REVIEW ARTICLE

MicroRNAs in the Blood-Brain Barrier in Hypoxic-Ischemic Brain Injury

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Abstract: Hypoxic-ischemic (HI) brain injury is a leading cause of acute mortality and chronic disability in newborns. Current evidence shows that cerebral microvascular response and compromised blood-brain barrier (BBB) integrity occur rapidly and could primarily be responsible for the brain injury observed in many infants with HI brain injury. MicroRNAs (miRNAs) are a type of highly conserved non-coding RNAs (ncRNAs), which consist of 21-25 nucleotides in length and usually lead to suppression of target gene expression. Growing evidence has revealed that brain-enriched miRNAs act as versatile regulators of BBB dysfunctions in various neurological disorders including neonatal HI brain injury. In the present review, we summarize the current findings regarding the role of miRNAs in BBB impairment after hypoxia/ischemia brain injury. Specifically, we focus on the recent progress of miRNAs in the pathologies of neonatal HI brain injury. These findings can not only deepen our understanding of the role of miRNAs in BBB impairment in HI brain injury, but also provide insight into the development of new therapeutic strategies for preservation of BBB integrity under pathological conditions.

1. INTRODUCTION

Hypoxic-ischemic encephalopathy (HIE) is the brain injury caused by deprivation of oxygen or impaired cerebral blood flow to the brain in conditions such as placental insufficiency, umbilical cord occlusion, asphyxia, cardiac arrest, and others. The term HIE is sometimes used interchangeably with neonatal encephalopathy (NE) in the literature [1]. It is estimated that HIE occurs in about 1.5 per 1000 live births [2, 3] and is usually associated with severe long-term disabilities including cognitive impairments, epilepsy and cerebral palsy [3, 4]. Similar to ischemic stroke, brain injury in HIE also results from a cascade of pathological events triggered by hypoxia/ischemia and evolves overtime [3-6]. The cerebral vascular cells are negatively affected over the course of HI pathology, leading to the opening of the blood-brain barrier (BBB), the structure that restricts material exchange between the blood and the brain parenchyma. Neonatal HIE showed rapid BBB disruption hours after the onset of HI insult in animal models [7-10]. Consistently, a clinical study found increased serum albumin in cerebrospinal fluid of neonates suffering from HI brain injury, and the permeability of BBB increased with the progression of HIE [11]. Therapeutic hypothermia is by far the only treatment available for HIE. Clinical trials have shown a reduction of infant

death and disability due to hypothermia therapy, but death and disability in infants with severe to moderate HIE remain to be a big challenge for HIE treatment [12].

MicroRNAs (miRNAs) are a class of small non-coding RNAs that are well known for their ability to post-transcriptionally modulate gene expression. They are increasingly recognized as master regulators of cellular processes through regulating one-third of the genes encoded. Mature miRNAs are single-stranded RNAs of 21-25 nucleotides in length and target specific messenger RNAs (mRNAs) for degradation or suppression by complementary binding to their 3'-untranslated region (3' UTR) [13, 14]. Encoded by about 1% of the genomic transcripts, thousands of miRNAs have been found in the human genome [15]. Cumulating evidence suggests that miRNAs may play a very important role in brain development and pathogenesis of neurological diseases such as ischemic stroke [13, 16, 17]. In the adult brain, the role of miRNAs in the modulation of BBB functions has been widely studied, and therapies based on miRNAs have shown to improve some outcomes of stroke in preclinical models of ischemic stroke. However, a majority of these studies focus on the mature brain, while BBB disruption and protection in the developing brain is less studied. Our understanding of the regulation of the BBB in the developing stage is still limited, thus the summary of findings from the adult brain could help us gain insights into BBB manipulations in the developing brain. However, cautions should be taken while extrapolating the data in consideration of the differences in the BBB between the mature and imma-

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ture brain. Herein, we have reviewed current knowledge on the BBB in the developing brain. We have summarized the progress of miRNAs in the modulation of BBB functions in ischemic stroke and highlighted several miRNAs that are implicated in the pathogenesis of neonatal HI brain injury.

2. COMPONENTS AND STRUCTURE OF THE BLOOD-BRAIN BARRIER IN THE IMMATURE BRAIN

The BBB is a diffusion barrier primarily located at the cerebral capillaries. In the traditional concept, the BBB includes brain microvascular endothelial cells (ECs), pericytes, astrocytes and basement membrane, while a more conventional concept of the neurovascular unit (NVU) also includes perivascular microglia, smooth muscle cells and neurons. This so-called NVU plays important roles in neurovascular coupling and maintaining vascular homeostasis in CNS [18-22]. The barrier function of BBB is primarily attributed to a non-fenestrated layer of ECs that are assembled by junctional complexes consisting of tight junctions (TJs) and adherens junctions (AJs). The TJs seal the intercellular cleft and restrict paracellular transport, while the AJs are responsible for initiating and stabilizing endothelial cell-cell contact [23, 24]. There are now over 40 proteins identified within TJs, including claudins, occluding, and zonula occludens (ZO) [25]. The barrier function of the ECs is complemented and regulated by the cellular and non-cellular components of the NVU.

Despite the early belief that the BBB is 'leaky' in the immature brain, experimental evidence reported that the BBB is fully functional during brain development [26, 27]. It was shown that TJ proteins such as occludin and claudin 5 are present in the barrier interface soon after the first vessels invading the brain [27]. The endothelial permeability is tightly restricted at embryonic day (E) 15 and the tight junctions are completely differentiated at E19 in mice [28]. ECs, pericytes, and basement membrane are all present in the BBB, while astrocytes are mostly absent at the early stage of BBB development [27]. Astrogenesis starts around E18 and lasts around a week [29]. The mature astrocytes are critically involved in regulating BBB function [27, 28, 30].

3. MECHANISMS FOR BBB DISRUPTION AFTER BRAIN ISCHEMIA

The cellular responses of the BBB and mechanisms of BBB dysfunction after ischemic stroke have been comprehensively reviewed elsewhere [31, 32]. Briefly, the injured ECs show cytoskeletal rearrangement and increased transcytosis of the TJ associated proteins, leading to the opening of BBB. Increased adhesion of immune cells to the injured endothelium further promotes TJ protein redistribution and immune cell infiltration [33]. Infiltrated neutrophils as well as other injured cells produce matrix metalloproteinases (MMPs), a type of calcium-dependent zinc-containing endopeptidase that contributes to the degradation of TJs and extracellular matrix (ECM) [31]. Cytokines and chemokines released during neuroinflammation further exacerbate BBB breakdown by activating healthy ECs and modifying TJ proteins. It is recently confirmed that BBB disruption proceeds infarction development and blocking of early BBB dysfunc-

tion provides parenchymal protection in the ischemic stroke model in mice [34, 35].

In the developing brain, the vulnerability of BBB to hypoxia/ischemia varies depending on the developmental stage. In the preterm brain, BBB in the germinal matrix has relatively low pericyte coverage, few astrocytic ensheathment, immature basal membrane, and high local production of endothelial growth factor (VEGF), angiopoietin-2 (angpt2) and MMPs that make the preterm brain prone to hemorrhage [36]. This condition is changed at term. Studies from neonatal arterial stroke animal models using transient middle cerebral artery occlusion (tMCAO) revealed that the BBB in the brain at term is more resistant to ischemic insult [37]. They found that some BBB-associated proteins that were profoundly changed in the adult stroke, such as collagen type IV α1 (col4a1), col4a2 and ECM proteins were better preserved in experimental HIE. Yet BBB disruption and brain edema were still rapidly observed in experimental HIE, especially in cases where a more severe injury is implemented [7, 8, 10]. In clinic, 86% of term neonates suffering from severe HIE develop brain edema, which is usually associated with poor neurological outcome [38]. Consistently, experimental HIE showed decreased TJ proteins such as claudin-5, occludin and ZO-1 [7, 8], as well as increased infiltration of neutrophil and other immune cells [10]. Increased MMP-9 and inflammatory cytokines are found in the serum of neonates with HIE [39]. Those changes are similar, though they may be less severe compared to the adult brain under the same conditions [36]. However, evidence on the cellular and molecular mechanisms for BBB disruption and repair in HIE is still limited. The data from ischemic stroke may not fully apply to HIE. Future efforts are needed to study the mechanism of BBB disruption, as well as its impact on the progress of neuropathology in the immature brain.

4. BIOGENESIS OF miRNAs

MiRNA genes are mainly located in either non-coding areas or introns within coding genes in the genome. The biogenesis of miRNAs has been described in detail elsewhere [40]. In the canonical pathway, the primary miRNAs (pri-miRNAs) are transcribed by polymerase II from miRNAs genes. Those long pri-miRNAs are then processed by RNase III protein Drosha to form precursor miRNA (pre-miRNAs) which is then transported to the cytoplasm. In the cytoplasm, the pre-miRNAs are cleaved by another RNase III protein Dicer and TRBP, giving rise to miRNA duplex. One strand of the duplex is selected to incorporate into the RNA-induced silencing complex (RISC) which degrades mRNAs in the guidance of loaded miRNA sequence. A few miRNAs are processed through non-canonical pathways that are independent of Drosha or Dicer [40, 41]. It is proposed that miRNAs act in networks. One miRNA influences multiple transcripts within the targeted signaling network, and several miRNAs can target a single mRNA or multiple mRNAs in a signaling pathway to achieve a biological effect [42]. The level of mature miRNA in cells is subjected to transcriptional regulations and RNA modifications that interfere with the maturation process [40, 43]. Thus, miRNAs are sensitive to environmental factors and external stimuli, such as the presence of growth factors, inflammation or hypoxia.

MiRNAs are also found extracellularly [44, 45]. They exist in biological fluids including blood plasma, cerebrospinal fluid, saliva, urine, breast milk, tears and many others [46], in which miRNAs are packaged in membrane vesicles such as apoptotic bodies, shedding vesicles and exosomes [47, 48], or bound to Argonaute (AGO) proteins which stabilize them from being degraded by RNases in the body fluids [49]. A diverse range of cell types contributes to the pool of extracellular miRNAs which may be part of the communication system between different cells or organs [50]. A number of studies have reported that miRNAs are packed in apoptotic bodies, and exosomes can be taken up by recipient cells and exert functional effects [50]. Therefore, both locally synthesized miRNAs and those found in the circulation system may be involved in the regulation of the BBB.

5. POTENTIAL ROLE OF miRNAs IN BBB DISRUPTION

The role of miRNAs in stroke and BBB protection has been widely studied. Many differentially expressed miRNAs can positively or negatively manipulate BBB functions in *in vitro* and/or *in vivo* model for stroke [32]. These miRNAs may fall into different categories according to their targets.

5.1. MiRNAs and Junction Proteins

Tight junction protein degradation is a major contributor to BBB disruption. The TJ and AJ proteins such as claudins, occludins and cadherins are subjected to degradation by MMPs, which is directly regulated by miRNAs. For instance, the expression of miR-132 was increased in the blood of stroke patients. Agomir-132 (exogenous miR-132) suppressed the transcript of MMP-9 and decreased the degradation of VE-cadherin in a mouse model of ischemic stroke [51]. Another study showed increased miR-539 expression in the brain tissue in rats after ischemia, which directly inhibits MMP-9 expression and protects ECs from oxygen-glucose deprivation (OGD)-induced EC monolayer hyperpermeability [52]. Moreover, other miRNAs have been found to directly target signaling pathways that regulate the expression, distribution and degradation of the junctional proteins. For example, miR-150 increased BBB permeability by targeting Tie-2 [53], an angiopoietin receptor that positively regulates vascular barrier function [54, 55]. MiR-143, which was upregulated after ischemic stroke in both human and animal models, was shown to target the E3 ubiquitin-protein ligase Hectd1 and enhance endothelial-mesenchymal transition associated with BBB disruption [56]. MiR-130a, which predominantly increased in ECs after ischemia, decreased tight junction protein expression by binding to transcription factor homeobox A5 [57]. MiR-155 targets claudin 1, and inhibition of which increases claudin1 and ZO-1 expression in human brain microvascular ECs [58]. In addition, miRNAs have been found to regulate junctional protein in other brain disorders [32].

5.2. MiRNAs and Cellular Components of the BBB

Endothelial cell injury after HI insult is the initial phase of BBB disruption. Thus, modulation of miRNAs related to endothelial cell damage is beneficial for preserving the BBB integrity. For example, miR-34a is upregulated in ECs after HI insult, which negatively affects mitochondria function in ECs by targeting Cytochrome c. Moreover, miR-34a knockout reduces BBB permeability, alleviates disruption of tight junctions, and improves stroke outcomes [59, 60]. MiR-26b inhibits autophagy and survival of ECs under OGD by targeting ULK2 and its endogenous sponge malat1 overturns the effect of miR-26b [61]. MiR-15a is upregulated in mouse cerebral ECs after OGD and induces EC death by targeting bcl-2. Further study showed that miR-15a is negatively regulated by peroxisome proliferator-activated receptor (PPAR) delta, a potential neuroprotectant in ischemic stroke [62]. Besides the primary contribution of ECs to the barrier function of the BBB, other cellular components such as astrocytes and pericytes also contribute to the regulation of the BBB permeability. Pericytes are the important regulator of BBB functions. Upon HI insult, pericytes separate and migrate away from the basement membrane, contributing to the BBB dysfunction. MiR-149-5p exerts its BBB protective effect by regulating pericyte migration. Further mechanical study revealed that miR-149-5p increased N-cadherin expression and decreased cell migration by negatively regulating sphingosine-1-phosphate receptor (S1PR) 2 and its downstream NF-kB/p65 pathway in cultured pericyte exposed to OGD [63]. Aquaporin-4 (AQP-4) is an active regulator of water flux, which is primarily expressed on the endfeet of astrocytes and plays an important role in edema formation. It has been documented that overexpression of miR-29b down-regulates AQP-4 and reduces cerebral edema in mice model of ischemic stroke [64]. Moreover, miR-130a and miR-320 were also shown to be transcription repressor and inhibitor of AQP-4 [65, 66]. However, cautions should be taken when designing therapeutics based on AQP-4 due to its reported ability to increase vasogenic edema [67]. AQP-4 activity is mainly associated with reduced cerebral edema in the neonatal brain [68].

5.3. MiRNAs and Neuroinflammation

Neuroinflammation is greatly increased after neonatal HI insult. The BBB at the interface of the blood and the brain parenchyma is prone to injury induced by immune cell infiltration and cytokine signaling. Some miRNAs can protect BBB integrity by reducing immune cell adhesion and pro-inflammatory cytokine expression. For instance, overexpression of miR-126-3p and -5p in the ischemic mice brain down-regulated pro-inflammatory cytokines and adhesion molecules, preserving BBB integrity and improving stroke outcome [69]. MiR-146a expression was increased in the brain tissue in a mouse model of ischemia stroke. Inhibition of miR-146a was shown to exacerbate BBB leakage after ischemic stroke by over-activating NF-kB signaling, increasing expression of inflammatory cytokines and its direct target, interleukin-1 receptor-associated kinase 1 (IRAK1)[70]. MiR-98, which is significantly reduced in the ECs after HI insults, was shown to reduce BBB permeability, leukocytes infiltration and microglia activation [71]. In addition to anti-inflammation, a number of miRNAs were shown to exhibit a pro-inflammatory effect and exacerbate BBB function after ischemic stroke. For instance, miR-210 up-regulates the expression of TNF-α, IL-1β, IL-6 CCL1 and CCL2 that are associated with pro-inflammatory response in a mouse model of ischemic stroke [72]. MiR-155 is strongly induced

by cytokines and mediates cytokine-induced hyperpermeability in ECs monolayer, whereas inhibition of miR-155 partially prevented monolayer damage [73]. Therapies based on those miRNAs may also show a potential protective effect on the BBB.

6. MiRNA IN THE DEVELOPING BRAIN AFTER HI BRAIN INJURY

Comparing to the large amount of studies investigating the role of miRNAs in brain injury in adults, only a few studies have focused on the expression of miRNAs in neonatal HIE [16]. Several miRNAs were found to be associated with HIE. For instance, miR-210 is up-regulated in the maternal blood of severely growth-restricted infants [74] and in the mouse hemisphere after HI brain injury [75]. MiR-210 is a master hypoxamir, which is regulated by HIF-1α and NF-κB during hypoxia [76]. It has been reported that miR-210 exerts a wide range of biological activities, including mitochondrial metabolism, angiogenesis and cell differentiation [13, 76]. In the normal brain, overexpression of miR-210 promotes angiogenesis and neurogenesis [77]. Our study found that HI insult significantly overexpressed miR-210 levels in the neonatal brain, which exacerbated BBB permeability by downregulating the expression of occludin and β-catenin after HI insult [78]. Moreover, inhibition of miR-210 exerted neuroprotective effect as well as anti-inflammation effect in the neonatal and adult brain [75, 79, 80]. Other studies have shown that miR-210 mediates the protective effect of vagus nerve stimulation on ischemic stroke and promotes neural precursor cell accumulation around ischemic region [81, 82]. It is possible that miR-210 have multiple targets in the brain to exert multiple functions that differ at injury and recovery stage of ischemic stroke and neonatal HIE. As a potential therapeutic target for HIE, more studies are needed to further determine the effect of miR-210 over the course of HI brain injury in neonates.

In addition to miR-210, other miRNAs, including miR-21, miR-374a, miR-424, miR-199a and miR-20b, are also potentially associated with neonatal HIE [74, 83]. MiR-21 upregulated TJ proteins in an animal model of traumatic brain injury [84] and a neuroprotective effect of miR-21 in ischemic stroke was also reported [85]. The effects of miR-374a, miR-199a and miR-424 have also been studied in ischemic stroke. However, their effects in the neonatal HIE are yet to be determined. Moreover, miR-146a, miR-155, miR-124 and let-7f have been implicated for the regulation of neuroinflammation, mainly microglia related response in the neonatal brain [86]. Among them, the miR-146a and let-7f showed a protective effect toward hypoxia in the neonatal brain [87, 88]. How neuroinflammation contributes to the BBB disruption in the neonatal brain after HI insult remains to be studied.

CONCLUSON

BBB protection has been widely recognized as a potential therapeutic strategy for the treatment of ischemic stroke. Cumulating evidence has shown that miRNA-based therapies such as miRNA mimics and inhibitors can manipulate miRNAs in the brain and protect BBB integrity in experimental stroke. However, those therapies are facing major challenges such as the lack of efficient drug delivery system to the brain, short half-life of the therapeutic molecules and the presence of off-target effects [89]. There may be still a long way to go to achieve success in the clinical translation of those therapeutics. Moreover, the molecular and cellular mechanism of BBB dysfunction in neonatal HI brain injury remains to be elucidated. The role of miRNAs in the pathogenesis of HIE is largely unknown. Despite the rich knowledge on BBB protection in ischemic stroke, the physiological difference between the developing and mature brain may limit the applicability of the data extrapolated from ischemic stroke. Future studies are needed to fill in the gap regarding BBB protection in the developing brain.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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