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The Emerging Roles of MicroRNAs in the Pathogenesis of Frontotemporal Dementia–Amyotrophic Lateral Sclerosis (FTD-ALS) Spectrum Disorders

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Abstract

Increasing evidence suggests that frontotemporal dementia (FTD) and amyotrophic lateral sclerosis (ALS) share some clinical, pathological, and molecular features as part of a common neurodegenerative spectrum disorder. In recent years, enormous progress has been made in identifying both pathological proteins and genetic mutations associated with FTD-ALS. However, the molecular pathogenic mechanisms of disease onset and progression remain largely unknown. Recent studies have uncovered unexpected links between FTD-ALS and multiple aspects of RNA metabolism, setting the stage for further understanding of the disorder. Here, the authors will focus on microRNAs and review the emerging roles of these small RNAs in several aspects of FTD-ALS pathogenesis.

Keywords

ALS; C9ORF72; CHMP2B; FTD; FUS; MicroRNA; neurodegeneration; progranulin; TDP-43

INTRODUCTION

Frontotemporal dementia (FTD) refers to a few clinically heterogeneous conditions characterized by progressive behavioral changes, deficits in executive function, and/or language impairments (Neary et al., 2005; Seelaar et al., 2011). Amyotrophic lateral sclerosis (ALS) is a degenerative motor neuron disease that causes progressive muscle wasting and eventual paralysis (Pasinelli & Brown, 2006). FTD and ALS are linked clinically, pathologically, and molecularly by several lines of evidence. First, about 15% of ALS patients have cognitive and behavioral impairments compatible with FTD (Wheaton et al., 2007), and some FTD patients meet the criteria for ALS (Lomen-Hoerth et al., 2002; Vercelletto et al., 1999). Moreover, in some familial cases, both FTD and ALS phenotypes occur between generations (Morita et al., 2006; Vance et al., 2006). Second, in both

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diseases, a few pathological proteins such as TDP-43, FUS, and p62 are found in neuronal aggregates (Al-Sarraj et al., 2011; Arai et al., 2003, 2006; Kwiatkowski et al., 2009; Neumann et al., 2006, 2009; Vance et al., 2009). Finally, mutations in the same genes, such as in vasolin-containing protein (*VCP*) (Johnson et al., 2010; Watts et al., 2004), charged multi-vesicular body protein 2B (*CHMP2B*) (Cox et al., 2010; Parkinson et al., 2006; Skibinski et al., 2005), Ubiquilin-2 (*UBQLN2*) (Deng et al., 2011), 43-kDa transactive response DNA-binding protein (*TARDBP*) (Borroni et al., 2009; Sreedharan et al., 2008), Fused in Sarcoma (*FUS*) (Kwiatkowski et al., 2009; Van Langenhove et al., 2010; Vance et al., 2009), and *C9ORF72* (DeJesus-Hernandez et al., 2011; Renton et al., 2011), can lead to either FTD or ALS. Unfortunately, all forms of FTD-ALS spectrum disorder are fatal, as no effective treatment is available.

MicroRNAs (miRNAs) are a class of a small (~21–23-nucleotide [nt]) noncoding RNAs that regulate gene expression mostly through 3' untranslated regions (3'UTRs) (Ambros, 2001; Huntzinger & Izaurralde, 2011). In the canonical miRNA biogenesis pathway (Figure 1), RNA polymerase II generates a long primary transcript that is rapidly cleaved by a nuclear complex formed by Drosha and DGCR8. This precursor miRNA (pre-miRNA) is exported to the cytoplasm to be further processed by Dicer. In the resulting imperfect RNA duplex, one strand (passenger strand) is usually degraded, and the other (guide strand) is loaded into an RNA-induced silencing complex. After target recognition, miRNA–mRNA interactions result in transcript degradation, translation inhibition, or both (Huntzinger & Izaurralde, 2011; Krol et al., 2010). Target sequences recognized by each miRNA are short enough to be found in up to hundreds of transcripts. As a result, miRNAs have the unique ability to coordinately regulate the levels of several genes in the same pathway (Herranz & Cohen, 2010).

Since their discovery (Lee et al., 1993; Wightman et al., 1993), miRNAs have emerged as important regulators of many biological processes (e.g., Gao, 2010; Inui et al., 2010; McNeill & Van Vactor, 2012; Pauli et al., 2011). More importantly, increasing evidence supports a role for miRNAs in human pathology, including many neurodegenerative diseases (e.g., Abe and Bonini, 2013; Esteller, 2011; Farazi et al., 2013; Gascon & Gao, 2012; Small & Olson, 2011). In this review, we discuss the latest evidence indicating the importance of miRNAs in the pathogenesis of FTD-ALS. As a starting point, we briefly summarize those miRNAs found to be dysregulated in the disease. Then, we point out how different genetic mutations causing FTD-ALS could alter miRNA pathways. Finally, we provide some mechanistic insights into how miRNAs might affect neuronal physiology and contribute to the onset and progression of disease.

miRNAs ARE DYSREGULATED IN FTD-ALS

Improvements in sequencing technologies have allowed exploration of genome-wide changes in the transcriptome of FTD-ALS patients (Chen-Plotkin et al., 2008; Rosen et al., 2011; Shtilbans et al., 2011). Each miRNA can regulate up to hundreds of mRNA targets, and these interactions often result in mRNA degradation. Thus, it is possible that transcriptome alterations detected in FTD-ALS patients derive, at least partially, from disruption of miRNA networks. Indeed, recent studies using miRNA microarrays or RNA

deep sequencing to assess alterations in the miRNA landscape in FTD-ALS (Campos-Melo et al., 2013; Chen-Plotkin et al., 2012; Hebert et al., 2013; Kocerha et al., 2011) have revealed extensive changes in the expression of miRNAs. A number of miRNAs (e.g., miR-132 and miR-34) are consistently dysregulated across independent cohorts of patients, suggesting misregulation of some miRNAs might be a common event in neurodegeneration. Recent data from animal and in vitro models provide experimental evidence for the contribution of these miRNAs to neuronal survival (Liu et al., 2012; Wong et al., 2013). Finally, several miRNAs are differentially expressed between FTD patients with progranulin mutations and FTD patients with other mutations, suggesting that different mutations result in disease subtype-specific miRNA signatures (Kocerha et al., 2011).

Although potentially interesting, these profiling data should be interpreted cautiously, owing to the limited number of patient samples and potential indirect effects, such as an exaggerated inflammatory response in diseased brains. Nonetheless, the data suggest that miRNAs are significantly altered in FTD-ALS, consistent with the notion that they may have a crucial role in disease pathogenesis.

POTENTIAL CONNECTIONS BETWEEN MIRNAS AND FTD-ALS-CAUSING MUTATIONS

Mutations in a number of genes cause both FTD and ALS. Here, we will briefly summarize the potential links between these genes and miRNAs (Figure 1). For more thorough coverage of the pathogenic mechanisms in FTD-ALS or the roles of miRNAs in other neurodegenerative diseases, readers are referred to recent review articles (Abe & Bonini, 2013; Gascon & Gao, 2012; Ling et al., 2013; Robberecht & Philips, 2013; Sleegers et al., 2010).

TARDBP

The groundbreaking discovery of TDP-43, encoded by the *TDP-43* gene, as the major constituent of tau-negative and ubiquitin-positive aggregates helped to establish the molecular link between FTD and ALS (Arai et al., 2006; Neumann et al., 2006). TDP-43 mutations were then found in ALS patients and also rarely in FTD patients (Borroni et al., 2009; Sreedharan et al., 2008; Winton et al., 2008). Although TDP-43 protein encompasses several identifiable motifs, most of these mutations map to the C-terminal glycine-rich domain (Da Cruz & Cleveland, 2011).

TDP-43 is a DNA/RNA-binding protein that has major roles in mRNA metabolism, such as transcription, splicing, transport and translation (Buratti et al., 2001; Da Cruz & Cleveland, 2011; Wang et al., 2008a). Interestingly, TDP-43 may also contribute to miRNA processing. TDP-43 was identified as part of a large protein complex containing Drosha but without microprocessor activity (Gregory et al., 2004). However, recent studies not only confirmed the association between TDP-43 and Drosha (Ling et al., 2010) but also showed that TDP-43 binds directly to a subset of pri-miRNAs to facilitate the production of pre-miRNAs (Kawahara & Mieda-Sato, 2012). Moreover, in HEK293 cells, cytoplasmic TDP-43 promotes pre-miRNA processing by binding to Dicer (Kawahara & Mieda-Sato, 2012). In

Drosophila, TDP-43 seems to regulate miR-9a levels by interacting with pri-miR-9a and likely promoting its stability (Li et al., 2013). Thus, TDP-43 may affect multiple steps in the miRNA pathway. In further support of the notion that TDP-43 regulates some but not all miRNAs, TDP-43 down-regulation in cultured HeLa cells, rodent neurons, or induced pluripotent stem cells (iPSC)-derived human neurons leads to changes in the expression levels of selected miRNAs (Buratti et al., 2010; Zhang et al., 2013). These observations have been recently confirmed in tissue from ALS patients (Freischmidt et al., 2013). Thus, it is possible that *TARDBP* mutations or sequestration of TDP-43 protein in neuronal aggregates results in dysregulation of TDP-43 activity, leading to miRNA alterations that might contribute to FTD-ALS pathogenesis.

FUS

FUS, a highly conserved RNA/DNA-binding protein, participates in multiple cellular functions, ranging from regulation of gene expression and RNA processing (splicing and transcription) to the DNA damage response and spine morphogenesis (Fujii et al., 2005; Uranishi et al., 2001; Wang et al., 2008b, 2013; Yang et al., 1998; Zinszner et al., 1997). Very much like TDP-43, FUS is also found in cytoplasmic aggregates in FTD-ALS patients (although in a much lower proportion of patients). Similarly, *FUS* mutations are largely associated to ALS and only occasionally to FTD and cluster mainly in the last 17 amino acids and in the glycine-rich region (Da Cruz & Cleveland, 2011; Kwiatkowski et al., 2009; Neumann et al., 2009; Vance et al., 2009).

FUS was also found in a large protein complex containing overexpressed Drosha (Gregory et al., 2004), but this finding was not confirmed in a subsequent study (Kawahara & Mieda-Sato, 2012). However, FUS might bind to pri-miRNAs at transcriptional sites as well and recruit Drosha for miRNA processing (Morlando et al., 2012). Interestingly, ALS-causing TDP-43 mutations result in more stable proteins with higher FUS binding affinity (Ling et al., 2010), raising the possibility these two disease proteins have overlapping functions in the miRNA pathway.

CHMP2B, Ubiquilin-2, and VCP

CHMP2B is a member of the ESCRT complex, a set of proteins involved in endosomal trafficking and autophagy (Henne et al., 2013; Hurley & Hanson, 2010). Mutations in *CHMP2B* were first identified in a Danish pedigree with autosomal dominant FTD (Skibinski et al., 2005) and were later linked, at lower frequencies, to ALS (Cox et al., 2010; Parkinson et al., 2006). Mutations tend to affect the C-terminal domain of the protein. Together with other ESCRT subunits, CHMP2B is primarily involved in membrane deformation/remodeling (Henne et al., 2013). It has been shown that, in eukaryotic cells, many aspects of mRNA biology take place at discrete cytoplasmic granules enriched in proteins involved in transcript degradation (i.e., decapping machinery) and translational repression known as P-bodies. Recent evidence suggests that interactions of P-bodies and endosomal membranes are required for optimal miRNA-mediated silencing (Gibbings et al., 2009; Lee et al., 2009). More importantly, both studies demonstrated that ESCRT mutants have impaired miRNA function, expanding the role of ESCRT machinery to miRNA-linked repression. In addition, mutant CHMP2B causes accumulation of abnormal autophagosomes

(Filimonenko et al., 2007; Lee & Gao, 2009; Lee et al., 2007; Lu et al., 2013). Intriguingly, autophagy might control miRNA activity by targeting Dicer and Ago2 for degradation (Gibbings et al., 2012; Zhang & Zhang, 2013). It remains to be determined how disease-associated mutant CHMP2B affects the functions of specific miRNAs.

Other FTD-ALS genes are *UBQLN2* and *VCP*. Mutations in *UBQLN2* could lead to either FTD or ALS, whereas those in *VCP* are preferentially linked to FTD. Both proteins are involved in autophagy. *UBQLN2* is a member of the ubiquilin family, which regulates degradation of ubiquitinated proteins through the ubiquitin proteasome system or autophagy (Kleijnen et al., 2003; Lee & Brown, 2012; Rothenberg et al., 2010). Mutations in *UBQLN2* affect mainly its proline-rich region and lead to abnormal protein degradation (Deng et al., 2011). *VCP*, a member of the diverse AAA-ATPase protein superfamily, has a role in autophagosome maturation (Tresse et al., 2010). The majority of the *VCP* mutations are localized in the ubiquitin-proteasome domain (Kimonis et al., 2008). Thus, it is tempting to speculate these two disease genes also affect the miRNA pathway by altering autophagy. In agreement with this hypothesis, stress granules, formed largely by RNA and RNA-associated proteins in eukaryotic cells, are cleared through autophagy (Buchan et al., 2013). This clearance is impaired by FTD-causing *VCP* mutations, indicating that it could be important under pathological conditions. Together, these observations suggest that impaired autophagy in patients with *UBQLN2*, *VCP*, or *CHMP2B* mutations might cause miRNAs alterations.

C9ORF72

In 2006, two studies identified a chromosome 9p locus associated with both FTD and ALS, providing an additional genetic link between the two diseases (Morita et al., 2006; Vance et al., 2006). The genetic mutation turned out to be GGGGCC repeat expansions in *C9ORF72* (DeJesus-Hernandez et al., 2011; Renton et al., 2011) and the most common genetic cause of both FTD and ALS (Majounie et al., 2012). Patients with *C9ORF72* expansion show TDP-43 aggregates but also TDP-43-negative and p62-positive inclusions (Al-Sarraj et al., 2011; Murray et al., 2011). Moreover, RNA foci containing the GGGGCC repeats (DeJesus-Hernandez et al., 2011) and dipeptide-repeat aggregates originating from repeat-associated non-ATG (RAN) translation were observed in patient brain tissues (Ash et al., 2013; Mori et al., 2013b).

Although the function of the *C9ORF72* gene product remains unknown, a recent report suggested that, in the mouse, expression of this locus is particularly high in those neuronal populations more vulnerable to the disease (Suzuki et al., 2013). *C9ORF72* repeat expansions may contribute to the pathogenesis of FTD-ALS by at least three potential mechanisms. First, the expression of some *C9ORF72* isoforms may be down-regulated, suggesting a potential haploinsufficiency mechanism (DeJesus-Hernandez et al., 2011; Majounie et al., 2012). Second, repeat-associated non-ATG (RAN) translation generates dipeptide-repeat proteins that aggregate in patient neurons (Ash et al., 2013; Mori et al., 2013b). Third, as in other repeat expansion diseases (Nelson et al., 2013), RNA species containing the repeats accumulate in nuclear foci in patient brains or iPSC-derived neurons (Almeida et al., 2013; DeJesus-Hernandez et al., 2011; Donnelly et al., 2013; Sareen et al.,

2013). Furthermore, antisense RNAs from repeats have been shown to form nuclear foci and can also be RAN translated (Gendron et al., 2013; Lagier-Tourenne et al., 2013; Mizielinska et al., 2013; Mori et al., 2013a; Zu et al., 2013).

RNA foci are toxic in other repeat diseases, such as myotonic dystrophy type 1, and have been proposed to be a major pathogenic mechanism (Lee & Cooper, 2009). By sequestering RNA-binding proteins (i.e., muscleblind in myotonic dystrophy 1), RNA foci disrupt specific aspects of RNA metabolism, such as transcription or splicing. Indeed, targeting RNA foci with antisense oligonucleotides could alleviate some of the disease's phenotypes and aberrant splicing (Donnelly et al., 2013; Lagier-Tourenne et al., 2013; Sareen et al., 2013). Whether RNA foci in C9ORF72 expansions could result in changes in the miRNA pathway remains unknown. CGG repeats in fragile X-associated tremor/ ataxia syndrome sequester the microprocessor and alter miRNA processing (Sellier et al., 2013). Given the sequence similarity, this observation raises the possibility that GGGGCC expansions might affect miRNA biogenesis through an analogous mechanism. Alternatively, miRNA might simply be altered in C9ORF72 patients because of TDP-43 aggregation. It will be interesting to determine which mechanism(s) are at work in C9ORF72 patients.

Progranulin

Mutations in the *GRN* gene cause autosomal dominant FTD (Baker et al., 2006; Gass et al., 2006). Progranulin, a secreted glycoprotein, is processed into granulins after extracellular cleavage (Ward & Miller, 2011). Although the function of progranulin and its role in neurodegeneration remain largely unknown, many pathogenic mutations in progranulin are null mutations that lead to haploinsufficiency (Baker et al., 2006; Gass et al., 2006). Indeed, reduced progranulin expression in heterozygous *GRN* mice or in human neurons derived from patient-specific iPSCs results in disease-relevant behavioral or cellular phenotypes (Almeida et al., 2012; Filiano et al., 2013).

miRNAs are important in regulating progranulin levels. For instance, a genetic polymorphism in the *GRN* 3'UTR is associated with a higher risk of FTD-ALS and affects the miR-659 binding site, resulting in decreased progranulin levels (Rademakers et al., 2008). Similarly, miR-29b and miR-107 directly regulate progranulin levels (Jiao et al., 2010; Wang et al., 2010). Moreover, three members of the miR-132 cluster are significantly down-regulated in FTD brains with TDP-43 inclusions; as a result, TMEM106B, a risk factor for FTD (Van Deerlin et al., 2010), is up-regulated, which in turn affects the progranulin pathways (Chen-Plotkin et al., 2012). Thus, multiple miRNAs may contribute to the pathogenesis of FTD due to progranulin deficiency.

CONCLUDING REMARKS

Although it is well established that global loss of miRNAs through Dicer knockdown results in neurodegeneration (Cuellar et al., 2008; Damiani et al., 2008; Davis et al., 2008; Haramati et al., 2010; Schaefer et al., 2007), the precise roles of specific miRNAs are a focus of current research. The onset of neurodegenerative diseases involves synaptic dysfunction in the absence of overt neuronal cell death (Bezprozvanny & Hiesinger, 2013; Selkoe, 2002). Misregulated miRNAs may contribute to eventual neuro-degeneration through chronic

changes in synaptic functions. For instance, miR-132 expression is dependent on neuronal activity (Nudelman et al., 2010) and regulates several aspects of synaptic plasticity (Mellios et al., 2011; Tognini et al., 2011). Another mechanism by which miRNAs might contribute to FTD-ALS pathogenesis is by acting upstream of the described mutations, such as miRNAs targeting TMEM106B or progranulin described above.

Additional molecular clues could be obtained by studying genetic risk factors for FTD-ALS in addition to known disease-causing mutations listed above. For example, alleles with intermediate CAG expansions (26–33 triplets) in *Ataxin-2* are linked to increased risk of ALS (Elden et al., 2010; Laffita-Mesa et al., 2013; Lee et al., 2011). In *Drosophila* olfactory neurons, Ataxin-2 interacts with Ago1 and regulates miRNA function (McCann et al., 2011), highlighting again a potential link between miRNAs and ALS. The role of miRNAs in ALS seems to extend beyond motor neurons. Muscular miRNAs such as miR-206 also contribute to progression of the disease in animal models (Williams et al., 2009).

Finally, it will be important to further explore potential therapies that target miRNAs, as expression of specific miRNAs could largely ameliorate disease symptoms and progression in ALS animal models (Koval et al., 2013; Williams et al., 2009). Exciting times are ahead as we begin to unravel how disruption of intricate miRNAs networks contributes to disease pathogenesis and learn to exploit the potential of these tiny but versatile RNA molecules as novel therapeutic tools.

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Figure 1.

Schematic representation of miRNA biogenesis, mechanism of action, and potential steps at which some FTD/ALS-causing mutations could disrupt the miRNA pathway. The inset represents an enlarged view of P-bodies and endosomal membrane, where miRNAs and miRNA-repressible mRNAs seem to be enriched (Gibbins et al., 2009; Lee et al., 2009). MVB = multivesicular body; ESCRT = endosomal sorting complexes required for transport.