag-ile X tremor/ataxia syndrome (FXTAS). FXTAS is associated with tremor, cerebella ataxia, cognitive decline, peripheral neuropathy, PD, autonomic dysfunction, proximal muscle weakness, multi-system atrophy, and dementia (Hagerman et al., 2005; Van Esch, 2006). Myotonic dystrophy, another trinucleotide disorder, is pre-dominantly a muscle disorder which exists in two neurological forms: DM1 with mental retardation, memory, visuo-spatial, and executive dysfunction, and DM2 with preferential executive dys-function (D’Angelo and Bresolin, 2006). DM1 is associated with CUG expansion within the 3′ UTR of the dystrophia myoton-ica protein kinase (DMPK) gene, and DM2 is linked to CCTG expansion in intron 1 of the zinc finger protein gene ZNF9 (Brook et al., 1992; Fu et al., 1992; Mahadevan et al., 1992; Ranum et al., 1998). These mutant RNAs orchestrate different forms of patho-geneses depending on the degree and type of expanded repeat length and their molecular interactions with the muscleblind-like (MBNL) family of RNA-binding proteins (Jiang et al., 2004; Pascual et al., 2006).

Several forms of spinocerebellar ataxia (SCA) are also impli-cated in different RNA-mediated pathological mechanisms. SCA8 results from CUG expansion of the 3′ UTR of an untranslated antisense RNA with partial overlap with the Kdch-like 1 (KILH1) gene (Koob et al., 1996; Nemes et al., 2000; Muttsuddi et al., 2004; Gatchel and Zoghbi, 2005). Utilizing SCA8 as a modifier screen, four novel mRNAs have been identified that show preferential neuronal expression (Mutsuddi et al., 2004). SCA10 is mediated by an unstable ATTCT repeat expansion in the 3′ end of a...
A gene regulatory network that allows normal functioning of the CNS governs this complex system. A deregulated complex involves the environment to the genome and plays important roles in a broad range of processes, from evolution to learning and memory. A to I RNA editing, besides altering protein function, also has the potential to alter splice site choice, miRNA target diversity, miRNA processing, and perhaps chromatin architecture. Furthermore, RNA editing alters RNA structure and thereby could potentially impact the biological functions of multiple types of ncRNAs. Therefore, RNA editing, RNA modification, small and long ncRNAs, and their complex regulatory network lead to a unifying theme of RNA-mediated regulatory circuitry for normal brain function.

ACKNOWLEDGMENTS

This research is supported by National Institute of Mental Health (MS) MH082234-02. The author would like to thank Dr. Kristina Thiel for critically reviewing the manuscript.

REFERENCES

Alderson, J. M., Nonaka, Y., O’Brien, B. J., Baek, S. Y., Stillman, A. A., Morgan, T. M., et al. (2003). Sequence variants in SLITRK1 are associated with Tourette’s syndrome. Science 306, 317–320.

Altheimer, S., Mhtamiri, M. M., Kieu, J. H., Iadarola, M., Florin, S. G., Bantock, N. W., E., J., (1993a). GABA receptor subtype gene expression in human prefrontal cortex: comparison of normal subjects and Tourette’s syndrome. Neuro. Com. 536, 556–560.

Altheimer, S., Smith, M. A., and Joffe, M. E. (1993). Is there an AMPA receptor subtype mRNA in prefrontal cortex and striatum in Alzheimer’s disease, Huntington’s disease and schizophrenia. Brain Dev. 15, 297–304.

Allen, S., Moor, E., Vigneault, F., Church, D., Athanasiadis, A., Rich, A., and Maas, www.frontiersin.org January 2013 | Volume 3 | Article 326 | 7

Bass, B. L. (2002). RNA editing by ADAR1. Gene 297, 87–94.

Beal, M. F., Jellinger, A., and Parkinson, J. M. (2007). The dystrophy and biology of RNA editing by adenosine deaminase acting on RNA (ADAR1). Brain Res. 1192, 85–94.

Bernard, A., Ferrah, L., Douzi, E., Chatain, G., Represa, A., Ben-Ary, Y., et al. (1999). QQR editing of the mouse GluR7 and GluR8 kainate receptors in vivo and in vitro: evidence for independent developmental, pathological, and cellular regulation. Eur. J. Neuroscience 11, 616–619.

Bass, S., and Sun, T. (2011). Functions of removing RNAs in neural development and neurological diseases. Mol. Neuroscience 46, 359–373.

Blow, M. J., Grocock, R. J., Van Dongen, A., S. M., Locatelli, F., Galeano, F., and d’Hondt, S. (2008). Systematic identification of edited microRNAs in the human brain. Genome Res. 18, 1533–1540.

Bock, B., A., Rich, A., and Mann, S. (2004). Widespread A-to-I RNA editing of Alu-containing miRNAs in the human transcriptome. PLoS Biol. 2, e391. doi: 10.1371/jour nal.pbio.0020391

Brunner, P., and Allman, F. H. (2012). ADAR proteins double-stranded RNA and Z-RNA binding domains. Curr. Top. Microbiol. Immunol. 353, 35–66.

Burk, D. J. (2004). MicroRNAs: genesis, biogenesis, mechanism, and function. Cell 116, 281–297.

Buckley, W. I., Johnson, R., Zuccato, C., Bittell, A., and Cattaneo, E. (2010). The role of RIST in transcriptional and epigenetic deregulation in Huntington’s disease. Neurobiol. Dis. 38, 28–39.

Burns, C. M., Cho, H., Ruizier, S. M., Huxley, L. K., Catron, H., Sanders-Bush, E., et al. (1997). Regulation of serotonin-2C receptor G protein-coupling by RNA editing. Nat. Rev. 3, 303–308.

Cathro, R. W., and Arnow, E. J. (2008). Origins and Mechanisms of miRNAs and siRNAs. Cell 136, 642–653.

Caralle, J., Butting, K., Konemann, M., Lalande, M., Brenton, C. G., Hoehnle, B., et al. (2000). Identification of brain-specific and imprinted RNA-editing enzymes. EMBO J. 19, 1594–1603.

Chen, Z., Wu, J., Yang, C., Fan, P., Balan, L., Jiao, Y., et al. (2012). Dissecting the role of critical region 8 (DGCR8)-protein-mediating microRNA biogenesis is Essential for Vascular Smooth Muscle Cell Development in Mice. J. Biol. Chem. 287, 19108–19128.

Childick, K. A., Wu, T., Liang, C., Schellenberg, M. J., Genev, E. M., Lynch, J. M., et al. (2006). FRET analysis of in vivo dimerization by RNA-editing enzymes. J. Biol. Chem. 281, 16350–16355.

Chen, D. S., Yang, W., I., Loo, T. J., Sukhova, R., Murray, J. M., and Nakamura, K. (2003). Requirement for dimerization by RNA editing activity of adenosine deaminases acting on RNA. J. Biol. Chem. 278, 17021–17027.

Clark, S. J., (2007). Action at a distance: epigenetic silencing of large chromosomal regions in carcinogenesis. J. Mol. Genet. 16, 848–859.

Costa, F. F. (2005). Non-coding RNAs: new players in eukaryotic biology. Gene 357, 83–94.

large intron of a gene of unknown function that may result in transcriptional silencing or in a different RNA-associated toxic mechanism (Matsura et al., 2009). SCA12 is caused by CAG expansion in the non-coding 5′ promoter or 5′ UTR of the PPP2R2B gene, which encodes a brain-specific regulatory subunit of protein phosphatase 2A (Holmes et al., 1999). All together these findings suggest that elucidating the IncRNA network is an important step toward understanding neurodegeneration and may reveal new targets to treat neurodegenerative diseases.

SUMMARY

RNA is a carrier of information and plays a central role in regulating development. A variety of regulatory non-protein-coding RNA molecules form complex multi-layered biological systems. A gene regulatory network that allows normal functioning of the CNS governs this complex system. A deregulated complex gene regulatory network plays a significant role in common neurodegenerative diseases. Furthermore, the list of known ncRNAs implicated in mammalian brain health and disease is growing.

RNA can alter the information in the genetic code without altering the hard-wired DNA through its splicing and RNA editing. ADAR substrates involved in RNA editing mechanisms provide functional complexity. RNA editing mediates the environmental cues by transmitting information to the epigenome. This mechanism connects the environment to the genome and plays important roles in a broad range of processes, from evolution to learning and memory. A to I RNA editing, besides altering protein function, also has the potential to alter splice site choice, miRNA target diversity, miRNA processing, and perhaps chromatin architecture. Furthermore, RNA editing alters RNA structure and thereby could potentially impact the biological functions of multiple types of ncRNAs. Therefore, RNA editing, RNA modification, small and long ncRNAs, and their complex regulatory network lead to a unifying theme of RNA-mediated regulatory circuitry for normal brain function.
RNA editing and non-coding RNAs

Davies, W., Isles, A. R., Burgoyne, D’Angelo, M. G., and Bresolin, N. (2006). Cognitive impairment at the epigenetic level: para-mutation from the plant to the mouse. Curr. Opin. Genet. Dev. 16, 193–198.

D’Angelo, M. G., and Brodvin, N. (2008). Cognitive impairment in neuromuscular disorders. Muscle Nerve 36, 16–55.

Davies, W., Isles, A. R., Burgoyne, P. S., and Wilkinson, L. S. (2004). X-linked imprinting effects on brain and behaviour. Behaviour 28, 35–44.

Davies, W., Isles, A. R., and Wilkinson, L. S. (2005). Imprinted gene expression in the brain. Neurobiol. Appetite. 29, 423–450.

Davies, W., Smith, B., Keeler, G., and Wilkinson, L. S. (2004). Expression patterns of the novel imprinted genes Nap1l5 and Peg1c and their non-imprinted host genes in the adult mouse brain. Gene Expr. Pattern 4, 741–747.

Davies, E., Czarnetzki, F., Tooyuki, I., Canuilla, J., Ferguson-Schroeder, C., Cocklett, N., et al. (2005). RNA-mediated allele-translation at the imprinted Rplq1 locus. Curr. Biol. 15, 745–749.

Dentorn, I. M., Keegan, L. P., Lafarga, M., Beric, M. T., O’Connell, M., and Carmo-Fonseca, M. (2003). Dynamic association of RNA-editing enzymes with the nucleus. J. Cell Sci. 116, 1805–1818.

Dimmig, S. (2004). Mitochondrial medicine. Rockefeller Ann. Rev. 16, 107–117.

Dimmig, S., and Davidson, G. (2005). Mitochondrial DNA and disease. Ann. Med. 37, 222–232.

Ding, F., Prinz, Y., Dhan, M. S., John- son, D. G., Karnachev-Montero, C., Niedobitek, G., B., et al. (2005). Lack of Prc1P in B10.A5 snRNA is critical for normal fertility in Prader-Willi syndrome mouse models. Mamm. Genome 16, 424–431.

Dinger, M. E., Peng, K. C., Mercer, T. R., and Mattick, J. S. (2006). Differentiation, protein-encoding, and noncoding RNA challenges and ambiguities. PloS Comput. Biol. 2:e1000176. doi: 10.1371/journal.pcbi.1000176

Doe, C. M., Relkovic, D., Garfield, A. S., Dinger, M. E., Pang, K. C., Mercer, T. R., et al. (2009). Loss of the imprinted host gene Nap1l5 and peg13 and their non-imprinted transcripts in the preimplantation mouse embryo. Nat. Genet. 41, 127–130.

Eisenberg, E., Nemzer, S., Kinar, Y., Harati, N., Sorek, R., Rechavi, G., and Lev- ervson, E. Y. (2005). A mushroom to-I RNA editing transcript spliced to a transcript coding for a putative RNA editing enzyme. Trends Genet. 21, 77–81.

Emmons, R. B., and Singh, M. (2005). “Adenosine to inosine RNA editing: substrates and consequences.” In RNA Editing: Frontiers in Molecular Biology. Eds. B. L. Bass, D. M., Morgan, T. E., et al. (2008). Differen- tial gene expression in mice lacking ADAR2 and epigenetic control of development. Proc. Natl. Acad. Sci. U.S.A. 105, 13929–13934.

Enca, A. M., Popovac, B. G., and Ghosh-Guinnavar, A. (2012). MicroRNAs in brain development and degeneration. Mol. Biol. Rep. 39, 2243–2252.

Englander, M., Dolans, M., Bhanuk, P., and Schumacher, C. (2005). How stress and fluorescent modu- late serotonin 2C receptor pre-mRNA editing. J. Neurosci. 25, 648–651.

Faghihi, M. A., Macosko, E. J., Khalil, A. M., Wood, D. E., Sakagun, B. G., Meegdon, T. E., et al. (2008). Expression of a novel editing-dependent RNA is elevated in Alzheimer’s disease and drives cortical fever in a model of beta-secretase. J. Med. 114, 725–730.

Fatidis, T., Buken, R., Vaughan, A. J., and Frances, K. (2006). Review of the literature on major muscle disorders in adult patients with mitochondrial disease. Physiotherapy 45, 1–7.

Feng, Y., Sansam, C. L., Singh, M., and Sansam, C. L., et al. (2011). 5-HT(2C) receptor RNA editing in mice lacking Adar2. J. Biol. Chem. 286, 652–654.

Ferron, L., Terret, H., Arango, V., Dower, A. I., Mann, J. J., and Schuman, S. (2002). Altered editing of serotonin 2C receptor pre-mRNA in the perirhinal cortex of depressed suicide victims. Neurop. 34, 541–550.

Finkelstein, E., A., Ayice, D. Y., Shriem, C. C., Siddi, M. S., and Santer, B., et al. (2006). 5-HT[4] receptor RNA editing in the amygdala of C57BL/6 and BALB/c mice. Neurosci. Res. 55, 96–104.

Fischer, E. J. T., Evans, M. Y., and Hagerman, P. J. (2005). Recent advances in fragile X: a model for autism and neurodevelopment. Curr. Opin. Psychiatry 18, 495–499.

Furuta, H., Kim, S. W., and Morris, K. V. (2007). Promoter-associated RNA is required for RNA-directed transcription. J. Biol. Chem. 282, 23422–23427.

Gallo, J. M., Jin, P., Thornton, C. A., Lin, S., and Obrietan, K. (2012). Anti-miRNA-155 and miRNA-152: a dynamic regulator of cognitive capacity. Brain Struct. Func. doi: 10.1007/s00381-012-2032-0 (in press ahead of print).

Ghildiyal, M., and Zamore, P. D. (2009). MicroRNAs in brain development involves tissue-selective pro- moter utilization and alternative splicing. J. Biol. Chem. 284, 15025–15026.

Gheorghian-Galateanu, A. (2012). DNA methylation in neurodegenera- tion. Brain Struct. Function 217, 1037–1053.

Gillis, J. M., Jin, F., Thornton, C. A., Lin, H., Robertson, J., and Dusana, S., et al. (2005). The role of RNA and RNA processing in neurodegeneration. J. Neurosci. 25, 10372–10375.

Gorick, E., Nemzer, S., Kinar, Y., Harati, N., Sorek, R., Rechavi, G., and Lev- ervson, E. Y. (2005). The role of RNA and RNA editing microRNAs in neurodegeneration in ALS spinal motor neurons. Neurobiol. Dis. 31, 1121–1128.

Gorick, E., Nemzer, S., Kinar, Y., Harati, N., Sorek, R., Rechavi, G., and Lev- ervson, E. Y. (2005). The role of RNA and RNA editing microRNAs in neurodegeneration in ALS spinal motor neurons. Neurobiol. Dis. 31, 1121–1128.

Gorick, E., Nemzer, S., Kinar, Y., Harati, N., Sorek, R., Rechavi, G., and Lev- ervson, E. Y. (2005). The role of RNA and RNA editing microRNAs in neurodegeneration in ALS spinal motor neurons. Neurobiol. Dis. 31, 1121–1128.

Gorick, E., Nemzer, S., Kinar, Y., Harati, N., Sorek, R., Rechavi, G., and Lev- ervson, E. Y. (2005). The role of RNA and RNA editing microRNAs in neurodegeneration in ALS spinal motor neurons. Neurobiol. Dis. 31, 1121–1128.

Gorick, E., Nemzer, S., Kinar, Y., Harati, N., Sorek, R., Rechavi, G., and Lev- ervson, E. Y. (2005). The role of RNA and RNA editing microRNAs in neurodegeneration in ALS spinal motor neurons. Neurobiol. Dis. 31, 1121–1128.

Gorick, E., Nemzer, S., Kinar, Y., Harati, N., Sorek, R., Rechavi, G., and Lev- ervson, E. Y. (2005). The role of RNA and RNA editing microRNAs in neurodegeneration in ALS spinal motor neurons. Neurobiol. Dis. 31, 1121–1128.
Ishimoto, K., Nakamura, N., Bando, M., Yoshikawa, T., and Kato, T. (2005). Altered RNA editing of serotonin 2C receptor in a rat model of depression. Neurosci. Res. 50, 69–78.
Jacobs, M. M., Fog, B. L., Emerson, R. B., and Stampfl, G. D. (2008). AIM202 and AIMAR expression and editing activity during forebrain development. Dev. Neurosci. 31, 223–237.
Jepson, J. E., and Roenan, R. A. (2010). Unraveling plasticity functions of A-to-I RNA editing in Drosophila. Fly (Austin) 4, 194–198.
Jiang, H., Markaki, A., Swansen, M. S., Morley, R. T., and Therion, C. A. (2004). Mysterious dystrophic type 1 is associated with nuclear foss of mutant RNA, sequestration of muscleblind proteins and desegregated alternative splicing in neurons. Hum. Mol. Genet. 13, 3879–3888.
Johnson, R. (2012). Long non-coding RNAs in Huntington’s disease neurodegeneration. Nucleic Acids Res. 40, 265–274.
Johnson, R., Richter, N., Jauch, R., Kawahara, Y., Sun, H., Ito, K., Kapranov, P., Cheng, J., Dike, S., Nix, D., et al. (2009). The long and protein-encoding RNAs in rhesus monkeys (M. mulatta). Hum. Mol. Genet. 18, 53–60.
Kim, J., Krichevsky, A., Grad, Y., Hayes, R. J., Murre, C., and Maniatis, T. (2002). A Cajal body-specific dsRNA-binding domain and required for RNA editing. Cell 109, 951–961.
Kim, J., Elbashir, M., and Bass, B. L. (2005). Inositol hexakaphosphate is bound in the ADAR2 members of the RNA-specific adenosine deaminase family. Nucleic Acids Res. 33, 5910–5916.
Kim, D. D., Kim, T. E., Wallah, T., Kobayashi, Y., Marino, C. T., Berekov, S., et al. (2004a). Widespread RNA editing of embryonic alu elements in the human transcriptome. Genome Res. 14, 1719–1729.
Kim, J., Kräcker, A., Goyal, V., Hayes, G. D., Koike, K. S., Church, G. M., et al. (2004b). Identification of many microRNAs that copiously with poly(A) addition in mammalian neurons. Proc. Natl. Acad. Sci. U.S.A. 101, 801–806.
Kohlbrenner, S., Khanna, A., Zhang, Z., Hua, J., Baecker, P. J., Soden, M., et al. (2010). A HOU1 RNA-binding module (SNORD 115) is processed into a 3′UTR: translation and splicing.
Kwak, S., Nishimoto, Y., and Yamashita, T. (2008). Noisy identity of AID-mediated A-to-I editing positions as a tool for ALS research. RNA Biol. 5, 193–197.
Laas, P., and de Strooper, B. (2010). Dysregulated microRNAs in neurodegenerative diseases. Senil. Cell Dev. Biol. 21, 768–773.
Leu, J. W., Busch, K., Nagel, L. A., Iaung, J., Longo-Guess, C. M., Cook, S. A., et al. (2006). Editing-defective RNA synthetase causes protein misfolding and neurodegeneration. Nature 440, 50–55.
Levato, E. Y., Eisenberg, E., Yelin, Y., Nemir, S., Hallegger, M., Scherbel, R., et al. (2004). Systematic identification of abundant A-to-I editing sites in the human transcriptome. Nat. Biotechnol. 22, 1001–1005.
Lewis, A., and Rod, W. (2006). How imprinting centre works. Cytogenet. Genome Res. 113, 81–89.
Luciano, D. J., Mirsky, H., Vendetti, N. J., and Mancini, T. (2011). Epigenetic principles and mechanisms underlying nervous system functions in health and disease. Prog. Neurobiol. 86, 305–348.
Mandel, M. F., and Mattick, J. S. (2007). Non-coding RNA: Flav. Med. Genet. 15, R17–R29.
Mattick, J. S., and Malik, M. F. (2008). RNA editing: DNA encoding and the evolution of human cognition. Trends Neurosci. 31, 223–227.
Mattie, K., Kanno, T., Huelter, D., Dasinger, L., and Mattie, A. J. (2007). Targets of RNA-directed DNA methylation. Curr. Opin. Plant Biol. 10, 512–519.
Meier, U. T. (2005). Epigenetic principles and mechanisms underlying nervous system functions in health and disease. Prog. Neurobiol. 86, 305–348.
Melcher, T., Maas, S., Herb, A., Sprenkel, P., Cheng, J., Dka, S., Nio, D. A., Dumont, R., Willingham, A. T., et al. (2007). RNA maps reveal new RNA classes and a possible function for pervasive transcription. Science 316, 1484–1488.
Mendel, J., Scola, D., and Mattick, J. S. (2009). The long and protein-encoding RNAs in rhesus monkeys (M. mulatta). Hum. Mol. Genet. 18, 53–60.
Mendel, M. F., and Mattick, J. S. (2007). Non-coding RNAs and RNA editing in brain development, functional divergence, and neurobiological disease. Physiol. Rev. 87, 799–823.
Mitschke, M. F., and Mattick, J. S. (2007). Non-coding RNAs and RNA editing in brain development: functional divergence, and neurobiological disease. Physiol. Rev. 87, 799–823.
Mitschke, M. F., and Mattick, J. S. (2007). The many facets of HUCA-ribonucleaseprotein. Chromosome 11A1–14.
Mitschke, M. F., Maas, S., Herb, A., Sprenkel, P., Cheng, J., Dka, S., Nio, D. A., Dumont, R., Willingham, A. T., et al. (2007). RNA maps reveal new RNA classes and a possible function for pervasive transcription. Science 316, 1484–1488.
RNA editing and non-coding RNAs

Singh

Page 10

Frontiers in Genomics | Non-Coding RNA

January 2013 Volume 3 Article 328 10

Mitsukori, Z., and Kovalchuk, I. (2011). Epigenetic memory in mam- mals. Front Genet. 2:48. doi: 10.3389/fgen.2011.00028

Miyake, K., Hirasawa, T., Koide, T., and Kubota, T. (2012). Epigenetics in autism and other neurodevelopmental dis- orders. Adv. Exp. Med. Biol. 724, 91–98.

Moschetti, M. V., Ahn, A. J., Hood, J. L., Kesterson, R. A., Jacobs, M. M., Kump, D. S., et al. (2010). Mice with altered serotonin 2C receptor RNA editing display characteristic behaviors of Prader–Willi syndrome. Neurobiol. Dis. 39, 168–181.

Morse, D. P., Amanzoe, P. J., and Bao, B. L. (2002). RNA hairpin in noncoding regions of human brain and Caenorhabditis elegans mRNA are edited by adenosine deaminases that act on RNA. Proc. Natl Acad. Sci. U.S.A. 99, 7906–7911.

Mutsuddi, M., Marshall, C. M., Ron- zone, K. A., Koob, M. D., and Reiley, J. (2004). The synaptic cisternal area 8 non-coding RNA causes neu- rodegeneration and associates with failed in Drosophila. Genes Brain Behav. 3, 302–308.

Nierman, Y., Levenon, E. Y., Jantsch, M. F., and Eisenberg, E. (2006). RNA editing level in the mouse is determined by the genomic repeat repertoire. RNA 12, 1802–1809.

Namas, J. P., Boren, K. A., Mosley, M. L., Ramsay, L. P., and Kroh, M. D. (2000). The SCA8 transcript is a brain-specific transcript encoding a novel actin- binding protein (KLHL1). J. Biol. Chem. 275, 35315–35322.

Pal-Bhadra, M., Bhadra, U., and Birch-Niswender, C. M., Copeland, S. C., Nishikura, K. (2006). Editor meets Morabito, M. V., Abbas, A. I., Hood, M. S., Davis, T. K., and Emeson, R. B. (1999). Regulation of alternative splicing by RNA editing. Nature 399, 75–80.

Parnell, S. L., O’Connell, M. A., and Keegan, L. P. (2012). Regulation and functions of ADAR in Drosophila. Curr. Opin. Immunol. 24, 221–226.

Pardap, M. C., O’Connell, M. A., Gers- bert, A. F., and Zitnik, S. (2008). Patterns of developmental expression of the RNA editing enzyme EDE1. Neurosci. 159, 809–879.

Pawson, H., Jorgenson, R., Fiskling, A., Nelson, F. C., Rournen, B., and Egelhoj, Y. (2006). Dimethylation of ADAR is mediated by the deubiquitinating enzyme UIMD. Nat. Neurosci. 9, 1171–1177.

Pearl, M. A., and Bass, B. L. (1995). Inte- site exists in mRNAs at tissue-specific levels and is most abundant in brain mRNA. EMBO J. 14, 3125–3137.

Pendzich, B., Freier, S. M., and Bennett, C. F. (1999). RNA editing through RNA nuclear retention. EMBO J. 18, 249–253.

Pieretti, M., and Mehlert, M. F. (2011). Non-coding RNA networks underlying cognitive disorders across the lifespan. Trends Mol. Med. 17, 387–398.

Quax, A. L., and Mehlert, M. F. (2012). Emerging roles of non-coding RNAs in brain evolution, development, plasticity and disease. Nat. Rev. Neurosci. 13, 121–138.

Ramam, L., Pfeiffer, P. F., Benson, K. A., Koob, M. D., and Day, J. W. (1997). Genetic mapping of a second mysotrophic dystrophia loci. Nat Genet. 19, 199–198.

Ronan, K. A. (2001). The RNA world meets behavior: A → U pre-RNA editing in animals. Trends Genet. 17, 53–56.

Rogelj, B., and Gieco, P. (2004). Expression and function of brain specific small RNAs. Rev. Neurosci. 15, 189–198.

Rogelj, B., Hartmann, C. E., Yeo, C. H., Bertrand, E., Muscatelli, F., and Cavaille, C. (2009). The imprinting mechanism. Curr. Opin. Genet. Dev. 19, 225–233.

Saita, E., and Ste Drepper, B. (2012). Non-coding RNAs with essential roles in neurodevelopmental disorders. Lancet Neurol. 11, 169–180.

Sarbach, H., Fong, C. G., Dixon, T. G., and Cygan, J. F. (2012). Gliadin signalling and obesity: at the inter- face of stress, mood and food reward. Pharmacol. Ther. 135, 316–320.

Schwender, C., Prasanth, S. G., Prasanth, K. V., Xuan, Z., Patel, M., Kump, D. S., et al. (2010). Mice misexpressing the RNA editing enzyme ADAR2 is mediated by the double-stranded RNA binding domain. EMBO J. 19, 1360–1369.

Singh, M., Kesterson, R. A., Jacobs, M. M., Joers, J. M., Gieco, P., and Emeson, R. B. (2007). Hyperphagia-mediated obesity in transgenic mice overexpressing the RNA editing enzyme ADAR 2. J. Biol. Chem. 282, 24480–24485.

Singh, M., Singh, M. M., Na, E., Agas- sundan, R., Zimmerman, M. B., and Johnson, A. K. (2011). Altered ADAR 2 expression and miRNA levels in the prefrontal cortex of ADAR 2 transgenic mice. Genes Brain Behav. 10, 437–447.

Singh, M., Singh, M. M., Na, E., Agas- sundan, R., Zimmerman, M. B., and Johnson, A. K. (2011). Altered ADAR 2 expression and miRNA levels in the prefrontal cortex of ADAR 2 transgenic mice. Genes Brain Behav. 10, 437–447.

Singh, M., Mous, B. T., Gieco, P., and Mehlert, M. F. (2007). The uniqueness of the RNA editing enzyme ADAR among animals. EMBO J. 26, 22448–22459.

Singh, M., Kesterson, R. A., Jacobs, M. M., Joers, J. M., Gieco, P., and Emeson, R. B. (2007). Hyperphagia-mediated obesity in transgenic mice overexpressing the RNA editing enzyme ADAR 2. J. Biol. Chem. 282, 24480–24485.

Sikosek, J., Babow, D. P., and Ilye, R. (2005). The uniqueness of the imprinting mechanism. Curr. Opin. Genet. Dev. 19, 225–233.

Souilli, M. S., Airoc, D. C., Lambert, W., Burnet, P. W., Harrison, J. S., and Sanders-Bush, E. (2005). A rapid new assay to detect RNA editing reveals encephalitic-derived changes in serotonin-2C receptors. Mol. Pharmacol. 68, 711–719.
RNA editing and non-coding RNAs in neurodegeneration

Singh M (2013) Dysregulated A to I RNA editing and non-coding RNAs in neurodegeneration. Front. Gene. 3:326.

doi: 10.3389/fgene.2012.00326

Conflict of Interest Statement: The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Received: 25 July 2012; accepted: 28 December 2012; published online: 22 January 2013.

Citation: Singh M (2013) Dysregulated A to I RNA editing and non-coding RNAs in neurodegeneration. Front. Gene. 3:326.

This article was submitted to Frontiers in Non-Coding RNA, a specialty of Frontiers in Genetics.

Copyright © 2013 Singh. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits use, distribution and reproduction in other forums, provided the original authors and source are credited and subject to any copyright notices concerning any third-party graphics etc.