MicroRNAs' Role in the Treatment of Subarachnoid Hemorrhage

Subjects: Health Care Sciences & Services

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Subarachnoid hemorrhage (SAH) is most commonly seen in patients over 55 years of age and often results in a loss of many productive years. SAH has a high mortality rate, and survivors often suffer from early and secondary brain injuries. Understanding the pathophysiology of the SAH is crucial in identifying potential therapeutic agents. One promising target for the diagnosis and prognosis of SAH is circulating microRNAs, which regulate gene expression and are involved in various physiological and pathological processes.

aneurysmal subarachnoid hemorrhage microRNAs neuroinflammation treatment

1. Subarachnoid Hemorrhage

Subarachnoid hemorrhage (SAH) typically affects patients over the age of 55, resulting in a significant loss of productivity. In 85% of cases, SAH is caused by the rupture of intracranial aneurysms (IA) which occur due to abnormal dilation of arteries resulting from increased pressure in the arteries and vessel structure disorders. Aneurysms often form at the bifurcation of arteries where the high flow of blood can damage the weakened wall of the artery [1]. While there has been a 17% increase in survival from aneurysmal subarachnoid hemorrhage, survivors commonly experience cognitive impairments that that can significantly impact their daily functioning, quality of life, and working capacity [2]. Not-traumatic SAH can lead to early and secondary brain injuries, with early brain injury occurring within 72 h of symptom onset [2] and secondary brain injury caused by cerebral vasospasm and delayed cerebral ischemia [3]. Approximately 50–90% of patients with angiography experience vasospasm [4].

2. MicroRNA

MicroRNAs (miRNAs) were discovered about 30 years ago in the nematode *Caenorhabditis elegans* [5]. At the same time, RNA interference pathways were discovered, and the most important one was the 21 nucleotide RNA triggers of silencing machinery. Further research showed that these two pathways are the same gene silencing pathway [6]. More than 2000 miRNAs have been discovered in humans, and it is believed that all of them participate in the regulation of one-third of the genes in the genome [6]. miRNAs are endogenous non-coding RNAs with 18–22 nucleotides. miRNAs interfere with the non-translatable 3′ (3′UTR) regions of the mRNAs and regulate gene expression at the post-transcriptional level. The importance of miRNAs was demonstrated by knocking out genes of the enzyme Dicer and Drosha (two enzymes that have critical function in miRNAs processing); knockout

of these genes in the mouse model resulted in embryonic lethality [7][8]. In the same way, any tissue-specific knockout of these genes causes defects in the tissue development [9]. The miRNA gene can be in the introns or exons or can be as standalone transcription units [10][11][12]. Their genes are not usually in the exons because their excision would lead to non-functional protein production [6]. Recent studies have shown that miRNAs are highly conserved in humans [13]. miRNAs have a prominent role in the cellular development and in the nervous system. They have an important role in neuroplasticity, development of neurons, dendritic spine development, neuronal remodeling, memory formation (in the amygdala), neuronal survival, and other neurobiological processes and diseases, and the expression profile can differ in pathological situations [14][15][16][17][18][19]. miRNAs regulate gene expression and are involved in different physiological and pathological processes. miRNAs are tissue-specific; for example, miR-9, miR-124a/b, miR-135, miR-153, miR-183, and miR-219 are expressed in differentiating neurons [20].

Neuroinflammation drives damage progression in IA and SAH. Because of its role in immune cell response regulation and inflammatory gene expression, miRNA could be a promising target for minimally invasive diagnostic and prophylactic purposes [21]. Tissue cells secrete miRNAs into the circulation and other biological fluids inside vesicles. miRNAs can be detected in the cells, tissues, and body fluids such as serum, plasma, tears, urine, or cerebrospinal fluid (CSF) [22]. For this reason, these circulating miRNAs are a novel target for the diagnosis and prognosis of a SAH [23].

3. MicroRNA-Based Therapies for SAH

In preclinical studies, miRNAs have been investigated as potential therapeutic agents and biomarkers for SAH or IA. In a murine SAH model, upregulation of miR-452-3p expression was observed along with increased pro-inflammatory factors and decreased anti-inflammatory factors. The inhibition of miR-452-3p reversed these trends by targeting histone deacetylase 3 (HDAC3). SAH also upregulated p65 acetylation, which was decreased by miR-452-3p inhibitor, leading to the upregulation of IκBα. However, Suberoylanilide hydroxamic acid (SAHA) reversed the protective effect of miR-452-3p inhibitor and aggravated mice brain injury. These findings highlight the potential effect of miR-452-3p and its inhibitor as therapeutic targets for SAH management [24].

Lai et al. discovered miR-193b-3p, a miRNA derived from bone mesenchymal stem cells, in an SAH model with male mice [25]. Systemic injection of miR-193b-3p downregulated HDAC3 and decreased p65 acetylation. Treatment with miR-193b-3p also reduced the levels of inflammatory cytokinesIL-1β, IL-6, and TNF-α in the brain tissue of mice following SAH [25]. These findings suggest that miRNAs and anti-miRNAs can modulate neuroinflammation through the HDAC3/NF-κB signaling in IA, early brain injury, and SAH (**Table 1**). In another study, Lou et al. demonstrated that the HDAC inhibitor SAHA protected against neuronal injury following SAH by increasing miR-340, which attenuated pyroptosis and the NEK/NLRP3 pathway [26].

Table 1. Micro-RNAs role in the diagnosis, treatment and prognosis of SAH.

First Author	Year	miRNA(s) Evaluated	Subjects Evaluated	Specimen Evaluated	Main Findings
Su XW	2015	miR-132-3p, miR-324-3p	Human	CSF	Circulating miR-132-3p and miR-324-3p may be potential biomarkers for acute aneurysmal SAH.
Wang WH	2016	miR-29a	Human	Blood	miR-29a may be a potential biomarker in the development of intracranial aneurysm.
Zaccagnini G	2017	miR-210	Mouse	Ischemic tissue	Overexpression and significance in ischemic tissue damage.
Sheng B	2018	miR-1297	Human	Serum	Early serum miR-1297 is an indicator of poor neurological outcome in patients with aSAH.
Sheng B	2018	miR-502-5p	Human	Serum	Persistent high levels of miR-502-5p are associated with poor neurologic outcome in patients with aneurysmal subarachnoid hemorrhage.
Feng X	2018	miR-143, miR-145	Human	Serum	Lower miR-143/145 levels and higher MMP-9 levels may be associated with intracranial aneurysm formation and rupture.
Li	2018	miR-24	Rat	Brain tissue	Upregulation of miR-24 expression led to vasospasm by suppressing endothelial nitric oxide synthase expression after SAH.
Yu S	2018	miR-22	Rat	Brain tissue	Neuroprotective effects in regulating inflammation and apoptosis.
Yang X	2019	miR-155	Human	Blood	A functional polymorphism in the promoter region of miR-155 predicts the risk of intracranial hemorrhage caused by ruptured intracranial aneurysm.
Zhao	2019	miR-206	Rat	Used as a therapeutic target	HucMSCs-derived miR-206-knockdown exosomes targeted BDNF, contributing to neuroprotection after SAH.
Wang S	2019	miR-140-5p	Rat	Used as a therapeutic target	Attenuated neuroinflammation and brain injury by targeting TLR4.
Geng W	2019	miRNA-126	Rat	Used as a therapeutic target	Exosomes from miRNA-126-modified ADSCs promote functional recovery after stroke in rats by improving

First Author	Year	miRNA(s) Evaluated	Subjects Evaluated	Specimen Evaluated	Main Findings
					neurogenesis and suppressing microglia activation.
Yang F	2020	miR-126	Human umbilical vein endothelial cell	Human umbilical vein endothelial cell	miR-126 may be involved in the development and rupture of intracranial aneurysms.
Lai	2020	miR-193b-3p	Mouse	Used as a therapeutic target	Systemic exosomal delivery of miR-193b-3p attenuated neuroinflammation and improved neurological function after SAH.
Chen	2020	miR-124	Rat	Used as a therapeutic target	CX3CL1/CX3CR1 axis promoted exosomal delivery of miR-124 from neuron to microglia, attenuating early brain injury after SAH.
Xiong L	2020	miRNA-129-5p	Rat	Used as a therapeutic target	Exosomes from bone marrow mesenchymal stem cells can alleviate early brain injury after subarachnoid hemorrhage through miRNA129-5p-HMGB1 pathway.
Gao X	2020	miRNA-21-5p	Rat	Used as a therapeutic target	Extracellular vesicle-mediated transfer of miR-21-5p from mesenchymal stromal cells to neurons alleviates early brain injury to improve cognitive function via the PTEN/Akt pathway after subarachnoid hemorrhage.
Wang	2021	miR-103-3p	Rat	Used as a therapeutic target	Inhibition of miR-103-3p preserved neurovascular integrity by upregulating caveolin-1 expression after SAH.
Deng	2021	miR-24	Rat	Used as a therapeutic target	miR-24 regulated inflammation and neurofunction by targeting HMOX1 expression in rats with cerebral vasospasm after SAH.
Liu Z	2021	miRNA-26b-5p	Rat	Used as a therapeutic target	MiR-26b-5p-modified hUB-MSCs-derived exosomes attenuate early brain injury during subarachnoid hemorrhage via MAT2A-mediated p38 MAPK/STAT3 signaling pathway.
Cai L	2021	circARF3	Rat	Used as a therapeutic target	Up-regulation of circARF3 reduces blood-brain barrier damage in rat subarachnoid hemorrhage model via miR-31-5p/MyD88/NF-κB axis.

First Author	Year	miRNA(s) Evaluated	Subjects Evaluated	Specimen Evaluated	Main Findings
Ru X	2021	miRNA-706	Mouse	Used as a therapeutic target	MiR-706 alleviates white matter injury via downregulating PKCα/MST1/NF-κB pathway after subarachnoid hemorrhage in mice.
Lu	2022	miR-452-3p	Rat	Used as a therapeutic target	miR-452-3p inhibited HDAC3 expression, leading to activation of NF-κB signaling and exacerbation of early brain injury after SAH.
Qian Y	2022	miR-140-5p	Mouse	Used as a therapeutic target	Alleviated M1 microglial activation in brain injury via miR-140-5p delivery.
Wang P	2022	miRNA-140-5p	Rat	Used as a therapeutic target	Exosome-encapsulated microRNA-140-5p alleviates neuronal injury following subarachnoid hemorrhage by regulating IGFBP5-mediated PI3K/AKT signaling pathway.
Cheng M	2022	miRNA-83-5p	Rat	Used as a therapeutic target	Extracellular vesicles derived from bone marrow mesenchymal stem cells alleviate neurological deficit and endothelial cell dysfunction after subarachnoid hemorrhage via the KLF3-AS1/miR-83-5p/TCF7L2 axis.
Zhou X	2022	miRNA-499-5p	Rat	Used as a therapeutic target	Suppression of MALAT1 alleviates neurocyte apoptosis and reactive oxygen species production through the miR-499-5p/SOX6 axis in subarachnoid hemorrhage.
Luo	2023	miR-340	Rat	Used as a therapeutic target	HDAC inhibitor SAHA upregulated miR-340 expression, which inhibited NEK7 signaling and attenuated pyroptosis after SAH.
Wang P	2023	miR-140-5p	Rat	Used as a therapeutic target	Attenuated microglia activation and inflammatory response via MMD downregulation.

CSF: cerebrospinal fluid, SAH: subarachnoid hemorrhage, MMP: Matrix metalloproteinase, BDNF: Brain derived neurotrophic factor, ADSC: Adipose derived stem cells.

In a rat SAH model, miR-103-3p was found to be upregulated and caused a decrease in Cav-1, leading to reduced neuroprotective effects. Therefore, inhibition of miR-103-3p could be a potential therapeutic strategy to preserve Cav-1 and maintain blood–brain barrier integrity, making it a novel target for SAH treatment (**Table 1**) [27].

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Research has identified significant roles for miRNAs and their regulation of TNF-α, both in pro- and anti-inflammatory contexts. Chen et al. investigated the effects of miR-124, the most abundant miRNA in the central nervous system, by CX3CL1 and CX3CR1 [28]. Upregulation of miR-124 in microglia inhibits CEBPα, a target protein, and downregulates TNF-α, thereby reducing microglia activation and signaling downstream cascades after SAH [28]. The study suggested that CX3CL1/CX3CR1-mediated transport of miR-124 in exosomes from neurons to microglia may regulate neuroinflammation in an SAH rat model [28].

MiRNA-24 targets the 3′UTR of endothelial nitric oxide synthase (NOS3), and elevated miRNA-24 levels have been associated with vasospasm in SAH patients [29]. Conversely, downregulation of miRNA-24 increases HMOX1 expression, resulting in inflammation reduction and improvement in neurological function in a rat SAH model [30].

MiRNA changes can also affect the brain-derived neurotrophic factor (BDNF)/tyrosine kinase B (TrkB)/cAMP-response element-binding protein (CREB) (BDNF/TrkB/CREB) pathway [21]. In a rat SAH model, Zhao et al. targeted BDNF with miR-206 delivered through exosomes derived from human umbilical cord mesenchymal stem cells (hucMSCs) [31]. Knockdown or down regulation of miR-206 increased BDNF expression in rats with SAH through the CREB pathway in vivo, resulting in improved neurological function [32]. CREB is a target of miR-34b, and downstream activation of the PI3K/Akt/NF-κB pathway is known to be influenced by phosphorylated CREB, leading to inhibition of NF-κB activation and a reduction in the proinflammatory response [33].

MiR-140-5p has demonstrated neuroprotective properties by suppressing toll-like receptor 4 (TLR4) and inhibiting downstream phosphatidylinositol 3-kinase/AK/nuclear factor-κB (PI3K/AKT/NF-κB) inflammatory signaling in rat brain tissue. A study showed that microglia-secreted extracellular vesicles (microglia-EVs) inhibited microglia activation and decreased TNF-α and IL-1β release after injection of miR-140-5p. Microglia-EVs were able to transfer miR-140-5p into microglia. Treating with microglia-EVs-miR-140-5p also reduced macrophage differentiation-associated (MMD) and blocked the inflammatory cascade and microglia response in SAH rats by suppressing the PI3K/AKT and Erk1/2 pathway [34][35]. Furthermore, increased miR-140-5p has been found to downregulate activin-like kinase 5 (ALK5) and NADPH oxidase 2 (NOX2), consequently inhibiting inflammatory M1 microglia activation in SAH mice [36]. These findings suggest that miR-140-5p may have therapeutic potential for the treatment of neuroinflammatory disorders such as SAH.

Makino et al. demonstrated in an aneurysm mouse model that tetracycline derivatives, including minocycline and doxycycline, have anti-inflammatory effects that could be used in aneurysm stabilization and rupture prevention [37]. Both minocycline and doxycycline treatments, through intraperitoneal injection and gavage, respectively, were found to have beneficial effects compared to their corresponding sham groups. While Makino et al. did not include a mechanistic investigation, subsequent studies have found that minocycline and doxycycline enhance brain-derived neurotrophic factor (BDNF) expression, decrease reactive oxygen production, and lessen inflammation through regulation of miR-155 and miR-210 [38][39]. These findings suggest that miR-155 and miR-210 may have therapeutic potential in the prevention of aneurysm rupture through their anti-inflammatory effects. In a murine SAH model, miR-22 was found to be upregulated compared to control mice without SAH, resulting in a decrease in IL-6 [40]. Lowering the expression of miR-22 increased IL-6 expression and led to neuroprotective effects. Increasing the

miR-22 expression also suppressed the caspase-3/Bax signaling pathway. These results suggest that miR-22 may be a potential therapeutic agent for the treatment of SAH [40].

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