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MicroRNAs in brain aging

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ABSTRACT

Brain aging is one of the most crucial biological processes that affect the physiological balance between health and disease. Age-associated dysfunction of brain leads to severe health problems in current aging society. MicroRNAs (miRNAs) have emerged as important regulators in most physiological processes including fine-tuning of the short-term, cellular regulatory functions as well as modulation of long-term organismal lifespan. In this review, we discuss critical roles of miRNAs in the progression of normal and pathological brain aging. 50% of all known miRNAs are found in brain including cortex and hippocampus. A significant number of expressed miRNAs were differentially regulated during aging, implicating miRNAs as regulators of brain aging. The ability of miRNAs to regulate multiple targets within a pathway or even multiple pathways allows for coordinated regulation of brain functions. miRNA-mediated, brain functional changes are evident in cognition, inflammation, neuroprotection, lipid metabolism, mitochondrial function and lifespan. Dysregulation of brain miRNAs contributes to accelerated cognitive decline and increased neurological disorders. Elucidating mechanisms by which miRNAs and their multiple targets are temporally and spatially regulated in normal and pathological brain aging will provide a deeper understanding on the process of interrelated pathways of brain aging, and a new insight into therapeutic interventions.

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1. Introduction

Brain aging is a complex biological process often associated with a decline in sensory, motor, and cognitive functions. Brain aging itself is not a disease, but is a significant risk factor for most commonneurodegenerative diseases. Although much research has focused on the pathological aspects of brain aging, relatively few studies have investigated the biology of brain aging in normal older adults (Yankner et al., 2008). The process of brain aging is often associated with several structural, chemical, and functional changes in the brain (Driscoll et al., 2003; Chételat et al., 2013; Blalock et al., 2003). Brain shrinkage is particularly observed in the prefrontal cortex and hippocampus, which are critical for learning, memory, planning, and other various complex cognitive processes (Driscoll et al., 2003; Chételat et al., 2013). Morphological and func-

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tional alterations in the blood vessels of the brain along with an increase in neuronal inflammation are apparent (Weiss et al., 2009). It also appears that additional brain regions can be activated in older adults as a part of the compensatory mechanism during brain aging (Spreng et al., 2010).

Aging without the incidence of concurrent diseases can be termed as normal aging. Studies of the neurobiology of normal aging are beginning to decode not only the mechanisms underlying the biology of brain aging, but also the mechanisms that make certain individuals more vulnerable to neurodegenerative diseases. Recent reports on aging human brains and model organisms suggest that brain aging process is accompanied with downregulation of genes controlling synaptic plasticity and mitochondrial function and upregulation of genes involved in stress responses (Lu et al., 2004) Studies also suggest that the aging brain retains functional plasticity, which is influenced and positively promoted by genes activated by various genetic and lifestyle factors; (Alegría-Torres et al., 2013).

A key characteristic feature of aging is the gradual decline in the quality control of components of biological systems. This complex surveillance system is required for the precise regulation of cell- and tissue-specific gene expression regulatory programs, which in turn are essential for the proper function of an organism. Previous reports have shown that deterioration of DNA and/or protein quality control plays a critical role in age-related diseases (Coppedè and Migliore, 2010; Morawe et al., 2012). For example, DNA damage is linked to age-related neurodegenerative diseases. The disruption of protein homeostasis is also closely associated with age-related cognitive diseases, including Alzheimer's disease and Parkinson's disease. Mutations in somatic DNA and proteotoxicity caused by the accumulation of misfolded proteins have also been shown to affect normal aging (Kourtis and Tavernarakis, 2011). However, compared with DNA and proteins, the role of RNA in brain aging remains poorly understood. Evidence from recent studies indicates that noncoding RNAs play important roles in normal and pathological aging, particularly, in the central nerve system (Eacker et al., 2009; Esteller, 2011; Abe and Bonini, 2013). Noncoding RNAs represent a diverse RNA species including miRNAs, tRNAs, rRNAs, snoRNA, and long noncoding RNA, and participate in a series of carefully orchestrated steps, including transcription and processing of primary transcripts into mature mRNAs, export of mRNAs to the cytoplasm, and translation of mRNAs into proteins. In this review, we concentrate exclusively on understanding the roles of miRNAs and their implications in brain aging.

2. MicroRNAs (miRNAs) in aging

miRNAs are small non-coding RNAs of 19–24 nucleotides in length that serve as regulators of gene expression at the post-transcriptional level in both plants and animals. They repress target gene expression by binding to the complementary sites on 3′ untranslated regions of target mRNAs to induce mRNA degradation or translational repression (Bartel, 2004). They are estimated to regulate as many as 60% of all human mRNAs, including mRNAs involved in practically all cellular and molecular functions. miRNAs are emerging as key regulators of neuronal development and function, in addition to being implicated in the pathogenesis of various neurodegenerative disorders (Giraldez et al., 2005; De Pietri Tonelli et al., 2008). Regulation of brain aging is associated with the differential expression of miRNAs, as revealed by a small RNA transcriptome analysis of the whole mouse brain (Eacker et al., 2011; Inukai et al., 2012). It was also recently reported that in the brain, out of 269 hippocampal miRNAs, 80 were differentially expressed between young and old stages of mice (49 of these were upregulated and 31 were downregulated) (Danka Mohammed et al., 2016). The ability of miRNAs to regulate multiple targets simultaneously in numerous interactions of key aging networks allows them to be a critical molecule necessary for various biological processes (Ambros, 2004; Lewis et al., 2005; Huntzinger and Izaurralde, 2001). Aging is a complex process involving the systematic regulation of multiple interconnected signaling pathways. Understanding the critical roles of miRNAs and identifying their downstream target genes in various model organisms reveals the molecular basis of brain deterioration during the aging process. The regulatory roles of miRNAs implicated in brain aging and their neurological functional consequences are discussed below with emphasis on cognition, inflammation, neuroprotection, mitochondrial function, lipid metabolism, and lifespan (Fig. 1). Representative miRNAs and their identified targets in various age-associated brain functions are summarized in

Table 1

3. miRNAs in synaptic plasticity and cognition

Cognitive ability is one of the key factors determining the quality of life in the elderly. Normal aging is often associated with cognitive decline and increased propensity for neurological diseases. Decline in cognitive functions is a characteristic of both normal and pathological aging, and although many studies have been conducted on the neurobiology of learning and memory, there is no general agreement on the factors underlying these neurobiological changes. The hippocampus has been the primary focus of research on the mechanisms underlying normal aging. There is a consensus that many deficits accompanying normal aging are similar to those observed in patients with bilateral hippocampal damage (Geinisman et al., 1995). Aging is one of the greatest risk factors for learning and memory deficits; many of these deficits closely resemble those exhibited during hippocampal atrophy. Previous reports of aging in animals have shown hippocampus-related memory decline, and this causality is highly likely to be extended to the case of humans. Structural and biochemical changes in the hippocampus are associated with normal aging, and these changes may be considered as a critical component of age-associated deterioration of hippocampal-dependent cognition (Driscoll et al., 2003). Patients with damage to the hippocampal formation have shown impairments in spatial and episodic memory. This finding has been confirmed in targeted lesion studies in various species from rodents to nonhuman primates. Aged rats demonstrated impairments in spatial navigation and learning, which are not attributable to visual defects (Rapp et al., 1987). More recent studies have shown an overall preservation of neuron number in the brains of aged rats, mice, monkeys, and humans (West, 1993). The preservation of neurons in terms of both numbers and basic cellular properties suggests that the cause of age-related alterations in memory function is rooted in the functional connections between these preserved neurons.

A recent miRNA profiling study using hippocampal tissues of normal young and old mice has shown that miR-204 is upregulated in aged hippocampal tissue (Danka Mohammed et al., 2016). Increased expression of miR-204 resulted in the downregulation of its target EphB2 by complementary binding to the 3′ UTR of EphB2, which in turn reduced the surface expression of the NR1 subunit of the NMDA (N methyl-D-aspartate) receptor, a key synaptic plasticity-regulating channel protein, in neurons. This mechanism may contribute to the reduction in synaptic plasticity in hippocampal neurons and age-associated decline of cognitive functions in the brain. Regulations of dendritic spine density by miRNAs have recently been reported (Hu et al., 2015). For example, GluR1 is a downstream target of miR-501 under physiological conditions. The expression levels of miR-501 and its target gene, GluR1, are inversely correlated during postna-

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