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Mini-review

microRNA involvement in developmental and functional aspects of the nervous system and in neurological diseases

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ABSTRACT

microRNAs, small non-coding RNAs that regulate gene expression at the post-transcriptional level, are emerging as important regulatory molecules involved in the fine-tuning of gene expression during neuronal development and function. microRNAs have roles during neuronal stem cell commitment and early differentiation as well as in later stages of neuronal development, such as dendritogenesis and synaptic plasticity. A link between microRNAs and neurological diseases, such as neurodegeneration or synaptic dysfunction, is becoming increasingly clear. This review summarizes the current knowledge of the function of microRNAs in the developing and adult nervous system and their potential contribution to the etiology of neurological diseases.

Introduction

The discovery of microRNAs (miRNAs) has introduced an important new layer of regulatory control of gene expression. miRNAs are short non-coding RNAs, about 21 nucleotides (nt's) long, that modulate gene expression at the post-transcriptional level by guiding cellular machinery to the 3′-untranslated region (3′-UTR) of specific messenger RNAs (mRNAs) to control their expression. Since the biogenesis and mechanism of action of miRNAs has been extensively described in other reviews [6,9], it will only be briefly discussed here. Most miRNAs are transcribed by polymerase II, although a few human miRNAs have been shown to be transcribed by polymerase III [8]. The primary transcript (pri-miRNA) can be up to several thousand nt's long and contains internal hairpin structures. Within the nucleus, the pri-miRNA is processed by the RNase III enzyme Drosha, resulting in a ~70 nt long hairpin precursor miRNA (pre-miRNA) containing a 2-nt 3′overhang. This overhang is recognized by Exportin-5, which transports the pre-miRNA into the cytoplasm. In the cytoplasm, the pre-miRNA is further cleaved by the RNase III enzyme Dicer. This results in the formation of an intermediary miRNA:miRNA* duplex consisting of the ~21 nt mature miRNA and its star sequence, miRNA*. Following unwinding of the miRNA duplex by a helicase, the mature miRNA is incorporated into the RNA-induced silencing complex (RISC), whereas the miRNA* is usually degraded. Binding of a miRNA to its target mRNA requires both RISC and the presence of Argonaute (Ago) proteins. miRNA target recognition usually involves strong base-pairing between residue 2–8 at the 5′-end of miRNAs, the so-called seed sequence, and complementary sequences in the 3′-UTR of the target mRNA. Depending on the degree of complementarity between the miRNA and its target, the target mRNA can either be cleaved and degraded or translationally repressed. Perfect complementarity induces degradation of the mRNA, whereas non-perfect complementarity results in translational inhibition. In animals, miRNA silencing of gene expression is predominantly mediated by translational blockade. To date, the mechanisms behind translational inhibition are elusive. Regulation at the step of translational initiation is believed to be the main mechanism to block translation, although evidence for regulation at post-initiation steps has also been put forward [51]. The miRNA induced translational inhibition appears to be reversible in a few instances [7,55], rendering the miRNA mediated regulation dynamic and responsive to specific cellular needs.

Vertebrate miRNA genes either occur as isolated genes or are located in large miRNA clusters that are coordinately transcribed as polycistronic primary transcripts [15]. Non-clustered miRNA genes can be transcribed from their own promoter, though 40% and 10% of human and mouse miRNA genes are located within introns and exons, respectively, of non-protein-coding or protein-coding transcripts and expressed along with their host gene [77].

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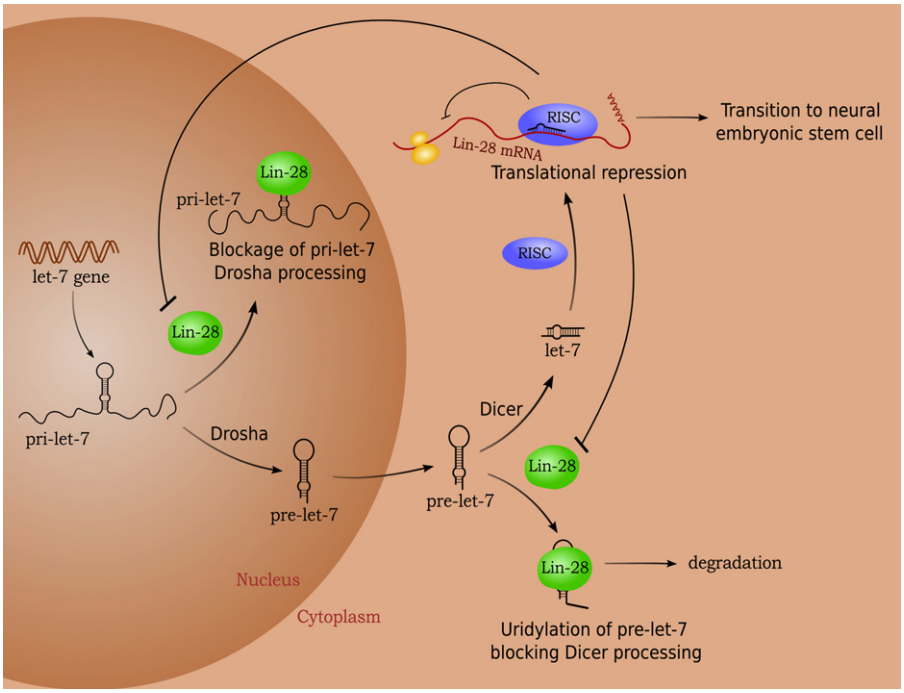

Fig. 1. Working model for the role of let-7 in neural cell lineage specification. Transition of embryonic to neural stem cells is controlled by let-7. The level of let-7 is regulated by a double-negative feedback loop between let-7 and Lin-28. Lin-28 protein suppresses let-7 at the post-transcriptional level, thereby maintaining embryonic stem cell identity. Translational inhibition of Lin-28 mRNA by let-7 allows processing of let-7, resulting in neural stem cell commitment. Lin-28 suppression of let-7 processing can be achieved by two mechanisms: (1) in the nucleus, Lin-28 binds to the loop of the hairpin structure in the pri-let-7 transcript, thereby blocking Drosha processing; (2) in the cytoplasm, Lin-28 induces uridylation of pre-let-7. Uridylated pre-let-7 is not recognized by Dicer and undergoes degradation.

miRNAs are very abundant in multicellular organisms and influence the expression of many protein-coding genes. To date, approximately 700 miRNAs have been described in the human genome [23] and the number is continuously expanding. Each miRNA has been estimated to target up to a few hundred target genes [33] and, altogether, miRNAs have been suggested to regulate as much as one third of the protein coding genes in animals [38]. miRNAs are divided into families based on similarities in their seed sequences. One-third of miRNA families are highly conserved across species, and as much as 60% conservation between mouse and human mature miRNAs is observed [52]. miRNAs have been implicated in diverse cellular processes such as developmental timing, apoptosis, metabolism, myogenesis and cardiogenesis [31].

Taking into account the high complexity of the brain and its neuronal circuits, it comes as no surprise that miRNAs are emerging as essential regulators of the development and function of the nervous system. miRNA research is still a relatively nascent field, and detailed mechanisms on miRNA involvement in the regulatory circuits of the nervous system are just beginning to be unveiled. This review presents an overview of the current knowledge about the involvement of miRNA regulatory pathways in the function of the developing and adult nervous system and in neurological diseases.

Role of Dicer and microRNAs in the nervous system

The brain is a rich source of miRNAs and several studies using miRNA expression profiling reveal that a significant fraction of miRNAs are enriched or specifically expressed in the nervous system [18,36], and that their expression is precisely regulated during brain development [34,46]. This initially indicated an important role of miRNAs in brain development, neuronal differentiation and regulation of brain and neuron specific gene expression. Genomic *Dicer* ablation results in the absence of all mature miRNAs and has been used as a valuable tool to study the general involvement of miRNA regulatory pathways in the nervous system. Severe brain morphogenesis deficits are observed in zebrafish *Dicer* knockout mutants. Lack of Dicer can be rescued by miR-430, a large family of miRNAs expressed during early zebrafish development, implicating an essential role for this miRNA family during brain development [22]. In mice, *Dicer* ablation causes neurodegeneration and cell death of subpopulations of neurons, such as dopamine neurons in the midbrain [29], postmitotic Purkinje cells of the cerebellum [54] and neocortical neurons [17]. In addition, loss of Dicer in cortex and hippocampus affects cellular and tissue morphology, axonal pathfinding and apoptosis [16]. This indicates that miRNAs are important in such diverse processes as neuronal and tissue morphogenesis, neuronal survival and possibly neurodegenerative diseases. *Dicer* silencing in neocortical progenitors impairs neuronal differentiation [17] and results in abnormal terminal differentiation of developing olfactory progenitors. Inhibiting the miR-200 family alone, a family of miRNAs highly expressed in olfactory tissue, phenocopies the abnormal terminal differentiation in olfactory progenitors [14]. As a whole, these results indicate a central role for miRNAs during neuronal differentiation.

The studies using *Dicer* mutants have revealed undoubtedly important roles for miRNAs in many diverse aspects of the nervous system. Nevertheless, the ablation of *Dicer* does not reveal anything about the function of individual miRNAs. The remaining of this review is focused on the impact of individual miRNAs on developmental and functional aspects of the nervous system.

microRNAs in neural cell lineage specification and differentiation

A number of studies have identified the importance of miRNA regulatory pathways in early events of neuronal development, such as neural stem cell commitment, differentiation and neurite outgrowth. let-7 was originally discovered in *Caenorhabditis elegans* as a regulator of developmental timing through the regulation of cell proliferation and differentiation [10]. This miRNA is highly