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Mini Review Article

A Review on the Role of MicroRNAs in Ischemic Stroke Recovery

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Abstract

Ischemic stroke has become is one of the primary causes of morbidity and mortality in the world. MicroRNAs (miRNAs), small ribonucleic acids (RNAs), negatively regulate gene expression on the post-transcriptional level via promoting degradation or translational suppression of their target mRNAs. In recent years, researchers have demonstrated that miRNAs have been implicated in the pathophysiological processes contributing to ischemia-reperfusion injuries and could serve as important mediators of recovery following ischemic stroke. This review, focuses on cerebral miRNAs regulating blood-brain barrier (BBB) function, apoptosis, inflammation, and oxidative stress in stroke. It has been shown that the regulation of miRNAs expression may be a potential therapeutic target in brain ischemia recovery.

Keywords: *Ischemic Stroke, MicroRNA, Neuroinflammation, Blood-Brain Barrier Integrity, Apoptosis, Oxidative Stress Burden.*

Introduction

Ischemic stroke is a cerebrovascular conditions resulting from arterial occlusion in the brain and leads to high morbidity and permanent physical disabilities [1, 2]. Restoration of blood flow after ischemia leads to severe brain damage, due to excessive generation of reactive oxygen species (ROS), intraneuronal overload with Ca2+, and increased blood-brain barrier (BBB) permeability [3, 4]. Ischemic brain injury triggers several pathogenic processes, such as neuroinflammation, excitotoxicity, oxidative stress, ionic imbalance, mitochondrial dysfunction, and apoptosis, causing neuronal cell death and impaired sensory, motor, and cognitive functions [5]. Although many experimental and clinical studies have done, there is no effective therapy for treatment of ischemic insults. Hence, there is a pressure need for discover novel therapeutic steerages to reduce ischemic neuronal insults.

MicroRNAs (miRNAs), belong to class of short-length (21-23 nucleotides) noncoding single-stranded RNA molecules. They are able to bind to the 3′ untranslated region (3′UTR) of target messenger RNA (mRNA) and regulate its stabilization and protein translation [6, 7]. miRNAs are presented in the cerebral system [8] and not only have regulative role in normal physiological and cellular processes (i.e. neuronal development, synaptic plasticity, proliferation, and apoptosis), but also are involved in neurodegenerative diseases via their target genes [9-12]. It is believed that expression of the microRNAs is changed following brain ischemia, and this change can target the translation of proteins that modulate neuroinflammation, cell death, as well as oxidative stress [13]. This review article aims to concentrate on the potential role of miRNAs for treatment of ischemic stroke neuronal injuries.

MicroRNAs in Ischemic Stroke Recovery

miRNAs and Blood-Brain Barrier

Mechanisms including ROS generation, matrix metalloproteinase (MMPs) activation as well as releasing of cytokines cause vascular disruption which eventually leads to BBB dysregulation [14, 15]. Evidence shows changes in BBB integrity and function may modulate by different classes of miRNAs in a way to restore their normal activities [16, 17]. The function of the MiR-132 affects synaptic plasticity and neuronal death. Also, it

is implicated in regulation of the post-stroke physiopathology such as BBB integrity [18]. In light of the negative effects on sexual function by affecting physiological factors (disorders of the vascular-nervous system-endocrine glands) and psychology (decreased self-confidence and changes i experimental and clinical studies, alternations of miR-124 expression in the blood ad brain were reported in ischemic stroke. Exogenous administration miRNA-132 could attenuate brain edema and infarction volume and improve neurological outcomes of the ischemia-reperfusion (I/R) insults in mice. Also, it is not only able to maintain the BBB integrity but also inhibit the expression of MMP-9 (direct target of miR-132), degradation of VE-cadherin and tight junction proteins β-catenin [19].

Cerebral ischemia induces overexpression of miR-130a, and its inhibition regulates ischemic stroke-induced BBB permeability by targeting Homeobox A5 [20]. miR-539 [21] and miR-21 [22] can preserve BBB integrity after brain ischemia through numerous mechanisms including increased expression of tight junctions, regulation of MMP-9, and inhibition of the mitogen-activated protein kinase (MAPK) signaling. As experimental findings shows, up-regulation of miR-149-5p reduces leakage of BBB and is associated with improvement of ischemia outcome through targeting sphingosine-1-phosphate receptor 2 in pericytes [23].

miRNAs and Inflammation, Oxidative Stress, and Apoptosis

Either neuroinflammation or oxidative stress have role in development of stroke insults, eventually leading to neuronal cell injury and apoptosis [24]. Brain ischemic insults trigger the microglial activation and releasing of the inflammatory mediators [25, 26]. During ischemic brain injury, pro-inflammatory cytokines (i.e. interleukin-18 (IL-18)) and interleukin-1β (IL-1β) mediate harmful effects of the inflammatory responses. Moreover, stroke induces excessive production of free radicals and ROS which stimulate N-methyl-D-aspartic acid (NMDA) receptors to increase influx of Ca^{2+} into the neuronal cells and subsequent mitochondrial disruption, as well as activation of neuronal nitric oxide synthase [27]. Intraneuronal overload with Ca^{2+} induces the release of mitochondrial cytochrome c into cytosolic space and its subsequent binding to both apoptotic protease-activating factor-1 and procaspase- 9 and activation of caspase-9 and caspase-3 proteins, causing neuronal apoptosis [28].

Several microRNAs participate in the regulation of oxidative stress, neuroinflammatory reactions and apoptosis [28]. As findings shows, MicroRNA-9a-5p (miR-9a-5p) participates in several physiological processes such as differentiation of neural progenitor cells, neurogenesis, angiogenesis as well as dendritic growth [27, 29]. MiR-9a-5p participates in NLRP1 inflammasome-induced brain ischemic damages. As findings shows, ischemic condition downregulates miR-9a-5p expression which mediate increase of NLRP1 inflammasome proteins, cleaved caspase- 1, IL-1b, and IL-18 levels, while their levels undergo a significant reduction upon overexpression of miR-9a-5pthe in cerebral structures [30]. Zhao et al. [31] reported that overexpression of miR-424 ameliorated neuronal insults after ischemic stroke via abolishing microglial activity. It has been shown that miR-let-7c-5p has anti-inflammatory and neuroprotective effects in cerebral ischemia via preventing of the microgliosis and repression of caspase-3 protein expression [32].

MiR-22 has neuroprotective and angiogenic effects by mediating the PI3K/Akt signaling in a rat model of focal cerebral ischemia [33]. Furthermore, the upregulation of miR-22 reduces I/R induced inflammation and apoptosis [34]. Also, overexpressed miR-31 alleviates inflammatory response and oxidative stress-mediated neuronal injury in ischemic stroke by inhibiting JAK/STAT3 pathway through downregulation of protein kinase D production [35].

CXC motif chemokine ligand 12 (CXCL12) is produced in brain endothelium and considered as a valuable marker for prognosis of the stroke risk. Its expression increases upon brain I/R insults [36, 37]. Clinical and experimental findings shows that miR-874-3p expression was reduced in ischemic conditions [38]. Overexpression of miR-874-3p suppresses CXCL12, induces angiogenesis, and inhibits inflammatory mediators through activation of the Wnt/β-catenin pathway [39]. MiR-579-3p expression has decreased in in vivo and in vitro modal of I/R injury and promoting miR-579-3p expression is associated with improvement in I/R damages and cell necrosis. MicroRNA-579-3p exhibits neuroprotective effects in brain ischemic through the modulation of neuroinflammatry reactions and apoptosis [40]. Upregulated microRNA-539-5p suppresses the neuroinflammatory responses and inhibits the development of brain I/R insults by histone deacetylase1 [41]. The expression of miR 421 was increased upon ischemic injuries. Prevention of miR-421 production through administering antagomir 2h after ischemia may have neuroprotective effects in I/R conditions via lowering oxidative stress burden and apoptosis [42]. Moreover, miR-424 and miR-124 are found to alleviate I/R damage through the reduction of apoptosis, ROS, and malondialdehyde and increasing of superoxide dismutase (SOD) and manganese SOD (MnSOD) [43]. Also, miR-106b-5p and miR-23a-3p have a neuroprotective effect against cerebral ischemia by increasing the MnSOD expression and inhibiting apoptosis [44, 45]. CCAAT enhancer-binding protein b (Cebpb) is involved in inflammation and the progression of brain injury after ischemic stroke [46]. Mitogen-activated protein kinase 8 (Map3k8) can activate p38, which promotes the generation of different kinds of inflammatory factors in neutrophils [47].

MicroRNA 381 3p confers protection against stroke via promoting angiogenesis and repressing the release of inflammatory factors by inhibiting Cebpb and Map3k8 [48]. MiR-195 participates in pro-apoptotic and anti-apoptotic processes. The cell stresses, including shock, hypoxia, and ROS active C-Jun N-terminal kinase (JNK), a subfamily of MAPK that plays a crucial role in apoptosis and inflammation [49]. The miR-195 overexpression protected nerve function and diminished neuronal apoptosis via inhibiting Kruppel-like factor5 (KLF5)-mediated activation of the JNK signaling pathway in rat model cerebral focal ischemia [50].

Table 1 summarized the function of microRNAs in brain ischemia.

Table 1. Mechanisms underlying miRNAs neuroprotective effects in ischemic stroke.

Type of Mechanisms	miRNA	References
Regulation of BBB integrity	miR-132	[19]
	miR-130a	[20]
	miR-539	[21]
	miR-21	[22]
	miR-145-5p	[23]
Reduction of inflammation	miR-9a-5p	[30]
	miR-22	[34]
	miR-31	[35]
	miR-874-3P	[38]
	miR-539-5P	[40]
	miR-381-3P	[48]
		[50]
Decreasing of apoptosis	miR-106b-5p	[44]
	miR-424	[31]
	miR-421	[42]
	miR-22	[34]
	miR-let-7c-5p	[32]
Reduction of oxidative stress	miR-424	[31]
	miR-31	[35]
	miR-421	[42]
	miR-424	[31]
	miR-106b-5p	[44]
	miR-23a-3p	[45]

conclusion

The miRNAs expression is dysregulated following brain ischemia, and these changes play a critical role in stroke pathophysiology. miRNAs modulation might be a new therapeutic approach in ischemic stroke (Figure 1). Further researches on miRNAs are supposed to shed new light on ischemic stroke therapy in the future.

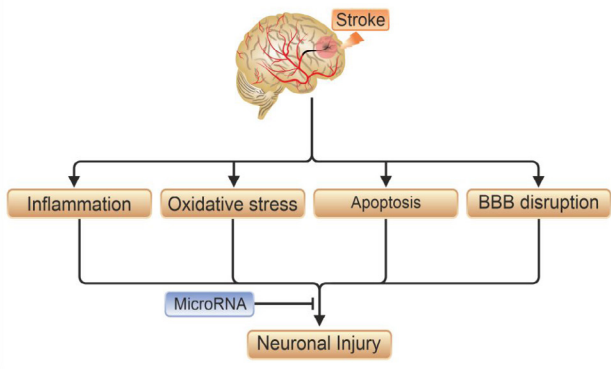

Figure 1. Schematic neuroprotective function of microRNAs in ischemic stroke. BBB: **blood-brain barrier.**

Acknowledgments

Not applicable.

Conflicts of Interest

The authors declare no conflict of interests.

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