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MicroRNAs Role in the Central Nervous System Development and Abnormalities

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Editorial

Initially, non-coding RNAs were thought to be "junk RNAs". MicroRNAs (miRNAs), a group of small non-coding RNA molecules, were discovered in 1993 [1,2]. However, their functions have been found to be associated with diverse biological procedures, including development, metabolism, immunity, hematopoietic differentiation, etc. [3]. It is estimated that miRNAs regulate the activity of approximately 60% of human protein-coding genes [4]. Abnormal miRNA expression may lead to a number of diseases, such as neoplasms [5,6], age-related diseases [7], and neurological disorders [8]. Advances in miRNA research have suggested that miRNAs not only help to understand molecular mechanisms of human CNS diseases, but also have potential to serve as biomarkers for early detection of neurological and/or neurodegenerative alterations.

miRNAs in the Central Nervous System (CNS)

Around 70% of the identified miRNAs are found in the brain [9]. Some miRNAs are specifically expressed and enriched in brain [10], suggesting their specific roles in regulating brain functions. Specifically, miRNAs are implicated in brain development: they regulate embryonic neural induction, development, differentiation, neuronal subtype specification, migration and integration, synaptogenesis and synaptic plasticity [11]. Any interference of miRNA regulations may be associated with aberrant neural development and neurological disorders.

The strikingly regulatory effects of miRNAs on the brain during development vary depending on developmental stages and/or the specific brain regions [10,12-14], contributing to the balance between neural stem cell proliferation and differentiation, therefore directing neural cell fates and brain morphogenesis. In general, miR-124, miR-125b, miR-137, miR-7 are contributing to neuronal differentiation, whereas miR-134, miR-184 are effective in maintaining neural stem cells at the undifferentiated status [15,16]. Indeed, miR-124 has been demonstrated to be the most abundantly expressed in adult brain [17] and is upregulated during neural progenitor cell differentiation and neuronal maturation [18]. miR-137 is found to increase neural stem cell proliferation and decrease differentiation during early development [19,20]. On the other hand, when neurons are differentiated, miR-137 promotes neuronal maturation by facilitating dendritic and axonal morphogenesis, synaptogenesis and spine development [21].

miRNAs have been indicated as important regulators in a number of neurological disorders, ranging from brain and nervous system neoplasms to neurodegenerative diseases such as Alzheimer's disease and Parkinson's disease [22-24]. Potential relationship between miRNAs and schizophrenia has also been identified in some patients [24]. For example, altered miRNA profiles in prefrontal cortex of schizophrenia patients has been detected from postmortem examination [23]. miRNAs bind to the target mRNAs to repress protein translation or increase mRNA degradation. Further identification of miRNA-targeting genes will help us better understand the mechanisms of neurological diseases, achieving our ultimate goal to develop miRNA-based diagnostic methods and effective therapies for clinical practice.

miRNAs as a Potential Biomarker for Early Detection of Neurological Disorders

miRNAs were first known to be inside of cells only, serving as regulators/mediators of cellular events. In 2008, they were found in plasma as well [25]. To date, miRNAs have been detected in most bio-fluids, such as plasma/serum, urine, cerebrospinal fluid (CSF), saliva [26-29]. In contrast to mRNA, extracellular miRNAs are stable and consistent within subjects of the same species [30]. Therefore, it has been proposed that extracellular miRNAs from bio-fluids may be able to serve as biomarkers for various disorders, including neurological diseases. Moreover, extracellular miRNAs alterations could indicate altered biological processes and possible therapies to target the pathological conditions.

Recently, application of miRNAs in easily accessible bio-fluids like plasma/serum as biomarkers for diseases has been widespread. However, current screening techniques used for miRNA biomarker identification are not sufficiently effective and sensitive. A generally used method to identify miRNAs as biomarkers is to compare miRNA profile from patients' bio-fluids with that from control group using miRNA array or next generation sequencing [31]. Although a great number of miRNAs can be analyzed simultaneously, it has been found that the sensitivity is much lower compared with traditional RT-PCR for individual miRNA examination due to the fact that the concentrations of most miRNAs in bio-fluids are very low. To improve the sensitivity, a two-step comparison is performed. Initially, a primary analysis of miRNAs from cells, tissues or organs that are obtained in pathological and normal conditions is performed. In the next step, the differentially expressed miRNAs is to be analyzed and verified [31]. Although there are reports that alteration of miRNAs in bio-fluids are not always consistent with those identified in cells, tissues or organs, this two-step approach has increased the sensitivity and reproducibility in some situations [31].

Similarly, the low concentrations of brain-enriched miRNAs in plasma/serum have resulted in a low detection rate of miRNAs, using current available techniques for identification of biomarkers of neurological diseases. Compared with plasma/serum, identification of

miRNA biomarkers from the CSF for neurological diseases can be advantageous: CSF is exclusively generated and circulating within the brain; the blood-brain barrier effectively prevents miRNAs generated from other sources entering CSF [31]. After miRNAs were first found in CSF [28], several more studies have demonstrated the presence of miRNAs in CSF and their potentials as biomarkers for neurological disease [32-35]. Further, a study comparing miRNA expression profile from serum and CSF has revealed that miRNA expression pattern is quite consistent among different subjects when miRNAs are from the same type of bio-fluid (serum or CSF). In contrast, the miRNA profile is less similar even the miRNAs are from the same subjects, but in different type of bio-fluids (serum or CSF) [36]. The difference suggests that changes in miRNAs relevant to neurological dysfunctions from plasma/serum could be masked by systemic miRNA changes that are not related to nervous system [36], and alteration of miRNA levels in CSF can be more relevant and sensitive for the early detection of neurological diseases.

Evaluation of miRNA in Neural Stem Cells to Study Neurotoxicity

It has been a fast progressing field of research to apply miRNAs as indicators to evaluate the severity of damage/injury for chemical/drug-induced toxicity. Research experimentation on neurotoxicity, especially developmental neurotoxicity is expensive and time-consuming. Establishing cost-effective and time-efficient experimental models and searching sensitive biomarkers for assessment of developmental neurotoxicity is therefore becoming increasingly necessary. As proposed by the National Research Council in 2007 (National Research Council, 2007), the future developmental neurotoxicity tests will depend mostly on *in vitro* models. Under such premise, utilization of human-derived neural stem cells may be the most relevant and effective model for understanding the roles of miRNA in mediating neurotoxic effects in human. In fact, the involvement of miRNAs in developmental neurotoxicity has been already observed in studies using human neural stem cell models [37-40]. The obtained results reveal that changes in miRNA expression may be a practical tool for assessing developmental neurotoxicity, understanding the underlined mechanisms, and developing strategies for therapeutic approaches.

Conclusion

The advances of miRNAs research have enriched our understanding of the CNS development and neurological disorders. Their diverse functions, multiple targets and complicated interacting network imply their profound involvement in the CNS development and functions. When generally the effects of a single miRNA are focused, interaction of multiple miRNAs may cause synergistic or even antagonistic effects. In the CNS, new roles of miRNAs in brain development and neurotoxicity have been just discovered. Although it is still difficult to clarify a cause/effect role of changes in miRNAs for the pathological conditions, application of miRNAs as biomarkers for neurological disorders and neurotoxic testing is promising [41,42].

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