Curr Tran Geriatr Gerontol Rep (2012) 1:214–218
DOI 10.1007/s13670-012-0030-5

FROM GENETICS TO EPIGENETICS: IMPLICATIONS IN NEURODEGENERATIVE DISORDERS (P JIN, SECTION EDITOR)

# MicroRNAs in Neurodegenerative Disorders

**Shunliang Xu**

Published online: 28 September 2012


**Abstract** MicroRNAs (miRNAs) are a class of small, noncoding RNAs (21–23 nucleotides in length) that can downregulate gene expression at the posttranscriptional level by either degrading or blocking the translation of messenger RNA targets. MicroRNAs are enriched in the brain and expressed in a spatially and temporally controlled manner. They play a key role in neuronal development, differentiation, biochemical pathways, and synaptic plasticity, and their expression is also tightly regulated. Mounting evidence shows that aberrant expression and dysfunction of brain-enriched microRNAs could be involved in the molecular pathogenesis of neurodegenerative disorders, such as Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), and amyotrophic lateral sclerosis (ALS). Here, we review recent research into aberrant miRNA expression in neurodegenerative disorders.

**Keywords** MicroRNA · Noncoding RNA · Neurodegeneration · Alzheimer's disease (AD) · Parkinson's disease (PD) · Huntington's disease (HD) · Amyotrophic lateral sclerosis (ALS) · Frontotemporal dementia (FTD) · Spinocerebellar ataxia (SCA) · Genetic · Epigenetic · APP · BACE1 · HTT · ATX1 · Dicer

## Introduction

Neurodegenerative disorders are a heterogeneous group of chronic progressive diseases characterized by neuronal dysfunction, progressive degeneration, and progressive neuronal loss; with the aging of general population, their prevalence is growing, and they are among the major contributors to disability and disease. Some of these disorders, such as spinocerebellar ataxia (SCA), are caused by the inheritance of gene mutations. In most cases, Alzheimer's disease (AD), Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS), and the prion diseases occur mainly sporadically. For some of the "sporadic" neurodegenerative disorders, rare genetic predispositions have been identified: carriers of these alleles can pass on the predispositions, and their offspring are at a relatively high risk of developing the disease. Moreover, though familial and "sporadic" idiopathic forms of the neurodegenerative disorders differ in several of their clinical features, it is clear that some shared common pathways underlie the neurodegeneration associated with each [1–4].

Mounting evidence suggests epigenetic factors, such as DNA methylation, histone acetylation, and noncoding RNA, could make up a fine regulatory network to control this critical process. Therefore, uncovering the functions of noncoding RNAs could greatly improve our understanding and treatment of human diseases. Noncoding RNAs, including microRNAs (miRNAs), Piwi-interacting RNAs (piRNAs), snoRNA, transcribed ultraconserved regions (T-UCRs), and large intergenic noncoding RNAs (lincRNAs), can shape diverse cellular pathways, from chromosome architecture, development, and growth control to apoptosis, and play a key role in neuronal development, differentiation, biochemical pathways, and neurosynaptic plasticity [5]. Among these noncoding RNAs, microRNA is the most widely studied. Increasing data show that aberrant expression and dysfunction of brain-enriched microRNAs specifically targeting and regulating the expression of disease-associated genes leads to neurodegeneration. Evidence for the reverse is also emerging, whereby a disease-linked protein regulates the microRNA machinery as an important mechanism that disturbs cellular homeostasis, accelerating the development of neurodegenerative diseases [6••, 7].

S. Xu (✉)
Department of Neurology, 2nd Hospital of Shandong University, Jinan, Shandong 250033, People's Republic of China
e-mail: sl_hsu@yahoo.com

Here, we present an overview of microRNA biogenesis and review recent studies on aberrant miRNA expression in neurodegenerative disorders.

## MicroRNA Biology

MiRNAs are small (~22-nucleotide) noncoding regulatory RNAs known to regulate translation of target mRNA molecules in a sequence-specific manner. In mammals, most endogenous miRNA genes are transcribed initially as primary transcripts (pri-miRNAs) that range from hundreds to thousands of nucleotides in length, and contain one or more extended hairpin structures [8••]. The nuclear RNase III enzyme Drosha, working with DGCR8, cleaves both strands near the base of the primary stem-loop and yields the precursor miRNA (pre-miRNA) (Fig. 1). After being exported to the cytoplasm by exportin-5/RanGTP, pre-miRNAs are further cleaved by the RNase III Dicer, along with a dsRNA-binding protein, TAR RNA-binding protein (TRBP) [8••]. The Dicer-TRBP complex is also required for the processing of short hairpin RNA (shRNA) into small interference RNA (siRNA) of ~21 bp. After cleavage by Dicer and unwinding by RNA helicase, one strand of the miRNA/miRNA* or siRNA duplex (the antisense, or guide strand) is then preferentially incorporated into the RNA-induced silencing complex (RISC), while the other strand (the sense, or passenger strand) is degraded (Fig. 1). The RISC is a large and heterogeneous multi-protein complex. Known components of the RISC include Dicer, TRBP, and Argonaute 2 protein (AGO2) [8••].

The RISC uses the guide RNA to find complimentary mRNA sequences via Watson–Crick base pairing, which leads to posttranscriptional gene silencing (PTGS) through inhibition of either translation initiation or elongation [8••, 9•]. MiRNA could also negatively regulate protein expression by targeting mRNA coding regions. Furthermore, miRNAs are found to upregulate the translation of target mRNAs in a cell cycle-dependent manner, switching between translational suppression in proliferating cells to translational activation in quiescent cells [10–12]. Hence, a single miRNA may simultaneously regulate the expression of multiple mRNA targets and thereby act as a rheostat to fine-tune protein expression.

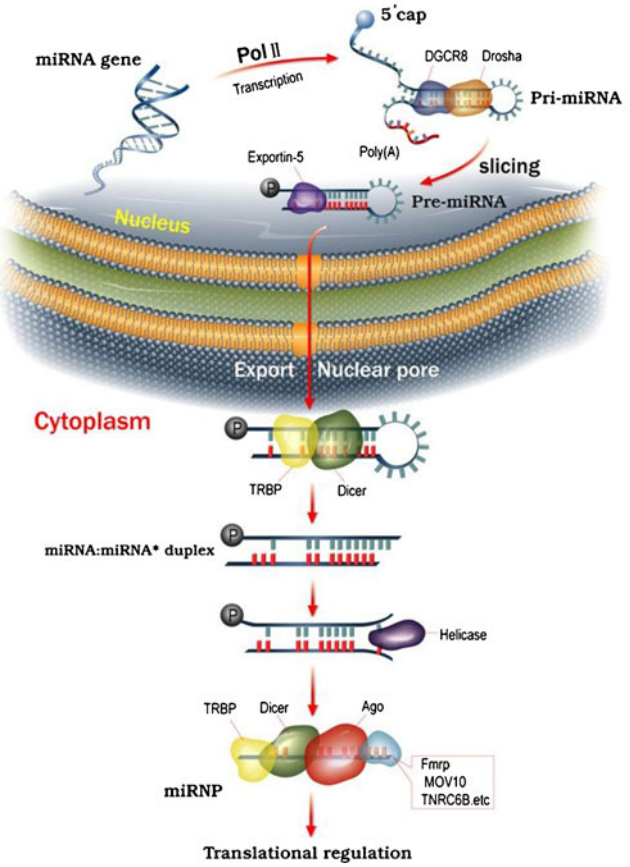


**Fig. 1** MicroRNA biogenesis. Genes encoding microRNAs are initially transcribed by RNA polymerase II or III to generate the primary miRNA transcripts (pri-miRNA) within the nucleus. The stem-loop structure of the pri-miRNA is recognized and cleaved on both strands by a Microprocessor complex, which consists of the nuclear RNase III enzyme Drosha and an RNA-binding protein, DGCR8, to yield a precursor miRNA (pre-miRNA), 60–70 nucleotides in length. The pre-miRNA is then exported from the nucleus through a nuclear pore by exportin-5 in a Ran-GTP-dependent manner and processed in the cytoplasm by the RNase III Dicer-TRBP. Sliced RNA strands are further unwound by an RNA helicase. One strand of the miRNA/miRNA* or siRNA duplex (the antisense, or guide strand) is then preferentially incorporated into the RNA-induced silencing complex (RISC, or miRNP for miRNAs) and will guide the miRNP to a target mRNA in a sequence-specific manner. Once directed to a target mRNA, the RISC can mediate translational regulation by inhibiting the initiation or elongation step, or via destabilization of the target mRNA. Alternatively, miRNAs may also upregulate translation of target mRNAs

## MicroRNA in Alzheimer's Disease

Alzheimer's disease (AD), the most common form of age-related dementia, is described as a gradual, progressive cognitive decline and dementia that results in the irreversible loss of neurons, especially in the cortex and hippocampus. The major neuropathological features of AD are the accumulation of extracellular senile plaques due to amyloid beta 42 peptide (Aβ42) aggregates and the intracellular neurofilament tangles (NFT) that are formed by hyperphosphorylated microtubule-associated protein tau. Aβ is derived from the sequential cleavage of amyloid precursor protein (APP) by β-site APP-cleaving enzyme 1 (BACE1) and the γ-secretase complex. Although the precise pathological mechanisms behind AD remain largely unknown, accumulating evidence indicates that aberrant regulation of miRNA-dependent gene expression is closely associated with molecular events responsible for Aβ production, NFT

formation, and neurodegeneration [13, 14, 15••]. For example, deregulation of miR-29b in the brain results in an increase of apoptotic markers in AD. Besides its potential role in apoptosis, miR-29 is also known to target BACE1. In humans and transgenic mice, the overexpression of miR-29 decreased endogenous BACE1 levels and increased Aβ production [15••]. Some miR-15 family members could target the expression of extracellular signal-regulated kinase 1 (ERK1), a direct Tau kinase, and might participate in neuronal Tau hyperphosphorylation in vivo [15••]. MiR-107 targets the genes BACE1 and cofilin, a component of the rod-like structures found in AD brains [16, 17•]. MiR-107 can also induce cell cycle arrest, and cell cycle re-entry is an early event in AD pathogenesis. Other evidence even suggests that miR-107 directly targets Dicer [18]. miR-9 targets Neurofilament H and Sirtuin (SIRT1), which correlate with axonal conduction and tau posttranslational modification [19]. Besides amyloid precursor protein and BACE1, others, such as serine-palmi toyltransferase (SPTLC1) and key proteins in the apoptosis pathway of AD, contain several miRNA target sites in their 3′-UTRs, including miR-16, miR-101, miR-106a, miR-520c, miR-137, and miR-181c [20]. More and more evidence suggests that miRNA deregulation is an essential pathogenic mechanism that can be induced by Aβ aggregation and contributes to the progression and severity of AD.

## MicroRNA in Parkinson's Disease

Parkinson's disease (PD), a common movement disorder, is clinically characterized by progressive rigidity, bradykinesia, tremor, and impaired balance. The primary neuropathological feature of PD is degeneration of the nigrostriatal dopaminergic pathway connecting the substantia nigra and the striatum. Another is the deposition of inclusion bodies (Lewy bodies) of α-synuclein (SNCA) in the substantia nigra, and mutation in this principle protein is reported in familial forms of PD. Mutations in SNCA, PARKIN, UCHL-1, PINK1, DJ-1, and LRKK2 cause familial cases of PD, although they account only for 5–10 % of patients [21, 22]. The amount of α-synuclein in neurons is an important determinant of its tendency to aggregate pathologically and increase neuronal susceptibility [23–25].

Recent reports demonstrate that the α-synuclein (SNCA) mRNA is under negative regulation by at least two brain-enriched miRNAs: mir-7 [26] and mir-153 [27], which have been shown to bind directly to the 3′-UTR of SNCA mRNA [24, 28]. Whether human aging and/or environmental factors alter miRNA expression levels in the midbrain and basal ganglia and therefore contribute to increased SNCA protein levels and PD risk should be explored further. Besides that, miR-133b, which physiologically targets Pitx3, a transcription factor involved in dopaminergic neuron differentiation, is found to be deficient in the PD midbrain, as well as in mouse models. A negative-feedback loop consisting of Pitx3 and miR-133b has been proposed, as Pitx3 induces transcription of miR-133b, which in turn suppresses Pitx3 expression, suggesting miR-133b function is a negative regulator of dopaminergic neuron differentiation [29, 30••]. miR-34b/34c downregulation was associated with a reduction in the expression of DJ1 and Parkin proteins, which are decreased in several affected brain regions in PD and incidental Lewy body disease and implicated in oxidative stress balance and mitochondrial integrity and function [31]. In a *Drosophila* model, leucine-rich repeat kinase 2 (LRRK2) PD-associated mutations negatively regulate the microRNAs, let-7 and miR-184*, leading to the overexpression of the E2F1/DP complex, which is involved in cell cycle and survival control and can cause dopamine neuron degeneration and impairment of locomotor activity, suggesting deregulated synthesis of E2F1/DP caused by miRNA pathway impairment is a key event in LRRK2 pathogenesis [6••, 30••].

## MicroRNA in Amyotrophic Lateral Sclerosis (ALS) and Frontotemporal Dementia (FTD)

Amyotrophic lateral sclerosis (ALS), the most common adult motor neuron disease, is clinically characterized as atrophy and paralysis of the lower limb and respiratory muscles due to degeneration of motor neurons. Loss of corticospinal upper motor neurons may produce stiffness (spasticity), abnormally active reflexes, and pathological reflexes. Loss of prefrontal neurons may result in special forms of cognitive impairment that include, most commonly, executive dysfunction, but may also include an altered awareness of the social implications of an individual's circumstances and, consequently, maladaptive social behaviors. In its fully expressed forms, the prefrontal dysfunction meets established criteria for frontotemporal dementia (FTD), the second most common early-onset dementia [32–34].

Familial ALS and FTD share some common pathogenesis on genes C9ORF72, VCP, and CHMP2B [33]. Moreover, the RNA-binding proteins TDP43 and FUS have been strongly implicated in both FTD and ALS. As an RNA-binding protein, TDP43 biochemically interacts with the miRNA-processing enzyme Drosha, raising the possibility that TDP-43 may play a role in miRNA processing [35, 36]. In a mouse model of ALS, mice that are genetically deficient in miR-206 form normal neuromuscular synapses during development, but the deficiency of miR-206 accelerates disease progression. Since miR-206 is required for efficient regeneration of neuromuscular synapses after acute nerve injury, this probably accounts for its salutary effects in ALS [20, 37]. MiR-9/9* is another microRNA potentially implicated in motor neuron disease; it is linked to the loss of spinal motor neurons (SMNs) that leads to spinal muscular atrophy [38].

## MicroRNA in Huntington's Disease

Huntington's disease (HD) is a genetic progressive neurodegenerative disease caused by abnormal CAG expansion at exon1 of the gene huntingtin (HTT) [39]. HTT associates with Argonaute2 in P-bodies, expanded HTT may sequester RNA processing factors in the cytoplasm, and depletion of HTT impairs miRNA-mediated gene silencing. Repressor element 1 silencing transcription (REST) factor, a major pathogenic pathway in HD, interacts with wild-type HTT. In pathological conditions, Htt mutation inhibits its interaction with REST and provokes REST accumulation in the nucleus of HD neurons, decreasing neuronal gene expression and leading to neuronal demise. As a transcriptional repressor, REST is found to regulate several neuronal genes and miRNAs. REST and its cofactor, coREST, possess functional target sites for miR-9 and miR-9*, respectively, and miR-9 and miR-9* (together with miR-7, miR-124, miR-132, and other miRNAs) are downregulated in HD patients [40, 41]. In addition, transcriptional repressors, including REST together with TP53, E2F1, and GATA4, could regulate the expression of 26 miRNAs in HD, and the altered expression of 12 intronic miRNAs was correlated with the expression of their target genes. Taken together, miRNAs likely play an important role in HD pathogenesis [42]. Recently, Monica et al. found CAG-expanded HTT RNA can be processed to generate CAG-repeated short RNAs with neurotoxic activity, and the toxic effect of expanded HTT is dependent on RNA-induced silencing complex (RISC) [43].

## MicroRNA in Spinocerebellar Ataxia (SCA)

Spinocerebellar ataxia (SCA), previously known as autosomal dominant cerebellar ataxia, is a group of close to 30 neurodegenerative diseases characterized by progressive incoordination of the limbs and trunk, unstable gait, dysarthric speech, nystagmus, and other symptoms, such as extrapyramidal dysfunction, dysautonomia, cognitive impairment, and motor and sensory impairments [44]. Six SCAs, including the more prevalent SCA1, SCA2, SCA3, and SCA6, along with SCA7 and SCA17, are caused by expansion of a CAG repeat in the coding region of their respective associated genes [44]. SCA1 is caused by polyglutamine-mutant ataxin 1 (ATX1); the level of the mutant protein affects disease severity, and miR-19, miR-101, and miR-130 can cooperatively lower the level of ATX1. In a cell culture model, inhibition of these miRNAs leads to increments of mutant ATX1, which enhanced cytotoxicity [45]. The miRNA bantam (ban) is found to modulate the pathogenicity of the human SCA3 model in *Drosophila*. The upregulation of ban alleviates the polyQ toxicity induced by the pathogenic polyglutamine protein ataxin 3, which is mutated in the human polyQ disease spinocerebellar ataxia type 3 (SCA3). Additionally, depletion of all the miRNAs by Dicer mutation dramatically enhances pathogenic polyQ protein toxicity in flies and human HeLa cells. The loss of Dicer and the decay of miRNAs from mouse Purkinje cells via the Purkinje cell-specific Pcp2 promoter-driven Cre recombinase had no immediate impact on the early life of mice, but the continuous lack of miRNAs led eventually to Purkinje cell loss by apoptosis, and animals developed ataxia with age [46]. For the other SCAs, the gene encoding TATA-binding protein (TBP), which is mutated in SCA type 17 (SCA17), is found to be downregulated by miR-146a. These studies suggest that miRNAs may be important for neuronal survival in neurodegenerative disease [47].

## Conclusion

Although the study of miRNA-mediated regulatory interaction is still in its infancy and numerous questions remain unanswered, the rapid expansion in our knowledge of miRNAs has opened up new avenues for neuroscience research to explore the mechanisms behind neurodegenerative disorders. With the great advances we have seen in sequencing, detection, and function analyses, the field is poised to uncover new biomarkers and potential therapeutic pathways to treat these debilitating diseases.

**Acknowledgments** We would like to thank Cheryl Strauss and Dr. Peng Jin for editing our manuscript. This work was supported by the Shandong Provincial Natural Science Foundation, China (ZR2011LH021) and the Independent Innovation Foundation of Shandong University (IIFSDU) (2010JC016).

**Disclosure** No potential conflicts of interest relevant to this article were reported.

## References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Urdinguio RG, Sanchez-Mut JV, Esteller M. Epigenetic mechanisms in neurological diseases: genes, syndromes, and therapies. Lancet Neurol. 2009;8(11):1056–72.
2. Yang JL, et al. Mitochondrial DNA damage and repair in neurodegenerative disorders. DNA Repair (Amst). 2008;7(7):1110–20.
3. Price DL, Sisodia SS, Borchelt DR. Genetic neurodegenerative diseases: the human illness and transgenic models. Science. 1998;282(5391):1079–83.
4. Hardy J, Gwinn-Hardy K. Genetic classification of primary neurodegenerative disease. Science. 1998;282(5391):1075–9.

5. Taft RJ, et al. Non-coding RNAs: regulators of disease. J Pathol. 2010;220(2):126–39.
6. •• Gehrke S, et al. Pathogenic LRRK2 negatively regulates microRNA-mediated translational repression. Nature. 2010;466(7306):637–41. *This paper uses Drosophila model show LRRK2 interacts with the microRNA (miRNA) pathway to regulate PD pathogenesis*.
7. Esteller M. Non-coding RNAs in human disease. Nat Rev Genet. 2011;12(12):861–74.
8. •• Du T, Zamore PD. microPrimer: the biogenesis and function of microRNA. Development. 2005;132(21):4645–52. *This and ref.[9] are classic reviews on microRNA biogenesis*.
9. • Bartel DP. MicroRNAs: genomics, biogenesis, mechanism, and function. Cell. 2004;116(2):281–97. *This and ref.[8] are classic reviews on microRNA biogenesis*.
10. Vasudevan S, Tong Y, Steitz JA. Cell-cycle control of microRNA-mediated translation regulation. Cell Cycle. 2008;7(11):1545–9.
11. Vasudevan S, Steitz JA. AU-rich-element-mediated upregulation of translation by FXR1 and Argonaute 2. Cell. 2007;128(6):1105–18.
12. Vasudevan S, Tong Y, Steitz JA. Switching from repression to activation: microRNAs can up-regulate translation. Science. 2007;318(5858):1931–4.
13. Satoh J. Molecular network of microRNA targets in Alzheimer's disease brains. Exp Neurol. 2012;235(2):436–46.
14. Hebert SS, Sergeant N, Buee L. MicroRNAs and the regulation of Tau metabolism. Int J Alzheimers Dis. 2012;2012:406561.
15. •• Delay C, Mandemakers W, Hebert SS. MicroRNAs in Alzheimer's disease. Neurobiol Dis. 2012;46(2):285–90. *Most recent review on microRNA in AD*.
16. Yao J, et al. MicroRNA-related cofilin abnormality in Alzheimer's disease. PLoS One. 2010;5(12):e15546.
17. • Wang WX, et al. The expression of microRNA miR-107 decreases early in Alzheimer's disease and may accelerate disease progression through regulation of beta-site amyloid precursor protein-cleaving enzyme 1. J Neurosci. 2008;28(5):1213–23. *First paper on miR-107 implicates to AD*.
18. Martello G, et al. A MicroRNA targeting dicer for metastasis control. Cell. 2010;141(7):1195–207.
19. Schonrock N, et al. Target gene repression mediated by miRNAs miR-181c and miR-9 both of which are down-regulated by amyloid-beta. J Mol Neurosci. 2012;46(2):324–35.
20. Gascon E, Gao FB. Cause or effect: misregulation of microRNA pathways in neurodegeneration. Front Neurosci. 2012;6:48.
21. Houlden H, Singleton AB. The genetics and neuropathology of Parkinson's disease. Acta Neuropathol. 2012;124(3):325–38.
22. Schiesling C, et al. Review: familial Parkinson's disease—genetics, clinical phenotype and neuropathology in relation to the common sporadic form of the disease. Neuropathol Appl Neurobiol. 2008;34(3):255–71.
23. Mandemakers W, Morais VA, De Strooper B. A cell biological perspective on mitochondrial dysfunction in Parkinson disease and other neurodegenerative diseases. J Cell Sci. 2007;120(Pt 10):1707–16.
24. Doxakis E. Post-transcriptional regulation of alpha-synuclein expression by mir-7 and mir-153. J Biol Chem. 2010;285(17):12726–34.
25. Singleton AB, et al. Alpha-Synuclein locus triplication causes Parkinson's disease. Science. 2003;302(5646):841.
26. Bak M, et al. MicroRNA expression in the adult mouse central nervous system. RNA. 2008;14(3):432–44.
27. Farh KK, et al. The widespread impact of mammalian MicroRNAs on mRNA repression and evolution. Science. 2005;310(5755):1817–21.
28. Junn E, et al. Repression of alpha-synuclein expression and toxicity by microRNA-7. Proc Natl Acad Sci U S A. 2009;106(31):13052–7.
29. Kim J, et al. A MicroRNA feedback circuit in midbrain dopamine neurons. Science. 2007;317(5842):1220–4.
30. •• Mouradian MM. MicroRNAs in Parkinson's disease. Neurobiol Dis. 2012;46(2):279–84. *Most recent review on microRNA in PD*.
31. Minones-Moyano E, et al. MicroRNA profiling of Parkinson's disease brains identifies early downregulation of miR-34b/c which modulate mitochondrial function. Hum Mol Genet. 2011;20(15):3067–78.
32. Ferrari R, et al. FTD and ALS: a tale of two diseases. Curr Alzheimer Res. 2011;8(3):273–94.
33. Orr HT. FTD and ALS: genetic ties that bind. Neuron. 2011;72(2):189–90.
34. Zago S, et al. Amyotrophic lateral sclerosis and frontotemporal dementia (ALS-FTD). Arch Ital Biol. 2011;149(1):39–56.
35. Huey ED, et al. FUS and TDP43 genetic variability in FTD and CBS. Neurobiol Aging. 2012;33(5):1016–e9–17.
36. Wang JW, et al. The ALS-associated proteins FUS and TDP-43 function together to affect Drosophila locomotion and life span. J Clin Invest. 2011;121(10):4118–26.
37. Williams AH, et al. MicroRNA-206 delays ALS progression and promotes regeneration of neuromuscular synapses in mice. Science. 2009;326(5959):1549–54.
38. Junn E, Mouradian MM. MicroRNAs in neurodegenerative diseases and their therapeutic potential. Pharmacol Ther. 2012;133(2):142–50.
39. Shastry BS. Neurodegenerative disorders of protein aggregation. Neurochem Int. 2003;43(1):1–7.
40. Savas JN, et al. Huntington's disease protein contributes to RNA-mediated gene silencing through association with Argonaute and P bodies. Proc Natl Acad Sci U S A. 2008;105(31):10820–5.
41. Lee ST, et al. Altered microRNA regulation in Huntington's disease models. Exp Neurol. 2011;227(1):172–9.
42. Witkos TM, Koscianska E, Krzyzosiak WJ. Practical aspects of microRNA target prediction. Curr Mol Med. 2011;11(2):93–109.
43. Banez-Coronel M, et al. A pathogenic mechanism in Huntington's disease involves small CAG-repeated RNAs with neurotoxic activity. PLoS Genet. 2012;8(2):e1002481.
44. Orr HT. Cell biology of spinocerebellar ataxia. J Cell Biol. 2012;197(2):167–77.
45. Lee Y, et al. miR-19, miR-101 and miR-130 co-regulate ATXN1 levels to potentially modulate SCA1 pathogenesis. Nat Neurosci. 2008;11(10):1137–9.
46. Schaefer A, et al. Cerebellar neurodegeneration in the absence of microRNAs. J Exp Med. 2007;204(7):1553–8.
47. Sinha M, et al. Altered microRNAs in STHdh(Q111)/Hdh(Q111) cells: miR-146a targets TBP. Biochem Biophys Res Commun. 2010;396(3):742–7.