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Review article

The role of microRNAs in synaptic plasticity, major affective disorders and suicidal behavior

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ABSTRACT

Major affective disorders are common widespread conditions associated with multiple psychosocial impairments and suicidal risk in the general population. At least 3–4% of all depressive individuals die by suicide. At a molecular level, affective disorders and suicidal behavior are recently associated with disturbances in structural and synaptic plasticity. A recent hypothesis suggested that small non-coding RNAs (ncRNAs), in particular microRNAs (miRNAs), play a critical role in the translational regulation at the synapse. We performed a selective overview of the current literature on miRNAs putative subcellular localization and sites of action in mature neurons analyzing their role in neurogenesis, synaptic plasticity, pathological stress changes, major affective disorders and suicidal behavior. miRNAs have played a fundamental role in the evolution of brain functions. The perturbation of some intracellular mechanisms as well as impaired assembly, localization, and translational regulation of specific RNA binding proteins may affect learning and memory, presumably contributing to the pathogenesis of major affective disorders and perhaps suicidal behavior. Also, miRNA dys-regulation has also been linked to several neuropsychiatric diseases. However, further evidence are needed in order to directly clarify the role of miRNAs in major affective disorders and suicidal behavior.

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1. Introduction

The last years have been characterized by relevant research aimed to understand the complex and interesting relationship between genes and proteins expression. Growing attention has been directed to investigate the correlation between genes encoding messenger RNAs (mRNAs) and human diseases, particularly

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neuropsychiatric disorders. In human brain, miRNAs are a prominent class of gene expression regulators involved in nervous system development and physiology, and disease (Bushati and Cohen, 2007; Fiore et al., 2008); also, they are emerging as having a fundamental role in various CNS physiopathological conditions (Mouillet-Richard et al., 2012).

During the evolution of brain functions miRNAs have served as metacontrollers of gene expression determining cellular changes critical for brain development and normal cognitive function. Therefore, understanding the molecular mechanisms regulating miRNAs expression is fundamental to understanding the pathophysiology of neuropsychiatric disorders (Dwivedi, 2011; Saugstad, 2010).

Flavell and Greenberg (2008) recently suggested that an activity-regulated transcriptional program in neurons consisting of hundreds of genes is critical for the development of neural circuits, activity-dependent changes and neural connectivity. They observed that genes, encoding retrograde signals to the presynaptic cell (such as brain-derived neurotrophic factor (BDNF)) or truncated, dominant-interfering forms of full-length proteins at the synapse level (such as homer1a), strongly influence dendritic and synaptic remodeling.

Similarly, Newman and Hammond (2010), postulating that miRNAs modulate a large variety of gene expression patterns during development and tissue homeostasis, investigated the specificity of the Microprocessor (the protein complex essential for maturation of canonical miRNAs) and the miRNA families requiring an interaction between RNA-binding proteins and cis-regulatory sequences within miRNA precursor loops. Post-transcriptional control of miRNA expression may be only partially regulated by the miRNA biogenesis pathway and largely depends on the interactions between the pri-miRNA and coactivator proteins providing a critical specificity. miRNA mis-regulation may impair important neurophysiological functions such as learning and memory playing a crucial role in major depression. Being metacontrollers of genetic expression, miRNAs appear to be possible genetic non-invasive biomarkers for the diagnosis, treatment and progression of important human diseases.

However, whether and how miRNAs regulation directly influences cellular signaling networks and biological functions contributing to the development of neuropsychiatric diseases, particularly major depression, remains still poorly understood. Considering this background, this review begins by summarizing the most relevant biochemical information about miRNAs. Then, the existing literature focusing on the role of miRNAs in neurogenesis and neuroplasticity mechanisms and their possible involvement in the development of pathological stress changes, affective disorders and suicidal behavior was carefully reviewed.

2. Methods

A reference search was performed across the Medline and ScienceDirect databases (January 1980 and December 2011). The search used the following terms: “microRNAs” AND “Neuroplasticity” OR “Synaptic plasticity” AND “Neurogenesis” AND “Affective Disorders” AND “Major Depression” OR “Major Depressive Disorder (MDD)” AND “Suicid*” (including suicidal behavior OR suicide ideation OR suicidal thoughts OR deliberate self harm OR suicidal attempt). In addition, the reference lists of all papers identified were reviewed.

GS reviewed the literature and drafted the manuscript. MP, PG and YD provided the intellectual impetuous and supervised the search strategy. MI, GG, and FM provided help in selecting and drafting the papers. LS provided language editing. All authors contributed to the conceptualization of the research, and approved the manuscript. Included papers were those published in peer-reviewed journals. Where a title or abstract seemed to describe a study eligible for inclusion, the full article was obtained and examined to assess its relevance. Two independent researchers conducted a two-step literature search. Any discrepancies between the two reviewers who, blind to each other, examined the studies for the possible inclusion were resolved by consultations with a senior author.

3. miRNAs: definition, diffusion and functions

In the brain, gene expression is regulated at multiple levels. Gene expression may be activated through transcriptional factors and alternative splicing, but also by a several noncoding RNA transcripts creating miRNAs, antisense RNAs, and other critical forms of RNAs (for more details see Dwivedi, 2011). miRNAs are widely expressed in mammalian brain tissue and act as regulators of developmental timing and cell fate (Kosik, 2006; Bushati and Cohen, 2007). Fig. 1 describes biogenesis and expression of miRNAs as well as mechanisms of miRNA-mediated translational processes. Approximately 1000 miRNAs have been identified in the human genome (miRBase, 2010); miRNAs are expressed in tissue and cell specific manner (Landgraf et al., 2007; Kapsimali et al., 2007; Choi et al., 2008). Approximately 20–40% miRNAs are expressed together during the brain development (Miska et al., 2004; Sempere et al., 2004). Smirnova et al. (2005) hypothesized that some miRNAs are expressed in neurons, whereas other in high concentrations in astrocytes. Several authors (Presutti et al., 2006; Fiore et al., 2008; Liu and Zhao, 2009; Vreugdenhil and Berezikov, 2009) suggested that miRNAs may locally regulate mRNA translation inducing changes in neurogenesis, synaptic and axon development, and neuronal plasticity. Also, miRNAs may contribute to the onset and maintenance of affective disorders at multiple levels as a result of abnormalities in synaptic plasticity and neurogenesis or by regulating the expression of genes critically involved in major depression (Dwivedi, 2011).

4. The role of miRNAs in neurogenesis and neuroplasticity mechanisms

Neurogenesis is known to be involved in learning and memory (Bekinschtein et al., 2011; Koehl and Abrous, 2011; Yirmiya and Goshen, 2011): environmental stimuli, exercise, and antidepressant drugs (ADs) enhance hippocampal neurogenesis (Lazarov et al., 2010) whereas pathological stress and major depression negatively affect hippocampal neurogenesis (DeCarolis and Eisch, 2010; Lucassen et al., 2010). The role of miRNAs in the regulation of neurogenesis is still a matter of debate. Table 1 summarizes the role of miRNAs and their clinical relevance as involved in synaptic plasticity, neurogenesis, and neuropsychiatric disorders.

More than 100 specific miRNAs, particularly miR-124a and let-7, miR-200 variants seem to be expressed by olfactory tissues (Choi et al., 2008). Cheng et al. (2009) suggested that miR-124 is a fundamental regulator of the temporal progression of adult neurogenesis. Specifically, the progression along the subventricular zone stem cell lineage to neurons was mediated by the regulation of the sex-determining region on Y (SRY)-box-9 (Sox9), induced by miR-124. Neuronal differentiation was blocked by the overexpression of Sox9 whereas enhanced neuronal formation was determined by Sox9 knockdown.

Szulwach et al. (2010) found that miR-137, which is regulated by Sox2, is critical for the proliferation and differentiation of adult neural stem cells. It has been observed that the overexpression and the reduction of miR-137, epigenetically induced by MeCP2 (a DNA methyl-CpG-binding protein), enhanced the

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