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MicroRNAs in Neural Cell Differentiation

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Abstract

The architecture and functioning of the mammalian nervous system is partly based on the complexity of combinatorial gene expression in the developing brain that results in a tremendous diversity of neural cells. MicroRNAs are small non-coding RNAs that are particularly abundant in the brain and are emerging as influential regulators of neural gene expression. This mini-review summarizes the recently discovered role of microRNAs in the development and maintenance of the nervous system. MicroRNAs are temporally expressed during neural differentiation, spatially regulated and embedded in molecular feedback loops that may contribute to the robustness of the neural networks.

Keywords

microRNAs; post-transcriptional regulation; development; nervous system; neurogenesis; differentiation

1. Introduction

MicroRNAs (miRNAs) are small (~ 21 nucleotides), non-coding RNAs that recognize binding sites located in the 3' Untranslated Region (3'UTR) of mRNA targets (Chekulaeva and Filipowicz, 2009). The miRNA genes are transcribed as primary miRNAs (pri-miRNAs) in the nucleus by RNA polymerase II and are further processed by the Rnase/Dgcr8 microprocessor complex into ~ 70 nucleotides (nts) long precursor miRNAs (pre-miRNAs), which fold into a classical stem-loop structure (Figure 1). These pre-miRNAs are then exported to the cytoplasm via the Xpo5/Ran complex, where they are further cleaved into ~21 nts duplexes by the RNase III-type enzyme Dicer1. Only one strand of the miRNA duplex, referred to as the miRNA, is incorporated into the RNA-induced silencing complex (RISC) while the opposite strand, also known as miRNA*, is generally not active – rather, it is poised for degradation. In animals, miRNAs predominantly bind to their targets by following imperfect complementary base pairing rules; of particular importance is the base pairing between positions 2 and 7 of the miRNAs (also known as the seed sequence) and their targets.

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The complexity of the nervous system originally arises during embryogenesis from a small number of neural stem cells (NSCs) (Merkle and Alvarez-Buylla, 2006). The large diversity of neural cell types present in the embryonic and adult brains is partly supported by the combinatorial complexity of the genetic programs orchestrated at the transcriptional level by transcription factors. Furthermore, the high abundance of miRNAs in the mammalian brain (Sempere et al., 2004), (Miska et al., 2004) strongly suggests that miRNAs may represent important post-transcriptional regulators of gene expression by adding subtle but influential changes to the genetic programs that normally occur in neural cells. In this mini-review, we will discuss the growing importance of miRNAs during neural proliferation and differentiation.

2. Neural stem cells: At the root of the neural lineage tree

During brain development, NSCs give rise to neurons, astrocytes and oligodendrocytes of the central nervous system (CNS). Typically, NSCs are multipotent and self-renewing (Gotz and Huttner, 2005). Before neurogenesis, the neural plate is composed of a single layer of neuroepithelial cells, which are highly polarized cells that first expand by symmetrical divisions. At the onset of neurogenesis, these neuroepithelial cells switch to an asymmetrical mode and produce radial glia cells and intermediate progenitor cells. Radial glia cells in the ventricular zone (VZ) undergo symmetric and asymmetric divisions to generate neurons (Anthony et al., 2004). In contrast, most intermediate progenitor cells are neuronal committed progenitors and divide symmetrically in the subventricular zone (SVZ) (Noctor et al., 2008). In the adult brain, neurogenesis becomes more limited even though some populations of NSCs are persisting through adult life either as a subset of astrocytes in restricted brain regions (Doetsch et al., 1999) or as Sox2⁺ cells residing in the subgranular zone (SGZ) of the hippocampus (Suh et al., 2007).

3. MiRNAs and early neurogenesis

The role of miRNAs in early neurogenesis has been assessed using mouse models in which the Dicer1 gene has been inactivated, resulting in a global loss of miRNAs in specific neuronal cell types such as Purkinje cells (Schaefer et al., 2007), hippocampal and cortical neurons (Davis et al., 2008). For instance, deletion of Dicer1 in Purkinje cells resulted in neuronal cell death suggesting an essential role of miRNAs in the survival of differentiated neurons. The deletion of Dicer1 in excitatory forebrain neurons led to reduced dendritic branch elaboration, increase in dendritic spines, microcephaly and ataxia by P15, confirming that miRNAs are important for the maintenance of differentiated neuronal cells and brain homeostasis. To determine whether miRNAs play a role at the earliest stages of neural differentiation, a mouse line with a Dicer1 floxed allele was crossed with an Emx1-Cre strain, resulting in the specific deletion of Dicer1 in neuroepithelial cells (De Pietri Tonelli et al., 2008). This deletion of Dicer1 in the E9.5 cortex led to a reduction in the size of the cortex by E12.5 and an increase in neuronal apoptosis in the cortical wall. By E14.5, there was depletion of apical and basal intermediate progenitor cells, thus showing that miRNAs play an indispensable role in the production of neurons during embryonic corticogenesis. Given that the miRNA repertoires of these neuronal cells have not been characterized, it would be of high interest to identify the specific miRNAs that are crucial during the transition from neuroepithelial cells to neuronal progenitor cells. Very recently, the miRNA repertoires of E11 and E13 rat neuronal progenitor cells revealed that several miRNAs were either up- or down-regulated at the onset of neurogenesis (Nielsen et al., 2009). Interestingly, miR-9 and miR-124, which have been initially reported as up-regulated during brain development (Krichevsky et al., 2003), were also found up-regulated during the lineage progression of neuronal progenitor cells, thus supporting a critical role for these two miRNAs during neuronal proliferation and differentiation (Table 1).

4. Temporal and spatial expression of miRNAs and control of neural differentiation

MicroRNAs are dynamically regulated during neural differentiation. For example, miR-138, miR-219 and miR-338 were found to be up-regulated during oligodendrocyte differentiation (Lau et al., 2008). These miRNAs are required for myelination, as demonstrated by two recent studies using conditional inactivation of Dicer1 in oligodendrocytes. Loss of myelin occurred after crossing the Dicer1 floxed mice with the PlpER^T line, resulting in the dysregulation of miR-219 which normally down-regulates Sox6 and Hes5, two inhibitors of oligodendrocyte differentiation (Zhao et al., 2010). In another study, Dicer1 inactivation obtained after crossing the Dicer1 floxed line with Cnp-cre or Olig2-cre lines resulted in abnormal CNS myelination (Dugas et al., 2010). In this transgenic model, lack of Dicer1 led to delay or disruption of oligodendrocyte differentiation; moreover, miR-219 was shown to regulate the expression of Sox6, Foxj3 and Zfp238, three transcription factors with potential role during oligodendrocyte proliferation. Pdgfra was also found to be a target of miR-219 and this observation is of importance since it has been known for decades that Pdgf is an important mitogenic signal for oligodendrocyte progenitor cells (Noble et al., 1988).

The levels at which miRNAs are expressed are critical for normal neural development, as documented by modulating the amounts of miR-9 in NSCs. One target of miR-9 is Tlx, a nuclear receptor involved in NSC renewal (Shi et al., 2004). *In utero* electroporation of miR-9 in the VZ of E13.5 mouse led to decreased Ki67⁺ cells and increased Dcx⁺ positive cells, suggesting that miR-9 accelerates neuronal differentiation by fine-tuning the expression of genes involved in the differentiation of neuronal progenitor cells (Zhao et al., 2009). Similar results were observed with another target of miR-9, Foxg1, a transcription factor involved in the generation of Cajal–Retzius (CR⁺) neurons (Hanashima et al., 2004). In the E12 mouse brain, miR-9 is located in the medial pallium and the VZ of the ganglionic eminences. Over-expression of miR-9 caused premature neuronal differentiation in the VZ, as identified by the early emergence of CR⁺ cells (Shibata et al., 2008). Of note, Foxg1 is expressed in the entire mouse telencephalon at E12 but is absent in the most medial pallium where miR-9 is highly expressed, introducing the notion that miRNAs are not only regulated during cellular differentiation, but also show defined expression patterns at precise time points during development. This spatial distribution may explain how miRNAs effectively dual-task: by being present in some tissues to actively repress gene expression and by being absent in the surrounding areas to allow a genetic program to occur by default in these adjacent tissues. In the zebrafish, miR-9 is absent from the midbrain-hindbrain boundary (MHB), an organization center of the neural tube, while present in adjacent areas of the midbrain and hindbrain (Leucht et al., 2008). Remarkably, the over-expression of miR-9 in the MHB triggered loss of the territory integrity, suggesting that the expression of miR-9 surrounding the MHB defines the boundaries of this territory. Furthermore, the inhibition of miR-9 in the surrounding areas led to reduction of HuC⁺ neuronal cells, consistent with an active role of miR-9 during the differentiation of neurons.

5. Fine-tuning of developmental transitions through temporal negative feedback loops

How is miR-9 up-regulated in progenitor cells committed to the neuronal lineage? In Huntington's Disease (HD), a polyglutamine expansion in the Htt protein abrogates its binding to REST, leading to its abnormal nuclear translocation in neuronal cells and decreased neuronal gene expression (Zuccato et al., 2003). Several miRNAs including miR-9, -9*, -29b, -124a and -132 were found as down-regulated in HD cases (Packer et al., 2008), suggesting that Rest normally regulates their expression in non-neuronal cells and NSCs by binding to upstream

RE1 silencing transcription factor (REST) elements of these miRNA genes. The existence of a feedback loop was suggested by the observation that REST inhibits miR-9 expression in NSCs and the subsequent down-regulation of REST during neuronal differentiation led to increased level of miR-9. Furthermore, miR-9 was also shown to down-regulate REST, thereby confirming a feedback loop between miR-9 and REST and a role for miR-9 in the removal of residual REST in neuronal committed progenitor cells. Other examples of feedback loops have been reported for miR-133b and Pitx3, which is a transcription factor required during the maturation of midbrain dopaminergic neurons (Kim et al., 2007) and for miR-9 and Tlx (Zhao et al., 2009). Of note, several of the miRNAs which are controlled by REST are also embedded in feedback loops and target REST or other components of the REST complex such as Rcor1/2 (Packer et al., 2008), Mecp2 (Klein et al., 2007) and Ctdsp1 (Visvanathan et al., 2007). For instance, Ctdsp1 normally acts as an anti-neural factor together with REST (Yeo et al., 2005) in non-neuronal cells and NSCs. Electroporations of 2'-O-methyl oligoribonucleotides targeting miR-124 in the chick neural tube increased the number of BrdU⁺ proliferating cells in the lateral post-mitotic zone and reduced NeuN⁺ neuronal cells, thus showing that miR-124 modulates neuronal cell differentiation (Visvanathan et al., 2007).

6. MiRNAs and functional homeostasis in neurons

When miR-124 was over-expressed in HeLa cells, the gene expression profile of these non-neuronal cells was directed toward a neuronal phenotype (Lim et al., 2005). There were ~170 down-regulated genes, each of which is generally absent or expressed at low levels in the brain, thus suggesting that a function for miR-124 in the nervous system is to repress unwanted or leaky transcripts. Such a fail-safe function (or “expression buffering”) is further supported by the observation that inhibition of miR-124 in primary cultures of terminally differentiated cortical neurons resulted in the increase of 10 non-neuronal transcripts (Conaco et al., 2006). However, the targets identified by these two studies are only the tip of the iceberg and the interplay between miR-124 and neurons extends beyond the primary down-regulation of targets. For example, miR-124 globally impacts splicing of neuronal genes by regulating the splicing factor Ptpb1, which allows inclusion of neuron-specific exons in transcripts (Makeyev et al., 2007) and is normally down-regulated in mature neurons (Boutz et al., 2007). Furthermore, miR-124 and Ptpb1 display reciprocal patterns of expression in the embryo, consistent with a function of miR-124 in maintaining neuronal integrity. Accordingly, the inactivation of Dicer1 in the telencephalon led to a high level of Ptpb1 protein throughout the entire span of the lateral telencephalic wall by E13.5, whereas Ptpb1 expression is normally restricted to the VZ of the telencephalon. This ectopic expression was accompanied by a loss of Map2⁺ post-mitotic neurons; however, this study did not address whether this resulted from abnormal proliferation of progenitor cells or increased neuronal apoptosis. Other important targets of miR-124 have been also identified during embryonic and adult neurogenesis. For example, over-expression of miR-124 during embryogenesis causes reduced proliferation of neural progenitor cells, repression of Actl6a, a component of the chromatin-remodeling Swi/Snf-like complex (Kuroda et al., 2002), and its replacement by Actl6b in post-mitotic neurons of the neural tube (Yoo et al., 2009). During adult neurogenesis, miR-124 also regulates neuronal progression at the transition of type C transit-amplifying cells to type A migrating neuroblasts (Cheng et al., 2009). Blocking miR-124 led to hyperplasia of type C cells, suggesting that these cells failed to differentiate into type A neuroblasts. Conversely, over-expression of miR-124 led to cell-cycle exit, increased neuronal differentiation and down-regulation of the transcription factor Sox9. The dynamics of the temporal and spatial regulation of miRNAs in the brain are schematized in Figure 2.

7. Concluding remarks

It is now clear that miRNAs play a critical role during neural cell proliferation and differentiation and that their dysregulation may lead to neurodegeneration (Lau and de Strooper, 2010). Moreover, the developmental regulation of gene expression by miRNAs in NSCs may be abnormally recapitulated in cancer stem cells. For example, miR-9 is not only highly expressed in fetal brain but also in oligodendroglioma and glioblastoma when compared to adult brain, normal oligodendrocytes and astrocytes (Nelson et al., 2006), (Nass et al., 2009). This snapshot of miRNA action thus captures not only the sophisticated regulatory network that operates during the nervous system development but also the miRNA dysregulation that could occur in pathophysiological conditions such as neurodegeneration or cancer. Further understanding of the complexities of these microregulators will uncover new developmental pathways and spawn innovative strategies aimed at promoting adult neurogenesis in neurodegenerative and demyelinating diseases as well as controlling brain cancers.

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Figure 1.

The biogenesis of miRNAs. The pri-miRNAs are composed of a stem, a terminal loop and two flanking sequences which are subject to cleavage by the Rnase/Dgcr8 microprocessor complex to produce pre-miRNAs (step 1). Through the Xpo5/Ran pathway, pre-miRNAs are translocated from the nucleus into the cytoplasm (step 2) where they are processed by Dicer1 into miRNAs (step 3). The miRNA duplexes are unwound and one strand of the duplex (namely the miRNA) is incorporated into the RISC complex (step 4). MiRNAs trigger post-transcriptional gene silencing through base pairing with the 3' UTR of mRNA targets, thereby leading to mRNA target degradation or translation repression.

Figure 2.

The miRNAs and the existence of molecular feedback loops. Three examples of negative feedback loops are shown for Pitx3-miR-133b, Tlx-miR-9 and Rest-miR-9. In the hypothetical model, the transcription factors (Pitx3, Tlx and REST) induce transcription of the miRNAs during neural differentiation. Those miRNAs are embedded in negative feedback circuits that normally suppress the expression of transcription factors. The proposed model also implies that miRNAs are dynamically regulated during neural differentiation (e.g. increase in expression) and expressed regionally or specifically in some cell types (dopaminergic neurons, neural stem cells or neurons). Because transcription factors and miRNAs are co-expressed during a specific time window, the proposed function of these miRNAs is to insure the proper timing of differentiation, as opposed to a more prevalent fail-safe function in maintaining cellular homeostasis in neural cells by preventing the expression of leaky transcripts (i.e. expression buffering characterized by mutual exclusion of miRNAs and mRNA targets, not described here).

Table 1

miRNAs and neural development

miRNA	Species	Targets	Function	Reference
miR-9	Human	REST	Promotes neurogenesis	Packer, 2008
miR-9	Mouse	Tlx	Promotes NSC differentiation	Zhao, 2009
miR-9	Mouse	Foxg1	Differentiation of CR+ neurons	Shibata, 2008
miR-9	Zebrafish	Fgf8, Fgfr1	Maintains organizer activity at the midbrain-hindbrain boundary	Leucht, 2008
miR-124	Mouse	Sox9	Promotes neurogenesis in the adult SVZ	Cheng, 2009
miR-124	Mouse	Actl6a	Neural specific chromatin-remodeling Swi/Snf-like complexes	Yoo, 2009
miR-124	Mouse	Ptbp1	Inclusion of neuron-specific exons in neuronal transcripts	Makeyev, 2007
miR-124	Chicken	Ctdsp1	Neural induction in the spinal cord of embryos	Visvanathan, 2007
miR-133b	Mouse	Pitx3	Differentiation of dopaminergic neurons	Kim, 2007
miR-219	Mouse	Sox6, Hes5	Promotes oligodendrocyte differentiation	Zhao, 2010
miR-219	Mouse	Sox6, Foxj3, Zfp238, Pdgfra	Promotes oligodendrocyte differentiation	Dugas, 2010