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miRNAs and deregulated gene expression networks in neurodegeneration

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Abstract

Neurodegeneration is characterized by the progressive loss of neuronal cell types in the nervous system. Although the main cause of cell dysfunction and death in many neurodegenerative diseases is not known, there is increasing evidence that their demise is a result of a combination of genetic and environmental factors which affect key signaling pathways in cell function. This view is supported by recent observations that disease-compromised cells in late-stage neurodegeneration exhibit profound dysregulation of gene expression. MicroRNAs (miRNAs) introduce a novel concept of regulatory control over gene expression and there is increasing evidence that they play a profound role in neuronal cell identity as well as multiple aspects of disease pathogenesis. Here, we review the molecular properties of brain cells derived from patients with neurodegenerative diseases, and discuss how a deregulated miRNA/mRNA expression networks could be a mechanism in neurodegeneration. In addition, we emphasize that the dysfunction of these regulatory networks might overlap between different cell systems and suggest that miRNA functions might be common between neurodegeneration and other disease entities.

Keywords

miRNAs; microarray; gene expression; neurodegeneration

Introduction

The main characteristic of neurodegeneration is the progressive dysfunction, deterioration and eventual loss of neurons in the nervous system. This can be caused by a variety of factors such as the intrinsic properties of the underlying neurodegenerative disorder, ischemia, inflammation, and toxic insult (Bossy-Wetzel et al., 2004; Jellinger, 2009). A pathological hallmark of many neurodegenerative diseases is a disturbed cellular homeostasis with accumulation of misfolded proteins in the form of cellular aggregates and the cytotoxicity of intermediate products, such as oligomers and protofibrils. Many of the mechanisms in neuronal cell function in physiology and pathophysiology are currently not well understood and the impact of neurodegeneration on patients is often devastating, since there are no or only insufficient therapies available.

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Neurodegenerative diseases can be roughly classified in two forms: The familial (early onset) forms that are associated with genetic mutations, such as the poly glutamine (polyQ) disorders (Ataxia and Huntington's disease - HD), and some forms of Parkinson's disease (PD), and the sporadic (late onset) forms, for which in many cases the cause is not known, e.g., sporadic Alzheimer's disease (AD), amyotrophic lateral sclerosis (ALS), and sporadic PD. Despite this distinction, there is also mounting evidence that sporadic neurodegeneration is a combination of genetic predisposition and environmental factors with overlapping disease mechanisms as seen in the familial disease forms (a comprehensive review on the genetic and biochemical classifications of neurodegenerative disease was recently published by (Jellinger, 2009)).

Although the understanding of the pathophysiology of neurodegeneration is still limited, research has progressed over the past years and, in particular, the development of new technologies has offered new insights into the molecular properties of the degenerating neuronal cell. Also, new discoveries have changed some of our understanding of disease mechanisms and this includes miRNAs, which introduce an entirely novel level of regulatory control over gene expression (Ambros, 2004). This new concept seems to be an important part in a diversity of cell systems in development, function and disease. In the nervous system, miRNAs are essential in developmental timing, cell proliferation, cell death and patterning as well as function and identity of neural cell populations (Ambros, 2004; Barbato et al., 2008; Fiore et al., 2008; Kuss and Chen, 2008; Satterlee et al., 2007; Schratt, 2009). In addition, there is also mounting evidence that miRNAs might play a role in neurodegeneration (Barbato et al., 2009; Bushati and Cohen, 2008; Eacker et al., 2009; Hebert and De Strooper, 2009; Hebert et al., 2009; Nelson et al., 2008; Singh, 2007). However, in contrast to an increasingly vast amount of knowledge about miRNA function in developmental systems and some disease entities such as, e.g., cancer (Croce, 2009; Garzon et al., 2009; Krichevsky and Gabriely, 2009), there is to date very little information of how miRNAs function in the pathogenesis of neurodegenerative diseases. This is in part due to the difficulties of evaluating miRNAs in patient populations - which represents a general caveat in studying neurodegeneration. Because of an often very subtle symptomatology at disease onset, the slow disease progression and long duration as well as the restricted accessibility of nerve cells, the availability of patients-derived neural tissue is limited. On the other hand, it is possible to study miRNAs in experimental in vitro and in vivo model systems for neurodegenerative diseases, and some of them have already served to generate new information about potential functions of these molecules in disease mechanisms (e.g. (Junn et al., 2009; Schaefer et al., 2007; Wang et al., 2009)). However, results from these studies tend to be limited to isolated disease aspects often leading to correlative conclusions that yet have to be confirmed in the complex biological systems of patients.

Concepts of miRNA function in neurodegenerative diseases have been extensively discussed (Barbato et al., 2009; Bushati and Cohen, 2008; Eacker et al., 2009; Hebert and De Strooper, 2007; Hebert and De Strooper, 2009; Nelson et al., 2008; Singh, 2007) and are based on information from miRNA function in other systems as well as on a few studies demonstrating experimental evidence of the potential role of miRNAs in pathogenetic mechanisms of neurodegeneration. In this review we will focus on the molecular properties based on data from gene expression profiles of patients-derived brain cells affected with neurodegenerative diseases and discuss how deregulated expression networks could be associated with miRNAs. In addition, we will extend our discussion to the view that the function of miRNAs in normal and abnormal regulatory networks might be common between neurons and other cell systems and how this view could influence the general understanding of pathogenetic mechanisms in neurodegeneration.

Gene expression profiling and general concepts of mechanisms in neurodegeneration

The combined feature of neurodegenerative diseases is the progressive degeneration, function, and loss of neuronal cells. However, despite this commonality, there are also clear differences as there is distinctive and localized neuronal cell loss in the brain. Neurodegeneration appears to be “cell-specific” predominantly affecting entorhinal and neocortical glutamatergic and nucleus basalis cholinergic neurons in AD, nigrostriatal neurons in PD, Purkinje cells in Spinocerebellar ataxia (SCA), and spinal motor neurons in ALS. Therefore, despite their pan-neuronal characteristics, the differences in phenotypic identity could be a cause or the consequence of vulnerability in neurodegenerative disorders. Gene expression profiling has revealed insight into the similarities as well as differences of the transcriptomes of these neurons and it appears that the differences seem to be more related to variability in gene expression levels, rather than to a “non-or-all” expression of particular genes or gene groups. This pattern is also observed in disease-affected neurons, where typically gene groups and subfamilies are deregulated that are linked to signaling pathways relevant in pathogenesis (Altar et al., 2009; Liang et al., 2008; Simunovic et al., 2009; Simunovic et al., 2010). Interestingly, many of these signaling pathways seem to overlap between neurons within one or across multiple disease entities (Altar et al., 2009; Bronner et al., 2009; Liang et al., 2008). These observations suggest a regulatory gene expression network that is responsible for phenotype identity and normal homeostasis and that is deregulated in neurodegeneration. On the molecular level, there are three aspects of this network: genetic predisposition, gene expression, and regulatory mechanisms (Figure 1). Genetic predisposition is the key aspect in familial forms of neurodegenerative disorders; in which defined mutations or enhanced expression levels of key genes are causative for neuronal cell death. Examples are the familial forms of PD with mutations or increased gene dosages of genes from the PARK family (Schiesling et al., 2008) or the polyQ diseases, such as HD and ataxia, which are genetically characterized by an extension of a CAG repeat in the huntingtin or ataxin gene (Bauer and Nukina, 2009), and some forms of familial-based ALS (Dion et al., 2009). In contrast, polymorphisms in sporadic neurodegeneration are more difficult to clearly associate to disease. Although it is commonly accepted that genetic predisposition is a risk factor, it is less clear how and to what extent it impacts disease onset and progression (Dion et al., 2009; Sutherland et al., 2009a; Webster et al., 2009).

Gene expression profiling, such as high throughput microarray and quantitative real-time (qRT)-PCR, has become a powerful methodology to delineate some of the molecular properties of neural cell populations derived from patients. Most of these studies have been focused on AD and PD. These studies revealed a vast amount of data and have reiterated the complexity of neuronal cell function as well as transformed the general understanding of their dysfunction (Mufson et al., 2006). However, it should be noted that the methodologies of gene expression profiling are also associated with many caveats ranging from patient-related parameters (diagnosis, age, disease-type, medication, gender), over technical issues (material collection, preparation, assay platforms, controls) to data analysis and interpretation (computational data transformation, methods of algorithms, statistics, significance, biological replicates), which account for the observed high variability between different data sets. An important caveat to mention here is the lack of cell-specificity in many microarray studies that are based on the analysis of dissected brain tissue specimens containing heterogeneous cell populations. This has now been overcome with the use of laser microdissection technologies and the profiling of single cell populations affected in neurodegeneration (Mufson et al., 2006) including substantia nigra DA neurons in PD (Cantuti-Castelvetri et al., 2007; Grundemann et al., 2008; Lu et al., 2004; Simunovic et al., 2009; Simunovic et al., 2010), brain-region specific pyramidal neurons in AD (Liang et al., 2008) or ALS (Jiang et al., 2005).

Despite differences between the various gene array studies there are also common observations relevant to the understanding of neurodegeneration: (1) Although the general expression profiles are similar between subjects, there is high individual variability in expression levels. This could reflect differences in disease progression based on, e.g., genetic predisposition, intrinsic and extrinsic environmental factors, medication, and others. (2) Expression profiles demonstrate both overlapping and distinct gene expression patterns between different neuronal subtypes and disease-affected neurons. These patterns refer in particular to signaling pathways that are deregulated in disease such as oxidative stress, excitotoxic insult, dysfunction of mitochondria, the ubiquitin-proteasome system, synapses, and the cytoskeleton, failure of axonal and dendritic transport, and a general disintegration of homeostasis (Altar et al., 2009; Jiang et al., 2005; Liang et al., 2008; Mufson et al., 2006; Simunovic et al., 2009). These findings support the view that neurodegeneration might be in part an accumulation of unifying events (Bossy-Wetzel et al., 2004; Jellinger, 2009). (3) Differences in levels of gene expression are often subtle between neuronal subtypes and in neurons affected by disease implying that even small changes in gene expression could have a profound impact on neuronal cell function and survival. In addition, diseased neurons exhibit deregulation with predominantly down-regulation of single (key) genes or groups of gene families relevant in signaling pathways of pathogenesis (although this seems to be less evident for ALS (Jiang et al., 2005)). Altogether, conceptually it appears that the entire gene expression networks underlie regulatory mechanisms that define the pan-neuronal phenotype as well as neuronal subtypes and these mechanisms are disturbed in neurodegeneration (Altar et al., 2009; Jiang et al., 2005; Liang et al., 2008; Mufson et al., 2006; Simunovic et al., 2009; Simunovic et al., 2010). miRNAs fit well in this concept, because of their function in mammalian neurogenesis, their role in determining neuronal phenotypes and function of postmitotic neurons, their distinct distribution in several brain regions and single neurons and their deregulation in neurodegeneration. miRNAs seem to play a profound role in steering and/or fine-tuning processes of neuronal cell function in both health and disease (Barbato et al., 2008; Schratz, 2009).

miRNAs in neurodegeneration

As discussed above, large-scale gene profiling has revealed new insights into the molecular properties of disease-affected neurons and an increasing body of data now offers the opportunity to tie together different aspects of normal and abnormal cell function, i.e., the influence of genetic predisposition (variability in coding and non-coding sequences), levels of gene expression, functionality of gene products (pre- and post-translation), gender, and the role of regulatory mechanisms, such as the miRNA system. These factors provide a complex regulatory expression network (Figure 1), which might or might not be unique to certain disease entities (see below).

The aspects of gene expression profiles in neurodegeneration as described above can be linked together with known features of miRNAs to develop a conceptual view of how these molecules might be involved in neurodegenerative disorders. So far, considerable screening efforts for miRNA expression have been performed on postmortem brain material from AD patients (summarized in (Hebert and De Strooper, 2009) and (Cogswell et al., 2008)) and, in one study, also in PD patients (Kim et al., 2007). As discussed above, it should be mentioned that in these studies dissected tissue samples containing heterogeneous cell populations were analyzed. This is an important parameter for data interpretation, since it is currently not clear how miRNA expression and function relates to individual cell types in the human brain and how they are involved in the complex interplay of neural subtypes. Nevertheless, in AD, these studies revealed some insight into possible mechanisms of pathogenesis. For example, the miRNAs miR-106a, -520c, -106b, -17-5p, and 20a could down-regulate amyloid beta precursor protein (APP) gene expression in vitro (Hebert et al., 2009; Patel et al., 2008), but so far only miR-106b

expression was found in sporadic AD patients (Hebert et al., 2009). In another study, reduction of miR-29b-1 and miR-29a in the temporal cortex of AD patients correlated with increased β -site APP cleaving enzyme 1 (BACE1) expression in the same sample population (Hebert et al., 2008; Hebert and De Strooper, 2009). Since BACE1 is a target for both miRNAs and the rate-limiting enzyme for A β production, these results could imply correlative evidence for a mechanism in this disease. Similarly, another study demonstrated diminished miR-107 expression in cortices from AD patients and biochemical analyses showed that BACE1 was a target for this miRNA (Wang et al., 2008b). Supportive information came also from a mouse model of AD, in which miR-298 and -328 could be identified as targeting miRNAs for BACE1 (Boissonneault et al., 2009). These data imply that critical genes in AD pathogenesis could be regulated by multiple miRNAs. Additional evidence for possible miRNA functions in AD was recently provided by data from the same AD mouse model as used by (Boissonneault et al., 2009) - i.e., APP^{swe}/PS Δ E9 transgenic mice, which contain a mouse-human hybrid of the APP gene with the Swedish mutation K594N/M595L and the PS1 Δ E9 transgene that encodes the exon-9-deleted human presenilin-1 (Wang et al., 2009). In this study miR-34a was functionally linked to downregulation of bcl2 expression, an anti-apoptotic protein involved in the regulation of the apoptotic proteins caspase 9 and 3. The authors could experimentally demonstrate that miR-34a indirectly regulates caspase 3 by targeting bcl2 and this correlated with an increased expression of miR-34a and caspase 3 in the cortices of the transgenic mice. These results indicated an involvement of miRNAs in the apoptotic signaling pathway, which is relevant in AD neurodegeneration (LeBlanc, 2005). Interestingly, miRNA arrays in the transgenic mice revealed deregulated expression of the AD-associated miRNAs miR-20a, -29a, -125b, -128a and -106b, but not others, such as miR-29b-1, -107, -298, and -328 (Wang et al., 2009). This profile also overlapped poorly with data from a recent large-scale miRNA screening using high throughput miRNA qRT-PCR technology on several brain regions and cerebral spinal fluid (CSF) from AD patients and age-matched controls (Cogswell et al., 2008). In this study, the authors reported a set of multiple miRNAs that were regionally and stage-specifically deregulated, but this included neither miR-29a/b-1 and miR-107 nor miR-298, -328, and -34a from the mouse studies. Despite the differences in the biological systems, little data overlap in miRNA profiling could be related to technical differences and difficulties in conducting the miRNA screening experiments (see (Hebert and De Strooper, 2009) for further discussion), considerable variations within patient populations as also seen in microarray studies (discussed e.g. in (Simunovic et al., 2009) and (Simunovic et al., 2010)), and/or could be related to distinct patterns in the biology of miRNA functions (see text below).

In contrast to AD, there is very little information of miRNA expression in PD-affected brains. So far, three miRNAs have been linked to the dopaminergic phenotype in relation to PD: (1) miR-133b that regulates the transcriptional activator Pitx3, which in mice is a key factor in the development of the DA neuronal phenotype (Kim et al., 2007). In this study, miR-133b was also upregulated in ventral midbrain tissue dissected from sporadic PD patients as determined by PCR of miRNA precursor molecules and Northern blots. (2) miR-7, which was shown to suppress α -Synuclein in mouse and human neuroblastoma cells (Junn et al., 2009). In this study miR-7 expression could be suppressed by oxidative stress in vitro and in vivo. Since dysfunctional α -Synuclein has been implicated in the impairment of the proteasome system - a major mechanism in PD pathogenesis - the authors suggested that oxidative stress might influence α -Synuclein levels via miR-7 inhibition. To substantiate this observation mice were treated with MPTP confirming a reduction of miR-7 in the ventral-midbrain. Although it was determined that miR-7 was more expressed in cultured neurons than in astrocytes, the in vivo experiments did not reveal the neuronal cell types that expressed miR-7. (3) miR-433, which in a large-scale genotyping study was linked to a mutation of its binding site in the 3'UTR region of the FGF20 gene (Wang et al., 2008a). Using a luciferase reporter gene assay, the authors confirmed that miR-433 could inhibit the translation of the FGF20 gene in vitro,

however, so far no in vivo data are available that demonstrate a direct link of functional miR-433 to PD pathogenesis.

Ongoing work from our laboratory on PD DA neurons has revealed some interesting observations that could be informative for PD and also for neurodegenerative diseases in general (Sonntag et al., unpublished data). Using laser microdissection (LMD), we isolated postmortem DA neurons from sporadic PD patients and aged-matched control subjects to determine the complete miRNA expression profiles by high throughput qRT-PCR (TaqMan® Human MicroRNA A Array v2.0, Applied Biosystems). These results revealed that DA neurons have a distinct miRNA expression profile independent of disease and gender and that expression levels varied within individual samples similar to observations made from microarray studies and, interestingly, also between genders. Also, there was an overall upregulation of miRNAs in PD. miRNA target correlations with genes that are deregulated in the same DA neurons (Simunovic et al., 2009) showed that miRNAs seem to act on the entire gene expression network including deregulated signaling pathways relevant in PD. Distribution of miRNAs demonstrated that they target single as well as multiple mRNAs and act alone or in groups. In addition, miRNAs seem to work on gene groups or multiple members of subfamilies, which are part of one or more signaling pathways, rather than major key genes that have been implicated in PD pathogenesis (e.g. PARK genes). Interestingly, comparison of results from our study on LMD DA neurons with the above discussed miRNAs on PD revealed that miR-133b was not expressed above detection threshold, while miR-433 was expressed, but not deregulated in PD and miR-7 was, unfortunately, not present on the TaqMan® Human MicroRNA A Array v2.0. As mentioned above, reasons for differences in miRNAs across studies could be due to technical as well as biological issues. For example, in the study by Kim et al. miRNA precursors were amplified by qRT-PCR, while our profiling was based on detecting mature miRNAs (Kim et al., 2007). Since miRNA processing is a highly regulated process, the expression of mature miRNAs can sometimes vary considerably from its precursor (Blow et al., 2006; Luciano et al., 2004). Alternatively, the use of LMD in our approach, instead of dissected midbrain tissue used by Kim et al., directly targeted DA neurons. Therefore, the lack of mature miR-133b expression in the isolated neurons could indicate that miR-133b might be expressed in a different cell population in the midbrain. It should also be noted that there is little evidence for a functional role of Pitx3 in mature PD-affected DA neurons (e.g., it is not deregulated in PD microarrays (<https://ncasr.griffith.edu.au/pdreview/2009/>)) indicating that a potential function of miR-133b in PD could be related to a different target in a different cellular phenotype.

Additional miRNAs have been identified in human brain tissue from HD and SCA1 patients (Lee et al., 2008; Packer et al., 2008). In the study by Packer et al., miR-9/9*, -29b, and -124a were significantly down-, while miR-29a and -132 were upregulated. The authors focused on a detailed analysis of miR-9/9*, which could be shown to target the RE1-silencing transcription factors REST and Co-REST that are important in neuronal cell function and dysfunctional in HD. Since REST is controlled by MeCP a target of miR-132 ((Klein et al., 2007) and see below), the authors suggested a double negative feedback network as a potential mechanism of miR-9/9* and miR-132 function in HD. Lee et al. identified that miR-19, -101, and -130 co-regulated ataxin 1 (ATXN1) levels in human cells and that inhibition of these miRNAs enhanced the cytotoxicity of the polyglutamine-expanded ATXN1 protein. Interestingly, miR-101 induced both mRNA degradation and inhibition of translation, while miR-19 and -103 only repressed translation. The authors also investigated the expression of these three miRNAs in mice cerebellum, since cerebellar Purkinje cells are vulnerable to mutant ATXN1 cytotoxicity. Indeed, all miRNAs were expressed in Purkinje cells suggesting that a functional role of miRNAs could be the regulation of toxic proteins (e.g. poly-Q or others) and that disturbances in this mechanism could be associated with neurodegeneration.

Regulatory miRNA/mRNA expression networks to develop new conceptual views of neurodegeneration

A key question in understanding the role of miRNAs in neurodegeneration is how to link their function to regulatory gene expression networks in neurons. There are three different parameters to be considered: A role of miRNAs in defining the pan-neuronal phenotype and in fine-tuning neuronal subtypes, a “common” role of miRNAs in neuronal cellular homeostasis, and a “specific” role of miRNAs in distinct neuronal cell function (Figure 2). This miRNA paradigm is closely linked to the gene expression machinery and affects signaling pathways that are deregulated in neurodegeneration. Supportive information for a role of miRNAs in defining the pan-neuronal phenotype comes from developmental studies. In particular miR-124 has been demonstrated to play a crucial role in neurogenesis in vitro (Krichevsky et al., 2006) and in vivo (Cheng et al., 2009; De Pietri Tonelli et al., 2008). The “neurogenic” properties of miR-124 were also demonstrated in a series of other studies (Cao et al., 2007; Cheng et al., 2009; Makeyev et al., 2007; Visvanathan et al., 2007) including an elegant experiment conducted by Lim et al., in which overexpression of miR-124 in HeLa cells could induce a neuron-specific expression profile (Lim et al., 2005). The miR-124 transfected cells downregulated 174 genes, and from these genes ~20% were also deregulated in PD DA neurons (Simunovic et al., 2009; Simunovic et al., 2010). Similarly, from a set of 27 validated targets after immunoprecipitation assays using HEK-293S cells transfected with miR-124a (Karginov et al., 2007), eight of the targets were deregulated in PD DA neurons. These results correlated with information from the MIRECORDS database (<http://mirecords.umn.edu/>), from which 49 (24%) genes out of 202 “validated” targets for miR-124 were deregulated in PD. Since miR-124 is abundantly expressed in the adult brain (Nelson et al., 2008; Nelson and Wilfred, 2009), one could speculate that this miRNA might be also involved in the DA neuronal phenotype and in PD pathogenesis or in both. Another example for pan-neuronal phenotype-specific miRNAs is miR-132, whose expression is activated by the transcriptional activator CREB, and which seems to form a feedback loop with its target MeCP2 and brain-derived neurotrophic factor (BDNF) – BDNF increases miR-132 expression, which downregulates MeCP2 that in turn decreases BDNF (Klein et al., 2007; Vo et al., 2005). Interestingly, BDNF inhibits the function of the spine-specific miRNA miR-132, which targets Lmtk1 a protein involved in dendritic spine densities (Schratt et al., 2006). These data attest to the function of miRNAs in regulating key aspects of neuronal cell function (Ooi and Wood, 2008).

Examples for “specific” miRNA function in neurodegeneration could be the discussed targeting of BACE1 by miR-29a/b-1 (Hebert et al., 2008), miR-107 (Wang et al., 2008b), or miR-298 and -328 (Boissonneault et al., 2009), α -Synuclein by miR-7 (when proven relevant in clinical PD) (Junn et al., 2009), the ATXN1-targeting miRNAs miR-19, -101, and -130 (Lee et al., 2008), or miR-659 that targets progranulin (GRN) in patients with frontotemporal dementia (Rademakers et al., 2008). However, probably most of the miRNAs would be linked to “common” mechanisms in neuronal cell function, such as exemplified by the correlation of miR-34a with bcl-2/caspase 3 expression in AD transgenic mice (Wang et al., 2009). Both molecules are part of a common apoptotic signaling pathways and many of its associated genes are also deregulated in neurons from patients with neurodegenerative diseases. Similarly miR-338 could be a “common” miRNA, since its target COXIV is a key component of the mitochondrial cytochrome c oxidase complex IV (Aschrafi et al., 2008). Oxidative stress and mitochondrial dysfunction is one of the hallmarks in neurodegeneration and many members of the COX family are deregulated in disease-affected neurons (e.g. DA neurons (Simunovic et al., 2009; Simunovic et al., 2010)). Other described miRNAs in the nervous systems with no obvious link to neurodegeneration might be important as well. For example, miR-504, which has been associated with the regulation of human dopamine receptor 1 expression (Huang and Li, 2009) or miR-219, which in rodents targets calmodulin kinase II γ , an important molecule

in the signaling cascade of the NMDA receptor (Kocerha et al., 2009). These proteins are also part of a set of deregulated genes related to signaling pathways in AD- or PD-diseased neurons. Thus, these miRNAs might or might not be involved in processes of neurodegeneration. A list of selected mammalian miRNAs with a potential for direct or indirect association with neuronal dysfunction in neurodegenerative diseases is provided in Table 1.

It is important to emphasize that in complex gene expression networks borders are not clearly drawn, as the function of both miRNAs and target genes are multifaceted and interwoven in the many aspects of cellular homeostasis. This has implication for understanding specific or overlapping features between different neurodegenerative diseases and also offers an even broader view, in that deregulated signaling pathways typical for neurodegeneration are also found in other diseases such as cancer, diabetes, psychiatric disorders, and others (Altar et al., 2009; Jellinger, 2009; Moran and Graeber, 2008; Mufson et al., 2006). As an example, an intriguing link could be the insulin-like growth factor (IGF-1) pathway, which has been associated with aging and which is over-represented in two recent studies on PD and Tauopathies (Bronner et al., 2009; Sutherland et al., 2009b). Important factors in IGF-1 signaling are forkhead transcription factors and, interestingly, miR-124a regulates the transcriptional activator FoxA2, which is a master regulator of pancreatic development and β -cell differentiation (Baroukh et al., 2007). In these cells, FoxA2 is not only involved in regulating genes for glucose metabolism and insulin secretion, but is also important for molecules that play a role in ATP-sensitive K^+ channel activity and glucose- or KCL-stimulated intracellular free Ca^{2+} concentrations - functions that are essential in neuronal homeostasis. Finally, FoxA2 is a key factor in midbrain dopaminergic cell development in both rodents and humans (Ang, 2009; Lin et al., 2009; Nelander et al., 2009) and its function is required for survival of DA neurons in aged mice implicating a role in PD (Kittappa et al., 2007). Altogether these data underscore that complex regulatory gene expression networks are overlapping between different cell systems and could indicate that miRNA functions might be common between neurodegeneration and other disease entities.

An important question in the role of miRNAs in neurodegeneration is whether these molecules are causative for or a consequence of the disease. Mounting evidence reveals that regulation of miRNA expression underlies similar mechanisms that occur for the transcription of mRNA. This includes genetic disparities, a complex interplay of transcriptional activators, feedback loops, and the maturation process of precursor molecules. Thus, miRNAs are part of an expression network acting on the same transcriptional and translational machinery that regulate their own function (Figure 1). Therefore, any scenario to modulate their expression could be possible, and it is feasible to speculate that miRNAs might also be influenced by the commonly known risk factors for neurodegenerative diseases, such as age, gender, environmental factors, and genetic predisposition. Indeed, several studies reporting that miRNAs can be regulated by toxic insult, such as $A\beta$ (Hebert et al., 2009), ROS-generating metal sulfates (Lukiw and Pogue, 2007) or oxidative stress in a MPTP mouse model of PD (Junn et al., 2009) support this notion.

Concluding remarks

In the past decade, it has become clear that miRNAs are essential key molecules in neuronal cell development, identity, and function. Moreover, there is increasing evidence that miRNAs also seem to play a role in neurodegeneration. However, this conceptual view is still in the early phases of being fundamentally substantiated by experimental data or patient-relevant studies that delineate the functions of miRNAs in the complex systems of neurodegenerative disorders. Advances in understanding miRNAs in neurodegeneration will require to go along with the dynamics of future research on neurodegeneration as a whole and will rely on advanced and refined technologies, improved experimental systems, the accessibility of patients-derived

material and the embracement of new conceptual views on the pathophysiology of these diseases.

The complexity of miRNA function is amplified by the complexity of neurobiological systems and the mechanisms involved in their demise. Therefore, understanding a role of miRNAs in neurodegeneration requires a general understanding of the pathogenetic processes involved in these disorders and emerging evidence suggests specific, but also unified, disease mechanisms that might overlap with other disease entities. Because of the diversity of their function, this concept could also be true for miRNAs, which could act as “specific” or “common” modulators in both normal and abnormal neuronal cell function. This view is in particular intriguing for sporadic neurodegeneration, since these disease forms are characterized by a chronic dysfunction of the cellular homeostasis that could be associated with subtle deregulation of gene expression levels and, thus, causing slow disease progression. This could be mediated by miRNAs and if proven relevant, it would be important to delineate the dynamics of miRNAs in onset and progression of neurodegeneration and to determine whether a disturbed miRNA system is cause or consequence or both for the development, sustainment or containment of neurodegenerative disorders. Changes in miRNA expression profiles have been already described in early and late life and in relation to neurodegeneration (Lukiw, 2007). The challenge will be to separate physiological functions of miRNAs during neuronal development and in postmitotic neurons from non-physiological and detrimental functions in disease. Altogether, dissecting out the specifics of miRNA regulation in neurodegenerative disorders and delineating overlapping functions within different disease entities will be the future challenge to further understanding this new concept of regulatory gene expression and to translate new knowledge into therapeutic intervention.

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Figure 1.

Biological systems in (neuronal) cell function. **(A)** Schematic representation of factors involved in cellular homeostasis. Cell function is orchestrated by a complex system of signaling pathways, which is tightly linked to a regulatory miRNA/mRNA network. These systems are influenced by genetic, epigenetic, and environmental factors and their deregulation is associated with the pathogenesis of (neuro)degeneration. **(B)** Schematic of the miRNA/mRNA regulatory network. miRNA expression follows similar steps as in mRNA expression: miRNA coding sequences are transcribed by RNA polymerase II or III as precursor RNAs and are processed into ~22 nucleotides mature miRNAs - some miRNAs can be post-transcriptionally edited and alter their target sequence. The main function of miRNAs is binding on mRNA targets for cleavage or blocking their translation (Bartel, 2004), a mechanism that can also be reversed under stress (Bhattacharyya et al., 2006a; Bhattacharyya et al., 2006b; Steitz and Vasudevan, 2009). The consequences of this regulation of gene expression are multifaceted and ultimately influence all aspects of cellular function including mRNA-splicing, DNA methylation, transcriptional activation, and translational processes. Since miRNAs also depend on this machinery, they are part of feedback loops that regulate their own expression. Finally, miRNAs expression and function can be modulated by intrinsic and extrinsic factors, such as genetic predisposition and stress underscoring their association with the pathogenesis of (neuro)degeneration.

Figure 2.

Schematic of miRNA involvement in neuronal cell development, function and degeneration. In mammals, miRNAs play a crucial role in pan-neuronal cell development (e.g., miR-124 and miR-9) (Cheng et al., 2009; De Pietri Tonelli et al., 2008; Krichevsky et al., 2006) and in the determination of neuronal subtypes (e.g. miR-133b (Kim et al., 2007)). In postmitotic neurons, it appears that miRNAs are part of pan-neuronal cell functions (“common” neuronal miRNAs) and could also be involved in the determination of neuronal subtype identities (“specific” neuronal miRNAs). This concept could have implication for a role of miRNAs in neurodegeneration as both overlapping and distinct disease processes are typical for neurodegenerative diseases. The deregulation of signaling pathways in neurodegeneration

could be a cause and/or a consequence of a deregulated miRNA/mRNA expression network that includes both “specific” and “common” miRNAs and their corresponding targets.

Selected mammalian miRNAs with validated targets and their potential association with neurodegeneration. miRNAs were organized according to their direct association with specific neurodegenerative diseases or to common targets that could be part of disease mechanisms.

Table 1

miRNA with direct disease association	species	validated target	disease	functional effect of miRNA	Reference
miR-29a/b-1	human	BACE1	AD	regulation of APP cleavage	(Hebert et al., 2008)
miR-107	human	BACE1	AD	regulation of APP cleavage	(Wang et al., 2008b)
miR-298	rodent	Bace1	AD	regulation of APP cleavage	(Boissonneault et al., 2009)
miR-328	rodent	Bace1	AD	regulation of APP cleavage	(Boissonneault et al., 2009)
miR-20a	human	APP	AD	regulation of APP expression	(Hebert et al., 2009)
miR-17-5p	human	APP	AD	regulation of APP expression	(Hebert et al., 2009)
miR-106b	human	APP	AD	regulation of APP expression	(Hebert et al., 2009)
miR-106a	human	APP	AD	regulation of APP expression	(Patel et al., 2008)
miR-520c	human	APP	AD	regulation of APP expression	(Patel et al., 2008)
miR-7	rodent	Snca	PD	regulation of a-Synuclein (e.g. UPS function)	(Junn et al., 2009)
miR-133b	rodent human	Pitx3	PD	feedback loop in DA neuronal cell development	(Kim et al., 2007)
miR-433	human	FGF20	PD	regulation of FGF20 (cell growth and survival)	(Wang et al., 2008a)
miR-9/9*	human	REST	HD	regulation of REST and CoREST	(Packer et al., 2008)
miR-19	human	ATXN1	SCA1	regulation of ATXN1 in Purkinje cells	(Lee et al., 2008)
miR-101	human	ATXN1	SCA1	regulation of ATXN1 in Purkinje cells	(Lee et al., 2008)
miR-130	human	ATXN1	SCA1	regulation of ATXN1 in Purkinje cells	(Lee et al., 2008)
miR-659	human	GRN	FTLD	regulation of GRN (cell growth)	(Rademakers et al., 2008)
miRNA with potential disease-associated targets	species	validated target	disease	functional effect of miRNA	Reference
miR-504	human	DRD1		regulation of dopamine receptor 1 expression	(Huang and Li, 2009)
miR-219	rodent	CamKII γ		modulates NMDA receptor function	(Kocerha et al., 2009)
miR-219	rodent	Scop		involvement in circadian clock	(Cheng et al., 2007)
miR-132	rodent	P250GAP		neuronal morphogenesis and dendritic plasticity	(Vo et al., 2005; Wayman et al., 2008)

miRNA with direct disease association	species	validated target	disease	functional effect of miRNA	Reference
miR-132	rodent	MeCP2		feedback loop with CREB and BDNF, homeostasis	(Klein et al., 2007)
miR-132	rodent	RFX4		involvement in circadian clock	(Cheng et al., 2007)
miR-134	rodent	Limk1		regulation of spine development and densities	(Schratt et al., 2006)
miR-134	rodent	Pum2		regulation of dendrite development	(Fiore et al., 2009)
miR-138	rodent	Apt1		dendritic spine morphogenesis	(Siegel et al., 2009)
miR-34a	rodent	bcl2		regulation of apoptosis	(Wang et al., 2009)
miR-124	rodent	multiple		multiple (see text)	see text
miR-338	rodent	CoxIV		oxidative phosphorylation, mitochondria function	(Aschrafi et al., 2008)

AD; Alzheimer's disease, PD; Parkinson disease, HD; Huntington's disease, SCA1; Spinocerebellar ataxia type 1, FTL D; Frontotemporal dementia