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Understanding microRNAs in Neurodegeneration

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Abstract

The recent explosion of interest in microRNAs (miRNAs) in the nervous system has recently expanded to the investigation of their role in neurodegeneration. These studies have begun to reveal the influence of miRNAs on neuronal survival and the accumulation of toxic proteins associated with neurodegeneration as well as providing clues as to how these toxic proteins can influence miRNA expression.

In recent years, several classes of small regulatory RNAs have been identified in a variety of tissues in many species. One such class of small RNAs are microRNAs (miRNAs), 18–25 nucleotide long RNAs that are generated by a series of cleavage events from long, polymerase II-transcribed RNA[1]. miRNAs act to guide the RNA-induced silencing complex (RISC) to mRNAs that have a target sequence that is complementary to the miRNA (Figure 1A). The interaction between miRNA and target need not be completely complementary: the most important pairing involves nucleotides 2–7 of the miRNA, the so-called ‘seed sequence’. With some rare exceptions[2], an mRNA targeted by RISC will be translationally silenced or will be destabilized and degraded[3]. In either case, the outcome is a decrease in protein production, with consequences for biological function that depend upon the mRNA targeted. In the nervous system these include effects on neurogenesis[4–6], dendritic outgrowth[7, 8] and dendritic spine formation[9, 10].

Alterations in the tuning of protein production can have serious consequences and is linked to many neurodegenerative diseases. For example, one extra copy of the normal α-synuclein gene was sufficient to cause Parkinson’s disease (PD) in one family[11]. Similarly, duplication of the gene encoding the amyloid precursor protein (*APP*)[12, 13] or mutations in its regulatory region that increase its transcriptional activity[14, 15] can lead to early onset Alzheimer’s disease (AD) or increased risk of AD, respectively. These examples highlight what is

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thought to be a central mechanism in neurodegenerative diseases: increased accumulation of toxic protein, leading to neuronal dysfunction.

miRNAs could modulate the accumulation of these toxic proteins by regulating the mRNA encoding the toxic protein itself or by regulating the mRNAs encoding proteins that modulate expression of the disease causing protein (Figure 1B). Furthermore, miRNAs might contribute to the pathogenesis of neurodegenerative disease downstream of the accumulation of toxic proteins by altering the expression of proteins that promote or inhibit cell survival. In this article, we discuss our current understanding of the contributions of miRNAs to neurodegenerative disease (Table 1) and consider how recent advances in technology may be implemented to advance the field.

miRNAs support neuronal survival

Neural cell death is the defining feature of all neurodegenerative diseases and the underlying cause of many functional deficits. Understanding the pathways that promote and prevent cell death in the nervous system is therefore essential for an understanding of disease pathology and to devise effective treatment strategies. Neuronal survival is supported by a variety of proteins, including those that provide trophic support such as brain-derived neurotrophic factor (BDNF), glial-derived neurotrophic factor (GDNF), and nerve growth factor (NGF). Pro-survival proteins such as BCL-2 and BCL-x_L, also act to inhibit cell death programs. miRNAs might regulate neuronal survival by inhibiting negative regulators of these pro-survival factors, or might regulate the pro-survival proteins themselves in response to survival cues such as neuronal activity.

A blunt, but useful, approach to define the roles of miRNAs in any function, including neuronal survival, is to disable the miRNA biogenesis pathway. In particular, these studies have been used to investigate the role of miRNAs in neuronal survival during development. One of the first studies to investigate the role of miRNAs in neuronal survival utilized a cerebellar Purkinje cell-specific knockout of *Dicer*, an enzyme essential for the generation of miRNA[16]. This resulted in the depletion of all mature miRNAs in these cells and was associated with a progressive neurodegenerative phenotype characterized by ataxia (loss of motor control) and Purkinje cell degeneration[17].

In another study, *Dicer* was inactivated under the control of the *dopamine receptor 1-Cre* (*DR1-Cre*) driver which caused the gene to be deleted in the DR1-expressing neurons of the striatum[18]. The *Dicer* mutants generated with *DR1-Cre* had significantly lower brain masses than their wild-type littermates, a phenotype that was suggestive of neurodegeneration. Surprisingly there were signs of reactive gliosis – a condition associated with neuronal cell death – but no clear sign of degeneration in the adult *DR1-Cre* mutants. The authors of the study therefore suggested that the decreased brain mass might have resulted from a combination of neuronal death during development and hypertrophy of *Dicer*-null neurons.

Similar observations were made in *Dicer* mutants generated using the *Calmodulin kinase II-Cre* (*CamKII-Cre*) driver, which inactivates *Dicer* in several regions, including the forebrain[19]. These mice had substantially smaller brains than control mice, which was shown to be due in part to increased cell death in the early postnatal period. The complexity

of the dendritic architecture of CA1 hippocampal neurons was also dramatically reduced in the *CamKII-Cre* knockouts, although it is not clear whether this was a degenerative or developmental effect. For both *DR1-Cre* and *CamKII-Cre Dicer* ablations, developmental neuronal death seemed to contribute to the gross reduction in brain mass, consistent with miRNAs playing a significant role in neuronal development. As is the case with most developmental processes, neuronal number is determined by balancing the levels of cell division and programmed cell death. Therefore, it is difficult to say whether the gross phenotypes observed in the *DR-1-Cre* and *CamKII-Cre Dicer* mutants are due to cell death, the absence of cell proliferation, or both. Deletion of *Dicer* in mature mouse olfactory neurons had little effect on the survival or function of these neurons, although ablation of *Dicer* in immature olfactory neurons results in failed differentiation of the neurons[20]. Deletion of *Dicer* in the developing cortex of mice using the *Emx1-Cre* line[5] results in the ablation of *Dicer* from embryonic day (E)9.5, which corresponds to the initiation of cortical neurogenesis. As in the olfactory system, cortical progenitor pools seem unaffected by the removal of miRNAs. Furthermore, the first wave of neurogenesis seems to occur normally; however, by E12.5 massive numbers of apoptotic cells were observed in the neuronal layer of the developing cortex.

Although problems associated with the long half-lives of miRNAs and Dicer made these experiments complicated, these results seems to suggest that miRNA are not required in the neural progenitors, but are required for the specification and survival of some types of mature neurons. Whether key individual miRNA/target pairs or broad regulation of the neuronal proteome is the critical factor for neuronal survival in these knockout models remains to be determined. Together these studies have established a critical role for miRNAs in the survival of neurons, but the precise mechanism by which miRNA promote survival will require further research.

A direct connection between a pro-survival gene and a miRNA in a neurodegenerative disease was made by the discovery of a common single nucleotide polymorphism (SNP) in the 3′ UTR of the *progranulin* (*GRN*) gene. GRN is a secreted protein with anti-apototic properties that have been described outside the CNS[21]. Significantly, mutations in *GRN* are linked to familial forms of frontotemporal lobe demntia (FTLD)[22–24]. This 3′ UTR SNP was found to be associated with a sub-type of frontotemporal lobe dementia [25] and enhances the ability of the human-specific *miR-659* to bind to and regulate the translation of *GRN* mRNA. The authors showed that GRN protein is reduced in tissue from patients with the disease-associated SNP. Using quantitative reverse transcription polymerase chain reaction (qRT-PCR), they found that *miR-659* is expressed in the brain. However, *miR-659's* relative abundance in the tissue affected in FTLD is unknown, making the relevance of this particular miRNA in the pathogenesis of FTLD currently unclear. Nevertheless, this study may provide the basis for further fruitful inquiry into the role of miRNA regulation in FTLD.

miRNAs alter protein accumulation

A common theme among many neurodegenerative conditions is the accumulation of proteins that are toxic to neurons. There are many points in the pathways leading to

production of toxic proteins at which miRNAs could conceivably act and at which changes in miRNA activity might be important. Most directly, there might be a loss of direct miRNA regulation of a toxic protein's mRNA. But perhaps equally as importantly, there could be a loss of miRNA-mediated regulation of proteins involved in the production or degradation of toxic proteins.

A recent study profiled miRNAs in AD patients and age-matched controls and found a small number of miRNAs with modestly altered expression levels[26]. Armed with this data, the authors used *in silico* predictions of miRNA targets to determine which miRNAs to pursue (Box 1). Among the down-regulated miRNAs, *miR-29a/b* were shown to be capable of regulating the *beta-site APP cleaving enzyme 1* (*BACE1*) 3′ UTR in a luciferase reporter assay. BACE1 has a central role in producing the toxic Aβ peptide, the principal component of the plaques that characterize AD. Indeed, the authors demonstrated a significant correlation between lower expression of *miR-29a/b* and higher expression of BACE1 in brain tissue. *miR-29a/b* is thought to be ubiquitously expressed in neurons and astroglia, suggesting that the specific reduction in its expression is not a secondary consequence of the death of specific neuronal populations. Transfection of *miR-29a/b* in HEK293 cells expressing APP – the precursor from which Aβ peptide is formed – significantly reduced the production of the Aβ peptide. This suggests that *miR-29a/b* is capable of significantly modulating BACE1 and consequently the production of the toxic Aβ peptide. Currently there is no evidence to indicate that genetic polymorphisms in *miR-29a/b* or the 3′ UTRs of *APP* or *BACE1* contribute to AD, suggesting that the *miR-29a/b-BACE1* interaction may not be causative in familial forms of AD[27].

Box 1

miRNA Target Prediction Programs

A miRNA requires very few base pair interactions to effectively silence a target mRNA. The most critical region for interaction is the 'seed sequence' (nucleotides 2–7 of the miRNA). Since a sequence of this length will occur with high frequency in the genome by chance alone, predicting functional miRNA target sites, even within the constraint of 3′ UTRs, is challenging. Most target prediction programs identify hundreds of potential targets for any given miRNA. This may lead to user bias since it is likely that there will be a gene of interest within the list of hundreds of predicted targets. This is particularly true for heavily studied genes with long, well annotated 3′ UTRs. Most successful target prediction alogrithims rely on evolutionary conservation to identify 6-mer, or longer, seed region homologies that may indicate functional homology. This obviously precludes clade-specific target sites that may have important functional significance. Two recent studies of miRNA mutants were used to investigate the impact of the loss of a single miRNA on proteome-wide protein level[41, 42]. These two studies agreed that the most comprehensive and accurate prediction programs are currently TargetScan and PicTar. Diana-microT has also been evaluated with favorable outcome. Despite the relatively good performance of TargetScan and PicTar, two-thirds of their predicted targets were not affected by the absence of the miRNA[41] (see REF 43 for a review).

Another mechanism by which miRNAs could affect protein accumulation in neurodegenerative disease is through polymorphisms in 3′ UTRs that could either add or eliminate miRNA target sites in mRNAs. For example, a recent study of risk factors for PD identified a point mutation in the 3′ UTR of the *fibroblast growth factor 20* (*FGF20*) gene that disrupts a *miR-433* binding site[28]. FGFs have been shown to regulate α-synuclein *in vitro*[29] and increases in α-synuclein expression can act as a causative agent in the development of PD[30]. The 3′UTR polymorphism can increase the expression of FGF20 and alter the expression of α-synuclein in cell culture. One major caveat of these findings is that the low level of *miR-433* detected in the brain may mean it is unlikely that this specific interaction has relevance to PD pathology. However, it is possible that *miR-433* is expressed in a minor cell population with relevance for PD. To address this possibility, future studies could use *in situ* hybridization to determine if dopamine neurons or neighboring cells are enriched in *miR-433* expression. This could lending credence to the hypothesis that a miRNA with a low expression level could effect α-synuclein expression though FGF signaling in disease-relevant cell types. However, it is also worth noting that a recent study was unable to reproduce any association between PD and FGF20[31].

One of the early observations that suggested that miRNAs might be involved in neurodegenerative disease was made in a *Drosophila* model of spinal cerebellar ataxia[32]. In this study, neurodegeneration caused by overexpression of a poly-glutamine expanded human ataxin in the *Drosophila* eye was enhanced by a heterozygous mutation in *Dicer1*. Conversely, overexpression of the *bantam* miRNA suppressed ataxin-induced neurodegeneration, although the mechanism by which the suppression occured remains unclear. Overexpression of poly-glutamine expanded human ataxin is also toxic in HEK293 cells; in this model, as in the fly eye, ataxin toxicity was enhanced by knockdown of Dicer suggesting that the enhancement is a generalizable phenomenon. Although this study did not produce evidence that miRNAs directly regulate ataxin expression, a related study showed that a variety of miRNAs were capable of regulating the human *Ataxin* mRNA in HEK293 cells[33]. Importantly, the authors showed that these miRNAs are expressed in Purkinje cells, one of the main target cell types of the disease. Either the knockdown of these miRNAs or the deletion of the miRNA binding sites in the 3′ UTR of the *Ataxin* mRNA accentuated Ataxin-induced toxicity in HEK293 cells. Experiments in Purkinje cells and *in vivo* will be required to further determine the importance of these miRNA-*Ataxin* interactions in the brain.

miRNAs downstream of toxic proteins

Although the accumulation of toxic proteins is thought to be the cause of many neurodegenerative conditions, the mechanism by which the toxic proteins cause cell death remains controversial. One possible mechanism by which they might do this is by interfering with miRNA-mediated regulation of pro-survival proteins.

Profiling of miRNA expression in tissue from patients with Huntington's Disease (HD) demonstrated significant decreases in *miR-9/9** expression as disease progressed[34].. The authors showed that alterations in *miR-9* and *miR-9** could affect the expression of the RE-1 silencing transcription factor (REST) and its co-repressor protein, CoREST. This was

significant because upregulation of the REST repressor complex can have deleterious effects on neuronal gene expression, repressing pro-survival genes like *BDNF* that may contribute to HD pathogenesis[35]. These results, together with those of other recently published HD studies suggest that a reciprocal transcription-translation circuit exists through which REST can in turn repress *miR-9* transcription. The activity of REST is increased by mutant Huntingtin protein[35], the protein that causes HD. Previous studies have shown that REST binds to DNA upstream of neuronally expressed miRNAs including the three genomic loci from which *miR-9* is transcribed, as well as *miR-124* and *miR-132*[36].

The interaction between REST and the upstream regions of *miRNA*s was confirmed by another group studying the impact of REST-mediated transcription in the context of HD[37]. These authors also investigated the expression of *miRNA* in post-mortem HD brain. Although many of the conclusions of these two studies were similar, there was little similarity between findings regarding the expression of miRNAs in post-mortem HD brain. For instance, REF 37 reported a significant decline in *miR-132* expression in post-mortem HD cortex, whereas REF 34 noted a significant increase in *miR-132* expression in late stage HD brain. This may be a consequence of differing methods of measuring miRNA expression levels, the noted heterogeneity in gene expression profiles in HD brains, or may indicate that the small sample size of each study is insufficient to power analysis of the data.

Profiling post-mortem tissue also identified reduced *miR-133b* in the midbrain of PD patients[16]. One trivial explanation for the reduction of *mR-133b* in PD patients is that it is enriched in the dopamine neurons that are lost during disease progression. This seems to be the case as *miR-133b* is enriched in the midbrain and is depleted in mouse models that are deficient in dopamine neurons, suggesting that loss of *miR-133b* is downstream of the accumulation of toxic protein and dopamine neuron death. However the authors of this study also uncovered a developmental feedback loop through which PITX3, a transcription factor that has a key role in dopamine neuron development, regulates *miR-133b* transcription and *miR-133b* in turn represses PITX3 synthesis. Whether this regulatory loop contributes to the survival of midbrain dopamine neurons, or whether *miR-133b* regulates other important factors in dopamine neurons remains to be determined.

Future Efforts

Exploiting miRNA biology to understand and treat neurologic disease is a novel and exciting opportunity. How will our understanding of miRNA in neurodegeneration intersect with therapeutics? miRNA-based interventions that enhance the endogenous neuroregenerative or neuroprotective capacity of the CNS are of course attractive. However, at the current time, targeting specific miRNAs in order to directly treat neurodegenerative diseases faces many challenges. The first challenge is understanding the breadth of the regulation of proteins by miRNAs. A single miRNA may regulate the expression of a few proteins or a large network of proteins. The cellular feedback loops and regulation of miRNA expression are not yet known. There is also a paucity of validated miRNA targets and there are difficulties in delivering of miRNA reagents to the brain. However, these are resolvable challenges. The delivery of oligonucleotides, ribozymes, siRNA and mRNA using viral and non-viral methods for gene therapy is currently the focus of extensive efforts

in medical research. Although effective delivery to neural tissues has yet to be realized, significant advances have been achieved through nanotechnology[38]. Using oligonucleotide-based miRNA therapy has the advantage of being transient, whereas viral or transgenic modification presents a variety of risks including viral-induced inflammation and oncogenesis.

Bearing in mind these challenges, there may nevertheless come a time when regulation of the expression or activity of miRNAs may be possible and have a clear therapeutic benefit. One possible strategy would be to enhance the expression miRNAs that target toxic proteins by providing either synthetic miRNA or virally expressed miRNA. Inhibiting miRNA-mediated repression of a neuroprotective mRNA may also represent an important therapeutic approach. Using miRNA in an *ex vivo* setting to expand cultures or to push stem cells to adopt appropriate fates also holds promise for models of neurodegenerative disease or replacement therapies. All of these approaches will require significant advances in delivery technology in order to be successful In addition, a precise understanding of miRNA-target relationships, including the cells in which each are expressed, is an absolute requirement for therapies to be effective. In order to arrive at this point there must be improvements in how we investigate miRNA expression and function.

One such improvement would be the use of cell-type specific miRNA expression profiles. Although there is clear value in expression profiling of tissue from disease patients, knowing where and when the miRNAs are expressed has important implications not only for disease mechanisms, but also for possible therapeutic intervention. Recent advancements in *in situ* hybridization techniques may rapidly improve what has been a largely ignored caveat to miRNA profiling studies[39]. Similarly, very few profiling experiments have begun to consider miRNA expression in neurons versus glia. This is an obvious and important question when considering the mechanism of miRNA action. Currently, our understanding of miRNA action suggests that they are stoichiometric inhibitors of mRNA translation. Therefore, only the most abundant miRNAs in a given tissue or cell type should be considered relevant to the biology of the tissue or cell. This further emphasizes the importance of localization of miRNAs to specific cell types in the identification of miRNAs that are likely to have relevance in neurodegenerative conditions.

Unbiased methodologies for miRNA target identification will also be an important advance. *In silico* methods for target identification are constantly improving (Box 1). Although already much improved, experimental methods are still emerging and will be essential tools for understanding how changes in miRNA expression will affect the proteome of a cell. A recent study may point the way toward resolving this question[40]. By using high-throughput sequencing coupled with cross-linking immunoprecipitation (HITS-CLIP) of RNA that is bound by RISC, the authors were able to identify both the miRNAs that are expressed in the brain and their likely mRNA targets. This represents an important leap forward in experimental miRNA target identification but still does not resolve questions of cell-type specific miRNA expression. It is likely that these technical advancements will yield significant details that will push forward our understanding of the neural miRNA system in health and disease.

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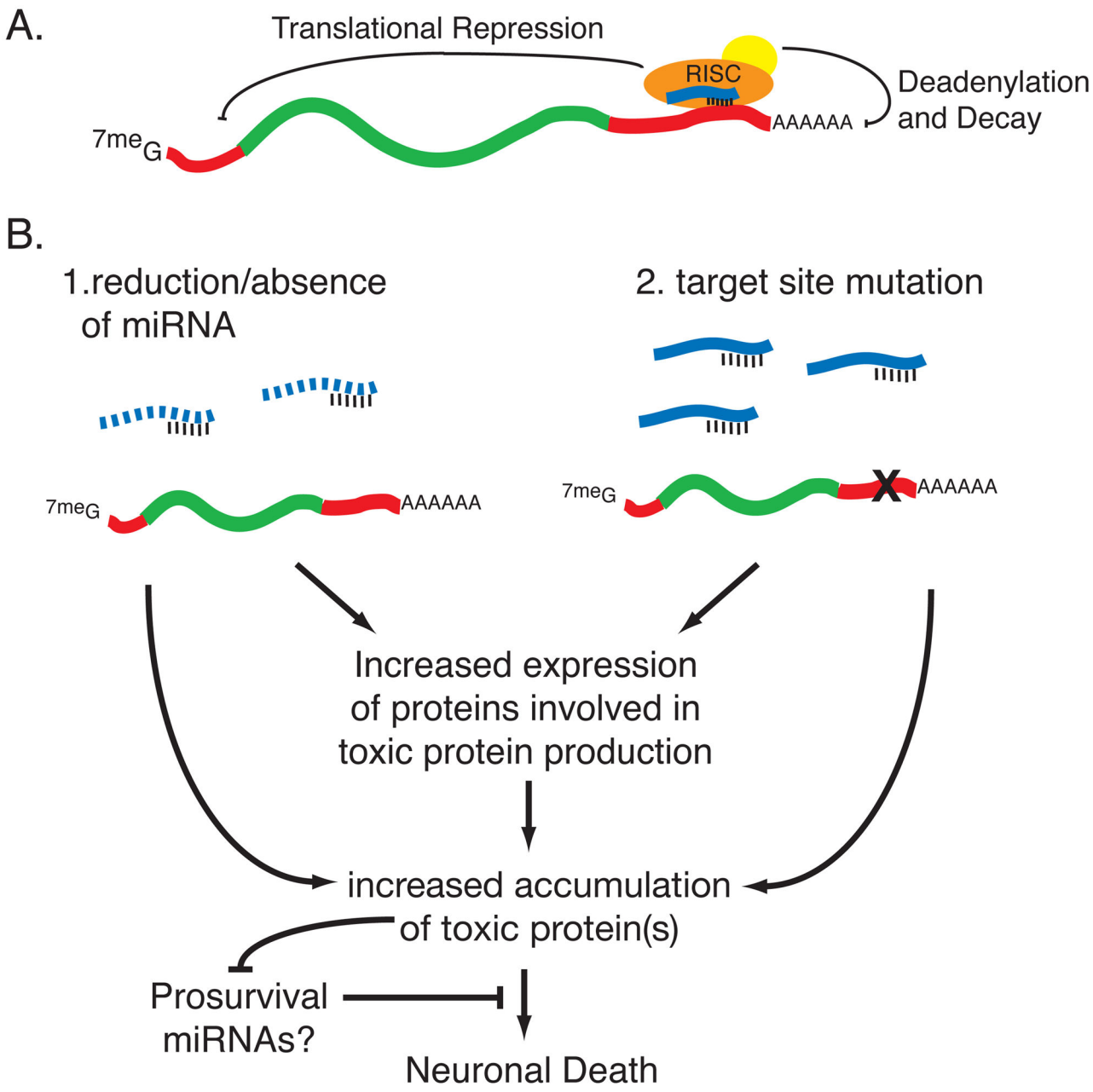

Figure 1.

Messenger RNA repression by microRNA and its affect on neuredegeneration. a| MicroRNAs (blue) bind their target mRNAs through sequences in the 3′ UTR. MicroRNAs require only a short span of sequence complementarity at the 5′ end of the miRNA to guide the RNA-induced silencing complex (RISC) to the mRNA, which promotes either translational repression or mRNA decay. Although many mechanisms for RNA silencing have been proposed, the prevailing view in the field is that RISC-mediated translational control occurs at the step of translation initiation. RISC-induced mRNA decay is thought to occur by deadenylation of the poly(A) tail followed by mRNA destruction. b| Proposed mechanisms by which miRNAs could influence neurodegeneration. Alterations in miRNA

function could result from changes in miRNA expression through genetic or epigenetic changes, resulting in either the reduction or absence of the miRNA. Alternatively, mutation of a miRNA binding site in the 3′-UTR of a target mRNA can disrupt miRNA-mediated repression. miRNAs have been shown to regulate proteins involved in the production of toxic proteins as well as toxic proteins themselves. Thus, reductions on miRNA activity may lead to the increased accumulation of toxic proteins which in turn could cause neuronal death or affect the expression of as of yet unidentified prosurvival miRNAs. *miR-9* may be an example of a prosurvival miRNA through its interaction with REST/CoREST[34].

Table 1

Human microRNAs linked to neurodegenerative disease

microRNA	Mode of Action	Targets	Ref.
miR-19, miR-101, miR-130	Supresses ATAXIN1 accumulation	*ATAXIN1*	33
*miR-9/miR-9**	Supresses negative interaction between Huntingtin and REST/CoREST	*REST* and *CoREST*	34
miR-29a/b	Supresses accumulation of toxic Aβ peptide	*BACE1*	26
miR-133b	Dopamine neuron specification and survival (?)	*PITX3*	16
miR-433	Indirectly supresses expression of α-synuclein	*FGF20*	28
miR-659	Represses GRN expression	*GRN*	25