The Role of microRNAs as Potential Biomarkers in Central Nervous System Disorders

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Abstract

MicroRNA is a non-coding single-stranded RNA able to alter and modulate gene expression. Sustained research in animal models increased the knowledge on the regulatory function of microRNA and its effect on gene expression at the posttranscriptional level in the central nervous system (CNS), with the final goal of developing new therapeutic and diagnostic strategies for CNS disorders.

The existence of a non-coding RNA, classified as microRNA (miRNA), offers new understanding of the molecular mechanisms that regulate cellular processes. miRNAs are a class of small (approx. 21-24 nucleotides) non-coding single-stranded RNAs that control gene expression by base pairing to mRNA transcripts and triggering translation repression or RNA degradation [1]. Since the initial studies performed in Caenorhabditis elegans 15 years ago [1], it is now clear that miRNA is able to alter and modulate the expression of thousands of genes involved in a wide spectrum of physiological processes. The human genome contains at least 695 miRNAs. Increasingly in recent years, the deregulation of miRNA networks has been increasingly implicated in a variety of human disease processes. Accordingly, many approaches are being made to generate knockout models and to provide scientific tools to explore and understand the pathways regulated by specific miRNAs in different tissues. In the last decade, research has expanded the knowledge of the posttranscriptional regulatory function of microRNA upon gene expression in the CNS. Evidence from post-mortem brain analysis and animal studies suggests that approximately 70% of the identified miRNAs are expressed in the CNS with a specific localization [2]. miR-124 is one of the well-known miRNAs involved in neuronal differentiation. Its expression has been detected in neurons, but not astrocytes, and the levels of miR-124 increase over time in the developing nervous system [2]. Gene-dosage effects are clearly implicated in neurodegenerative disorders. For instance, amyloid beta precursor protein (APP) gene duplications [3] or trisomy 21 [4] (which provides an extra copy of the APP gene) are closely correlated with the development of Alzheimer’s disease (AD). Evidence of increased miRNA expression in peripheral blood mononuclear cells (PBMC) has been found in sporadic AD. This may contribute to a new dimension in understanding the pathogenesis of AD and provide accessible blood-based diagnostic and prognostic biomarkers for this condition [5]. The expression of disease-coding genes may be regulated by specific miRNAs and it is logical to assume that changes in this miRNA expression could lead to the accumulation of disease-causing proteins and to neuronal dysfunction and death.

The up-regulation of miR-125b and down-regulation of miR-9 and miR-210 have been implicated in several studies on miRNA expression as indicators of the AD-affected brain [6]. Few miRNAs were found to be consistently changed in AD versus non-demented brains, including miR-107. An observed decrease of miR-107 levels associated with mild cognitive impairment (MCI) was of particular note, as it suggests that decreased miR-107 expression occurs in the earliest stages of AD [7]. Other miRNAs differed between non-demented and AD patients but did not appear to change in the subclinical stages of AD. For example, miR-103 is a close paralogue of miR-107, differing only at a single 3-base locus and was detected only in the clinical phase of AD [5]. The up-regulation of miR-103 was of particular note, as it suggests that decreased miR-107 expression occurs in the earliest stages of AD [7]. Other miRNAs differed between non-demented and AD patients but did not appear to change in the subclinical stages of AD. For example, miR-103 is a close paralogue of miR-107, differing only at a single 3-base locus and was detected only in the clinical phase of AD [5]. Recently, increasing evidence supports the hypothesis that the progressive up-regulation of inflammatory gene expression and inflammatory signaling by miR-146 is linked to the development and progression of AD [8]. The use of anti-miR-146a to repress the effects of up-regulated miR-146a may be a potential therapeutic approach. In 2012, Wang L and Huang Y suggested that applying anti-miR-146a to AD transgenic mouse models is the immediate step towards anti-miR-146a clinical trials for AD [8]. Control of neurodegenerative disease profiling studies is difficult, as it not
possible to compare healthy and diseased tissue from the same source. The underlying mechanisms of how and why miRNAs become deregulated in disease remain largely unknown. Aging and accumulating damage may affect the miRNA genes or miRNA, which would constitute an example of a primary cause of sporadic disease. Recent papers acknowledged that several problems remain unsolved: “(1) to what extent, the peripheral alterations reflect changes in central nervous system; (2) the mechanisms underlying the relationship between miR-146a alterations and the pathological progressive process in AD” [9]. Similar questions also exist in the investigations of miRNA in strokes and other neurological disorders [9,10]. Understanding the roles of miRNAs in human neurological diseases, including traumatic CNS injuries and neurodegenerative diseases, is an important phase in creating new drugs [11]. MiRNAs reduce steady-state protein levels for the targeted gene(s) by posttranscriptional regulation [12]. Modified RNAs can be transiently delivered as a synthetic, preprocessed miRNA, or anti-miRNA oligonucleotides [13]. MiRNAs are important regulators of diverse neurobiological processes such as neurogenesis, neurodifferentiation, growth, proliferation, and apoptosis. A study done by Coriat and Vincent in 2012 showed that anesthetic agents caused microRNA expression to change and the expression pattern was distinct for each anesthetic agent [14]. More studies need to be done in order to link microRNA deregulation with acute processes like emergence delirium and postoperative delirium. Identifying the gene targets and signaling pathways responsible for their neurological effects is critical for future studies, with the final goal being the development of new therapeutic and diagnostic strategies for CNS disorders.

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REFERENCES