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Review

MicroRNA function in neuronal development, plasticity and disease

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Abstract

The development and function of the nervous system is orchestrated by a plethora of gene regulatory mechanisms. MicroRNAs (miRNAs), an abundant class of small non-coding RNAs, are emerging as important post-transcriptional regulators of gene expression in the brain. MiRNAs function at all stages of neuronal development, ranging from the initial specification of neuronal cell types to the formation and plasticity of synaptic connections between individual neurons. Moreover, links between miRNA dysfunction and neurological diseases become more and more apparent. The study of this novel layer of gene regulation therefore promises to enrich our knowledge of brain function and pathology.

Keywords: MicroRNA; Differentiation; Synapse; Nervous system; Neurological disease

1. Introduction

Post-transcriptional regulation of gene expression is a mechanism used in multiple aspects of neuronal development and function in the CNS. The importance and complexity of this pathway has been emphasized by the discovery of microRNAs (miRNA). This class of small non-coding RNAs induces translational repression or degradation of a target mRNA upon imperfect base pairing to its 3′ untranslated region (3′UTR). The biogenesis and mechanism of action of miRNAs are covered in detail in a number of excellent reviews [1,2], and will therefore be just briefly summarized here. Structurally, mature miRNAs are single stranded RNA molecules of about 21 nucleotides (nt) derived from a 70 to 100 nt hairpin-precursor (pre-miRNA). MiRNA genes are mostly transcribed by RNA-polymerase II, the exception being some human genes that are transcribed by RNA-polymerase III [3]. The primary transcript, which can be up to hundreds of nt long, is then processed by the RNAse III enzyme Drosha in the nucleus, to yield a pre-miRNA. The pre-miRNA is subsequently translocated to the cytoplasm by an exportin-5 dependent mechanism. Once in the cytosol, pre-miRNAs are further processed by a second RNAse III enzyme, Dicer. Cleavage generates an imperfect, siRNA-like duplex that is unwound and whose strand with the weakest base pairing at the 5′ end is preferentially loaded into the RNA-induced silencing complex (RISC). Binding of the miRNA to its target occurs within the RISC and target silencing requires the presence of proteins belonging to the Argonaute (AGO) family. Complementarity between the 5′ end of the miRNA, the seed region, and the 3′ UTR of the target mRNA appears to be critical for the binding, while more variability is tolerated in the base pairing at the 3′ end of the miRNA [1,2]. The mechanism by which miRNAs silence gene expression is still an active and controversial field of investigation. One of the main mechanisms appears to be a block of translational initiation, but other mechanisms are likely involved [4–6]. A critical structure for miRNA-mediated deadenylation and degradation are processing bodies (P-bodies), cytoplasmic foci which were originally identified as sites of mRNA storage and degradation. In addition to P-bodies neurons contain a variety of functionally related high molecular weight ribonucleoprotein particles (nRNP) that are involved in storage, dendritic trafficking (see Section 4) and translational control of neuronal mRNAs [7,8].

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MiRNAs are involved in a variety of physiological and pathological processes in multicellular organisms, ranging from patterning to cancer development [9]. Since the CNS is a rich source of miRNAs that often display a brain specific expression pattern (see below), and since a single miRNA is able to target up to a few hundreds of different mRNAs [10], it is hardly surprising that the number of roles assigned to miRNAs during all stages of CNS development and function is rapidly expanding.

In this review, we will first briefly describe the isolation of miRNAs expressed in the CNS and the unique features of brain specific miRNA genes. We will then focus on the role of miRNAs in the developing and adult nervous system. Finally the last section will address emerging connections between the miRNA pathway and neurological diseases.

2. Isolation and expression of miRNA in the nervous system

The first hint that miRNAs might play a variety of roles within the nervous system came from cloning and expression analysis of miRNAs. A surprisingly high number of unique miRNAs was isolated from brain and neuronal cell lines [11]. A large number of these microRNAs were associated with polyribosomes [12,13], a hallmark of ongoing translation indicating that in the nervous system, like in other tissues, miRNAs might be involved in the regulation of translation. With the development of suitable probes for microarray profiling and detection by *in situ hybridization* (ISH), it was possible to show that miRNA expression in the nervous system can be both regulated dynamically and in a tissue specific manner [14]. For instance, some miRNAs, such as mir-138 and mir-124, are expressed predominantly in the CNS; other miRNAs display a region or cell type specific expression: zebrafish mir-222 is present only in the telencephalon [15], whereas mir-26 and mir-29 are predominantly expressed in astrocytes [16]. On the other hand, a number of brain microRNAs appear to be developmentally regulated, with high expression observed in neuronal progenitors (e.g. mir-92b) but not in differentiated neurons, or vice versa (e.g. mir-124). Recently, the temporal and regional specificity of miRNA expression in the CNS has been confirmed and expanded by two extensive expression studies. First, in zebrafish the distribution of 38 conserved miRNAs expressed in the nervous system was analyzed by ISH [17]. Second, in mammals a miRNA expression atlas has been generated by large-scale small RNA cloning and sequencing [18]. Both studies confirmed the presence of CNS specific microRNAs and identified new ones, such as mir-218, a miRNA that is expressed only in motor neurons in zebrafish, and mir-29a, a family of miRNAs that is absent in embryonic tissues but highly expressed in the adult cortex. Taken together, these descriptive studies represented the basis for more functional studies in the following years. Furthermore, they revealed some unique features of CNS miRNAs regarding evolutionary conservation. On one hand some miRNAs, such as let-7, were found to be highly conserved from nematodes to primates [19], suggesting that these miRNAs might regulate general aspects of nervous system development. On the other hand, some miRNAs are expressed only in the primate brains [20]. The function of these evolutionarily young miRNAs is unknown, but it is tempting to speculate that they might contribute to the astoundingly high cellular diversity found in the brain of higher organisms, and in the cellular mechanisms underlying higher cognitive function.

Although transcriptional mechanisms already generate a high degree of complexity, the variety of brain specific miRNAs can be further increased by post-transcriptional regulation. For example, the three members of the mir-376 family (376a, -b and -c) have been shown to undergo editing in humans and mouse and, interestingly, this modification occurs specifically in the brain [21]. Furthermore, an example of brain specific processing has recently been described. Whereas the pre-mir-138 is ubiquitously expressed, the functionally mature mir-138 is exclusively found in the brain and fetal liver. Since pre-mir-138 cytoplasmic export is normal, this suggests that the tissue specific expression of the mature mir-138 is due to regulated Dicer processing [22]. Furthermore, members of the let-7 family have been shown to undergo regulated processing during early embryogenesis, and deregulated let-7 processing is responsible for the altered levels of this microRNA observed in several primary tumors [23].

3. MicroRNAs in the developing nervous system

Historically miRNAs have first been identified as regulators of cell fate determination in *Caenorhabditis elegans* [24–27]. Thus, many studies explored the potential role of miRNAs in neuronal differentiation and fate determination using various model systems such as *C. elegans*, *Drosophila melanogaster* and zebrafish. More recently, the analysis has been extended to several mammalian animal and cellular models.

Suppression of miRNA biogenesis by disrupting the zebrafish Dicer gene has provided the first evidence that miRNAs are necessary for the development of the nervous system [28]. Dicer mutants showed severe defects in neural tube morphogenesis, and this phenotype likely arose from abnormal neuronal differentiation, as opposed to defects in early patterning or specification. Introduction of mature mir-430 , a large family of related zebrafish miRNAs, into the mutant fish partially rescued the phenotype, suggesting that the miR-430 family specifically was responsible for some of the phenotypes. It is unknown if Dicer plays a similar role during early neural development in mammals as Dicer deficient mice die at embryonic day 7.5 before neurulation occurs [29]. However, recent conditional gene targeting approaches have shed some light on the role of the miRNA pathway in the CNS in mammals. Deletion of Dicer in the telencephalon by mid-gestation results in a size reduction of the forebrain likely caused by apoptosis of differentiating neurons [30]. Similarly, progressive cell death was observed when Dicer was inactivated postnatally in the cerebellum[31] or in dopaminergic neurons in the forebrain [32]. Taken together this genetic analysis is consistent with a general role for miRNAs in cell survival and differentiation in the CNS. However, it is important to note that a causal link between specific miRNAs and the observed phenotype in mammalian Dicer knockout animals has not been formally proven. Since Dicer is necessary